Arch. Pharm. Res. (2021) 44:903–986
https://doi.org/10.1007/s12272-021-01354-2

Online ISSN 1976-3786
Print ISSN 0253-6269

Archives of Pharmacal Research
www.springer.com/12272

REVIEW

Genus *Sophora*: a comprehensive review on secondary chemical metabolites and their biological aspects from past achievements to future perspectives

Howaida I. Abd-Alla[1] · **Dalila Souguir**[2] · **Mohamed O. Radwan**[1,3]

Received: 16 July 2020 / Accepted: 29 October 2021 / Published online: 15 December 2021

Abstract *Sophora* is deemed as one of the most remarkable genera of Fabaceae, and the third largest family of flowering plants. The genus *Sophora* comprises approximately 52 species, 19 varieties, and 7 forms that are widely distributed in Asia and mildly in Africa. *Sophora* species are recognized to be substantial sources of broad spectrum biopertinent secondary metabolites namely flavonoids, isoflavonoids, chalcones, chromones, pterocarpans, coumarins, benzofuran derivatives, sterols, saponins (mainly triterpene glycosides), oligostilbenes, and mainly alkaloids. Meanwhile, extracts and isolated compounds from *Sophora* have been identified to possess several health-promising effects including anti-inflammatory, anti-arthritic, antiplatelets, antipyretic, anticancer, antiviral, antimicrobial, antioxidant, anti-osteoporosis, anti-ulcerative colitis, antidiabetic, anti-obesity, antidiarrheal, and insecticidal activities. Herein, the present review aims to provide comprehensive details about the phytochemicals and biological effects of *Sophora* species. The review spotlighted on the promising phytonutrients extracted from *Sophora* and their plethora of bioactivities. The review also clarifies the remaining gaps and thus qualifies and supplies a platform for further investigations of these compounds.

Keywords Fabaceae · *Sophora* · Phytochemicals · Biological activities · Distinctive-alkaloids

✉ Howaida I. Abd-Alla
howaida_nrc@yahoo.com

✉ Mohamed O. Radwan
mohamedradwan@kumamoto-u.ac.jp

[1] Chemistry of Natural Compounds Department, National Research Centre, El-Bohouth Street, Giza-Dokki 12622, Egypt

[2] Institut National de Recherches en Génie Rural, Eaux et Forêts (INRGREF), Université de Carthage, 10 Rue Hédi Karray, Manzeh IV, 2080 Ariana, Tunisia

[3] Medicinal and Biological Chemistry Science Farm Joint Research Laboratory, Faculty of Life Sciences, Kumamoto University, 5-1 Oe-honmachi, Chuo-ku, Kumamoto 862-0973, Japan

Introduction

Medicinal plants have been identified and utilized throughout human history. Plants could synthesize a wide variety of bioactive compounds that have several biological functions (Sweelam et al. 2018; Boozari et al. 2019b; Elberry et al. 2020). Fabaceae (Leguminosae, the legume family) is the third largest family of flowering plants (Borges et al. 2013). Fabaceae includes about 20,000 species within 750 genera and it includes herbal trees, herbs, and shrubs distributed worldwide (Simpson 2010). One of the most important genera of this family is *Sophora* which contains ~ 52 species, 19 varieties, and 7 forms that are widely distributed in Asia and mildly spread in Africa (Simpson 2010; Borges et al. 2013).

More than 15 species of this genus have been historically used in the traditional medicines, shifting the scientific community attention on their bioactive components with multi pharmacological and/or therapeutic benefits (Aly et al. 2019; Boozari et al. 2019b; Cai et al. 2020; Wang et al. 2020a, b, c). Despite the importance of genus *Sophora*, only few species have been chemically evaluated as previously covered in several reviews (Aly et al. 2019; Boozari et al. 2019b; Elberry et al. 2020). Herein, we illustrated the structure of > 360 isolated compounds from different *Sophora* species, including alkaloids, chalcones, chromones, pterocarpans, coumarins, benzofuran derivatives, sterols, isoflavonoids, flavonols, flavones, saponins, and stilbene oligomers (Cao

and He 2020; Jin et al. 2020; Zhang et al. 2020a). These phytonutrients showed numerous pharmacological activities including anti-inflammatory, anti-arthritic, antiplatelets, antipyretic, anticancer, antiviral, antimicrobial, antioxidant, anti-osteoporosis, anti-ulcerative colitis, antidiabetic, anti-obesity, antidiarrheal, insecticidal, and hair growth promoting, besides their uses in the treatment of skin diseases i.e. eczema, colitis, and psoriasis (Huang et al. 2018a, b; Aly et al. 2019; Boozari et al. 2019b; Wang et al. 2019a, b, 2020a, b, c; Guo et al. 2020; Mao et al. 2020; Li et al. 2021b; Ma et al. 2021).

The review by Krishna et al. (2012) summarized the literature to document the ethnomedical and secondary metabolites that characterize and differentiate between *Sophora* species. Further, Aly et al. have surveyed the findings during 8 years (2011–2019) on the bioactivities of *Sophora* species, with particular focus on their anticancer and anti-inflammatory properties. Wang and co-authors have also assessed the reported biological activities of important class of compounds, quinolizidine alkaloids of *Sophora* species (Wang et al. 2019a), while Boozari et al. has a particular focus on active prenylated flavonoids and their structure–activity relationship (Boozari et al. 2019b). The purpose of the present critical study is to highlight the recent advances in current knowledge on *Sophora* species. However, the aim is not only to represent the recorded data, but also to address all the defects and gaps required for further future investigation. In the current review, figures are used as the simplest way to simplify the hugely recorded data of *Sophora* species into informative points. We employed those figures to elaborate and suggest the future scientists' role for a better prospective investigation regarding *Sophora* genus. We do believe that this kind of ordered knowledge will guide the researchers to extend their research and explore the *Sophora* for drug development.

Phytochemistry

Sophora is a crucial genus, because of the broad variation in its chemical composition. This genus was reported to be rich in polyphenols such as flavanols, flavones, and isoflavonoids along with pterocarpans, chalcones, chromones, and benzofuran derivatives (Tables 1, 2, 3, 4, 5, 6). As tabulated in Tables 7, 8, 9, 10, 11 and 12, stilbenes, oligomers, sterols, triterpenes, coumarins, alkaloids, phenolic acids, and other phenolated compounds were identified from different *Sophora* species. Other constituents include hydrocarbons and fatty acids methyl esters identified by gas chromatography/mass spectrometry (GC/MS) from *Sophora* species was also demonstrated in Table 13.

Traditional uses of main *Sophora* species

Traditionally *Sophora* species were widely utilized in the treatment of many diseases and ailments (Ahn 1998). *Sophora* plants, such as the roots of *S. flavescens*, the roots of *S. tonkinensis*, and the seeds of *S. alopecuroides* were commonly used in traditional Chinese medicines for the treatment of fever, bacterial infections, heart disease, rheumatism, eczema, colitis, acute pharyngolaryngeal infection, sore throat, acute dysentery and gastrointestinal hemorrhage, and other gastrointestinal diseases (Fang et al. 2018; Fan et al. 2019; Gu et al. 2020; Jin et al. 2020; Li et al. 2020d; Wang et al. 2020b; Zhang et al. 2020a; Ti et al. 2021). The main species of *Sophora* that are commonly used in traditional medicine were the following:

S. flavescens

The dried roots of *S. flavescens* Aiton are traditionally used as an antipyretic medicine to reduce the inflammation (Aly et al. 2019; Wang et al. 2019c). The herb is also used for the treatment of skin and mucosal ulcers, sores, diarrhea, gastrointestinal hemorrhage, arrhythmia, and eczema (Aly et al. 2019; Boozari et al. 2019b). The root of *S. flavescens* has been extensively used in the clinic to treat cancer, hematochezia, dysentery, jaundice, pruritus vulvae, hepatitis, eczema, and skin diseases in traditional Chinese medicine (Yang et al. 2021). Traditionally, *S. flavescens* was used for asthma, sores, gastrointestinal hemorrhage and allergy, inflammation, anti-ulcerative, and treating of diarrhea and eczema (Ahn 1998; Chen et al. 2020b).

S. japonica and *S. viciifolia*

Recently the flower buds of *S. japonica* have been used as cosmetic whitening agent (Kim et al. 2021). The flower buds of *S. japonica*, which are a major traditional medicine in many Asian countries, are used to stop bleeding (Kim et al. 2021), and therefore, they are used to treat bleeding haemorrhoids, hypertension, and pyoderma. Meanwhile, *S. japonica* L. was used as a haemostatic agent to treat hemorrhoids and hematemesis (Aly et al. 2019; Elberry et al. 2020), where *S. viciifolia* roots were utilized as a Chinese drug to treat fever, cystitis, haematuria, and edema (Ao et al. 2019). The S. *davidii* plant is synonymous with, and formerly known as, S. *viciifolia.* The roots of *S. davidii* have been traditionally used to clear heat, sooth a sore throat, blood cooling, swelling reducing, and treat each of hematochezia, cough, and dysentery, etc. (Li et al. 2021b).

Table 1 Flavonols and flavones isolated from *Sophora* species

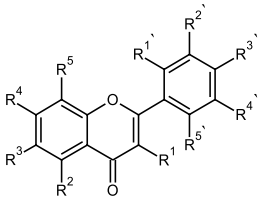
No.	Name	Plant species	Structure	References
1	Quercetin	*S. alopecuroides* *S. flavescens* *S. japonica* *S. tonkinensis* *S. viciifolia*		Lin et al. (2019a), Elberry et al. (2020), Gu et al. (2020), Jin et al. (2020)
2	Kaempferol	*S. interrupta* *S. japonica*		Cao and He (2020), Elberry et al. (2020)
3	Rutin	*S. japonica* *S. tonkinensis*	**1**: $R^1=R^2=R^4=R^{2`}=R^{3`}=OH$; $R^3=R^5=R^{1`}=R^{4`}=R^{5`}=H$ **2**: $R^1=R^2=R^4=R^{3`}=OH$; $R^3=R^5=R^{1`}=R^{2`}=R^{4`}=R^{5`}=H$	Chen et al. (2018d), Elberry et al. (2020), Guo et al. (2020), Jin et al. (2020)
4	Luteolin	*S. alopecuroides* *S. davidii* *S. viciifolia*	**3**: $R^2=R^4=R^{2`}=R^{3`}=OH$; $R^1=O$-glc-rh; $R^3=R^5=R^{1`}=R^{4`}=R^{5`}=H$ **4**: $R^2=R^4=R^{2`}=R^{3`}=OH$; $R^1=R^3=R^5=R^{1`}=R^{4`}=R^{5`}=H$	Lin et al. (2019a), Gu et al. (2020), Li et al. (2021b)
5	Vicenin-2			
6	Saponarin			
7	Geraldol	*S. tomentosa* *S. secundiflora*	**5**: $R^2=R^4=R^{3`}=OH$; $R^3=R^5=$glc; $R^1=R^{1`}=R^{2`}=R^{4`}=R^{5`}=H$ **6**: $R^2=R^{3`}=OH$; $R^3=$glc; $R^4=O$-glc; $R^1=R^5=R^{1`}=R^{2`}=R^{4`}=R^{5`}=H$ **7**: $R^1=R^4=R^{3`}=OH$; $R^{2`}=OCH_3$; $R^2=R^3=R^5=R^{1`}=R^{4`}=R^{5`}=H$	Boozari et al. (2019b), Aly et al. (2020b)
8	7,4′-Dihydroxyflavone	*S. subprostrata* *S. japonica*	**8**: $R^4=R^{3`}=OH$; $R^1=R^2=R^3=R^5=R^{1`}=R^{2`}=R^{4`}=R^{5`}=H$	Boozari et al. (2019b), Farhadi et al. (2019)
9	*des-O*-Methylan-hydroicaritin	*S. tomentosa*	**9**: $R^1=R^2=R^4=R^{3`}=OH$; $R^5=$isoprenyl group; $R^3=R^{1`}=R^{2`}=R^{4`}=R^{5`}=H$	Boozari et al. (2019b)
10	Tomentosanol C		**10**: $R^1=R^2=R^4=R^{3`}=OH$; $R^5=$geranyl group $R^3=R^{1`}=R^{2`}=R^{4`}=R^{5`}=H$	
11	Rhamnosyl vitexin	*S. microphylla*	**11**: $R^2=R^4=R^{3`}=OH$; $R^5=$rh- glc; $R^1=R^3=R^{1`}=R^{2`}=R^{4`}=R^{5`}=H$ **12**: $R^2=R^4=R^{3`}=OH$; $R^3=$rh- glc; $R^1=R^5=R^{1`}=R^{2`}=R^{4`}=R^{5`}=H$	Bisby et al. (1994)
12	Rhamnosyl isovitexin		**13**: $R^2=R^{3`}=OH$; $R^4=O$-glc; $R^1=R^3=R^5=R^{1`}=R^{2`}=R^{4`}=R^{5`}=H$ **14**: $R^2=OH$; $R^4=O$-glc-rh; $R^{3`}=O$-glc; $R^1=R^3=R^5=R^{1`}=R^{2`}=R^{4`}=R^{5`}=H$	
13	Apigenin-7-*O*-glucoside	*S. tetraptera*	**15**: $R^2=R^4=R^{2`}=OH$; $R^{3`}=OCH_3$; $R^1=O$-glc-rh; $R^3=R^5=R^{1`}=R^{4`}=R^{5`}=H$ **16**: $R^2=R^4=R^{3`}=OH$; $R^5=OCH_3$; $R^1=O$-glc-glc; $R^3=R^{1`}=R^{2`}=R^{4`}=R^{5`}=H$	
14	Apigenin-7-*O*-rhamnosyl-glucoside-4′-*O*-glucoside		**17**: $R^2=R^{3`}=OH$; $R^4=O$-glc; $R^{2`}=R^{4`}=OCH_3$; $R^1=R^3=R^5=R^{1`}=R^{5`}=H$	
15	3′,5,7-Trihydroxy-4′-methoxyflavone-3-*O*-α-L-rhamnopyranosyl(1 → 6)-β-D-glucopyranoside	*S. davidii* *S. viciifolia*		Lin et al. (2019a), Li et al. (2021b)
16	8-*O*-Methylherbacetin-3-*O*-sophoroside			
17	Tricin-7-*O*-β-D-glucopyranoside			

Table 1 (continued)

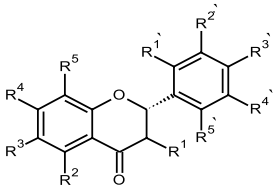
No.	Name	Plant species	Structure	References
18	Alopecurone G	*S. alopecuroides*		Li et al. (2020a)
19	Sophoraflavanone G	*S. alopecuroides* *S. davidii* *S. exigua* *S. flavescens* *S. leachiana* *S. pachycarpa*		Boozari et al. (2019a, b), (Yang et al. 2019, 2020c), Li et al. (2020a), Long et al. (2020)
20	Leachianone A	*S. alopecuroides* *S. davidii* *S. leachiana*	**18**: $R^4=R^{3`}=OH$; $R^5=$lavandulyl group; $R^{1`}=OCH_3$; $R^1=R^2=R^3=R^{2`}=R^{4`}=R^{5`}=H$ **19**: $R^2=R^4=R^{1`}=R^{3`}=OH$; $R^5=$lavandulyl group; $R^1=R^3=R^{2`}=R^{4`}=R^{5`}=H$	Yang et al. (2019), Li et al. (2020a), Ma et al. (2021)
21	Lehmannin	*S. lehmannii*	**20**: $R^2=R^4=R^{3`}=OH$; $R^5=$lavandulyl group; $R^{1`}=OCH_3$; $R^1=R^3=R^{2`}=R^{4`}=R^{5`}=H$	Yang et al. (2019)
22	Exiguaflavanone G	*S. exigua*	**21**: $R^4=R^{1`}=R^{3`}=OH$; $R^5=$lavandulyl group; $R^1=R^2=R^3=R^{2`}=R^{4`}=R^{5`}=H$	Boozari et al. (2019b), Cho et al. (2020), Li et al. (2020a)
23	Kurarinone	*S. flavescens*	**22**: $R^2=R^4=R^{1`}=R^{3`}=R_{5`}=OH$; $R^5=$lavandulyl group; $R1=R3=R_{2`}=R_{4`}=H$	Boozari et al. (2019b), Cho et al. (2020)
24	2′-Methoxy-kurarinone		**23**: $R^4=R^{1`}=R^{3`}=OH$; $R^5=$lavandulyl group	Boozari et al. (2019b)
25	Vexibidin	*S. alopecuroides*	$R^2=OCH_3$; $R^1=R^3=R^{2`}=R^{4`}=R^{5`}=H$	Boozari et al. (2019b), Li et al. (2020a)
26	Vexibinol		**24**: $R^4=R^{3`}=OH$; $R^5=$lavandulyl group; $R^2=R^{1`}=OCH_3$; $R^1=R^3=R^{2`}=R^{4`}=R^{5`}=H$	Li et al. (2020a)
27	Exiguaflavanone M	*S. exigua*	**25**: $R^2=R^4=R^{3`}=OH$; $R^3=$lavandulyl group; $R^{1`}=OCH_3$; $R^1=R^5=R^{2`}=R^{4`}=R^{5`}=H$	Li et al. (2020a)
28	Kushenol	*S. flavescens*	**26**: $R^2=R^4=R^{1`}=R^{3`}=OH$; $R^3=$lavandulyl group; $R^1=R^5=R^{2`}=R^{4`}=R^{5`}=H$	Boozari et al. (2019b), Chen et al. (2019a), Cho et al. (2020), Kwon et al. (2020)
29	Kurarinol		**27**: $R^2=R^4=R^{1`}=R^{3`}=R^{5`}=OH$; $R^1=R^3=R^{2`}=R^{4`}=H$ $R^5=$2-(2-hydroxypropan-2-yl)-5-methylhex-4-enyl	
30	7,4′-Dihydroxy-5-methoxy-8-(γ, γ-dimethylallyl) –flavanone	*S. flavescens*	**28**: $R^2=R^4=R^{1`}=OH$; $R^1=R^3=R^{2`}=R^{3`}=R^{4`}=R^{5`}=H$ $R^5=$5-hydroxy-2-isopropenyl-5-methyl hexyl	Cho et al. (2020), Gu et al. (2020)
31	Tonkinochromane J	*S. tonkinensis*	**29**: $R^2=R^4=R^{1`}=R^{3`}=OH$; $R^1=R^3=R^{2`}=R^{4`}=R^{5`}=H$ $R^5=$5-hydroxy-2-isopropenyl-5- methyl hexyl	Jin et al. (2020)
32	Isoxanthohumol	*S. flavescens*	**30**: $R^4=R^{3`}=OH$; $R^5=\gamma$, $\gamma$-dimethylallyl; $R^2=OCH_3$; $R^1=R^3=R^{1`}=R^{2`}=R^{4`}=R^{5`}=H$	Boozari et al. (2019b)
33	3 α,7,4′-Trihydroxy-5-methoxy-8-(γ, γ -dimethylallyl) –flavanone		**31**: $R^4=R^{3`}=R^{4`}=OH$; $R^5=R^{2`}=$isoprenyl group; $R^1=R^2=R^3=R^{1`}=R^{5`}=H$ **32**: $R^4=R^{3`}=OH$; $R^5=$isoprenyl group; $R^2=OCH_3$; $R^1=R^3=R^{1`}=R^{2`}=R^{4`}=R^{5`}=H$ **33**: $R^1=R^4=R^{3`}=OH$; $R^5=$isoprenyl group; $R^2=OCH_3$; $R^3=R^{1`}=R^{2`}=R^{4`}=R^{5`}=H$	

Table 1 (continued)

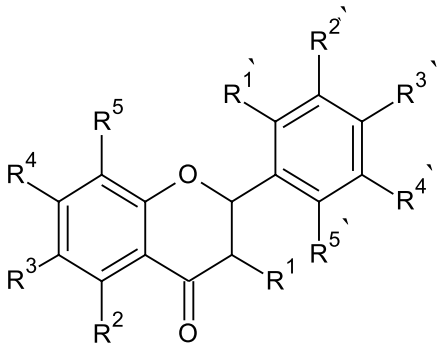
No.	Name	Plant species	Structure	References
34	Exiguaflavanone E	*S. exigua*	 **34**: $R^2=R^{1`}=R^{3`}=OH$; R^5 = lavandulyl group; $R^4=R^{4`}=OCH_3$; $R^1=R^3=R^{2`}=R^{5`}=H$	Li et al. (2020a)
35	Exiguaflavanone F	*S. exigua*	**35**: $R^2=R^{2`}=R^{5`}=OH$; R^5 = lavandulyl group; $R^4=OCH_3$; $R^1=R^3=R^{1`}=R^{3`}=R^{4`}=OH$	Boozari et al. (2019b), Li et al. (2020a)
36	5,7,2′-Trihydroxy-8-lavandulyl flavanone		**36**: $R^2=R^{2`}=R^{5`}=OH$; R^5 = lavandulyl group; $R^1=R^3=R^4=R^{1`}=R^{3`}=R^{4`}=H$	
37	Exiguaflavanone J	*S. exigua*	**37**: $R^2=R^4=R^{1`}=R^{3`}=R^{5`}=OH$; $R^1=R^{2`}=R^{4`}=H$; R^3 = isoprenyl group; R^5 = lavandulyl group	Farhadi et al. (2019), Li et al. (2020a), Yang et al. (2020c)
38	Exiguaflavanone K		**38**: $R^2=R^4=R^{3`}=OH$ $R^5$ = isoprenyl group $R^{2`}=OCH_3$ $R^1=R^3=R^{1`}=R^{4`}=R^{5`}=H$	
39	Leachianone D	*S. leachiana*	**39**: $R^2=R^4=R^{3`}=OH$; $R^{5`}=OCH_3$ R^5 = 5-hydroxy-2-isopropenyl-5-methyl hexyl; $R^1=R^3=R^{1`}=R^{2`}=R_4`=H$	Boozari et al. (2019b), Li et al. (2020a)
40	Leachianone E		**40**: $R^2=R^4=R^{3`}=OH$; $R^5$ = lavandulyl group; $R^1=R^3=R^{1`}=R^{2`}=R^{4`}=R^{5`}=H$	
41	Prostratrol F	*S. prostrata*	**41**: $R^4=R_3`=OH$; $R^5$ = lavandulyl group; $R^1=R^2=R^3=R^{1`}=R^{2`}=R^{4`}=R^{=`}=H$	Li et al. (2020a)
42	Prostratrol G		**42**: $R^4=R^{3`}=OH$; $R^3=R^5=R^{2`}$ = isoprenyl group; $R^1=R^2=R^{1`}=R^{4`}=R^{5`}=H$	
43	Glabrol	*S. prostrata* *S.alopecuroides*	**43**: $R^4=R^{3`}=OH$; $R^5=R^{2`}$ = isoprenyl group; $R^1=R^2=R^{1`}=R^{4`}=R^{5`}=H$	Li et al. (2020a)
44	3-Hydroxy glabrol	*S. prostrata*	**44**: $R^1=R^4=R^{3`}=OH$; $R^5=R^{2`}$ = isoprenyl group; $R^2=R^3=R^{1`}=R^{4`}=R^{5`}=H$	Li et al. (2020a)
45	6-γ, γ-Dimethylallyl-5,7,3′,4′-tetrahydroxy flavanone	*S. secundiflora*	**45**: $R^2=R^4=R^{3`}=R^{4`}=OH$; R^3 = isoprenyl group; $R^1=R^5=R^{1`}=R^{2`}=R^{5`}=H$	Aly et al. (2019, 2020a)
46	2′,4′,7-Trihydroxy-6,8-*bis*(3-methyl-2-butenyl) flavanone	*S. tonkinensis*	**46**: $R^4=R^{3`}=R^{5`}=OH$; $R^3=R^5$ = isoprenyl group; $R^1=R^2=R^{1`}=R^{2`}=R^{4`}=H$	Li et al. (2020a)
47	Glabranin	*S. tomentosa*	**47**: $R^2=R^4=OH$; R^5 = isoprenyl group; $R^1=R^3=R^{1`}=R^{2`}=R^{3`}=R^{4`}=R^{5`}=H$	Boozari et al. (2019b)
48	Sophoraflavanone B		**48**: $R^2=R^4=R^{3`}=OH$; $R^5$ = isoprenyl group; $R^1=R^3=R^{1`}=R^{2`}=R^{4`}=R^{5`}=H$	
49	Tomentosanol D		**49**: $R^2=R^4=R^{3`}=OH$; $R^5$ = 2-hydroxy-3-methylbut-3- enyl $R^1=R^3=R^{1`}=R^{2`}=R^{4`}=R^{5`}=H$	
50	Tomentosanol E		**50**: $R^2=R^4=R^{1`}=R^{3`}=R^{5`}=OH$; $R^3$ = geranyl group; $R^5$ = isoprenyl group; $R^1=R^{2`}=R^{4`}=H$	

Table 1 (continued)

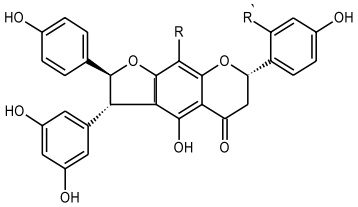
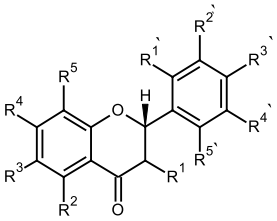
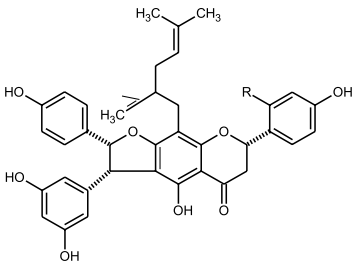
No.	Name	Plant species	Structure	References
51	Sophoraflavanone A	*S. tomentosa*	**51**: $R^2=R^4=R^{3`}=OH$; $R^5$ = geranyl group; $R^1=R^3=R^{1`}=R^{2`}=R^{4`}=R^{5`}=H$	Boozari et al. (2019b)
52	Sophoraflavanone C		**52**: $R^2=R^4=R^{3`}=R^{1`}=OH$; R^5 = geranyl group; $R^1=R^3=R^{2`}=R^{4`}=R^{5`}=H$	
53	Sophoraflavanone D	*S. koreensis* *S. tomentosa*	**53**: $R^2=R^4=R^{1`}=R^{3`}=R^{5`}=OH$; $R^3$ = geranyl group; $R^1=R^5=R^{2`}=R^{4`}=H$	Boozari et al. (2019b), Li et al. (2020a)
54	Sophoraflavanone E			
55	Isosakuranin	*S. viciifolia*	**54**: $R^2=R^4=R^{1`}=R^{3`}=R^{5`}=OH$; $R^5$ = geranyl group; $R^1=R^3=R^{2`}=R^{4`}=H$	Lin et al. (2019a)
56	Lonchocarpol A	*S. tetraptera*	**55**: $R^2=R^{3`}=OH$; $R^4$ = *O*-glc; $R^{3`}=OCH_3$; $R^1=R^3=R^5=R^{1`}$ $R^{2`}=R^{4`}=R^{5`}=H$	Li et al. (2020a)
			56: $R^2=R^4=R^{3`}=OH$; $R^3=R^5$ = isoprenyl group; $R^1=R^{1`}=R^{2`}=R^{4`}=R^{5`}=H$	
57	Alopecurone A	*S. alopecuroides*		Li et al. (2020a)
58	Alopecurone C		**57**: R = lavandulyl group; R` = OH	
59	Alopecurone D		**58**: R = isoprenyl group; R` = H	
60	Alopecurone F		**59**: R = lavandulyl group; R` = OCH_3	
			60: R = isoprenyl group; R` = OH	
61	Exiguaflavanone A	*S. flavescens* *S. exigua*		Boozari et al. (2019b), Li et al. (2020a), Yang et al. (2020c)
62	Exiguaflavanone B			Boozari et al. (2019b), Li et al. (2020a)
63	Exiguaflavanone C			
64	Exiguaflavanone D		**61**: $R^2=R^4=R^{1`}=R^{5`}=OH$; R^5 = lavandulyl group; $R^1=R^3=R^{2`}=R^{3`}=R^{4`}=H$	
			62: $R^2=R^{1`}=R^{5`}=OH$; $R^1=R^3=R^{2`}=R^{3`}=R^{4`}=H$; $R^4=OCH_3$; R^5 = lavandulyl group	
			63: $R^2=R^4=R^{1`}=R^{3`}=R^{5`}=OH$; $R^3$ = Lavandulyl group; $R^1=R^5=R^{2`}=R^{4`}=H$	
			64: $R^2=R^4=R^{1`}=R^{5`}=OH$; R^3 = isoprenyl group; R^5 = lavandulyl group; $R^{3`}=OCH_3$; $R^1=R^{2`}=R^{4`}=H$	
65	Alopecurone B	*S. alopecuroides*		Li et al. (2020a)
66	Alopecurone E		**65**: R = OH **66**: R = OCH_3	

Table 1 (continued)

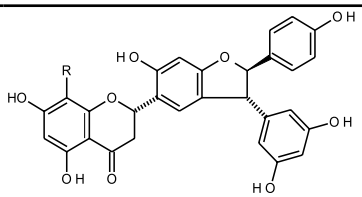
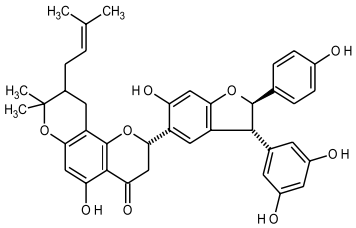
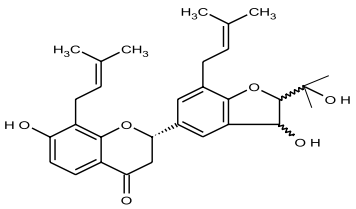
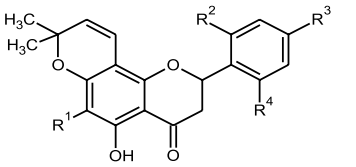
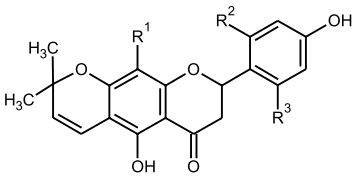
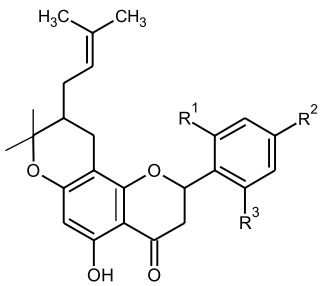
No.	Name	Plant species	Structure	References
67	Sophoraflavanone I	*S. davidii* *S. leachiana*	 **67**: R = lavandulyl group **68**: R = isoprenyl group	Aly et al. (2019), Yang et al. (2019)
68	Leachianone I	*S. flavescens* *S. leachiana*		Li et al. (2020a)
69	Leachianone C	*S. leachiana*		Li et al. (2020a)
70	Tonkinochromane K	*S. tonkinensis*		Li et al. (2020a)
71	Euchrenone	*S. tetraptera*	 **71**: R^1 = isoprenyl group; R^2 = R^3 = OH; R^4 = H **72**: R^1 = lavandulyl group; R^2 = R^3 = R^4 = OH	Li et al. (2020a)
72	Exiguaflavanone I	*S. exigua* *S. flavescens*		Farhadi et al. (2019), Li et al. (2020a)
73	Lupinifolin	*S. tetraptera*	 **73**: R^1 = isoprenyl group; R^2 = R^3 = H **74**: R^1 = lavandulyl group; R^2 = R^3 = OH	Zhang et al. (2020a)
74	Exiguaflavanone H	*S. exigua* *S. flavescens*		Li et al. (2020a)
75	Exiguaflavanone L	*S. exigua*	 **75**: R^1 = R^3 = OH; R^2 = H **76**: R^1 = H; R^2 = OH; R^3 = OCH_3	Li et al. (2020a)

Table 1 (continued)

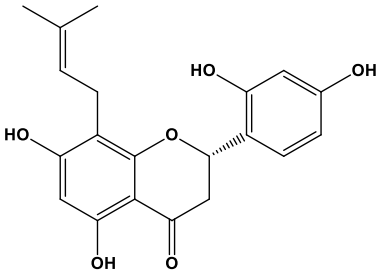
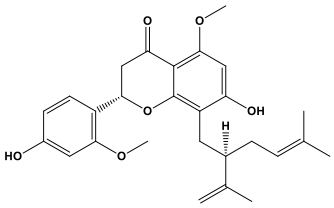
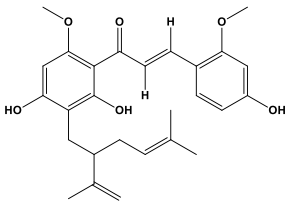
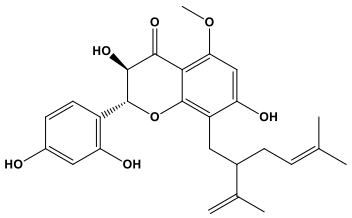
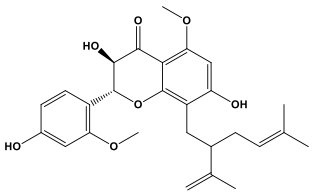
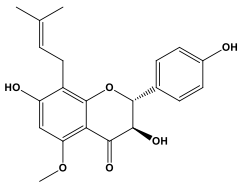
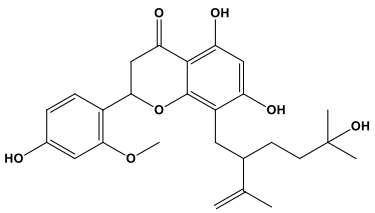
No.	Name	Plant species	Structure	References
76	Leachianone B	*S. leachiana*		Boozari et al. (2019b), Li et al. (2020a)
77	Leachianone G	*S. flavescens*		Yang et al. (2021)
78	(2*S*)-5,4-Dimethoxy-8-lavandulyl-7,2-dihydroxyflavanone	*S. flavescens*		Yang et al. (2021)
79	Kushenol D	*S. flavescens*		Yang et al. (2021)
80	Kushenol I	*S. flavescens*		Yang et al. (2021)
81	2′-Methoxy kushenol I	*S. flavescens*		Yang et al. (2021)
82	Kushenol K	*S. flavescens*		Yang et al. (2021)
83	Kushenol P	*S. flavescens*		Yang et al. (2021)

Table 1 (continued)

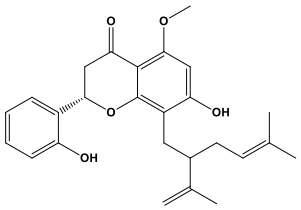
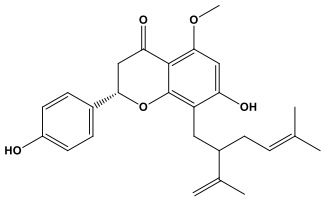
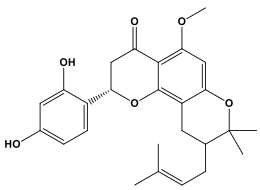
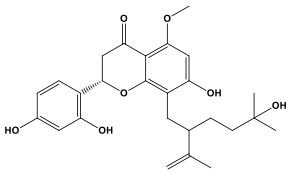
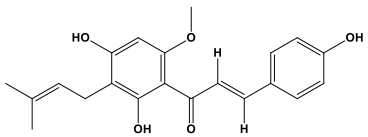
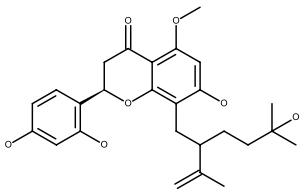
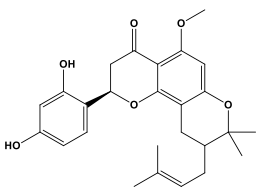
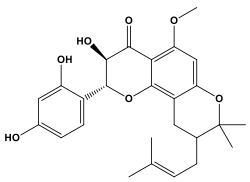
No.	Name	Plant species	Structure	References
84	Kushenol R	*S. flavescens*		Yang et al. (2021)
85	Kushenol U	*S. flavescens*		Yang et al. (2021)
86	(2*S*)-2,4-Dihydroxy-5-methoxy-6″,6″-dimethyl-5″-prenyldihydropyrano[2″,3″:4,3] flavanone	*S. flavescens*		Yang et al. (2021)
87	(2*R*,3*R*)-5-Methoxy-7,4′-dihydroxy-8-[3,3-dimethylallyl]flavanonol	*S. flavescens*		Yang et al. (2021)
88	Xanthohumol	*S. flavescens*		Yang et al. (2021)
89	Norkurarinol	*S. flavescens*		Yang et al. (2021)
90	Sophoraflavenochromane G	*S. flavescens*		Yang et al. (2021)
91	Sophoraflavanonol A	*S. flavescens*		Yang et al. (2021)

Table 1 (continued)

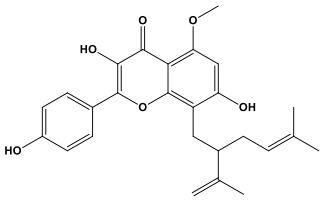
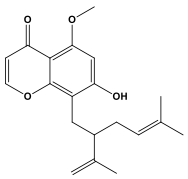
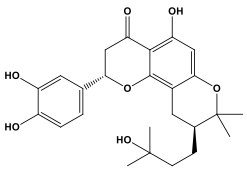
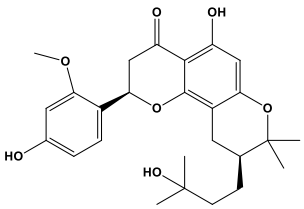
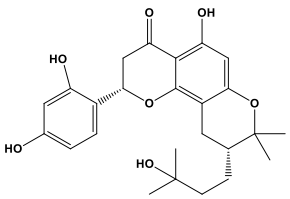
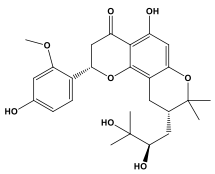
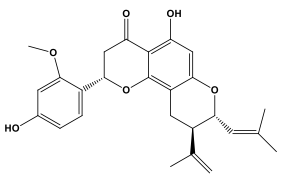
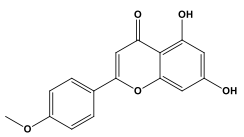
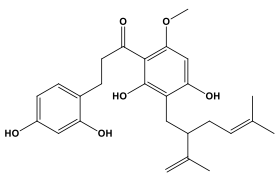
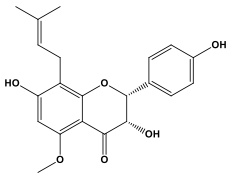
No.	Name	Plant species	Structure	References
92	5-Methoxy-7,4′-dihydroxy-8-lavandulylflavonol	*S. flavescens*		Yang et al. (2021)
93	5-Methoxy-7-hydroxy-8-lavandulylbenzochromone	*S. flavescens*		Yang et al. (2021)
94	Davidone A	*S. davidii*		Ma et al. (2021)
95	Davidone B	*S. davidii*		Ma et al. (2021)
96	Davidone C	*S. davidii*		Ma et al. (2021)
97	Davidone D	*S. davidii*		Ma et al. (2021)
98	Davidone E	*S. davidii*		Ma et al. (2021)
99	Acacetin	*S. davidii*		Ma et al. (2021)
100	2-Methoxy-2′,4′,4,6-tetrahydroxy-5-lavanduly dihydrochalcone	*S. flavescens*		Yang et al. (2021)

Table 1 (continued)

No.	Name	Plant species	Structure	References
101	Sophoraflavanone M	*S. flavescens*		Han et al. (2021)

S. alopecuroides

It is benefited for its anti-dysentery effect, a property that is commonly observed in other *Sophora* genus phytomedicines (Zhou et al. 2020).

S. tonkinensis

In traditional Chinese medicine theory, the root and rhizome are toxic and mainly used in the treatment of pharyngeal and laryngeal diseases (Zhang et al. 2021b).

S. subprostrata and *S. mollis*

Another example about the roots of *S. subprostrata* and *S. mollis*, which were used as an antipyretic, analgesic with a potential anti-tumor activity (Ao et al. 2019; Wang et al. 2019a; Zhang et al. 2020a; Quradha et al. 2021). These roots are also used as a Korean traditional medicine for the treatment of fever, inflammation, peptic ulcer, and cancer (Aly et al. 2019, 2020a; Boozari et al. 2019b; Chen et al. 2020b; Wang et al. 2020b; Yang et al. 2020b). Several *Sophora* species including *S. subprostrata* displayed various activities in dispelling dampness, clearing heat, sedation, detoxification, and relieving swelling and pain (Zhou et al. 2020).

S. exigua

Sophora exigua Craib is commonly used in Thailand to increase postpartum breast milk production in women who have hypogalactia and reduce fever (Kaewdana et al. 2021).

Biological effects

Active molecules from the genus *Sophora*

Worldwide, about 4 billion people today rely on plants as sources of drugs even in the developed countries (Sweelam et al. 2018; Aly et al. 2019; Boozari et al. 2019b). Freshly, medicinal plants gained the attention in term of identifying and exploiting safe and effective remedies for treatment of several chronic and infective diseases (Boozari et al. 2019a, b; Wang et al. 2020a ,b; Zhou et al. 2020). The phytoextracts of *Sophora* species are rich sources of bioactive phytochemicals, such as prenylated flavonoids, quinolizidine-type alkaloid, terpenes, etc. with health-promoting properties (Tables 14, 15). Biological activities of many *Sophora* species bioactive compounds are depending on the structure of those constituents.

Cytotoxic and anti-tumor activity

Prenylated flavonoids from *Sophora* species exert dependently inhibited the Alzheimer's disease, primarily through their skeleton's structure (chalcones, flavonols, flavanones), and their lipophilic chain length (lavandulyl and prenyl groups) (Aly et al. 2019; Boozari et al. 2019b). Due to the promising and diverse bioactivities on multitarget tissues of prenylated flavanones, research on such components were recently spotlighted (Awad et al. 2014, 2018; Boozari et al. 2019b; Wang et al. 2020b). For example, sophoraflavanone G (**19**; from *S. flavescens*) has revealed cytotoxicity for several tumor cells with IC_{50}-values of 20 mM, which was like cisplatin, commonly used as a recent chemotherapy drug to treat different cancers (Long et al. 2020). It also has reported to induce apoptosis in triple-negative breast cancer cells (Huang et al. 2019, 2020). Kurarinone (**23**) induced apoptosis in small cell lung carcinoma (SCLC) cells via multiple mechanisms and delayed SCLC-cell's migration and invasion (Chung et al. 2019). By its underlying mechanism, Kurarinone promoted Fas and TRAIL receptor-1 and -2 expression via the caspase-8/Bid pathway.

A prenylated flavanone from the roots of *S. flavescens* has recorded anti-proliferative activity against human hepatoma cells (HepG2) (Yang et al. 2021). This lavandulyl flavonoid 2-methoxy-2′,4′,4,6-tetrahydroxy-5-lavanduly dihydrochalcone (**100**) significantly activated autophagic flux and trigger

Table 2 Isoflavonoids isolated from *Sophora* species

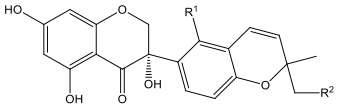
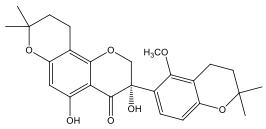
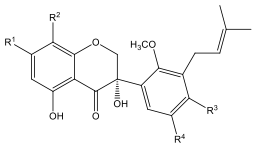
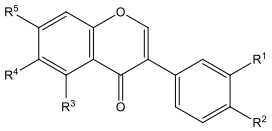
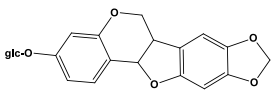
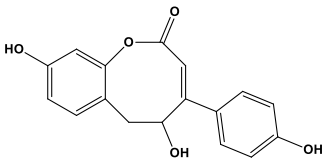
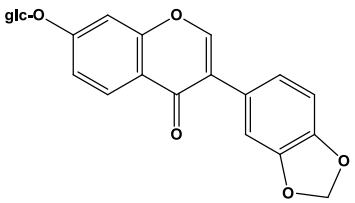
No.	Name	Plant species	Structure	References
102	Sophoronol A	*S. mollis*		Boozari et al. (2019b), Uzor (2020), Kaewdana et al. (2021)
103	Sophoronol B		**102**: $R^1 = OH$; $R^2 = H$ **103**: $R^1 = OCH_3$; $R^2 = OH$	
104	Sophoronol C			
105	Sophoronol D			
106	Sophoronol E		**105**: $R^1 = OH$; $R^2 = H$; $R^3 = OCH_3$; $R^4 = OH$	
107	Sophoronol F		**106**: $R^1 = OH$; $R^2 =$ isoprenyl; $R^3 = OCH_3$; $R^4 = H$ **107**: $R^1 = OCH_3$; $R^2 =$ isoprenyl; $R^3 = OH$; $R^4 = H$	
108	Daidzein	*S. japonica*		Chen et al. (2018d), Elberry et al. (2020), Guo et al. (2020), Song et al. (2021)
109	Ononin	*S. japonica* *S. tonkinensis*	**108**: $R^1 = R^3 = R^4 = H$; $R^2 = R^5 = OH$ **109**: $R^1 = OH$; $R^2 = OCH_3$; $R^3 = R^4 = H$; $R^5 =$ glucose	
110	Glycitin	*S. japonica*	**110**: $R^1 = R^3 = H$; $R^2 = OH$; $R^4 = OCH_3$; $R^5 =$ glucose	
111	Glycitein-4′-*O*-β-D-glucoside	*S. japonica*	**111**: $R^1 = R^3 = H$; $R^2 =$ glucose; $R^4 = OCH_3$; $R^5 =$ OH	
112	Calycosin-7-*O*-glucoside	*S. fraseri* *S. japonica* *S. secundiflora*	**112**: $R^1 = OH$; $R^2 = OCH_3$; $R^3 = R^4 = H$; $R^5 =$ glucose **113**: $R^1 = R^3 = R^4 = H$; $R^2 =$ glucose; $R^5 =$ glucose	
113	Paratensein-7-*O*-glucoside	*S. japonica*		
114	Isotrifolirhizin	*S. japonica* *S. tonkinensis*		Chen et al. (2018d), Elberry et al. (2020), Guo et al. (2020), Song et al. (2021)
115	Puerol A	*S. japonica*		Chen et al. (2018d), Elberry et al. (2020), Guo et al. (2020)
116	5-hydroxypseudobaptigenin-7-*O*-glucoside	*S. japonica*		Chen et al. (2018d), Elberry et al. (2020), Guo et al. (2020)

Table 2 (continued)

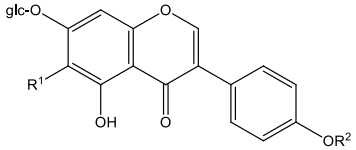
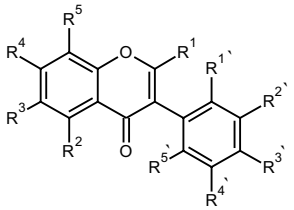
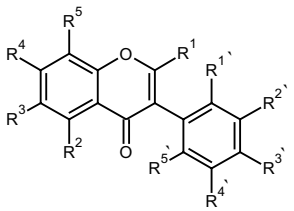
No.	Name	Plant species	Structure	References
117	Sissotrin	*S. japonica*		Kim and Yun-Choi (2008), Chen et al. (2020d)
118	Tectoridin	*S. japonica*	**117**: $R^1 = H$; $R^2 = CH_3$ **118**: $R^1 = OCH_3$; $R^2 = H$	Kim and Yun-Choi (2008), Chen et al. (2020d)
119	Genistin	*S. japonica* *S. tonkinensis*	**119**: $R^1 = H$; $R^2 = H$	Kim and Yun-Choi (2008), Chen et al. (2020d), Song et al. (2021)
120	Genistein	*S. moorcroftiana* *S. secundiflora*		Huang et al. (2018c), Su et al. (2018), Boozari et al. (2019b), Li et al. (2020a)
121	2′-Hydroxygenistein	*S. alopecuroides*		Li et al. (2020a)
122	3′-Isoprenyl genistein	*S. flavescens* *S. japonica* *S. tomentosa*		Boozari et al. (2019b), Li et al. (2020a)
123	Fraserinone A	*S. fraseri*	**120**: $R^2 = R^4 = R^{3`} = OH$; $R^1 = R^3 = R^5 = R^{1`} = R^{2`} = R^{4`} = R^{5`} = H$	Li et al. (2020a)
124	Calycosin	*S. fraseri* *S. japonica* *S. secundiflora*	**121**: $R^2 = R^4 = R^{1`} = R^{3`} = OH$; $R^1 = R^3 = R^5 = R_{2`} = R^{4`} = R^{5`} = H$	Boozari et al. (2019b), Li et al. (2020a)
125	Formononetin	*S. flavescens* *S. secundiflora* *S. tonkinensis*	**122**: $R^2 = R^4 = R^{3`} = OH$; $R^{2`}$ = isoprenyl group; $R^1 = R^3 = R^5 = R^{4`} = R^{5`} = H$ **123**: $R^2 = R^4 = R^{3`} = OH$; $R^1 = R^3 = R^5 = R^{2`} = R^{5`} = H$ $R^{1`} = OCH_3$; $R^{4`}$ = 1,1-dimethyl-2- propenyl **124**: $R^4 = R^{2`} = OH$; $R^{3`} = OCH_3$; $R^1 = R^2 = R_3 = R^5 = R^{1`} = R^{4`} = R^{5`} = H$ **125**: $R^4 = OH$; $R^{3`} = OCH_3$ $R^1 = R^2 = R^3 = R^5 = R^{1`} = R^{2`} = R^{4`} = R^{5`} = H$	Boozari et al. (2019b), Cho et al. (2020), Jin et al. (2020), Li et al. (2020a)
126	Orobol (Isoluteolin)	*S. davidii* *S. japonica* *S. secundiflora*		Boozari et al. (2019b), Elberry et al. (2020), Guo et al. (2020), Li et al. (2021b)
127	Secundiflorol B	*S. gypsophila* *S. secundiflora*	**126**: $R^3 = R^4 = R^{2`} = R^{3`} = OH$; $R^1 = R^2 = R^5 = R^{1`} = R^{4`} = R^{5`} = H$	Boozari et al. (2019b), Li et al. (2020a)
128	Secundiflorol C	*S. flavescens* *S. japonica* *S. tomentosa*	**127**: $R^2 = R^4 = R^{1`} = R^{2`} = OH$; $R^{3`} = OCH_3$; $R^{4`}$ = 1,1-dimethyl-2- propenyl; $R^1 = R^3 = R^5 = R^{5`} = H$	Boozari et al. (2019b), Li et al. (2020a)
129	Pratensein	*S. secundiflora*	**128**: $R^4 = R^{1`} = R^{2`} = OH$; $R^{3`} = OCH_3$; $R^{4`}$ = 1,1-dimethyl-2- propenyl; $R^1 = R^2 = R^3 = R^5 = R^{5`} = H$	Boozari et al. (2019b), Li et al. (2020a)
130	Biochanin	*S. interrupta* *S. japonica* *S. secundiflora*	**129**: $R^2 = R^4 = R^{2`} = OH$; $R^{3`} = OCH_3$; $R^1 = R^3 = R^5 = R^{1`} = R^{4`} = R^{5`} = H$ **130**: $R_2 = R^4 = OH$; $R^{3`} = OCH_3$; $R^1 = R^3 = R^5 = R^{1`} = R^{2`} = R^{4`} = R^{5`} = H$	Boozari et al. (2019b), Rammohan et al. (2020)
131	Prunetin	*S. flavescens* *S. secundiflora* *S. tonkinensis*	**131**: $R^2 = R^{2`} = R^{3`} = R^{5`} = OH$; $R^4 = OCH_3$; $R^1 = R^3 = R^5 = R^{1`} = R^{4`} = H$	Boozari et al. (2019b), Cho et al. (2020), Jin et al. (2020), Li et al. (2020a)
132	Irisolidone	*S. tomentosa*	**132**: $R^2 = R^4 = OH$; $R^3 = R^{3`} = OCH_3$; $R^1 = R^5 = R^{1`} = R^{2`} = R^{4`} = R^{5`} = H$	Boozari et al. (2019b)

Table 2 (continued)

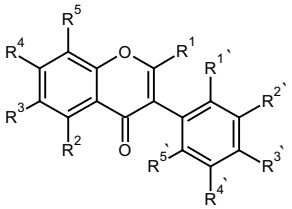
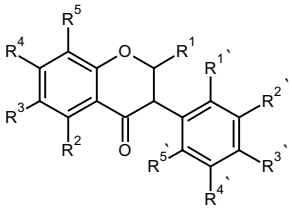
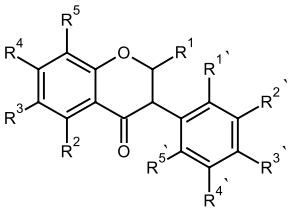
No.	Name	Plant species	Structure	References
133	Iristectorigenin A	*S. gypsophila* *S. secundiflora* *S. viciifolia*	 **133**: $R^2=R^4=R^{2`}=OH$; $R^3=R^{3`}=OCH_3$; $R^1=R^5=R^{1`}=R^{4`}=R^{5`}=H$	Boozari et al. (2019b), Lin et al. (2019a), Li et al. (2020a)
134	Sophoricoside		**134**: $R^2=R^4=OH$; $R^{3`}=O$-glc; $R^1=R^3=R^5=R^{1`}=R^{2`}=R^{4`}=R^{5`}=H$	
135	Sophoraisoflavanone A	*S. flavescens* *S. fraseri* *S. japonica* *S. tomentosa*	 **135**: $R^2=R^4=R^{3`}=OH$; $R^{1`}=OCH_3$; $R^{2`}$ = isoprenyl group; $R^1=R^3=R^5=R^{4`}=R^{5`}=H$	Boozari et al. (2019b), Li et al. (2019c)
136	Kenusanone H	*S. koreensis* *S. tomentosa*	**136**: $R^2=R^4=R^{1`}=R^{3`}=OH$; R^5 = lavandulyl group; $R^1=R^3=R^{2`}=R^{4`}=R^{5`}=H$	Aly et al. (2019), Boozari et al. (2019b), Li et al. (2020a)
137	Prostratol A	*S. flavescens* *S. prostrata*	**137**: $R^4=R^{1`}=R^{3`}=OH$; $R^{4`}$ = geranyl group; $R^1=R^2=R^3=R^5=R^{2`}=R^{5`}=H$	
138	Prostratol B	*S. tomentosa*	**138**: $R^4=R^{1`}=R^{3`}=OH$; $R^3=R^{4`}$ = isoprenyl group; $R^1=R^2=R^5=R^{2`}=R^{5`}=H$	Boozari et al. (2019b)
139	Prostratol C		**139**: $R^4=R^{1`}=OH$; $R^{3`}=OCH_3$; $R^{4`}$ = isoprenyl group; $R^1=R^2=R^3=R^5=R^{2`}=R^{5`}=H$	
140	Secundiflorol D	*S. secundiflora*	**140**: $R^4=R^{1`}=R^{2`}=OH$; $R^{3`}=OCH_3$; $R^1=R^2=R^3=R^5=R^{5`}=H$ $R^{4`}$ = 1,1-dimethyl-2- propenyl	Aly et al. (2019), Li et al. (2020a)
141	Secundiflorol E	*S. flavescens* *S. fraseri* *S. japonica* *S. tomentosa*	 **141**: $R^2=R^4=R^{2`}=OH$; $R^{1`}=R^{3`}=OCH_3$; $R^{4`}$ = 1,1-dimethyl-2- propenyl; $R^1=R^3=R^5=R^{5`}=H$	Boozari et al. (2019b), Li et al. (2019c)
142	Secundiflorol H	*S. secundiflora*	**142**: $R^2=R^4=R^{2`}=OH$; $R^{1`}=R^{3`}=OCH_3$; $R^1=R^3=R^5=R^{4`}=R^{5`}=H$	Boozari et al. (2019b)
143	Arizonicanol C	*S. arizonica* *S. tomentosa*	**143**: $R^2=R^4=R^{2`}=OH$; $R^3=\gamma,\gamma$-dimethylallyl; $R^{1`}=R^{3`}=OCH_3$; $R^1=R^5=R^{4`}=R^{5`}=H$	Boozari et al. (2019b), Chang et al. (2019a, b)
144	Arizonicanol D		**144**: $R^2=R^4=R^{2`}=OH$; $R^{1`}$ = isoprenyl group; $R^{3`}=OCH_3$ $R^1=R^3=R^5=R^{4`}=R^{5`}=H$	
145	Tomentosanol A		**145**: $R^2=R^4=R^{3`}=OH$; $R^3$ = isoprenyl group; $R^{1`}=OCH_3$; $R^{4`}$ = 1,1-dimethyl-2- propenyl; $R^1=R^5=R^{2`}=R^{5`}=H$	

Table 2 (continued)

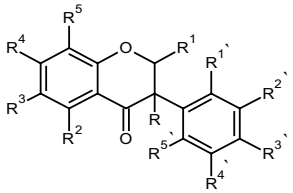
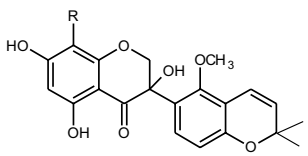
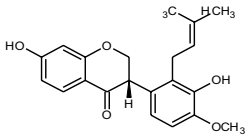
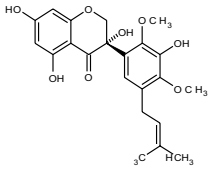
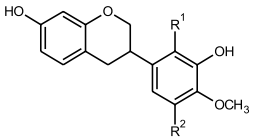
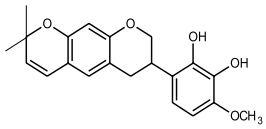
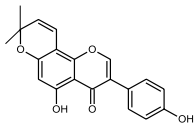
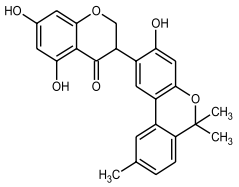
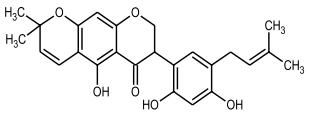
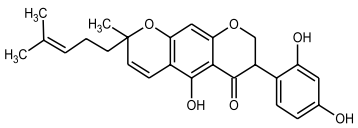
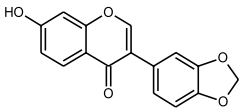
No.	Name	Plant species	Structure	References
146	Isosophoranone	*S. secundiflora* *S. tonkinensis* *S. mollis*	**146**: $R^2=R^4=R^{3`}=OH$; $R^3=R^{2`}=$ isoprenyl group; $R^{1`}=OCH_3$; $R^1=R^5=R^{4`}=R^{5`}=H$	Aly et al. (2019), Li et al. (2020a), Song et al. (2021)
147	Kenusanone A	*S. tetraptera*	**147**: $R^2=R^4=R^{3`}=R^{5`}=OH$; $R^{2`}=$ lavandulyl group; $R^1=R^3=R^5=R^{1`}=R^{4`}=H$	
148	Tetrapterol C	*S. secundiflora*	**148**: $R^2=R^4=R^{3`}=OH$; $R^5=$ lavandulyl group; $R^{1`}=OCH_3$; $R^1=R^3=R^{2`}=R^{4`}=R^{5`}=H$	Boozari et al. (2019b)
149	Tetrapterol D	*S. arizonica*	**149**: $R^2=R^4=R^{3`}=OH$; $R^{2`}=$ lavandulyl group; $R^1=R^3=R^5=R^{1`}=R^{4`}=R^{5`}=H$	Boozari et al. (2019b)
150	Tetrapterol E	*S. arizonica*	**150**: $R^4=R^{3`}=OH$; $R^{2`}=$ lavandulyl group; $R^1=R^2=R^3=R^5=R^{1`}=R^{4`}=R^{5`}=H$	Boozari et al. (2019b)
151	Tetrapterol G	*S. tomentosa*	**151**: $R^2=R^4=R^{1`}=R^{3`}=OH$; $R^3=R^{4`}=$ isoprenyl group; $R^1=R^5=R^{2`}=R^{5`}=H$	Aly et al. (2019), Li et al. (2020a)
152	Tetrapterol H	*S. mollis* *S. tetraptera*	**152**: $R^2=R^4=R^{1`}=OH$; $R^5=R^{4`}=$ isoprenyl group; $R^{3`}=OCH_3$; $R^1=R^3=R^{2`}=R^{5`}=H$	
153	Tetrapterol I	*S. secundiflora* *S. koreensis* *S. tomentosa*	**153**: $R^4=R^{3`}=OH$; $R^1=R^3=$ isoprenyl group; $R^2=R^5=R^{1`}=R^{2`}=R^{4`}=R^{5`}=H$	Aly et al. (2019), Boozari et al. (2019b), Li et al. (2020a)
154	Secundiflorol A	*S. tomentosa* *S. fraseri* *S. mollis*	 **154**: $R=R^2=R^4=R^{1`}=R^{2`}=OH$; $R^{3`}=OCH_3$; $R^{4`}=$ 1,1-dimethyl-2- propenyl; $R^1=R^3=R^5=R^{5`}=H$	
155	Secundifloran		**155**: $R=R^4=R^{1`}=R^{2`}=OH$; $R^{3`}=OCH_3$; $R^{4`}=$ 1,1-dimethyl-2- propenyl; $R^1=R^2=R^3=R^5=R^{5`}=H$	
156	Kenusanone F		**156**: $R=R^2=R^4=R^{3`}=OH$; $R^{1`}=OCH_3$; $R^{2`}=$ isoprenyl group; $R^1=R^3=R^5=R^{4`}=R^{5`}=H$	
157	Tomentosanol B		**157**: $R=R^2=R^4=R^{3`}=OH$; $R^{1`}=OCH_3$; $R^3=R^{2`}=$ isoprenyl group; $R^1=R^3=R^5=R^{4`}=R^{5`}=H$	Aly et al. (2019), Boozari et al. (2019b), Chang et al. (2019a, b), Li et al. (2020a)
158	Sophoronol	*S. tomentosa* *S. mollis* *S. tetraptera*	 **158**: $R=H$	
159	Tetrapterol F		**159**: R = isoprenyl group	

Table 2 (continued)

No.	Name	Plant species	Structure	References
160	Secundiflorol F	*S. secundiflora* *S. mollis*		Boozari et al. (2019b), Ismail et al. (2020), Li et al. (2020a)
161	3,5,7-Trihydroxy-3-[3′-hydroxy-2′,4′-dimethoxy-5-(3-methyl-2-butenyl)]-phenyl-1-benzopyran-4-one			
162	5′-γ, γ-Dimethylallyl-7,3′-dihydroxy-2′,4′-dimethoxyisoflavan (Unaniisoflavan)	*S. gypsophila* *S. secundiflora* *S. davidii*	 **162**: $R^1 = OCH_3$; $R^2 = \gamma, \gamma$-dimethylallyl	Aly et al. (2019), Li et al. (2020a, 2021b)
163	Secundiflorol G	*S. secundiflora*	**163**: $R^1 = OH$; $R^2 = \gamma, \gamma$-dimethylally	Boozari et al. (2019b)
164	Arizonicanol A	*S. arizonica*	**164**: $R^1 = OH$; $R^2 = H$	Boozari et al. (2019b), Chang et al. (2019a, b)
165	Arizonicanol B	*S. arizonica*		Li et al. (2020a)
166	Derrone	*S. secundiflora*		Li et al. (2020a)
167	Tetrapterol A	*S. tetraptera* *S. mollis*		Aly et al. (2019)
168	Cajanone	*S. tetraptera*		Li et al. (2020a), Boozari et al. (2019b), Li et al. (2020a)
169	Lespedeol B	*S. secundiflora*		
170	Pseudobaptigenin	*S. japonica* *S. secundiflora*		

reactive oxygen species (ROS) release in HepG2. Studies of its mechanism suggested that this compound mediates its anti-proliferative effects through autophagic cell death, which is an apoptosis independent. Western blot experiments demonstrated that the prenylated flavanone **100** could also activate the key signaling protein of autophagy and ROS, while it does not affect the main protein of the apoptosis signaling pathway (Yang et al. 2021).

The lavandulylated flavanones, 2′-methoxykurarinone (**24**) and kurarinone (**23**), were isolated from the root of *S. flavescens*, together with two known lavandulyl flavanones, sophoraflavanone G (**19**) and leachianone A (**20**), were exhibited cytotoxic activity against human myeloid leukemia HL-60 cells (Chang et al. 2019a, Huang and Xu 2020). Matrine (**246**) was recoded to promote human myeloid leukemia cells apoptosis through Warburg effect mediated by hexokinase 2 (Lin et al. 2019b). It (**246**) also inhibited the growth of natural killer/T-cell lymphoma cells by modulating CaMKIIγ-c-Myc signaling pathway (Gu et al. 2020).

The structure of exiguaflavanones A (**61**) and B (**62**), purified from *S. exigua* has approximately the same carbon skeleton orientation as frullanolide. This compound exhibited potent anti-breast cancer activity in breast cancer cell lines, including MDA-MB- (-231and -468) and MCF-7 (Boozari et al. 2019b; Farhadi et al. 2019; Li et al. 2020a; Yang et al. 2020c).

The isoflavonoid, formononetin (**125**) isolated from the phytoextract of *S. flavescens* (PSf), has been well-documented for its anticancer and the status of **125** in cancer therapeutics varied from arresting cell cycle, fights progression of cancer via inducing apoptosis, and halting metastasis via targeting various pathways (Jiang et al. 2019a). It also (**125**) targeted the fibroblast growth factor 2 and protein kinase-B signaling pathways, leading to the suppression of tumor growth and angiogenesis. The in vivo antiangiogenetic synergetic ability of low dose of oxaliplatin, the most used chemotherapy drug for colorectal cancer, combined with an injection of *S. flavescens* (Sf-I) against the growth of human umbilical vein endothelial cells was reported (Elberry et al. 2020).

Compounds with 2 isoprenyl groups (one in A-ring and the other in B-ring) tetrapterol G (**151**) and compound with α, α-dimethylallyl group at C-5′ of B-ring such as secundiflorol D (**140**), secundiflorol E (**141**), secundiflorol A (**154**), and secundifloran (**155**), showed relatively high cytotoxic activity against tumor and normal human cell lines (Guo et al. 2020; Ledoux et al. 2018). The cytotoxicity effect of different isoflavone glucosides and maackiain (**172**), isolated from *S. alopecuroides* seeds, against MCF-7, Hep3B, HeLa, and H1299 cells was reported (Rong et al. 2020; Tsai et al. 2020). The arylbenzofuran, 2-(2′,4′-dihydroxyphenyl)-5,6-methylene dioxybenzofuran (**192**), isolated from the roots of PSf and the roots and PSt rhizome, potently inhibited IL-6 production and cytotoxic activity against the KB epidermoid carcinoma cell line (Boozari et al. 2019b; Li et al. 2019c; Jin et al. 2020).

Compound Kushen Injection (CKI), as a formula mainly consisted of matrine **246**, has been employed into clinical applications in the adjuvant treatment of breast, lung, colon, gastric, esophageal, liver, and pancreatic cancer (Cho et al. 2018; Ao et al. 2019; Chen et al. 2019c; Hong et al. 2019; Liang et al. 2020; Yao et al. 2021). The reported mechanism of this component (**246**), to suppress KRAS-driven pancreatic cancer growth, was by inhibiting autophagy-mediated energy metabolism (Cho et al. 2018). Kushen is the root of *S. flavescens* based-formula inhibited angiogenesis in a collagen-induced arthritis rat model (Ao et al. 2019; Elberry et al. 2020). Kurarinone (**23**), a lavandulyl flavanone, isolated from the roots of PSf, was reported to have a cytotoxic activity ($IC_{50} = 22.2$ μM) against human MCF-7/6 breast cancer cells, but with a weak estrogenic activity (Boozari et al. 2019b). The inhibitory effects of flavonoid-rich extract of *S. flavescens* on indoleamine 2, 3-dioxygenase 1 (IDO1), a tryptophan catabolising enzyme, is known as a tumor cell survival factor that causes immune escape in several types of cancer (Kwon et al. 2019). Kushenol (**28**), a flavonoid isolated from PSf, was reported as IDO1-inhibitor and might be useful in the development of immunotherapeutic agents against cancer.

The matrine (**246**) has been proved in many studies to inhibit cancer cell proliferation and metastasis, arrest cell cycle, promote apoptosis, and reduce the toxicity of anticancer drugs with reversing effects on anticancer drug resistance (Chen et al. 2019d; Cao and He 2020; Fu et al. 2020; Liu et al. 2020a, b; Zhang et al. 2020a). A nontoxic concentration of Matrine (**246**) also facilitated intrinsic apoptosis pathway and suppressed the expression of ATP-binding cassette subfamily B member 1 drug transport (Chen et al. 2019d). The same compound induced papillary thyroid cancer cell apoptosis in vitro and suppressed the in vivo tumor growth by downregulating miR-182-5p (Li et al. 2019b; Fu et al. 2020). The inhibitory effect of **246** on human nasopharyngeal carcinoma CNE-2 cells was reported (Wang et al. 2018c). Matrine (**246**) reversed multidrug resistance of breast cancer MCF-7/ADR cells through PI3K/AKT signaling pathway (Zhou et al. 2018b). Another study suggested that the dependence of **246** suppression of self-renewal, on regulation of LIN28A/Let-7 pathway in breast cancer stem cells (Li et al. 2020c). The quinolizidine-type alkaloid (**246**) can inhibit the proliferation of breast cancer MCF7, BT-474, and MDA-MB-231 cells, which may be related to the inhibition of inhibitory κB kinase β (IKKβ) regulation of nuclear factor κB (NF-κB) signaling pathway (Cao and He 2020; Zhang et al. 2020a).

The anticancer property of a derivative of matrine **246** was explored (Zhou et al. 2019). The activity of N-methyl

cytisine (**268**) in inhibiting breast cancer cell metastasis was previously demonstrated (Chen et al. 2020a).

Leachianols (**208**–**211**), are naturally occurring oligostilbenes; the resveratrol trimers were isolated from *S. leachiana* roots (Yang et al. 2019; Boozari et al. 2019a). These stilbenoids exhibited a wide range of biological activity including a positive result in a cell-based assay for antimitotic activity using HeLa cells with a cytotoxic effect. A prepared injection from *S. flavescens* and *Heterosmilax chinensis* was reported to disrupt cell cycle and induce apoptosis in breast cancer (Nourmohammadi et al. 2019). This injection strongly reduced migration of HT-29 and MDA-MB-231 cells, moderately slowed brain cancer cells on migration and invasion of colon, brain, and breast cancer cell lines. The prepared injection decreased metastasis by impairing migration in hepatocellular carcinoma cells and repressing RNA markers associated with tumor metastasis in MCF-7 cells.

Oxysophoridine **242** is an alkaloid extracted from *S. alopecuroides* Linn. Many in vitro cellular and in vivo animal studies showed that **242** has various pharmacological activities. It suppressed the growth of hepatocellular carcinoma (Yao et al. 2012) and colorectal cancer cells (Jin et al. 2017) by regulating apoptosis associated with the Bcl-2/Bax/caspase-3 signalling pathway, and alleviation of spinal cord injury via anti-inflammatory, anti-oxidative stress, and anti-apoptosis effects (Cao et al. 2018).

The protective effects of oxymatrine (**249**) on homocysteine-induced endothelial injury were reported (Wu et al. 2019a). The involvement of mitochondria-dependent apoptosis and Akt-eNOS-NO signaling pathways was suggested. The ability of sophoridine (**240**) to suppress rat liver BRL-3A cells viability in a concentration- and time-dependent manner was also recorded (Qiu et al. 2018). This compound (**240**) increases cytotoxicity, ROS accumulation, and cell apoptosis in a concentration-dependent manner (Qiu et al. 2018). Sophoridine (**240**) and oxymatrine (**249**) exerted a good anti-tumor effect in clinical applications (Cao and He 2020; Liu et al. 2020a, b).

Oxymatrine (**249**) exerted cytotoxicity against cancer cells through regulation various oncogenic signaling pathways such as the Akt, nuclear factor kappa B (NF-κB) cascades, and epidermal growth factor receptor (EGFR) (Halim et al. 2019). This QA **249** induced A549 human non-small lung cancer cell apoptosis via extrinsic and intrinsic pathways (Zhou et al. 2018d; Izdebska et al. 2019). Another study presented the influence of oxymatrine on non-small cell lung cancer cells (Halim et al. 2019; Izdebska et al. 2019). It suggested that this compound has induced dose-dependent cell death, mainly through ER stress-induced apoptosis pathway. Oxymatrine **249** also reduced the metastatic potential by inhibiting the cancer epithelial-mesenchymal transition process (Chen et al. 2019c). A recent study showed that through in vitro inhibiting colon cancer cell epithelial-mesenchymal transition and NF-κB signaling, the compound **249** reversed the resistance of 5-fluorourfacil (Liang et al. 2020).

The role of matrine (**246**), oxymatrine (**249**), and PSf alkaloid gel in cervical cancer has been also investigated (Zhou et al. 2018e). The gel has recorded to restrain cervical cancer cell proliferation, induce cellular apoptosis through stimulation of Bax and E-cadherin, induce cell cycle arrest in G2/M phase, inhibit metastasis, and suppression of MMP2, Bcl-2 and cyclin A. The regulation of the cervical cancer cells was suggested via the suppression of AKT/mTOR signaling pathway (Zhou et al. 2018e). Through activating p53 and Hippo signaling pathways, sophoridine (**240**) inhibited lung cancer cell growth and enhanced the cisplatin sensitivity (ur Rashid et al. 2020; Zhou et al. 2018d, 2020). The same compound **240** was reported to exert tumor-suppressive activities via promoting ESRRG-mediated β-catenin degradation in gastric cancer (Peng et al. 2020b). Sophoridine (**240**) also reported to suppress macrophage-mediated immunosuppression through TLR4/IRF3 pathway, and subsequently upregulate CD8 + T cytotoxic function against gastric cancer (Zhuang et al. 2020). Sipi soup, a traditional Chinese medicine, which is consists of the aqueous extract derived from 4 plants including PSj, was reported as an anti-inflammatory component. This medicine has suggested that it may prevent the progression of cervical cancer by inhibiting the activation of CAF, and the inflammatory process by reducing HIPK1-AS expression (Zhou et al. 2018a).

Cytotoxic activities of phenolic acids (**324**–**331**) from the seeds of *S. alopecuroides* and the roots of *S. tonkinensis* against hepato-cellular carcinoma, HepG2, and Hep3B cell lines were investigated (Song et al. 2018; Hou et al. 2020; Zhang et al. 2021c). Butein (**331**) significantly inhibited the cancer cell growth in a concentration-dependent manner (Song et al. 2018). Another study confirmed that the weak anticancer activity of compounds (**325**–**328**) and (3S,2R)-methyl 2-(4-hydroxybenzyl)tartrate (**332**) against the same two cell lines (Song et al. 2019).

HPLC fingerprint of chloroform extract from *S. tonkinensis* Gagnep revealed the presence of ononin (**109**), genistin (**119**), genistein (**120**), isosophoranone (**127**), trifolirhizin (**154**), isotrifolirhizin (**155**), and maackiain (**172**) (Song et al. 2021; Chen et al. 2020c). The authors explored the mechanisms of this extract on suppression tumors of nasopharyngeal carcinoma cells. They found that the extract inhibited cell viability, clonal growth, and induced cell apoptosis in a dose-dependent manner. This effect was exerted by silencing the PI3K/AKT/mTOR signaling pathway, which is associated with upregulation of cleaved PARP, cleaved caspase 3/7/8/9, caspase 3/7/8/9, Bax, and downregulation of PI3K, P-PI3K, PARP, AKT,P-AKT, mTOR, and P-mTOR and Bcl-2 (Ao et al. 2019; Cao and He 2020; Chen et al. 2020d).

Compounds **246** and **249** had direct killing effects on various tumor cells, such as HepG2, BEL-7402, and SGC-7901, and could inhibit the invasion and metastasis of gastric cancer last cells (Huang et al. 2018c; Elberry et al. 2020; Zhang et al. 2020a). Matrine (**246**) has been reported to inhibit the progression of prostate cancer by promoting expression of GADD45B (Huang et al. 2018a). Oxymatrine (**249**) exhibits anti-tumor activity in a gastric cancer through inhibiting IL-21R-mediated JAK2/STAT3 pathway and the proliferation of vascular endothelial cells (Huang et al. 2018c; Su et al. 2018; Fan et al. 2019).

Combined chemotherapy can effectively reduce or stabilize the tumors, improve quality of life, and significantly alleviate the cancer-induced pain (Fan et al. 2019). Radix *S. flavescens* contained serum can inhibit cell proliferation and induce apoptosis of human colon cell line SW480 (Liang et al. 2020). This induction of apoptosis was reported as one of the suggested anti-neoplasm mechanisms of the medicine (Elberry et al. 2020). With the effective components of oxysophocarpine (**236**), matrine (**246**), and oxymatrine **249** (Cao and He 2020), it has been widely applied to treating various kinds of malignant tumors in China, including colon carcinoma (Liang et al. 2020; Liu et al. 2020a, b). Matrine (**246**) effectively inhibited the proliferation and anchorage-independent growth of human colon cancer HT29 cells (Fang et al. 2018).

Exposure of gastric cancer cells (AGS and HGC 27) to oxymatrine (**249**), contributed to the suppression of cell proliferation and invasion (Huang et al. 2018c). The anti-tumor effect of **249** was exhibited via regulation of JAK/STAT signaling pathway. Anti-proliferation effects of phytoextract of *S. moorcroftiana* (PSm) seeds on HepG2 were also reported (Su et al. 2018). Sophocaprine (**235**), matrine (**246**), and aloperine (**284**) were identified in the extract of PSm with low polarity. Matrine (**246**) has reported to reverse the Warburg effect and it suppresses colon cancer cell growth via negatively regulating HIF-1α (Hong et al. 2019). This compound (**246**) has reported to trigger colon cancer cell apoptosis and G0/G1 cell cycle arrest, where **284** has induced apoptosis and G2/M cell cycle arrest in HepG2 (Liu et al. 2019a, 2020b). Matrine (**246**) induced apoptosis in human esophageal squamous cancer KYSE-150 cells through increasing ROS and inhibiting mitochondrial function (Jiang et al. 2018). It also inhibited the growth of oral squamous cell carcinoma cells in vitro and in vivo (Li et al. 2019d). Matrine (**246**) has exhibited its effect via mediation of microRNA-22 (ur Rashid et al. 2019; Liu et al. 2020b), where aloperine (**284**) was through PI3K/Akt signaling pathway (Liu et al. 2019a).

Matrine (**246**) has also involved in the progression of gastric cancer through inhibiting miR-93-5p and upregulating the expression of target gene AHNAK (Liu et al. 2020b). The effect of matrine (**246**) from *S. flavecens* on hepatocellular carcinoma, the one of the most prevalent and lethal cancer with high metastasis and recurrence rates, has been investigated (Dai et al. 2021). This significant anti-metastatic effect was attributed to enhanced miR-199a-5p expression and subsequently impaired hypoxia-inducible factor-1α signaling and epithelial-mesenchymal transition. Thus, matrine (**246**) was suggested as a promising component with anti-metastatic medication for hepatocellular carcinoma therapy.

The mechanism of allomatrine (**248**), isolated from the bark of *S. japonica*, in invasion and proliferation inhibition of human lung cancer A549 cell line was also investigated. This alkaloid inhibited the proliferation and invasion in vitro by promoting apoptosis, inducing ROS production, inhibiting ubiquitin proteasome, arresting cell cycle, and regulating tumor related gene expression (Liu et al. 2020a, b).

The quinolizidine-type alkaloid aloperine (**284**) extracted from PSa, showed some therapeutic effects against multiple myeloma and colon cancer though increasing cell apoptosis (Yin et al. 2018; Li et al. 2020d).

The quinolizidine alkaloid **284** exerted the most potent cytotoxic activity on leukemia cell lines U937, HL-60, and K562, lung cancer cells, glioma cells, ovarian cancer cells, oesophageal cancer EC109 cells, and HepG2 cell lines (Qiu et al. 2020b; Zhou et al. 2020).

The combination of compound **284**-Adbic (adenoviral vector expressing $p14^{ARF}/p53$) can produce a synergistic effect as anti-cancer mixtures at low doses. This may offer less toxic and more effective treatment strategy for non-small cell lung cancer (Muhammad et al. 2020). Research conducted by Song's group has recorded that **284** significantly inhibited the viability of bladder cancer cells, mostly via suppressing hypoxia induced epithelial-mesenchymal transition activation of mTOR/p70S6K/4E-BP1 pathway (Zhou et al. 2020).

The anti-tumor effect of total alkaloids of *S. alopecuroides* (TASa) in H22 tumor-bearing mice was investigated. It was found that different dose groups of TASa extract could apparently inhibit the solid H22 tumor in mice, with a clear dose–effect relationship (Huang et al. 2018c; Jia et al. 2020).

The potential cytotoxic, antimicrobial, antioxidant, and anti-enzyme of *S. alopecuroides* L. seeds was recently reported (Zahra et al. 2021). Twelve quinolizidine alkaloids; sophalodes A–L (**307–319**), which were matrine-type alkaloids isolated from *S. alopecuroides* seeds (Li et al. 2021a). Structurally, sophalodes A-D (**307–310**) were the examples of C-11 oxidized matrine-type alkaloids from *Sophora* plants.

The sophalodes (**307–319**) A-L inhibited nitric oxide production induced by lipopolysaccharide in RAW 264.7 macrophages, among them, compounds sophalode K **318**

Table 3 Pterocarpans isolated from *Sophora* species

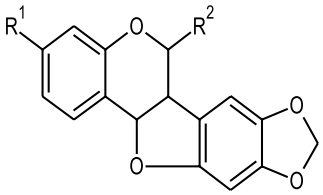
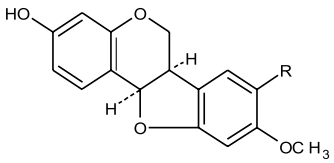
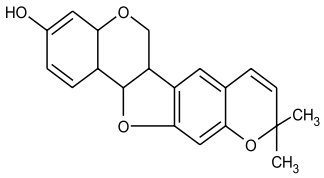
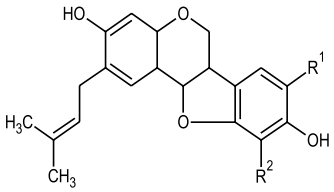
No.	Name	Plant species	Structure	References
171	Sophorocarpan B	*S. alopecuroides* *S. davidii* *S. fraseri*	 **171**: $R^1 = OH$; $R^2 = OCH_3$	Aly et al. (2019), Yang et al. (2019)
172	Maackiain	*S. davidii* *S. exigua* *S. flavescens* *S. fraseri* *S. gypsophila* *S. interrupta* *S. leachiana* *S. prostrata* *S. subprostrata* *S. tetraptera*	**172**: $R^1 = OH$; $R^2 = H$	Boozari et al. (2019b), Yang et al. (2019), Cho et al. (2020), Huh et al. (2020), Rammohan et al. (2020)
173	Trifolirhizin	*S. flavescens* *S. subprostrata* *S. tonkinensis*	**173**: $R^1 = O$-glc; $R^2 = H$	Boozari et al. (2019b), Cho et al. (2020), Song et al. (2021)
174	3-Hydroxy-8,9-methylene dioxy-pterocarpan	*S.alopecuroides* *S. mollis*	**174**: $R^1 = OH$; $R^2 = H$	Ismail et al. (2020), Wang et al. (2020a, b, c)
175	Prostratol D	*S. prostrata*		Aly et al. (2019), Boozari et al. (2019b)
176	Prostratol E	*S. prostrata* *S. tetraptera*	**175**: R = γ, γ-dimethylallyl **176**: R = geranyl group	
177	Isoneorautenol	*S. prostrata* *S. tetraptera*		Aly et al. (2019), Boozari et al. (2019b)
178	Ficifolinol	*S. prostrata*	 **178**: R^1 = γ, γ-dimethylallyl; $R^2 = H$	Boozari et al. (2019b)
179	Erythrabyssin II		**179**: R^2 = γ, γ-dimethylallyl; $R^1 = H$	

Table 3 (continued)

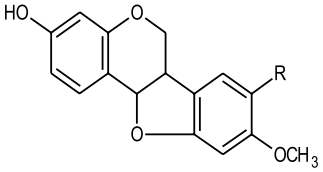
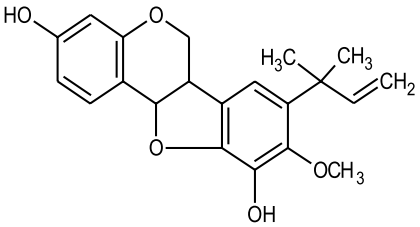
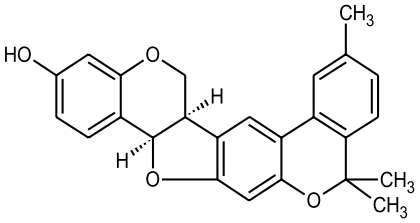
No.	Name	Plant species	Structure	References
180	Secundiflorol I	*S. gypsophila* *S. secundiflora*	 **180**: R = OCH_3	Aly et al. (2019), Boozari et al. (2019b)
181	Medicalpin	*S. gypsophila*	**181**: R = H	
182	Arizonicanol E	*S. arizonica*		
183	Tetrapterol B	*S. mollis* *S. tetraptera*		Boozari et al. (2019b)

Table 4 Chalcones isolated from *Sophora* species

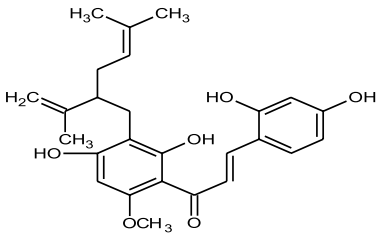
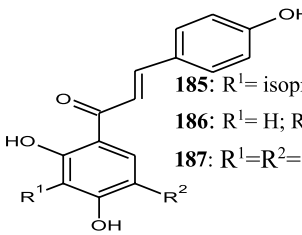
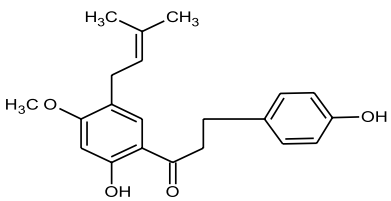
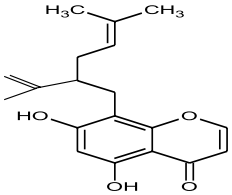
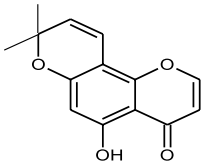
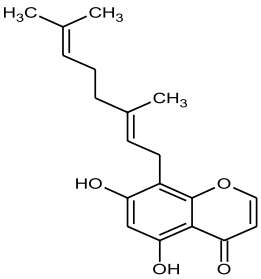
No.	Name	Plant species	Structure	References
184	Kuraridin	*S. flavescens*		Boozari et al. (2019b), Cho et al. (2020)
185	Isobavachalcone	*S. interrupta* *S. prostrata*	 **185**: R^1= isoprenyl group; R^2= H **186**: R^1= H; R^2= isoprenyl group **187**: R^1=R^2= H	Aly et al. (2019, 2020a, b, c)
186	Bavachalcone			
187	Isoliquiritin	*S. arizonica* *S. gypsophila*		Boozari et al. (2019b)
188	Tonkinochromane L	*S. tonkinensis*		Jin et al. (2020)

Table 5 Chromones isolated from *Sophora* species

No.	Name	Plant species	Structure	References
189	Exiguachromone A	*S. exigua*		Aly et al. (2019), Farhadi et al. (2019)
190	Exiguachromone B			Boozari et al. (2019b), Farhadi et al. (2019)
191	Sophorachromone A	*S. tomentosa*		Chang et al. (2019a, b)

exhibited the most significant activity with IC_{50}-values of 29.19 µM.

Evaluation of anticancer activity of isolated compounds from *S. mollis* (Royle) Graham Ex Baker, including scopoletin **216** and β-sitosterol glucoside **218** have revealed weak effect against HeLa and 3T3 cell lines (Quradha et al. 2021). The major compounds derived from *Sophora* species that having cytotoxic and anti-tumor activities were illustrated in Table 16.

Neurological activity

Many studies have reported the neuroprotective effects of QA isolated from *Sophora* (Wang et al. 2019a, d). The useful use of PSf and the isolated active alkaloid (**246**), as natural alternatives for hypnotic medicine, was suggested (Wang et al. 2019a). They have alleviated the hyperactivity induced by caffeine and promoted a shift toward non-rapid eye movement sleep. The mechanism was suggested to decrease wake time by the activation of the neurons of ventrolateral preoptic nucleus, and through modulating serotonergic transmission (Wang et al. 2019a). Aloperine (**284**) has significant neuroprotective effects, in an Alzheimer's disease cellular model, attributing to its anti-oxidative stress (Wang et al. 2019d). This compound **284** ameliorated oxidative stress patterns in presenilin 1 exon 9 deletion mutant cells by reducing the production of 4-hydroxy-2-nonenal and ROS (Zhao et al. 2018). Its treatment increased mitochondrial membrane potential (MMP) in N2a/Swe.D9 cells as Alzheimer's disease cellular model.

The phytoextract of *S. flavescens* (PSf) and its prenylated flavonoids; possessing low molecular weights and lipophilic moieties, may be potent therapeutic and preventive candidates for Alzheimer's disease (Boozari et al. 2019b; Cho et al. 2020).

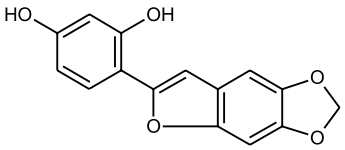
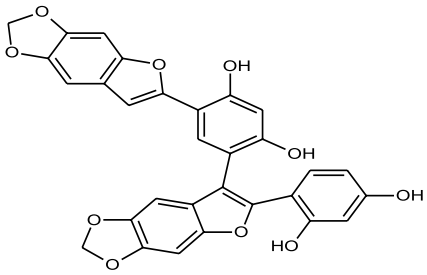
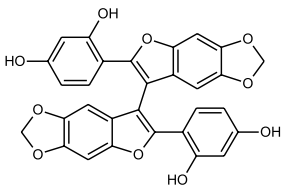
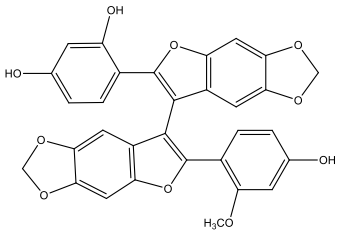
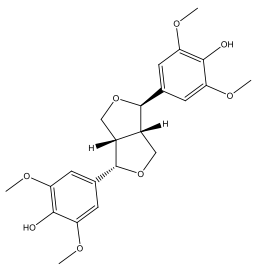
β-Site APP cleaving enzyme 1 (BACE1) activities in Alzheimer's disease were significantly inhibited by kushenol (**28**), isoxanthohumol (**32**), leachianone A (**20**), and kuraridin (**184**) with IC_{50}-values of 5.45, 7.19, 8.56, and 6.03 µM, respectively. These compounds were isolated from the lead bioactive fractions EtOAc and CH_2Cl_2 of the crude PSf (Boozari et al. 2019b; Chen et al. 2019a).

Maackiain (**172**) has emerged as a valuable agent for Parkinson's disease treatment, with remarkable improvements in food-sensing behavior and lifespan (Tsai et al. 2020) mainly by inhibiting monoamine oxidase B. Maackiain (**172**) significantly reduced dopaminergic neuron damage in 6-hydroxydopamine-exposed worms of the BZ555 strain. The neurological activity was illustrated in Table 17.

Antimicrobial activity

Sophora exigua has reported with antimicrobial activities against *Candida albicans*, *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa* (Kaewdana et al. 2021).

Table 6 Benzofuran derivatives isolated from *Sophora* species

No.	Name	Plant species	Structure	References
192	2-(2′,4′-Dihydroxy-phenyl)-5,6-methylene dioxy benzofuran	*S. davidii* *S. fraseri* *S. tetraptera*		Aly et al. (2019), Boozari et al. (2019b), Li et al. (2021b)
193	Shandougenine A	*S. davidii* *S. tonkinensis* *S. davidii* *S. tonkinensis*		Boozari et al. (2019b), Li et al. (2019c, 2021b)
194	Shandougenine B			
195	Shandougenine C	*S. davidii*		Li et al. (2021b)
196	(+)-Lirioresinol-A	*S. davidii*		Li et al. (2021b)

Sophoraflavanone G (**19**), isolated from *S. exigua* also exerted an antibacterial effect by reducing the fluidity of cellular membranes (Boozari et al. 2019b; Farhadi et al. 2019).

Flavanones (**19**) and (**23**) exhibited potent antibacterial activities (10 µg/disk) against Gram-positive bacteria (Farhadi et al. 2019). The phytoextract of *S. alopecuroides* roots and its content of pterocarpan derivative, maackiain (**172**) helped individuals with androgenetic alopecia as the derivative promoted the proliferation of human hair keratinocytes (Chang et al. 2018; Wang et al. 2018f; Huh et al. 2020).

Sophoraflavanone B (**48**) also caused cell wall weakening and consequently membrane damage had occurred, and intracellular constituents leaked from the cell as the proposed mechanism of its antimicrobial activity against methicillin-resistant-*Staph. aureus* (anti-MRSA) (Farhadi et al. 2019; Hadadi et al. 2020). An antibacterial synergism of compound (**48**) with antibiotics, including ampicillin, gentamicin, and oxacillin anti-MRSA, was previously determined (Farhadi et al. 2019). While the other prenylated flavonoid, sophoraflavanone G (**19**; from *S. flavescens* and *S. exigua*) potentiated the effect of ampicillin or oxacillin against the MRSA infection (Farhadi et al. 2019). In addition, the compound (**19**) showed significant antibiofilm formation against *Bacillus subtilis*, *Staph. aureus*, and *Staph. epidermidis* with MIC-values ranging from 3.1 to 12.5 µg mL^{-1} (Farhadi et al. 2019). The lavandulyl flavanones isolated from the roots of *S. exigua* (PSe) (Li et al.

Table 7 Stilbene oligomers isolated from *Sophora* species

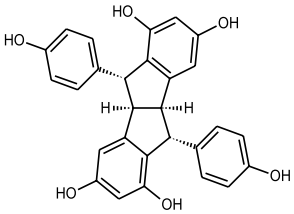
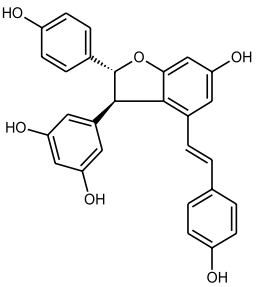
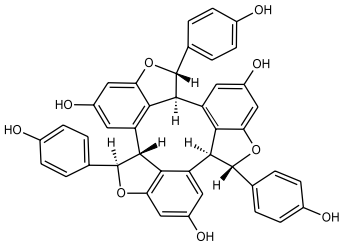
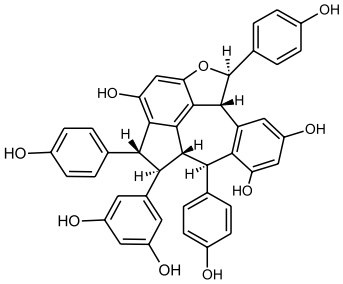
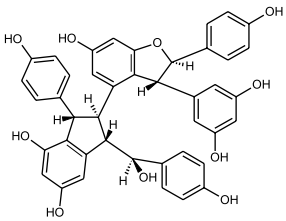
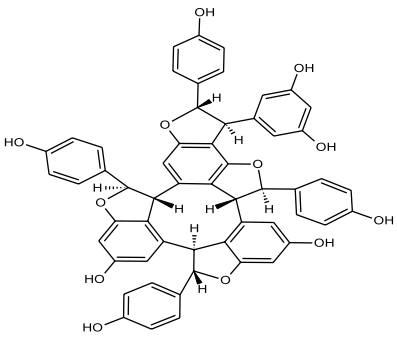
No.	Name	Plant species	Structure	References
197	Pallidol	*S. alopecuroides*		Wang et al. (2020b)
198	Viniferin	*S. alopecuroides* *S. davidii* *S. leachiana* *S. moorcroftiana*		Su et al. (2018), Yang et al. (2019), Wang et al. (2020b)
199	Davidol E	*S. davidii* *S. moorcroftiana*		Yang et al. (2019), Wang et al. (2018a, b, c, d, e, f)
200	Davidol A	*S. davidii*		Yang et al. (2019)
201	Davidol B	*S. davidii*		Yang et al. (2019)
202	Davidol C			

Table 7 (continued)

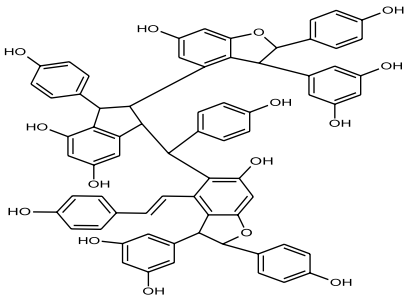
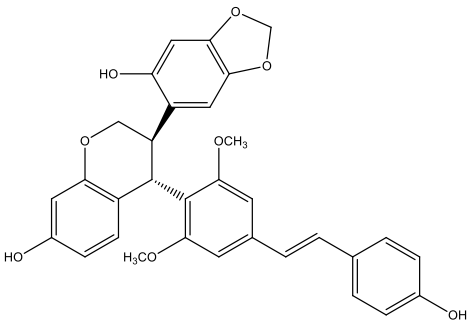
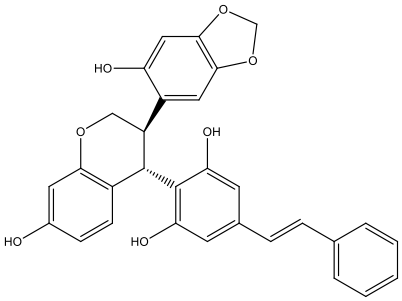
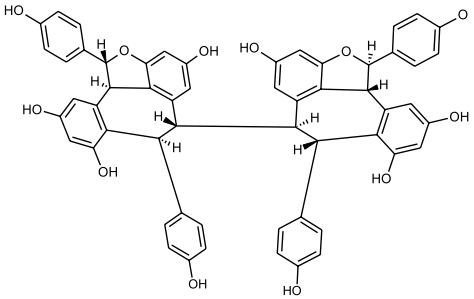
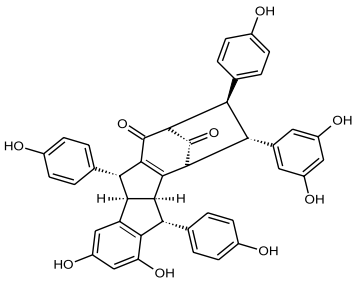
No.	Name	Plant species	Structure	References
203	Davidol D	*S. davidii*		Yang et al. (2019)
204	Davidiol E	*S. davidii*		Li et al. (2021b)
205	Davidiol F	*S. davidii*		Li et al. (2021b)
206	Hopeaphenol	*S. leachiana*		Aly et al. (2019)
207	Leachianol A	*S. alopecuroides* *S. leachiana*		Boozari et al. (2019b), Wang et al. (2020a, b)

Table 7 (continued)

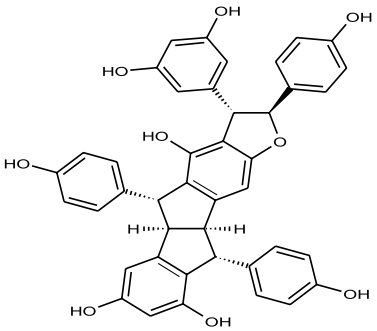
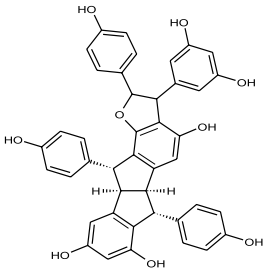
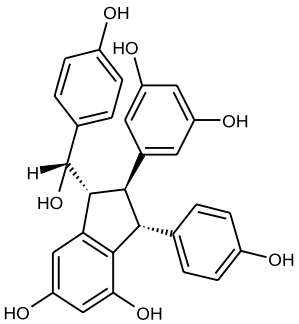
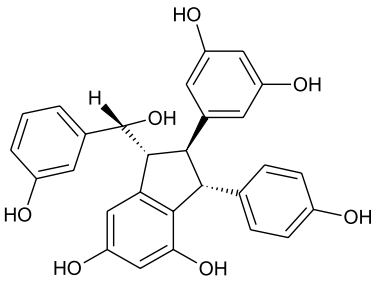
No.	Name	Plant species	Structure	References
208	Leachianol D	*S. leachiana*		Boozari et al. (2019b)
209	Leachianol E	*S. leachiana*		Boozari et al. (2019b)
210	Leachianol F	*S. alopecuroides* *S. leachiana*		Boozari et al. (2019b), Wang et al. (2020a, b)
211	Leachianol G	*S. alopecuroides* *S. leachiana* *S. davidii*		Yang et al. (2019), Wang et al. (2020a, b)

Table 7 (continued)

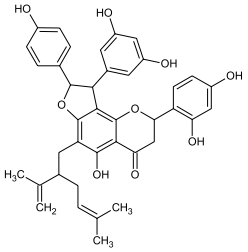
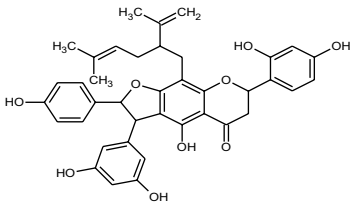
No.	Name	Plant species	Structure	References
212	Alopecurone H	*S. alopecuroides*		Wang et al. (2020a, b)
213	Alopecurone K	*S. alopecuroides*		Wang et al. (2020a, b)

Table 8 Coumarins isolated from *Sophora* species

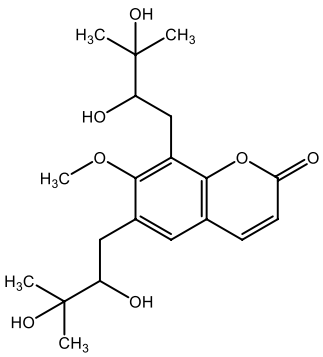
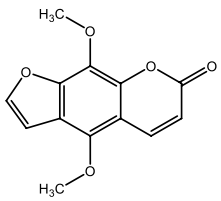
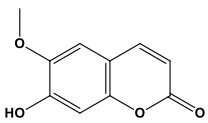
No.	Name	Plant species	Structure	References
214	7-Methoxy-6,8-*bis*-(2,3-dihydroxy-3-methylbutyl)-coumarin	*S. alopecuroides* *S. interrupta*		Aly et al. (2019), Wang et al. (2019a)
215	Isopimpinellin	*S. interrupta*		Boozari et al. (2019b)
216	Scopoletin	*S. mollis*		Quradha et al. (2021)

Table 9 Sterol and steroid glucosides isolated from *Sophora* species

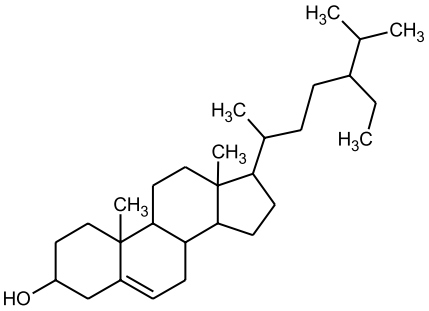
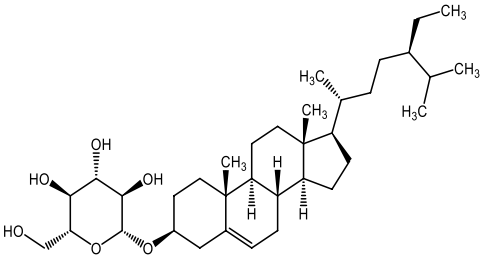
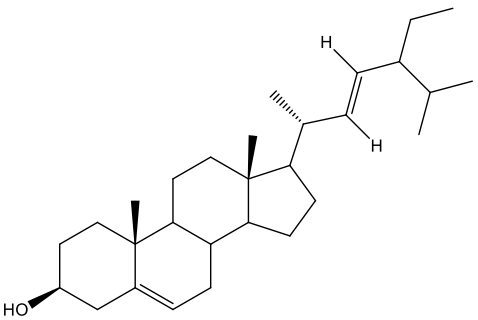
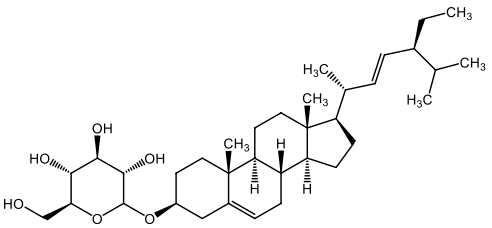
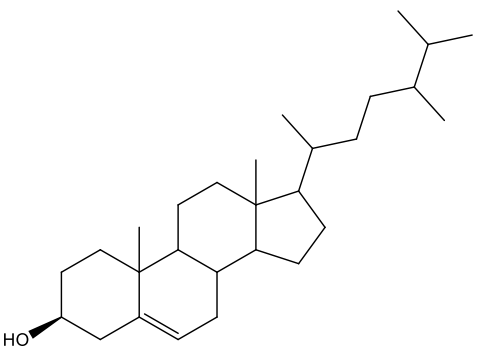
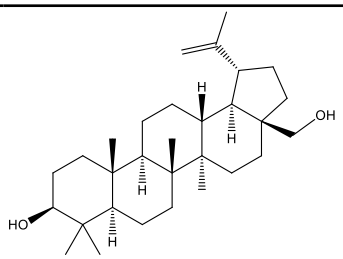
No.	Name	Plant species	Structure	References
217	β-Sitosterol	*S. alopecuroides* *S. mollis* *S. secundiflora* *S. tomentosa*		Aly et al. (2020a), Wang et al. (2020b)
218	Sitosterol 3-*O*-glucoside	*S. mollis* *S. pachycarpa*		Boozari et al. (2019a), Quradha et al. (2021)
219	Stigmasterol	*S. secundiflora* *S. tomentosa*		Aly et al. (2020a)
220	Stigmasterol 3-*O*-glucoside	*S. alopecuroides* *S. pachycarpa*		Wang et al. (2020b)
221	Campesterol	*S. secundiflora* *S. tomentosa*		Aly et al. (2020a)

Table 9 (continued)

No.	Name	Plant species	Structure	References
222	Lup-20(29)-ene-3, 28- diol (Betulin)	*S. mollis* *S. tomentosa* *S. secundiflora*		Aly et al. (2020a), Quradha et al. (2021)

2020a; Yang et al. 2020c) were proposed to be potent phytotherapeutic agents against MRSA infection (Farhadi et al. 2019). A complete growth inhibition of 21 MRSA-strains (3.13–6.25 µg mL^{-1}) was exerted by exiguaflavanones-A (**61**) and B (**62**), the isolated flavanones from PSe with a lavandulyl residue (Farhadi et al. 2019). Partial synergistic effects with anti-MRSA antibiotics, such as minocycline, rifampicin, and vancomycin, were also reported. Lavandulyl flavanones were also reported as anti-malarial, anti-inflammatory, and cytotoxic agents (Boozari et al. 2019b; Li et al. 2020a; Kaewdana et al. 2021).

The potentials of total alkaloids of *S. alopecuroides* (TASa) and matrine (**246**) in prevention of biofilm formation in *Staph. epidermidis* infections were indicated (Jia et al. 2019). A previous study evidenced that the isoflavonoid genistein (**120**), isolated from *S. moorcroftiana,* could be a potential inhibitor of NorA, a multi-drug transporter of *Staph. aureus* (Farhadi et al. 2019). The mode of action of the aglycone on different bacterial cells was studied and the changes exerted in the cell morphology of bacteria were suggested as the underlying mechanism. Additionally, mixing this compound with the bacterial culture immediately and significantly inhibited the global synthesis of RNA and DNA (Farhadi et al. 2019).

The chalcone isobavachalcone (**185**) has reported with the lowest MIC-value (0.3 µg mL^{-1}) of Gram-positive bacteria, which was fourfold lower than the MIC-value (4.9 µg mL^{-1}) of the conventional drug gentamicin (Aly et al. 2019; Farhadi et al. 2019; Rammohan et al. 2020).

Matrine (**246**) and oxymatrine (**249**) have anti-*Helicobacter pylori* (Hp) infection effects, the closely related to the digestive diseases (Li et al. 2020d; Wang et al. 2020b, c). The compounds used for oral ulcers and have the potential of antibacterial inflammation, and alleviating swelling, pain, and sore myogenic (Li et al. 2020d; Wang et al. 2020b). Additionally, ASa combined with omeprazole or bismuth pectin has promising antimicrobial activity against Hp, and conventional triple therapy through inhibition of Hp-induced IL-8, COX-2, and NF-κB expression. Summary of findings on the antimicrobial activity of *Sophora* compounds was also illustrated in Table 18.

Anti-osteoporosis activity

In a sub-cytotoxic concentration range, a derivative of genistein (**120**) showed a significant proliferative activity in estrogen-dependent cell line of MCF-7. In a previous report, prominent anti-osteoporosis effect of the CH_2Cl_2 fraction from PSj fruits was attributed to the high content of isoflavone (**120**). This aglycone has a peculiar anti-osteoporotic dual mode of action. It was recorded to be the most effective isoflavone in preserving bone health and rebalancing bone turnover towards bone formation through its positive ability to regulate bone cell metabolism (Yang et al. 2020c). This isoflavone inhibited osteoclast and stimulated osteoblast function, mainly through the osteoprotegerin-sRANKL system.

Compounds genistein **120** and sophoricoside **134** from *S. japonica* was also reported to prevent the osteoporosis (Yang et al. 2020c). Chemically, isoflavonoids are compounds with ring C in position 3 instead of position 2. The isoflavone aglycone genistein (**120**) and flavonol aglycone kaempferol (**2**) were found to be the main phytoestrogens in the naringinase-treated phytoextract of *S. japonica* (PSj) seeds (Yang et al. 2020c). *S. japonica* seeds extract PSj prevented bone loss, partly by inhibiting the osteoclastic activity. The alcoholic PSj showed a significant estrogenic activity only after naringinase treating. Kaempferol (**2**), was nearly equipotent to genistein (**120**) as an estrogen agonist (Yang et al. 2020c), which was reported to prevent the osteoporosis (Yang et al. 2020c). Fructus Sophorae (FS) or Huaijiao, the dry mature fruit of *S. japonica*, were proved to prevent bone loss in ovariectomized rat's model (Shim et al. 2005). The effect of flavonoids, including rutin (**3**), genistein (**120**), pratensein (**129**), biochanin (**130**), prunetin (**131**) sophoricoside (**134**), and rutin (**3**), on rat osteoblasts was also reported (Yang et al. 2020c). They were act as estrogen-like reagents and significantly increased the cellular activity of MC3T3-E1 cells. Another study disclosed the effects of alkaloids on osteoblasts infected with *Staph. aureus* and osteoclasts (Wang et al. 2018e).

Matrine (**246**) inhibited TGF-β induced Smad2/3 phosphorylation and transcription of runt-related transcription

Table 10 Triterpenes isolated from *Sophora* species

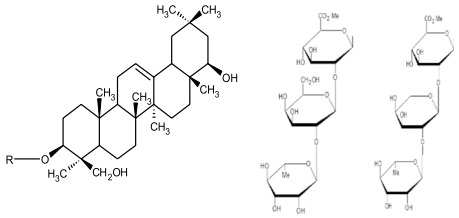
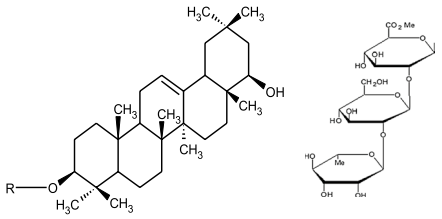
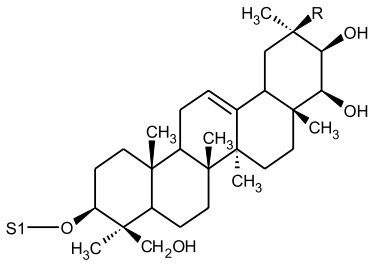
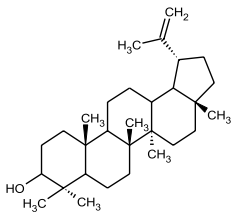
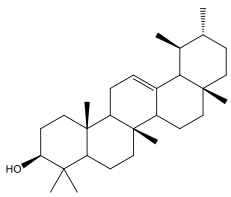
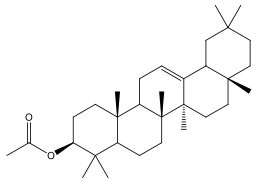
No.	Name	Plant species	Structure	References
223	Soyasaponin I methyl ester	*S. flavescens* *S. japonica* *S. subprostrata*		Yang et al. (2020b)
224	Soyasaponin II methyl ester		**223**: R = S1 **224**: R = S2	
225	Kaikasaponin III methyl ester	*S. subprostrata*		Yang et al. (2020b)
226	Kaikasaponin I methyl ester		**225**: R = S1 **226**: R = S3	
227	Soyasaponin A_3 methyl ester	*S. subprostrata*		Yang et al. (2020b)
228	Kuzusapogenol A methyl ester		**227**: R = CH_3 **228**: R = CH_2OH	
229	Lupeol	*S. flavescens* *S. japonica* *S. subprostrata*		Wang et al. (2020b)
230	α-Amyrin	*S. tomenosa* *S. secundiflora*		Aly et al. (2020a)
231	β-Amyrin acetate	*S. tomenosa* *S. secundiflora*		Aly et al. (2020a)

Table 11 Alkaloids isolated from *Sophora* species

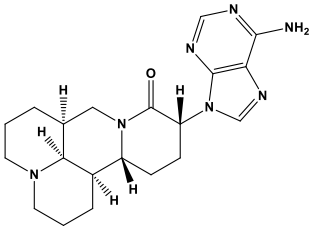
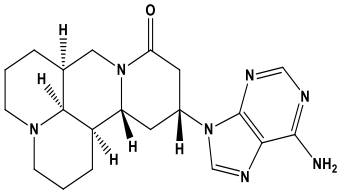
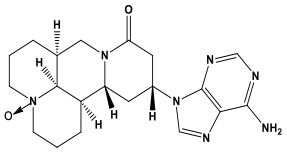
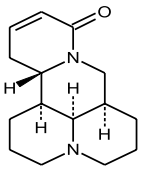
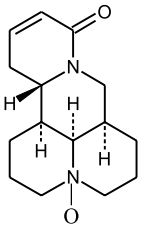
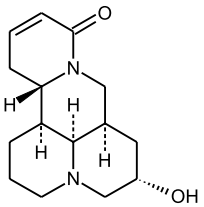
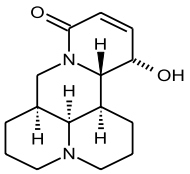
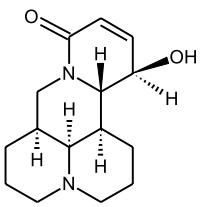
No.	Name	Plant species	Structure	References
232	Sophovicine A	*S. davidii*		Zhang et al. (2021c)
233	Sophovicine B	*S. davidii*		Zhang et al. (2021c)
234	Sophovicine C	*S. davidii*		Zhang et al. (2021c)
235	Sophocarpine	*S. alopecuroides* *S. flavescens* *S. japonica* *S. moorcroftiana* *S. tonkinensis* *S. viciifolia*		Ao et al. (2019), He et al. (2019), Cao and He (2020), Li et al. (2020d)
236	Oxysophocarpine	*S. flavescens*		Wang et al. (2019a)
237	9 α-Hydroxysophocarpine	*S. flavescens*		Wang et al. (2019a)
238	12α-Hydroxysophocarpine	*S. flavescens* *S. viciifolia*		Ao et al. (2019), Wang et al. (2019a)
239	12 β -Hydroxy-sophocarpine	*S. alopecuroides*		Li et al. (2020d)

Table 11 (continued)

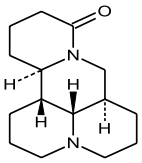
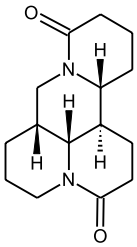
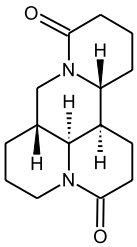
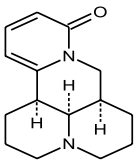
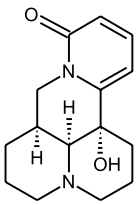
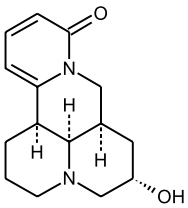
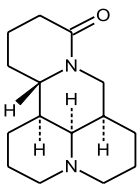
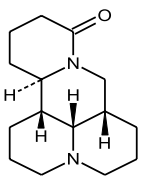
No.	Name	Plant species	Structure	References
240	Sophoridine	*S. alopecuroides* *S. flavescens* *S. japonica*		Zhang et al. (2018b), Wang et al. (2019a), Li et al. (2019c), Cao and He (2020), Li et al. (2020d)
241	Isosophoridine	*S. flavescens* *S. japonica*		Zhang et al. (2018b)
242	10-Oxysophoridine	*S. flavescens* *S. japonica*		Zhang et al. (2018b)
243	Sophoramine	*S. alopecuroides* *S. flavescens* *S. japonica* *S. viciifolia*		Zhang et al. (2018b,c), Ao et al. (2019), Cao and He (2020), Elberry et al. (2020), Guo et al. (2020), Li et al. (2020d), Wang et al. (2020b)
244	7 α –Hydroxysophoramine	*S. alopecuroides* *S. japonica*		Li et al. (2020d)
245	9 α-Hydroxysophoramine	*S. flavescens*		Wang et al. (2019a)
246	Matrine	*S. alopecuroides* *S. chrysophylla* *S. flavescens* *S. japonica* *S. moorcroftiana* *S. subprostrata* *S. tomentosa* *S. tonkinensis* *S. viciifolia*		Ao et al. (2019), Fan et al. (2019), Li et al. (2019c), Wang et al. (2019a), Aly et al. (2020b), Cao and He (2020), Elberry et al. (2020), Guo et al. (2020), Li et al. (2020d), Zhang et al. (2020a, b, c)
247	Isomatrine	*S. flavescens*		Wang et al. (2019a)

Table 11 (continued)

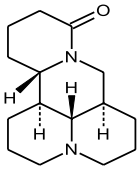
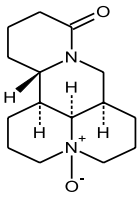
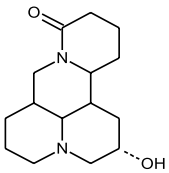
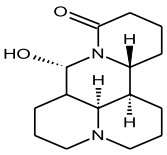
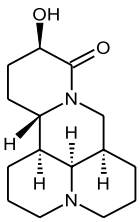
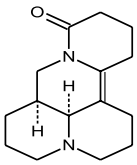
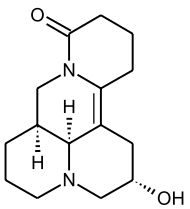
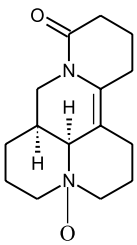
No.	Name	Plant species	Structure	References
248	Allomatrine	*S. flavescens* *S. japonica*		Zhang et al. (2018b), Wang et al. (2019a)
249	Matrine N-oxide (Oxymatrine)	*S. alopecuroides* *S. chrysophylla* *S. flavescens* *S. japonica* *S. macrocarpa* *S. moorcroftiana* *S. subprostrata* *S. tomentosa* *S. viciifolia*		Zhang et al. (2018b, 2020a, b, c), Ao et al. (2019), Wang et al. (2019a), Cao and He (2020), Elberry et al. (2020), Gao et al. (2020), Guo et al. (2020), Li et al. (2020d), Liu et al. (2020a,b)
250	9α-Hydroxymatrine	*S. alopecuroides* *S. flavescens* *S. macrocarpa* *S. viciifolia*		Ao et al. (2019), Cao and He (2020), Gao et al. (2020), Li et al. (2020d)
251	5α-Hydroxymatrine [(+)-Sophoranol]	*S. flavescens* *S. tonkinensis*		Zhang et al. (2018b), He et al. (2019)
252	14β-Hydroxymatrine	*S. flavescens*		Zhang et al. (2018b)
253	7,11-Dehydromatrine (Leontalbinine)	*S. flavescens* *S. japonica*		Zhang et al. (2018b, 2020a, b, c), Wang et al. (2019a), Cao and He (2020), Elberry et al. (2020), Guo et al. (2020)
254	9 α-Hydroxy- 7,11-dehydromatrine	*S. flavescens*		Wang et al. (2019a)
255	7,11-Dehydro-oxymatrine	*S. flavescens*		Zhang et al. (2018b)

Table 11 (continued)

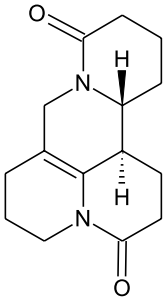
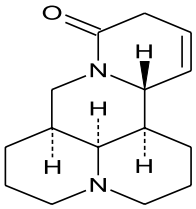
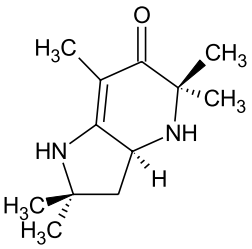
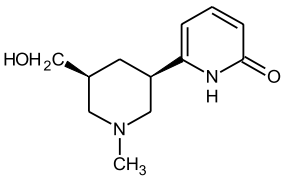
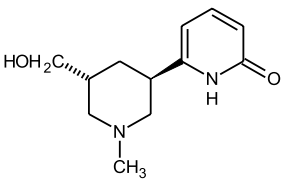
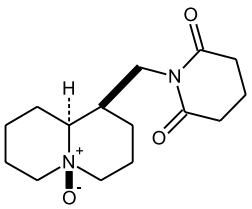
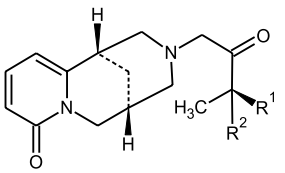
No.	Name	Plant species	Structure	References
256	10-Oxy-5,6 dehydromatrine	*S. flavescens*		Zhang et al. (2018b)
257	Lehmanine	*S. flavescens*		Wang et al. (2019a)
258	Flavascensine	*S. flavescens*		Wang et al. 2019a
259	Kurarimine	*S. flavescens*		Wang et al. (2019a)
260	Isokurarimine	*S. flavescens*		Wang et al. (2019a)
261	Epilamprolobin-N-oxide	*S. tomentosa*		Chang et al. (2019a, b), Wang et al. (2019a), Aly et al. (2020b)
262	Sophorasine A	*S. griffithii*		Zhang et al. (2020a, b, c)
263	Sophorasine B		**262**: R^1 = OH; R^2 = H **263**: R^1 = H; R^2 = OH	

Table 11 (continued)

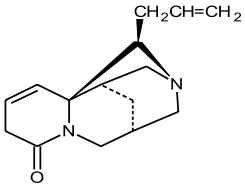
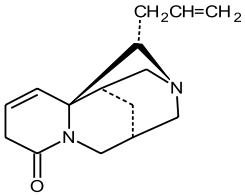
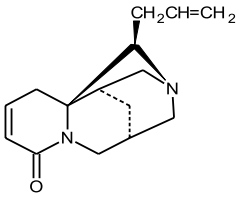
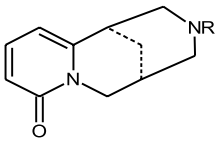
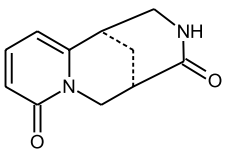
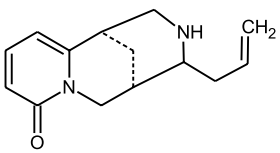
No.	Name	Plant species	Structure	References
264	Tsukushinamine A	*S. franchetiana*		Boozari et al. (2019b)
265	Tsukushinamine B	*S. franchetiana*		Wang et al. (2019a)
266	Tsukushinamine C	*S. franchetiana*		Zhang et al. (2020a, b, c)
267	Cytisine	*S. alopecuroides* *S. chrysophylla* *S. franchetiana* *S. korensis* *S. macrocarpa* *S. secundiflora* *S. tomentosa*	 **267**: R = H	Wang et al. (2019a), Chen et al. (2020d), Gao et al. (2020), Huang and Xu (2020a), Li et al. (2020d), Wang et al. (2020b), Zhang et al. (2020a, b, c)
268	N-methyl cytosine	*S. alopecuroides* *S. chrysophylla* *S. flavescens* *S. korensis* *S. macrocarpa* *S. secundiflora* *S. tomentosa*	**268**: R = CH_3	Ao et al. (2019), Aly et al. (2020b), Cao and He (2020), Chen et al. (2020a), Huang and Xu (2020a), Gao et al. (2020), Li et al. (2020d), Wang et al. (2019a, 2020b)
269	N-formyl cytosine	*S. alopecuroides* *S. chrysophylla* *S. franchetiana* *S. korensis* *S. secundiflora* *S. tomentosa*	**269**: R = CHO	Wang et al. (2019a, 2020b), Aly et al. (2020b), Chen et al. (2020a), Gao et al. (2020), Huang and Xu (2020a), Li et al. (2020d)
270	Rhombifolin	*S. chrysophylla* *S. flavescens* *S. franchetiana* *S. korensis* *S. secundiflora*	**270**: R = CH_2-CH_2 = CH_2	Wang et al. 2019a; Aly et al. 2020b; Cao and He 2020; Gao et al. 2020; Zhang et al. 2020a, b, c
271	11-Oxocytisine	*S. secundiflora*		Wang et al. (2019a), Aly et al. (2020b), Chen et al. (2020a), Gao et al. (2020), Huang and Xu (2020a)
272	11-*Allyl*-cytisine	*S. secundiflora*		Wang et al. (2019a), Aly et al. (2020b), Chen et al. (2020a), Gao et al. (2020), Huang and Xu (2020a)

Table 11 (continued)

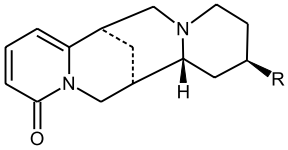
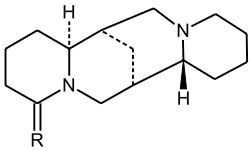
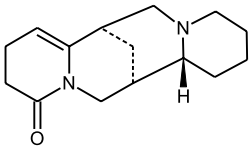
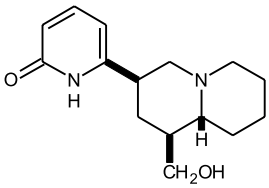
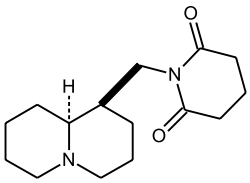
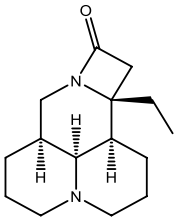
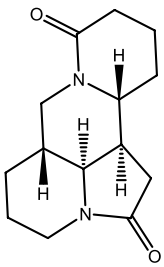
No.	Name	Plant species	Structure	References
273	Anagyrine	*S. chrysophylla* *S. flavescens* *S. franchetiana* *S. korensis* *S. secundiflora* *S. tomentosa* *S.tonkinensis*	 **273**: R = H **273′**: R = OH	He et al. (2019), Wang et al. (2019a), Aly et al. (2020b), Cao and He (2020), Gao et al. (2020), Zhang et al. (2020a)
274	Lupanine	*S. flavescens* *S. japonica* *S. korensis* *S. secundiflora* *S. subprostrata*	 **274**: R = O	Aly et al. (2019, 2020a), Wang et al. (2019a), Cao and He (2020), Elberry et al. (2020), Gao et al. (2020), Guo et al. (2020), Zhang et al. (2020a)
275	Sparteine	*S. secundiflora*	**275**: R = H_2	Aly et al. (2019, 2020a), Wang et al. (2019a)
276	5,6-Dehydrolupanine	*S. chrysophylla* *S. korensis* *S. secundiflora*		Aly et al. (2019, 2020a), Wang et al. (2019a), Cao and He (2020)
277	Mamanine	*S. chrysophylla* *S. flavescens*		Wang et al. (2019a), Cao and He (2020), Gao et al. (2020)
278	Epilamprolobin	*S. tomentosa*		Wang et al. (2019a)
279	Sophaline A	*S. alopecuroides*		Zhang et al. (2018c)
280	Sophaline B	*S. alopecuroides*		Zhang et al. (2018c)

Table 11 (continued)

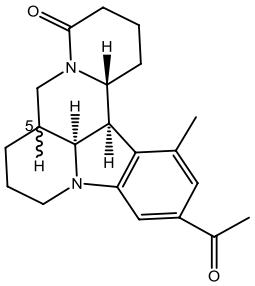
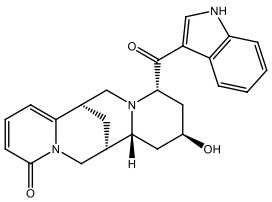
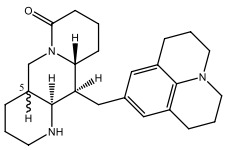
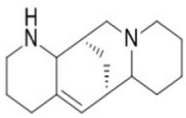
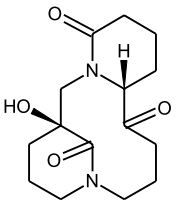
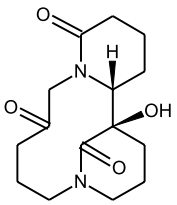
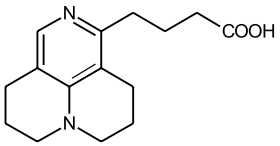
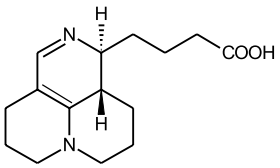
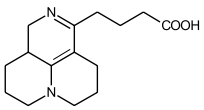
No.	Name	Plant species	Structure	References
281	Sophaline.C.(5*R*) Sophaline D (5*S*)	*S. alopecuroides*		Zhang et al. (2018b)
282	Sophaline E	*S. alopecuroides*		Zhang et al. (2018c)
283a **283b**	Sophaline G (5-αH) Sophaline H (5-βH)	*S. alopecuroides*		Zhang et al. (2018c)
284	Aloperine	*S. alopecuroides*		Yin et al. (2018), Ye et al. (2020)
285	Alopecurine A	*S. flavescens*		Zhang et al. (2018b)
286	Alopecurine B	*S. flavescens*		Zhang et al. (2018b)
287	Flavesine G	*S. flavescens*		Zhang et al. (2018b)
288	Flavesine H	*S. flavescens*		Zhang et al. (2018b)
289	Flavesine I	*S. flavescens*		Zhang et al. (2018b)

Table 11 (continued)

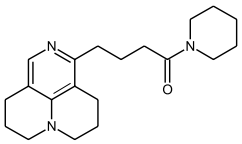
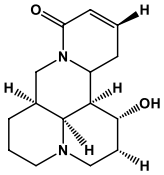
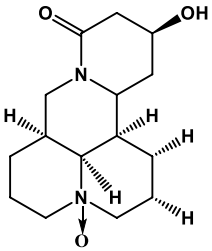
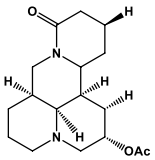
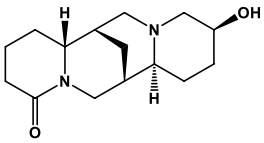
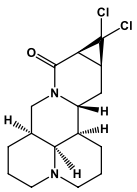
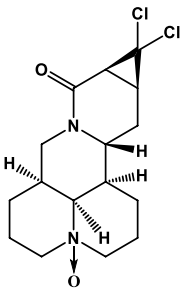
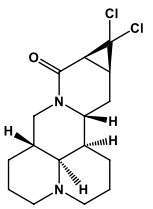
No.	Name	Plant species	Structure	References
290	Flavesine J	*S. flavescens*		Zhang et al. (2018b)
291	8α-Hydroxysophocarpine	*S. viciifolia*		Gao et al. (2020)
292	13β-Hydroxyoxymatrine	*S. viciifolia*		Gao et al. (2020)
293	9α-Acetoxymatrine	*S. viciifolia*		Gao et al. (2020)
294	14β-Hydroxylupanine	*S. viciifolia*		Gao et al. (2020)
295	Alopecine A	*S. alopecuroides*		Wang et al. (2020b, c)
296	Alopecine B	*S. alopecuroides*		Wang et al. (2020b, c)
297	Alopecine C	*S. alopecuroides*		Wang et al. (2020b, c)

Table 11 (continued)

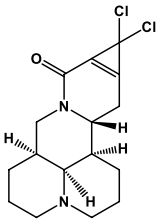
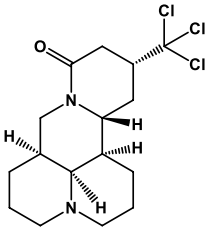
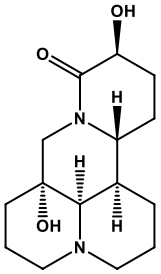
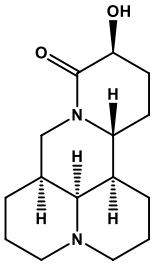
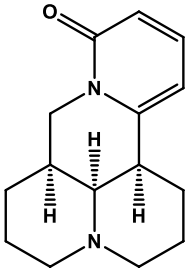
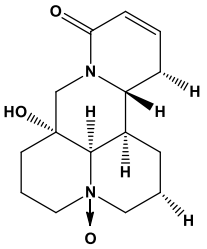
No.	Name	Plant species	Structure	References
298	Alopecine D	*S. alopecuroides*		Wang et al. (2020b, c)
299	Alopecine E	*S. alopecuroides*		Wang et al. (2020b, c)
300	5α,14β-Dihydroxymatrine	*S. tonkinensis*		He et al. (2019)
301	14β-Hydroxymatrine	*S. tonkinensis*		He et al. (2019)
302	7β-Sophoramine	*S. tonkinensis*		He et al. (2019)
303	(+)-5α-Hydroxyoxysophocarpine	*S. tonkinensis*		Pan et al. (2015)

Table 11 (continued)

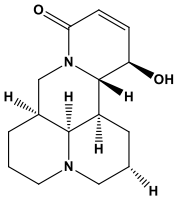
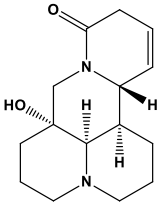
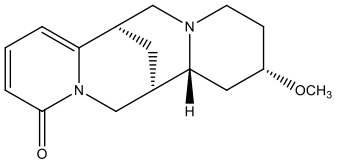
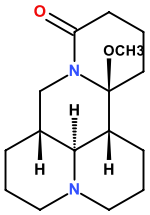
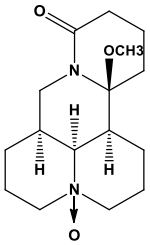
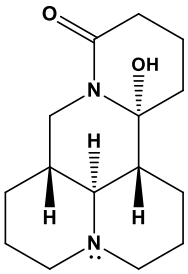
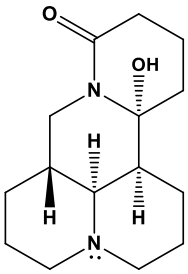
No.	Name	Plant species	Structure	References
304	(-)-12β-Hydroxyoxysophocarpine	*S.tonkinensis*		Pan et al. (2015)
305	(+)-5α-Hydroxylemannine	*S. tonkinensis*		Pan et al. (2015)
306	13-Methoxyanagyrine	*S. secundiflora*		Aly et al. (2021)
307	Sophalode A	*S. alopecuroides*		Li et al. (2021a, b)
308	Sophalode B			
309	Sophalode C			
310	Sophalode D			

Table 11 (continued)

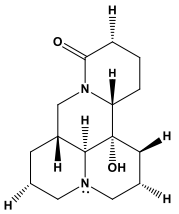
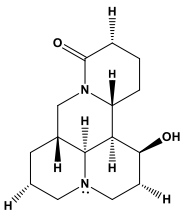
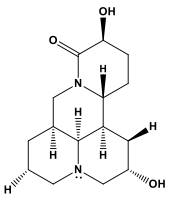
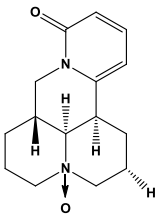
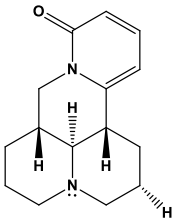
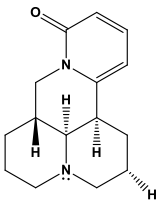
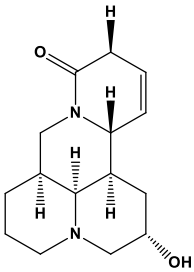
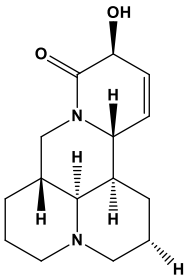
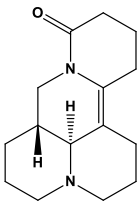
No.	Name	Plant species	Structure	References
311	Sophalode E	*S. alopecuroides*		Li et al. (2021a)
312	Sophalode F			
313	Sophalode G			
314	Sophalode H	*S. alopecuroides*		Li et al. (2021a)
315	Sophalode I			
316	Neosophoramine			

Table 11 (continued)

No.	Name	Plant species	Structure	References
317	Sophalode J	*S. alopecuroides*		Li et al. (2021a)
318	Sophalode K			
319	Sophalode L			

factor-2, alkaline phosphatase, and osteocalcin after osteoinduction (Mao et al. 2020). Matrine **246** inhibited heterotopic ossification by suppressing the migration and osteogenic differentiation of TGF-β (Mao et al. 2020).

Sophocarpine (**235**) also exerted a protective effect against ox-LDL-induced endothelial damage (Fang et al. 2020), via regulating NF-κB signaling pathway (Wu et al. 2019b). The same compound (**235**) suppressed NF-κB signalling pathway and attenuated wear particle-induced implant loosening by inhibiting osteoclastogenesis and bone resorption (Zhou et al. 2018c).

Hepatoprotective activity

Sophora fruit tea is a traditional Chinese herb tea rich in sophoricoside (**134**). This compound is an isoflavone glycoside (genistein-4′-*O*-β-D-glucopyranoside) isolated from dried *S. japonica* fruit (Li and Lu 2018). The hepatoprotective effect of **134** was exerted against fructose-induced liver injury via regulating oxidation, lipid metabolism, and inflammation in mice. Other alkaloids, such as sophoridine (**240**) and oxymatrine (**249**), were the key components of *S. flavescens* (Sf -I). The Sf-I can improve immunity, protect the liver against oxidation, and provide a chemotherapeutic sensitivity (Cao and He 2020; Liu et al. 2020a, b). The possible mechanism of hepatotoxicity induced by phytoextract of *S. flavescens* (PSf) has been explored (Jiang et al. 2020c). It has been suggested that PSf exhibited a metabolism disturbance of the bile acids, fatty acids, glycerophospholipids, and amino acids of orally exposed rats. The hepatoprotective activity of the benzoic acid derivatives sophophenoside A (**322**) and sophophenoside B (**323**) on the cytotoxic effect of D-galactosamine in HL-7702 cells was assayed (Jiang et al. 2020b). Sophophenoside A (**322**) exhibited a moderate hepatoprotective activity at a concentration of 10 μM. A combinational treatment of *S. moorcroftiana* alkaloids with albendazole displayed better therapeutic effects than albendazole alone against liver echinococcosis, and alleviated liver injury (Zhang et al. 2018a). A recent study also suggested that aloperine (**284**) could prevent the early development of hepatocellular carcinoma like lesions in rat liver (Shi et al. 2019).

Muscle and vasorelaxation activity

Kushenol (**28**) and sophoraflavanoneB (**48**) strongly induced the relaxation of porcine coronary arteries with respective ED_{50}-values of 8.6 and 12.4 μM, separately (Aly et al. 2019). Relaxation of bladder smooth muscle by flavonoids of *S. flavescens* was also recorded (Han et al. 2018), via

Table 12 Phenolic acids and other phenolic compounds isolated from *Sophora* species

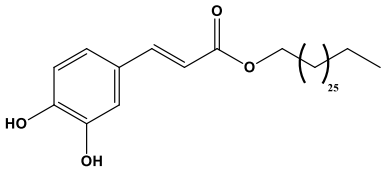
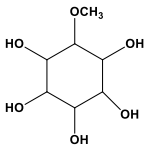
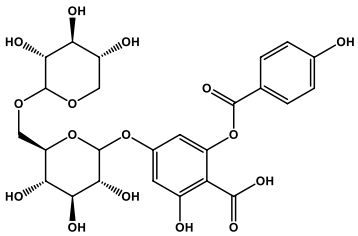
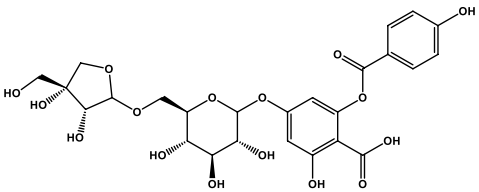
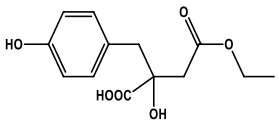
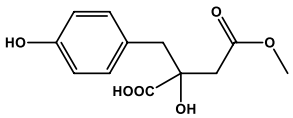
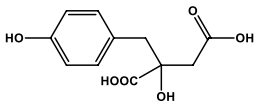
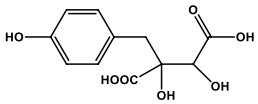
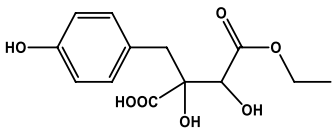
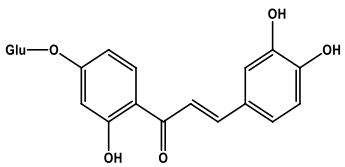
No.	Name	Plant species	Structure	References
320	2-Propenoic acid, 3-(3,4-dihydroxyphenyl)-octacosyl ester	*S. mollis*		Quradha et al. (2021)
321	Pinitol	*S. mollis*		Quradha et al. (2021)
322	Sophophenoside A	*S. alopecuroides* *S. mollis*		Jiang et al. (2020b)
323	Sophophenoside B	*S. pachycarpa*		Jiang et al. (2020b)
324	Ethyl 2-(4-hydroxybenzyl) malic acid	*S. alopecuroides*		Song et al. (2018)
325	Methyl eucomate	*S. alopecuroides*		Song et al. (2018)
326	Eucomic acid	*S. alopecuroides*		Song et al. (2018)
327	Piscidic acid	*S. alopecuroides*		Song et al. (2018)
328	Ethyl 2-(4-hydroxybenzyl) tartrate	*S. alopecuroides*		Song et al. (2018)
329	Butein-4′-*O*-β-D-glucopyranoside	*S. alopecuroides*		Song et al. (2018)

Table 12 (continued)

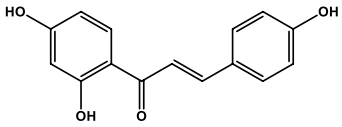
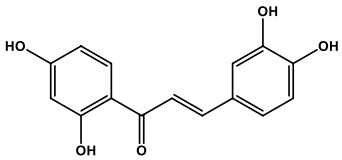
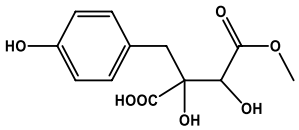
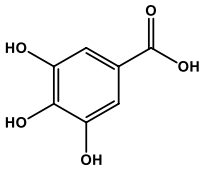
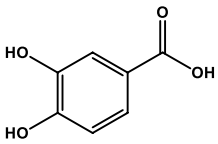
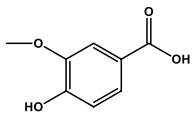
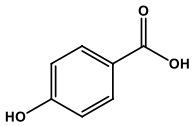
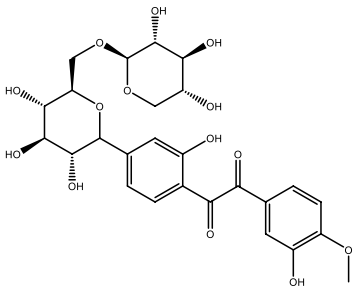
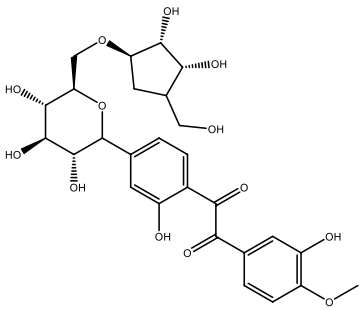
No.	Name	Plant species	Structure	References
330	*Iso*-liquiritigenin	*S. alopecuroides*		Song et al. (2018)
331	Butein	*S. alopecuroides*		Song et al. (2018)
332	(3*S*,2*R*)-Methyl 2-(4-hydroxybenzyl) tartrate	*S. alopecuroides*		Song et al. (2018)
333	Gallic acid	*S. alopecuroides*		Hou et al. (2020)
334	Protocatechuic acid	*S. alopecuroides*		Hou et al. (2020)
335	Vanillic acid	*S. alopecuroides*		Hou et al. (2020)
336	*p*-Hydroxybenzonic acid	*S. alopecuroides*		Hou et al. (2020)
337	Sophodibenzoside A	*S. flavescens*		Shen et al. (2013)
338	Sophodibenzoside B	*S. flavescens*		Shen et al. (2013)

Table 12 (continued)

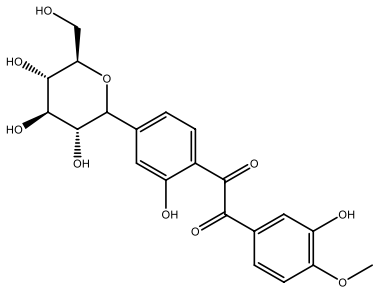
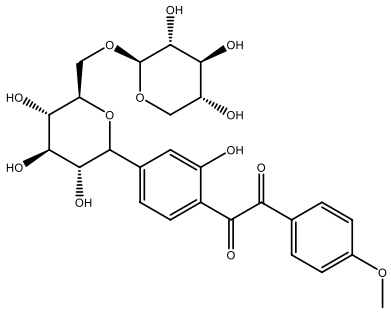
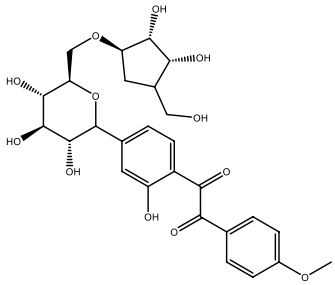
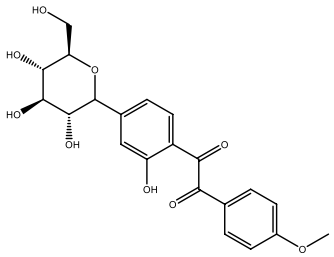
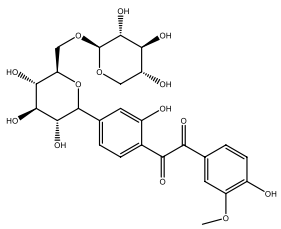
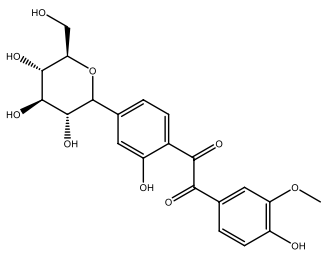
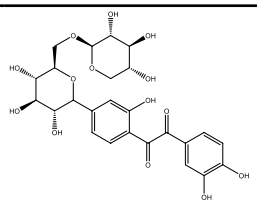
No.	Name	Plant species	Structure	References
339	Sophodibenzoside C	*S. flavescens*		Shen et al. (2013)
340	Sophodibenzoside D	*S. flavescens*		Shen et al. (2013)
341	Sophodibenzoside E	*S. flavescens*		Shen et al. (2013)
342	Sophodibenzoside F	*S. flavescens*		Shen et al. (2013)
343	Sophodibenzoside J	*S.flavescens*		Shen et al. (2013)
344	Sophodibenzoside K	*S. flavescens*		Shen et al. (2013)

Table 12 (continued)

No.	Name	Plant species	Structure	References
345	Sophodibenzoside L	*S. flavescens*		Shen et al. (2013)

direct activation of the large-conductance calcium-activated potassium channel. Matrine (**246**) also improved skeletal muscle atrophy by mostly inhibiting E3 ubiquitin ligases and activating the Akt/mTOR/FoxO3α signaling pathway (Chen et al. 2019b). Authors also demonstrated that comound (**246**) could increase muscle fiber size and muscle mass in an in vivo CT26 colon adenocarcinoma cachexia mouse model (Chen et al. 2019b). Furthermore, Yang et al. 2018 suggested that aloperine (**284**) induced vasodilatory effects, in rat aorta, mainly due to the operations of voltage-operated potassium channels and ATP-sensitive potassium channels. The vascular relaxant effect of ethanolic extract of *S. flavescens* roots was found, via endothelium-dependent NO-soluble guanylyl cyclase–cGMP signaling pathway (Aly et al. 2019; Boozari et al. 2019a, b).

Antiviral activity

In addition to the ability of various plants secondary metabolites to interfere directly with viral replication, these metabolites may also modulate the host immune response against infection with limited side-effects (Abd-Alla et al. 2009; Yang et al. 2019; Ma et al. 2020a). *S. subprostrata* Chun and *T. chen* radix ($EC_{90} = 82.2 \pm 8.2$ and 27.5 ± 1.1 µg mL^{-1}, respectively with SI = 11.1) was one of the most active 22 plants against mouse hepatitis virus (MHV)-A59-infected mouse dihydrolipoamide-branched chain transacylase E2 cells. The plant extract significantly reduced the viral replication after 6 h of exposure following infection. In another screening study on 19 plants, *S. flavescens* Aiton radix was confirmed to be an effective on the viral replication in MHV-A59-infected cells (Kim and Yun-Choi 2008; Orhan and Deniz 2020). Interestingly, *S. subprostrata* has the capacity to inhibit coronaviruses replication in vitro which holds a promise for a prospect drug against the emerging COVID-19 (Fuzimoto and Isidoro 2020; Ghoran et al. 2021).

The lavandulylated flavanone, kurarinol (**29**), chalcone, and kuraridin (**184**), isolated from *S. flavescens* roots have been reported to have antiviral activities (Boozari et al. 2019b; Yang et al. 2019). Compound (**29**) also inhibited rotavirus-induced cytopathic effects, probably due to its ability to modulate the rotavirus replication and toll-like receptor 3-mediated inflammatory pathways. This chalcone inhibited the adsorption and replication of reoviruses (human type 1–3 reoviruses and Korean porcine reovirus), by inhibiting viral RNA, protein synthesis, hemagglutination, and shedding (Boozari et al. 2019b; Chen et al. 2020d). Many flavonoids, including 6 isoflavones and three pterocarpans, isolated from *S. davidii* flowers have reported to exhibit protective effects against Tobacco Mosaic virus replication with a higher inhibition rate than ningnanmycin as a positive control (Wang et al. 2018d; Yang et al. 2019).

Exiguaflavanone A (**61**) has been reported as one of the anti-Zika virus phytochemicals, by strongly interacting with the ATP site of helicase (Farhadi et al. 2019). The anti-influenza activity of the decoction of San Wu Huangqin D-SWH, a traditional Chinese medicine formula, was suggested to be related with its regulation ability on the immune system or/and inhibitory effects on major virus proteins (Ma et al. 2018, 2020a, b; Li et al. 2020d). Interestingly, Chinese patients (~ 80%) with the chronic hepatitis B and ~ 4 billion of the world population rely on traditional herbal medicines (Liu et al. 2018b; Mohamed et al. 2019). The main herbal component of this formula is *S. flavescens*, the well-known phytoextract, having a wide spectrum of biological properties. *S. flavescens* exerted broad antiviral effects versus influenza, hepatitis B virus (HBV) (both wild-type and entecavir-resistant), enterovirus71, coxsackie B3, and respiratory syncytia, due to its key bioactive substances, including flavonoids, triterpenoids, and quinolizidine-type alkaloid (QA) (Liu et al. 2018b; Ma et al. 2018, 2020a, b; Ren et al. 2019; Wang et al. 2019a).

QA were extracted from many *Sophora* species (Table 11) and have been exerted various excellent activities such as sophocarpine (**235**), sophoridine (**240**), matrine (**246**), oxymatrine (**249**), and aloperine (**284**) (Huang et al. 2018c; Ao et al. 2019; Zhang et al. 2020a).

Matrine-family alkaloids, as tetracycloquinolizindine analogues, have aroused great interests over the past decades (Chen et al. 2018d; Wang et al. 2018b; Fu et al. 2020; Cai et al. 2020), which possessed various pharmacological activities (Wang et al. 2019a; Cai et al. 2020). These alkaloids showed a potent antiviral activity against HBV-infection (Zhang et al. 2018b, c; Parvez et al. 2019). Matrine (**246**)

Table 13 Other constituents identified by gas chromatography/mass spectrometry (GC/MS) from *Sophora* species

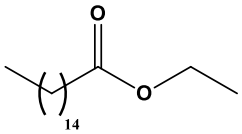
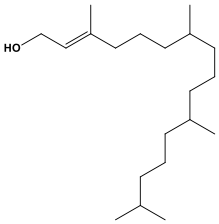
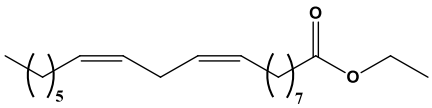
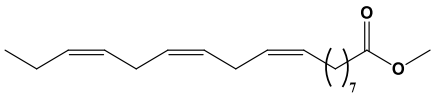
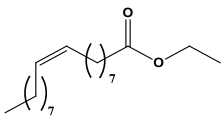
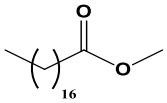
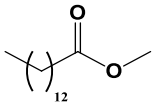
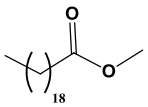
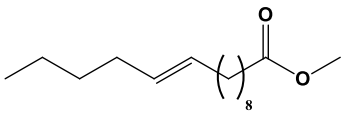
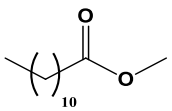
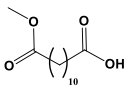
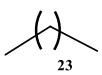
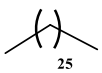
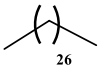
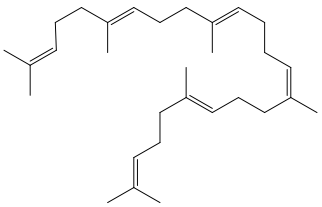
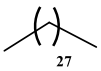
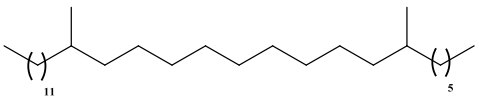
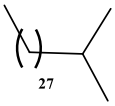
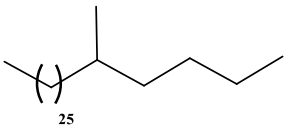
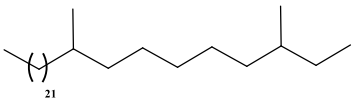
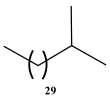
No.	Name	Plant species	Structure	References
346	Palmitic acid methyl ester	*S. tomentosa* *S. secundiflora*		Aly et al. (2020a)
347	Phytol			
348	Linoleic acid methyl ester			
349	Linolenic acid methyl ester			
350	Oleic acid methyl ester			
351	Stearic acid methyl ester			
352	Myristic acid methyl ester			
353	Eicosanoic acid methyl ester			
354	*cis*-10-Pentadecenoic acid methyl ester			
355	Dodecanoic acid methyl ester			
356	Dodecanedioic acid methyl ester			
357	Heptadecanoic acid methyl ester			
358	*n*-Pentacosane			
359	*n*-Heptacosane			

Table 13 (continued)

No.	Name	Plant species	Structure	References
360	*n*-Octacosane			
361	*trans*-Squalene			
362	*n*-Nonacosane			
363	7,17-Dimethylnonacosane			
364	2-Methyltriacontane			
365	5-Methylhentriacontane			
366	3,9-Dimethylhentriacontane			
367	2-Methyldotriacontane			

and oxymatrine (**249**), as common alkaloids, have been used for the clinical treatment of hepatitis in China (Zhang et al. 2020a). Many matrine-type alkaloids isolated from the PSf roots were investigated for their antiviral activities against HBV (Zhang et al. 2018b, 2020a). The combined matrine (**246**) and oxymatrine (**249**) capsules were used for the treatment of chronic HBV infection (Parvez et al. 2019). Many matrine-type alkaloids, isolated from the rhizomes of *S. tonkinensis*, have also exhibited antiviral activity (Pan et al. 2015).

9α-Hydroxysophocarpine (**237**), 12β-hydroxyoxysophocarpine (**239**), 5α-hydroxymatrine, and sophoranol (**251**) have been exhibited antiviral activity against the coxsackie virus B3, with IC_{50}-values of 26.62–252.18 μM (Pan et al. 2015; Ti et al. 2021). The alkaloids 12α-hydroxysophocarpine (**238**), **239**, and sophoramine (**243**) inhibited influenza virus A/Hanfang/359/95 replication with IC_{50}-values of 63.07–242.46 μM. Oxymatrine (**249**), sophoridine (**240**), alopecurine B (**286**), flavesine G (**287**), and flavesine J (**290**) also effectively inhibited HBsAg secretion at noncytotoxic concentrations than lamivudine, as a positive control (Ti et al. 2021).

Matrine (**246**) in vitro inhibited the replication of porcine reproductive and respiratory syndrome virus co-infection in PAM cells. The underlying antiviral mechanism of **246** may be mediated through its ability to partly regulate TLR3,4/NF-κB/TNF-α pathway (Sun et al. 2018; Ti et al. 2021).

The polysaccharide isolated from *S. subprosrata* regulated the inflammatory response of mouse mononuclear macrophage cell line RAW264.7 cells infected with porcine circovirus type 2 (Li et al. 2019a; Yang et al. 2020b). The bush *Sophora* root polysaccharide and its sulfate as well as baicalin-phospholipid complex (BPC) inhibited duck hepatitis A virus type 1 (DHAV-1) adsorption, replication, and release (Chen et al. 2018a, b). This effect may be due to drop the RNA synthesis and the protein translation via reducing the 3D protein stability, inhibiting cellular Hsp70 expression, and suppressing DHAV-1 IRES activity (Chen et al. 2018c).

Table 14 Biological activities previously reported for genus *Sophora*

Biological activity	Species	Part used	References
Antiproliferative	*S. flavescens*	Roots	Aly et al. (2019), Boozari et al. (2019a, b)
Anti-tumor and immunomodulating	*S. japonica*	Leaves	Luo et al. (2018), Boozari et al. (2019a), Cao and He (2020), Elberry et al. (2020), Liu et al. (2020a, b), Ma et al. (2020a), Zhang et al. (2020a), Quradha et al. (2021)
	S. moorcroftiana	Roots	
	S. mollis	Aerial parts	
	S. pachycarpa	Seeds	
Anticancer	*S. japonica*	Flower buds	Huang et al. (2018a), ur Rashid et al. (2019, 2020), Rammohan et al. (2020), Zhang et al. (2020a)
	S. interrupta	Roots	
		Radix	
Apoptosis	*S. moorcroftiana*	Seeds	Su et al. (2018), Li et al. (2019c, 2020a), Cao and He (2020), Fu et al. (2020), Quradha et al. (2021)
	S. flavescens	Aerial parts/seeds	
	S. tonkinensis	Seeds	
Angiogenesis inhibitors			
Cytotoxic	*S. japonica*	Leaves	Elberry et al. (2020), Quradha et al. (2021)
	S. mollis	Aerial parts	
	S. tomentosa	Leaves	
	S.secundiflora	Leaves	
Antiproliferative	*S.Japonica*	Roots	Elberry et al. (2020)
Antioxidant	*S. chrysophylla*	Leaves	Boozari et al. (2019b), Rammohan et al. (2020)
	S. interrupta	Roots	
	S. subprostrata	Roots	Boozari et al. (2019b)
	S. viciifolia	Flowers/Leaves/Fruits	Lin et al. (2019a), Guo et al. (2020)
	S. japonica	Leaves	Elberry et al. (2020), Guo et al. (2020)
	S. tomentosa	Roots	Chang et al. (2019a, b)
	S. denudata	Roots	Ledoux et al. (2018)
	S. exigua	Roots	Kaewdana et al. (2021)
	S. mollis	Aerial parts	Quradha et al. (2021)
Antiviral	*S. flavescens*	Roots	Ledoux et al. (2018), Zhang et al. (2018b, c), Aly et al. (2019), Ao et al. (2019), Elberry et al. (2020), Ma et al. (2020a), Wang et al. (2020b), Zhang et al. (2021b)
	S. alopecuroides		
	S. denudata		
	S. davidii		
	S. japonica		
	S. tonkinensis	Rhizomes/Roots	Li et al. (2019c), Jin et al. (2020)
Reduction of membrane fluidity	*S. exigua*	Roots	Boozari et al. (2019b), Farhadi et al. (2019)
Antimicrobial and cytotoxicity			Farhadi et al. (2019)
	S. flavescens	Roots	Ao et al. (2019)
	S. pachycarpa	Roots	Boozari et al. (2019a, b), Chang et al. (2019a), Aly et al. (2020a), Hadidi et al. (2020), Kaewdana et al. (2021)
	S. tomentosa	Roots	
	S. exigua	Leaves	
	S. secundiflora	Leaves	
Antibacterial	*S. alopecuroides*	Roots	Su et al. (2018), Farhadi et al. (2019), Lin et al. (2019a), Wang et al. (2020b), Quradha et al. (2021)
	S. moorcroftiana	Seeds	
	S. viciifolia	Roots	
	S. mollis	Aerial parts	
Cardioprotective	*S. flavescens*	Roots/ Leaves	Aly et al. (2019), Boozari et al. (2019b), Wang et al. (2020b), Zhang et al. (2020a)
	S. japonica	Leaves	
	S. alopecuroides	Roots	
Hair growth promoting	*S. flavescens*	Roots	Aly et al. (2019), Chang et al. (2018)
	S. alopecuroides	Leaves	
	S. tonkinensis	Leaves/Branches	
	S. japonica	Flowers	
	S. secundiflora	Aerial parts	
	S. interrupta	Roots	
Antipsoriatic			Aly et al. (2019), Boozari et al. (2019b)

Table 14 (continued)

Biological activity	Species	Part used	References
Anti-inflammatory			Aly et al. (2017, 2020a, b, c), Boozari et al. (2019b), Elberry et al. (2020), Cho et al. (2020), Li et al. (2019c, 2020b), Rammohan et al. (2020), Ye et al. (2020)
Anti-arthritic	*S. flavescens*	Aerial parts/Roots	Ao et al. (2019), Elberry et al. (2020)
Anti-osteoporosis	*S. flavescens*	Fruits/Aerial parts	Li et al. (2020d), Mao et al. (2020), Yang et al. (2020c)
Nematicidal	*S. flavescens*	Aerial parts	Aly et al. (2019)
Anti-parasitic	*S. moorcroftiana*	Aerial parts	Luo et al. (2018)
Insecticidal	*S. alopecuroides*	Aerial parts	Boozari et al. (2019b), Zhang et al. (2020a, b, c), Zhou et al. (2020)
	S. secundiflora	Branches/Seeds/Leaves	Aly et al. (2019, 2020a, 2021), Shoukat et al. (2020)
	S. flavescens	Roots/Branches/Leaves	
	S. tomentosa	Leaves	Aly et al. (2021)
Pesticidal	*S. flavescens* *S. alopecuroides* *S. moorcroftiana*	Roots	Aly et al. (2019), de Andrade et al. (2020), Li et al. (2020b)
	S. mollis	Herb	
Antifeedant	*S. flavescens*	Seeds	Aly et al. (2019), Boozari et al. (2019b)
Anti-protozoal	*S. flavescens*	Herb Seeds	Luo et al. (2018), Aly et al. (2019), Boozari et al. (2019b)
Antipyretic	*S. flavescens* *S. interrupta* *S. subprostrata*	Roots	Aly et al. (2019), Zhang et al. (2020a, b, c)
Antiplasmodial	*S. mollis*	Roots	Zhang et al. (2020a)
Neuroprotective	*S. flavescens* *S. tomentosa*	Roots Leaves, Roots	Chang et al. (2019a, b), Wang et al. (2019d), Aly et al. (2020c)
Antiulcer			Chen et al. (2020b)
Anti-allergic			Aly et al. (2019)
Antidiabetic	*S. alopecuroides* *S.davidii* *S. flavescens* *S. japonica* *S. secundiflora*	Seeds Leaves/Roots Flowers Buds Seeds	Aly et al. (2017), Huang et al. (2018b), Wang et al. (2019b), Yang et al. (2019), Cho et al. (2020), Elberry et al. (2020), Zhang et al. (2020b), Li et al. (2021b)
	S. tomentosa *S. interrupta* *S. japonica*	Roots	Chang et al. (2019a, b) Rammohan et al. (2020)
Antiplatelets	*S.Japonica*	Fruits Leaves	Kim and Yun-Choi (2008), Aly et al. (2019, 2020a), Boozari et al. (2019b)
Anti-Parkinsonism	*S.Japonica*	Flowers/Buds	Boozari et al. (2019b); Chang et al. (2019a), Tsai et al. (2020)
Anti-obesity	*S. alopecuroides*	Leaves	Elberry et al. (2020)
Estrogenic	*S. Japonica*	Seeds	Elberry et al. (2020), Yang et al. (2020c)
Cerebral infarction reduction	*S. Japonica*	Flowers	Elberry et al. (2020)
Ulcerative colitis	*S. alopecuroides* *S. flavescens*	Total alkaloids Aerial parts in capsule	Chen et al. (2020b), Jia et al. (2020), Li et al. (2020d)
Antidiarrheal	*S. alopecuroides*	Seeds/Leaves	Boozari et al. (2019b), Majnooni et al. (2021)
	S. flavescens	Roots	Boozari et al. (2019b)
	S. tonkinensis	Rhizome	Li et al. (2019c)

Sophoridine (**240**) has exhibited obvious antiviral effects both in vitro and in vivo against CoxsackievirusB3 (CV-B3), by regulating cytokine expression. It is likely that the alkaloid (**240**) itself, not its metabolites, is mainly responsible for the antiviral activities (Ma et al. 2018; Ren et al. 2019). The serum samples obtained from rats with oral administration of compound **240** reduced this virus, a major pathogen for acute and chronic viral myocarditis, titers in infected myocardial cells. Matrine (**246**) has been reported to suppress the viral RNA copy number on rhabdomyosarcoma cells (Ma et al. 2018; Ren et al. 2019). Moreover, **246-** treatment of mice challenged with a lethal dose of human enterovirus 71, one of the major causative agents of hand, foot, and mouth disease in children less than 6 years old, reduced the mortality and relieved clinical symptoms (Ren et al. 2019). The matrine-type alkaloid sophoridine (**240**) inhibited EV71 infection in Vero cells, and it was highly effective against EV71 when Vero cells were pretreated with **240** for 2 h. This compound was highly effective at inhibiting EV71 attachment at a concentration over 250 μg mL^{-1} (Ren et al. 2019; Ti et al. 2021). The role of **249** and anagyrine (**273**), as the potent anti-respiratory syncytial virus components (Ma et al. 2018; Parvez et al. 2019) that have been isolated from the active PSf was recorded. The suggested mode of **284** to inhibit human immunodeficiency virus (HIV)-1 infection, was by blocking virus entry and inhibited the virus envelope-mediated cell–cell fusion (at low concentrations) (Aly et al. 2019; Wang et al. 2019a). This compound has approximately sevenfold more potent activity against HIV-1 than influenza virus (Wang et al. 2019a).

Matrine-based alkaloids (**279**–**281**), isolated from *S. alopecuroides* seeds, were reported with a similar or even better efficacy compared to the treatment with lamivudine and/or interferons (Wang et al. 2019a). Compounds **279** and **280** possess unprecedented 6/6/6/4 and 6/5/6/6 ring systems, respectively, while **281** has a pair of stereoisomeric matrine-acetophenone alkaloids with an unusual skeleton. A rare 1,4-diazaindan-type alkaloid; flavascensine (**279**) was also isolated from *S. flavescens* roots (Wang et al. 2019a; Ti et al. 2021). Sophaline E (**282**), the first example of sparteine-indolizine alkaloid, sophaline G (**283a**) and sophaline H (**283b**), the epimeric normatrine-julolidine alkaloids with unusual skeletons were isolated from *S. alopecuroides* and have showed antiviral activities against HBV (Wang et al. 2019a; Li et al. 2020d; Majnooni et al. 2021). A quinolizidine alkaloid with an unusual endocyclic ring system, aloperine (**284**) was extracted from the seeds and leaves of *S. alopecuroides* L. (Majnooni et al. 2021). Compound **284** has been identified as a potent hepatitis virus C inhibitor with EC_{50}-value of 4.23 ± 0.99 μM (Dang et al. 2016; Ti et al. 2021).

HIV-1-NL4-3 NanoLuc-sec virus infection of MT4 cells was performed, in the presence of various concentrations of **284** to evaluate its anti-HIV activity. The quinolizidine alkaloid **284** showed anti-HIV activity with EC_{50}-value of 1.75 ± 0.59 μM. BMS-806-resistant, Env-mediated cell–cell fusion, such as that mediated by YU2-T198P and 8x, may be inhibited by **284** (Ti et al. 2021). Through endocytosis inhibition, the quinolizidine alkaloid **284** effectively prevents the propagation of hepatitis virus C (HCV) in Huh7.5 cell line and primary human hepatocytes without cytotoxicity (Lv et al. 2020; Zhou et al. 2020).

Recently, Zhang et al. 2021c isolated unusual matrine–adenine hybrids from *S. davidii* with inhibitory effects on human cytomegalovirus (HCMV). Sophovicines B (**233**) and C (**234**) can inhibit HCMV replication effectively with IC_{50}-values of 7.12 and 7.32 μM, respectively.

Pulmonary hypertension

The alterations of phosphodiesterase (PDE) isozyme related to various pathologies and the design of specific PDE inhibitors might lead to the development of new specific therapeutic strategies in numerous pathologies (Farhadi et al. 2019). The prenylated flavonol, kushenol (**28**), mediated mTOR pathway by inhibiting PDE and Akt activity to induce apoptosis in non-small-cell lung cancer cells (Chen et al. 2019a). PDE5-inhibiting drugs are also used in the treatment of erectile dysfunction and pulmonary hypertension. A strong and selective inhibitory activity against rat diaphragm phosphodiesterase 5 (IC_{50} = 4.77 mg/mL) was exerted by the methanolic extract of *S. flavescens* roots (Boozari et al. 2019b). The isoflavonoid aglycones, biochanin (**130**) and prunetin (**131**), have selectively inhibited phosphodiesterase (PDE) isozyme PDE4. Orobol (5,7,3′,4′-tetrahydroxyisoflavone) was obtained from the ethyl acetate fraction of *S. davidii* (Franch.) Skeels (Li et al. 2021b). One of orobol synonyms is isoluteolin (**126**). A derivative of the flavone luteolin (**4**) exhibited a dual inhibition on PDE2/PDE4 with an IC_{50} ~ 40 μM, where quercetin (**1**) selectively inhibited PDE3/PDE4 (Boozari et al. 2019b; Farhadi et al. 2019).

A study from Chang and his coauthors provided information about the role of **284** to suppress human pulmonary vascular smooth muscle cell proliferation via inhibiting inflammatory response (Chang et al. 2019b). Aloperine (**284**) could protect the mice against bleomycin -induced pulmonary fibrosis by attenuated fibroblast proliferation and differentiation (Yin et al. 2018; Chang et al. 2019b). Mechanistic studies revealed that **284** could regulate the phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) and TGF-β/Smad signaling pathways by reducing fibroblast proliferation and differentiation, respectively (Yang et al. 2018; Yin et al. 2018; Wang et al. 2019d). While the quinolizidine alkaloids, isolated from *S. viciifolia* flowers including three matrine-type alkaloids (**291–293**) and the sparteine-type alkaloid

Table 15 Common biological activities of different species of *Sophora*

Plant species	Substance used	Main pharmacological activity	Action	References
S. flavescens (PSf)	CH_2Cl_2 fraction of roots and prenylated flavonoids	Alzheimer's disease	Selective β-secretase and cholinesterase inhibition	Boozari et al. (2019b), Cho et al. (2020)
	A combination of extract and stevioside	Diarrhea	Improve small intestinal lesion score in piglets, alleviate diarrhea and decrease rotaviral shedding in feces	Boozari et al. (2019b), Wang et al. (2019a)
	Prenylated flavonoids from roots	Vasorelaxant	Induces the relaxation of porcine coronary arteries	Aly et al. (2019)
	Ethanol extract of roots	Relax vascular smooth muscle	This via endothelium-dependent NO–sGC –cGMP signaling pathway	Aly et al. (2019)
	Prenylated flavornoidsfrom roots	Psoriasis	Inhibits cell growth and production of pro-inflammatory mediators	Chang et al (2018), Boozari et al. (2019b), Yang et al. (2020a, b, c)
	Total methanol extract of roots	Antipruritic agent	Inhibit 5-HT-induced scratching in a dose-dependent manner, without any effects on the locomotor activity	Aly et al. (2019)
	Aqueous extract included in a formula	Anti-allergic asthma airway hyperreactivity	Inhibits acetylcholine induced airway smooth muscle contraction in tracheal rings from allergic asthma	Yoo et al. (2019)
	Total extract	Protection against lung granuloma	Inhibit inflammation and infiltration of macrophages	Liu et al. (2018a)
	Total extract	Anti-caries	Inhibitory activities against *Streptococcus mutans* biofilms and antibacterial properties against several strains of mutans *streptococci* (Farhadi et al. 2019; Wang et al. 2019a)	Farhadi et al. (2019), Wang et al. (2019a)
	Prenylated flavonoids from the roots	Anti-allergic	Inhibition of the release of β-hexosaminidase from cultured RBL-2H3 cells	Boozari et al. (2019b)
	Prenylated flavonoids	Cancer immunotherapeutic	Ihibitory effects on indoleamine 2, 3-dioxygenase 1 activity	Kwon et al. (2019)
	Total alcoholic extract	Cytotoxic	Against human myeloid leukemia HL-60 cells	Chang et al. (2019a, b)
	Total alcoholic radix extract	Colon cancer	Inhibit cell proliferation and induce apoptosis of human colon cell line SW480	Liang et al. (2020)
	Prepared formula containing this plant	Angiogenesis	Inhibit angiogenesis in a collagen-induced arthritis rat model	Ao et al. (2019), Elberry et al. (2020)
	Total extract injection	Antiangiogenetic activity colorectal cancer	Inhibits the growth of human umbilical vein endothelial cells in vitro	Elberry et al. (2020)
	Total extract injection	Colorectal cancer	Reverses the drug resistance of oxaliplatin/SW480 and fluorouracil/SW480 Enhance expression of annexinA1	Ao et al. (2019), Cao and He (2020), Chen et al. (2020d)

Table 15 (continued)

Plant species	Substance used	Main pharmacological activity	Action	References
	In a prepared injection	Colon and breast cancer	Strongly reduced migration of HT-29 and MDA-MB-231 cells	Nourmohammadi et al. (2019)
	EtOAc and CH_2Cl_2	Alzheimer's disease	Inhibit β-Site APP cleaving enzyme 1	Boozari et al. (2019b), Chen et al. (2019a)
	Total alcohol extract	For healthy hair	Improvement in the inspected alopecia scores in the lotion plus phytoextract group were significant over a period of six months	Chang et al. (2018)
	Total alcohol extract	Pulmonary hypertension	Strong and selective inhibitory activity against rat diaphragm phosphodiesterase 5	Chen et al. (2019a)
		Improve immunity	Protect the liver against oxidation and provides chemotherapeutic sensitivity	Cao and He (2020), Liu et al. (2020a, b)
	In a formula decoction of the rootstock	Anti-inflammatory	Treatment of skin inflammation and wound healing	Chang et al. (2018)
		Contact dermatitis	Inhibits the release of histamine and β-hexosaminidase, and migration	Aly et al. (2019), Yoo et al. (2019), Yang et al. (2020a, b, c)
	Docoction of a medicine formula I	Anti-tumor	In clinical applications	Cao and He (2020), Liu et al. (2020a, b)
		Antiviral	Ability on the immune system or/and its inhibitory effects on major virus proteins	Ma et al. (2018, 2020a, b), Li et al. (2020d)
	Ethanol exract	The antimicrobial activities of seed and roots	Against *Bacillus subtilis*, *Escherichia coli*, *Micrococcus tetragenus* and *Proteus* species were compared by agar well diffusion method	Zhao et al. (2021)
	Total flavonoids	Relaxation of bladder smooth muscle	Via direct activation of the large-conductance calcium-activated potassium channel	Han et al. (2018)
	Total alkaloid gel	Cervical cancer	Via the suppression of AKT/mTOR signaling pathway	Zhou et al. (2018e)
	The total alkaloids from roots	Antiviral	Against HBV	Zhang et al. (2018b, 2020a)
	Total extract of radix	Antiviral	It is effective on viral replication in mouse hepatitis virus (MHV)-A59-infected cells	Orhan and Deniz (2020)
	S. flavescens nanoparticles	Antimicrobial	*Staphylococcus epidermidis* inactivation	Sim et al. (2014)
S. alopecuroides	The total alkaloids from roots	Colitis	Protection associated with downstream pro-inflammatory mediators and inhibition of nuclear transcription factor κB (NF-κB) activation	Halim et al. (2019), Chen et al. (2020b)

Table 15 (continued)

Plant species	Substance used	Main pharmacological activity	Action	References
	The total alkaloids from seeds	Improve depression in mice	Modulating gut microbiota	Zhang et al. (2021a)
	The total methanolic extract from seeds	Cytotoxic, antimicrobial, antioxidant, and enzyme inhibition	Significant total antioxidant capacity, highest α-amylase inhibition (methanol extract) and strong anti-leishmanial activity	Zahra et al. (2021)
	The total alkaloids from seeds	Anti-tumor effect in H22 tumor-bearing mice	Inhibits solid tumor in the spleen and thymus	Huang et al. (2018c), Jia et al. (2020)
	The total alkaloids from roots	Clinically for chronic prostatitis and psoriasis	Suppression of p63 expression	Aly et al. (2019), Boozari et al. (2019b), Hadadi et al. (2020)
	The total alkaloids from seeds	In *Staphylococcus epidermidis* infection	Prevents biofilm formation	Jia et al. (2019)
	Total extract from seeds	It Reduces the acute opioid withdrawal symptoms	Decreases the clinical opiate withdrawal scale score	Kianbakht et al. (2020)
	Flavonoid-rich extract from seeds	It ameliorates dyslipidemia, hyperglycemia, and insulin resistance in diabetic mice	Partly through activating PKC/GLUT4 pathway and regulated PPARα and PPARγ expression in white adipose tissue and liver, thereby ameliorating dyslipidemia	Lv et al. (2021)
	Total extract	Anti-larvae activity	High mortality against the larvae of *Aedes albopictus*	Shoukat et al. (2020)
S. tomentosa (PSt)	Total alcoholic extract	Prevents MPTP-induced parkinsonism in C57BL/6 mice	via the inhibition of GSK-3β phosphorylation and oxidative stress	Chang et al. (2019a)
	Lipoidal matters of leaves	Cytotoxic activity towards HCT-116 carcinoma cell line	IC_{50} value was of 38.76 µg/mL	Aly et al. (2020a)
		Antimicrobial activity	At concentration of 50 mg/mL and using the technique of agar well diffusion	Aly et al. (2020a)
S. tonkinensis (PSton)	Prenylated flavonoids from rhizomes and roots	Effect on the expression of inflammatory mediators has recorded	Effect on proprotein convertase subtilisin/kexin type 9 (PCSK9)	Ahn et al. (2019), Zhang et al. (2021b)
		Antioxidant and antibacterial activities	Free radical scavenging activity and antibacterial against different strains	Zhang et al. (2021b)
	The chloroform extract of roots	Suppression tumors of nasopharyngeal carcinoma cells	It inhibited cell viability, clonal growth, and induced cell apoptosis in a dose-dependent manner	Song et al. (2021)
S. exigua (PSe)	The aqueous extract of roots	Antimalarial activity	Exhibited 60.46% suppression of parasitemia (at 600 mg/kg)	Kaewdana et al. (2021)
	Total ethanolic extract of roots (Kheaw-Hom remedy)	Antioxidant activity	in vitro free radical scavenging, inhibition of DPPH radicals, superoxide anions, and hydroxyl radicals, and cell-based antioxidant activities	Kaewdana et al. (2021)
	Lavandulyl flavanones from the roots	Anti-MRSA infection	Complete growth inhibition of twenty-one strains of MRSA	Li et al. (2020a), Yang et al. (2020c)

Table 15 (continued)

Plant species	Substance used	Main pharmacological activity	Action	References
	Total alcoholic extract	Potent anti-breast cancer	Against MDA-MB- (-231and -468) and MCF-7	Boozari et al. (2019b), Farhadi et al. (2019), Li et al. (2020a), Yang et al. (2020c)
S. leachiana	Extract and isolated oligostilbenes	Anti-mitotic activity and cytotoxic effect	Against HeLa cells	Yang et al. (2019), Boozari et al. (2019a)
S. japonica (PSj)	Total extract of bark	Anti-proliferative activity	Promotes apoptosis and inducing reactive oxygen species ROS production	Liu et al. (2020a, b)
	Methanol extract of the flower buds	Treating contact dermatitis	Therapeutic mechanism is explained by relations between major flavonoids and 13 contact dermatitis-related genes	Kim et al. (2021)
	Acombination with *Scutellaria baicalensis* Georgi	Anti-hypertensive effect and improve kidney injury	Regulating gut microbiota in spontaneously hypertensive rats	Guanet al. (2021)
	CH_2Cl_2 fraction from fruits	Anti-osteoporosis activity	Regulates bone cell metabolism	Yang et al. (2020c)
	Total alcoholic extract from seeds	Anti-osteoporosis activity	Prevents bone loss Partly by inhibiting osteoclastic activity	Yang et al. (2020c)
	Aqueous extract included in traditional medicine, Sipi soup	Anti-inflammatory in cervical cancer	Prevents the progression of cancer by inhibiting the activation of CAF and the inflammatory process by reducing HIPK1-AS expression	Zhou et al. (2018a)
	Total alcoholic extract from mature fruit	Anti-osteoporosis activity	Prevents bone loss in ovariectomized rat's model	Shim et al. (2005)
	The alkaloids from seeds	Anti-osteoporosis activity	The effect on osteoblasts infected with *Staphylococcus aureus* and osteoclasts	Wang et al. (2018e)
	Mixture of total extract with *Artemisia sphaerocephala* gum	Edible antioxidant film	Increases DPPH scavenging activity of the film	Guo et al. (2020)
S. interrupta	Total extract	Antiulcer activity		Boozari et al. (2019b), Chen et al. (2020b), Yang et al. (2020b)
S. moorcroftiana (PSm)	Total extract and extracted isoflavones	Antimicrobial activity	Inhibitor of NorA, a multi-drug transporter of *Staph. Aureus*	Farhadi et al. (2019)
S. moorcroftiana (PSm)	Total extract of seeds	Anti-proliferative activity	Inhibits human hepatocarcinoma HepG2	Su et al. (2018)
	CH_2Cl_2 fraction of seeds	Protoscolicidal activity *in vivo*	Inhibiting effect against growth of *Echinococcus granulosus* cyst	Luo et al. (2018)
	A combinational treatment of alkaloids with albendazole	Alleviate liver injury	therapeutic effects against liver echinococcosis	Zhang et al. (2018a)
S. subprostrata	Total extract	Antiulcer activity	Inhibits the free and total acid output of gastric juice	Chen et al. (2020b), Yang et al. (2020b)

Table 15 (continued)

Plant species	Substance used	Main pharmacological activity	Action	References
	Total extract of radix	Potent inhibitor of mouse hepatitis virus (MHV)-59/CoV than ribavirin	Decreased production and the intracellular viral RNA and protein expression	Fuzimoto and Isidoro (2020)
	Total polysaccharides	Anti-inflammatory activity	Regulation on inflammatory response of mouse mononuclear macrophage cell line RAW264.7 cells infected with porcine circovirus type 2	Li et al. (2019a), Yang et al. (2020b)
	A combination of bush root polysaccharide and baicalin-phospholipid complex	Inhibit duck hepatitis A virus type 1 adsorption, replication and release	Drop the RNA synthesis and the protein translation	Chen et al. (2018a, b)
S. tonkinensis	Prenylated flavonoids	Anti-allergic effect	Inhibiting IL-6 production	Boozari et al. (2019b)
S. davidii = *S. viciifolia*	A flavonoid-rich extract	Antidiabetic activity	via activation of AMP-activated protein kinase in KK-Ay mice	Huang et al. (2018b), Wang et al. (2019b), Yang et al. (2019)
	Stems and leaves extract	Anti-itching activity	Decrease the number and the duration of itching	Yoo et al. (2019)
	Flowers and unusual matrine–adenine hybrids	Antiviral activity	inhibitory effect on human cytomegalovirus	Zhang et al. (2021c)
S. secundiflora	Lipoidal matter of leaves	Cytotoxic activity towards HCT-116 carcinoma cell line	IC_{50} value was of 97.00 µg/mL	Aly et al. (2020a)
		Antimicrobial activity	At concentration of 50 mg/mL and using the technique of agar well diffusion	Aly et al. (2020a)

Table 16 Summary of findings on the cytotoxic and anti-tumor activity of compounds derived from *Sophora* species

Compound	Plant species	Cytotoxic and anti-tumor activity	Action	References
Sophoraflavanone G (**19**)	*S. flavescens*	Cytotoxicity for several tumor cells	Induces apoptosis in triple-negative breast cancer cells	Huang et al. (2019, 2020), Long et al. (2020)
sophoraflavanone G (**19**), leachianone A (**20**), kurarinone (**23**), 2′-methoxykurarinone (**24**)	*S. flavescens* *S. davidii*	Cytotoxic activity	Against human myeloid leukemia HL-60 cells	Chang et al. (2019a, b), Ma et al. (2021)
Kurarinone (**23**)	*S. flavescens*	Cytotoxic	Against human breast cancer	Boozari et al. (2019b)
		Induce apoptosis in small cell lung carcinoma	Promots Fas and TRAIL receptor-1 and -2 expression via the caspase-8/Bid pathway	Chung et al. (2019)
Formononetin (**125**)		Suppression of tumor growth and angiogenesis	Targets the fibroblast growth factor and protein kinaseB signaling pathway	Elberry et al. (2020)
Exiguaflavanones A (**61**) and B (**62**)	*S. exigua*	Potent anti-breast cancer	MDA-MB- (-231and -468) and MCF-7	Boozari et al. (2019b), Farhadi et al. (2019), Li et al. (2020a), Yang et al. (2020c)
Secundiflorol D (**140**), secundiflorol E (**141**), secundiflorol A (**154**), secundifloran (**155**)	*S. flavescens*	Cytotoxic	Cytotoxic activity against human tumor cell lines and normal human cells	Ledoux et al. (2018), Guo et al. (2020)
Maackiain (**172**)	*S. alopecuroides* seeds	Cytotoxic	Against MCF-7, Hep3B, HeLa and H1299 cells	Rong et al. (2020), Tsai et al. (2020)
Leachianols (**208–211**)	*S. leachiana*	Anti-mitotic activity and cytotoxic effect	Against HeLa cells	Boozari et al. (2019a), Yang et al. (2019)
Sophoridine (**240**)	*S. alopecuroides*	Lung cancer cell growth	Through activation of the p53 and Hippo signaling pathways	Zhou et al. (2018d, 2020), ur Rashid et al. (2020)
	Sophoridine (**240**) hydrochloride injection	Anticancer drugs derived fromtraditional Chinese medicine	It is indicated in nausea lymphoma, gastrointestinal tumor	Yao et al. (2021)
Oxysophoridine (**242**)	*S. alopecuroides*	Hepatocellular carcinoma	Suppression of the growth by regulating apoptosis associated with the Bcl-2/Bax/caspase-3 signalling pathway	Yao et al. (2012)
		Colorectal cancer cells	Suppression of the growth by regulating apoptosis associated with the Bcl-2/Bax/caspase-3 signalling pathway	Jin et al. (2017)
Sophoridine (**240**)	*S. flavescens*	Gastric cancer	Upregulates CD8 + T cytotoxic function	Zhuang et al. (2020)
		Tumor-suppressive activities	This via promoting ESRRG-mediated β-catenin degradation in gastric cancer	Peng et al. (2020a, b)
Oxysophocarpine (**236**), matrine (**246**) and oxymatrine (**249**)		Colon cancer	Anti-neoplasm mechanisms	Cao and He (2020), Elberry et al. (2020)

Table 16 (continued)

Compound	Plant species	Cytotoxic and anti-tumor activity	Action	References
Matrine (**246**)		Hepatocellular carcinoma	Stronger anti-proliferative action on Bel7402 and SMMC-7721 cells under hypoxia than that in normoxia	Dai et al. (2021)
		Colon cancer	Inhibited the proliferation and anchorage-independent growth	Fang et al. (2018)
		Prostate cancer	Inhibit the progression Promoting expression of GADD45B	Huang et al. (2018a)
		Myeloid leukemia	Promots human myeloid leukemia cells apoptosis	Lin et al. (2019b)
		Inhibits the growth of natural killer/T-cell lymphoma cells	Modulating CaMKIIγ-c-Myc signaling pathway	Gu et al. (2020)
		Breast cancer	Reversed multidrug resistance of MCF-7/ADR cells through PI3K/AKT signaling pathway	Zhou et al. (2018b)
		Anti-proliferation	Inhibition of inhibitory κB kinase β regulation of nuclear factor κB signaling pathway	Cao and He (2020), Zhang et al. (2020a)
	S. moorcroftiana	Colon cancer	Reverse the Warburg effect and suppresses cell growth Negative regulating HIF-1α Triggers colon cancer cell apoptosis and G0/G1 cell cycle arrest	Hong et al. (2019)
	S. alopecuroides	Gastric cancer	Re Inhibits the progression through inhibiting miR-93-5p and upregulating the expression of target gene AHNAK	Liu et al. (2020b)
	S. flavescens	Thyroid cancer	Induces papillary thyroid cancer cell apoptosis in vitro and suppresses tumor growth in vivo by down-regulating miR-182-5p	Li et al. (2019b), Fu et al. (2020)
Matrine (**246**)		Nasopharyngeal cancer	Inhibit human nasopharyngeal carcinoma CNE-2 cells	Wang et al. (2018c)
	S. flavescens	Esophageal squamous cancer	Induces apoptosis in KYSE-150 cells -Increases (ROS) and inhibiting mitochondrial function	Jiang et al. (2018)

Table 16 (continued)

Compound	Plant species	Cytotoxic and anti-tumor activity	Action	References
		Oral squamous cancer	Inhibits the growth of cell carcinoma cells in vitro and in vivo Exhibits it via mediation of micro-RNA-22	Li et al. (2019d), ur Rashid et al. (2019), Liu et al. (2020b)
	In Compound Kushen Injection formula (*S. flavescens*)	Pancreatic cancer	Inhibiting autophagy-mediated energy metabolism	Cho et al. (2018), Ao et al. (2019), Nourmohammadi et al. (2019), Yao et al. (2021)
Allomatrine (**248**) inh	*S. japonica*	Inhibits proliferation and invasion	Promoting apoptosis, inducing ROS production, inhibiting ubiquitin proteasome, arresting cell cycle and regulating tumor related gene expression	Liu et al. (2020a, b)
Matrine (**246**) and Oxymatrine (**249**)	*S. flavescens*	Gastric cancer	Direct killing effects on HepG2, BEL-7402, and SGC-7901 Inhibit the invasion and metastasis of gastric cancer last cells	Huang et al. (2018c), Elberry et al. (2020), Zhang et al. (2020a)
Oxymatrine (**249**)		Apoptosis- Endothelial injury	The involvement of mitochondria-dependent apoptosis and Akt-eNOS-NO signaling pathways	Wu et al. (2019a)
		Gastric cancer	Suppression of cell proliferation and invasion	Huang et al. (2018c)
			Inhibition of IL-21R-mediated JAK2/STAT3 pathway	Su et al. (2018), Fan et al. (2019)
		A549 human non-small lung cancer cell apoptosis	This via extrinsic and intrinsic pathways	Zhou et al. (2018d), Izdebska et al. (2019)
		Induces dose-dependent cell death of non-small lung cancer	This through ER stress-induced apoptosis pathway	Halim et al. (2019); Izdebska et al. (2019)
		Reverses epithelial-mesenchymal transition in breast cancer cells	This via depressing αVβ3 integrin/FAK/PI3K/Akt signaling activation	Chen et al. (2019c)
		Inhibition of colon cancer cell epithelial-mesenchymal transition and NF-κB signaling	Reverses 5-fluorouracil resistance	Liang et al. (2020)
		Psoriasis vulgaris	Anti-proliferation effect on human skin keratinocytes and suppression of p63 expression	Huang et al. (2018a, b), Aly et al. (2019)
N-methyl cytisine (**246**)	*S. alopecuroides*	Breast cancer	Inhibiting breast cancer cell metastasis	Chen et al. (2020a)
Aloperine (**284**)	*S. japonica*	Colon cancer	Against multiple myeloma and colon cancer though increasing cell apoptosis	Yin et al. (2018), Li et al. (2020d)

Table 16 (continued)

Compound	Plant species	Cytotoxic and anti-tumor activity	Action	References
	S. alopecuroides	Ovarian cancer	It induces apoptosis by ROS activation mechanism in human ovarian cancer cells	Qiu et al. (2020a)
		Lung cancer	Compound **284**–Adbic (adenoviral vector expressing $p14^{ARF}/p53$) combined treatment on Non-small cell lung cancer cells synergistically produced induced apoptosis, anti-proliferative effects, and arrested cell cycle at the G1 phase	Muhammad et al. (2020)
		Bladder cancer	It significantly inhibits the viability of bladder cancer cells. This was exerted via suppressing hypoxia induced epithelial-mesenchymal transition activation of mTOR/p70S6K/4E-BP1 pathway	Zhou et al. (2020)
	S. flavescens	Oral squamous cancer	Through the PI3K/Akt signaling pathway	Liu et al. (2019a)
	S. moorcroftiana	Liver cancer	Induces apoptosis and G2/M cell cycle arrest in hepatocellular carcinoma	Liu et al. (2019a, 2020b)
Anagyrine (**273**)		Cytoxic activity against MCF-7 and HEPG-2	It exhibited IC_{50} values of 27.3 ± 0.7 and 30.2 ± 0.9 µg/mL against MCF-7 and HEPG-2 cancer cells, respectively	Aly et al. (2021)
Phenolic acids (**324**–**331**)	*S. tonkinensis*	Cytotoxic	Against hepato-cellular carcinoma cell lines, HepG2 and Hep3B	Song et al. (2018), Hou et al. (2020)
Butein (**331**)	*S. tonkinensis*	Cytotoxic	Inhibits the cancer cell growth	Song et al. (2018)

Table 17 Summary of findings on the neurological activity of compounds derived from *Sophora* species

Compound	Activity	Action	References
Kushenol (**28**), isoxanthohumol (**32**) and leachianone A (**20**), kuraridin (**184**)	Inhinitβ-Site APP cleaving enzyme 1 (BACE1)	IC_{50} of 5.45, 7.19, 8.56, 6.03 µM	Boozari et al. (2019b), Chen et al. (2019a)
Formononetin (**125**)	Anti-dementia	Neuroprotective effects on scopolamine-induced dementia	Aly et al. (2020c)
Maackiain (**172**)	Agent for Parkinson's disease treatment	Improvements in food-sensing behavior and life-span Reduce dopaminergic neuron damage in 6-hydroxydopamine-exposed worms of the BZ555 strain	Tsai et al. (2020)
Aloperine (**284**)	Neuroprotective	Ameliorate oxidative stress patterns	Zhao et al. (2018)

Table 18 Summary of findings on the antimicrobial activity of compounds drived from *Sophora* species

Compound	Activity	Action	References
Flavanones (**19**) and (**23**)	Potent antibacterial	IC50 of 10 µg/disk) against Gram-positive bacteria	Farhadi et al. (2019)
Quercetin (**1**), kaempferol (**2**) and sophoraflavanone G (**19**)	Anti-caries	Inhibitory activities against *Streptococcus mutans* biofilms and antibacterial properties against several strains of mutans *Streptococci*	Farhadi et al. (2019), Wang et al. (2019a)
	B enefit individuals with androgenetic alopecia	Promotes the proliferation of human hair keratinocytes	Chang et al. (2018), Huh et al. (2020)
Sophoraflavanone G (**19**)	anti-MRSA	Antibiofilm formation against microbe	Farhadi et al. (2019)
SophoraflavanoneB (**48**)	anti-MRSA	Cause cell wall weakening and membrane damage	Farhadi et al. (2019), Hadadi et al. (2020)
Exiguaflavanones A (**61**) and B (**62**)	Anti-MARS	Growth inhibition of twenty-one strains	Farhadi et al. (2019)
Genistein (**120**)	**Anti-**bacterial	Changes exerted in the cell morphology of bacteria	Farhadi et al. (2019)
Matrine (**246**)	Antimicrobial	Prevention of biofilm formation in *Staphylococcus epidermidis* infections	Jia et al. (2019)

(**294**), showed no activity as anti-inflammatory and anti-influenza virus (Gao et al. 2020).

Anti-inflammatory activity

Kushenol (**28**) was reported to inhibit autophagy and impairs lysosomal positioning via VCP/p97 inhibition (Kwon et al. 2020). A recent study has demonstrated that kushenol dose-dependently suppressed the production of inflammatory mediators in lipopolysaccharide-stimulated RAW264.7 macrophages (Cho et al. 2020). In HaCaT cells, the compound exerted antioxidant stress activity and prevented DNA damage as well as cell death by upregulating the endogenous antioxidant defense system.

The potent inflammasome-activating effect of maackiain (**172**) was also reported (Huh et al. 2020). The compound (**172**) has been suggested to exert an immunostimulatory effect by promoting IL-1β production via activation of the inflammasome/caspase-1 pathway and this may be clinically useful as an acute immune-stimulating agent.

The plant phytoextracts are also used for conditions involving the liver, heart, intestinal tract, and skin (Boozari et al. 2019b; Quradha et al. 2021). Experimental investigations indicated that its phytoextracts stimulated anticancer, antibacterial, antiviral, anti-inflammatory, and antipruritic responses with wound healing benefits (Huang et al. 2018a; Su et al. 2018; Boozari et al. 2019b).

Recently, *S. gibbosa* extract-loaded microemulsion-impregnated gelatin/chitosan was suggested to be a potential candidate for the wound healing (Shalaby et al. 2021).

The prenylated flavonoids, namely kushenol (**28**) and sophoraflavanone B (**48**), are used in wound healing (Chen et al. 2019a) and also exerted anti-inflammatory and anti-oxidative stress activities (Cho et al. 2020). Compound (**28**) is a noncompetitive potent inhibitor of tyrosinase, the enzyme responsible for synthesizing melanin, thereby has

potential cosmetic applications as a skin whitener (Boozari et al. 2019a, b; Cho et al. 2020). Decoction of an herbal Chinese formula comprises the *S. flavescens* rootstock, has been reported as a botanical remedy for treatment of skin inflammation (Chang et al. 2018). ASa was clinically used for the treatment of chronic prostatitis and psoriasis (Aly et al. 2019; Boozari et al. 2019b; Hadadi et al. 2020). The isolated prenylated flavonoids from *S. flavescens* roots also can inhibit the cell growth and production of pro-inflammatory mediators which were related to skin diseases such as psoriasis (Chang et al 2018; Boozari et al. 2019b; Yang et al. 2020a, b, c). The anti-proliferation effect of oxymatrine (**249**) on human skin keratinocytes has been reported to be related with the suppression of p63 expression. This compound does not affect the formation of basement membrane, which is very important to maintain the normal function of human skin keratinocytes (Aly et al. 2019; Wang et al. 2020a, b).

Many dosage forms were prepared from *S. alopecuroides* and applied to the clinical therapy *e.g.,* the tablet (colitis enteritis and dysentery), suppository (cervical erosion and gynecological inflammation), and oil liniment (neurodermatitis and eczema) (Chen et al. 2020b; Jia et al. 2020; Li et al. 2020d).

The effect of many prenylated flavonoids, isolated from roots and rhizomes of *S. tonkinensis*, on the expression of inflammatory mediators and proprotein convertase subtilisin/kexin type 9 (PCSK9) was also studied (Ahn et al. 2019). Lonchocarpol A (**56**) at concentrations of 20 μM downregulated PCSK9 mRNA expression in HepG2 cells (Ahn et al. 2019).

Matrine (**246**) can induce endoplasmic reticulum stress in MCF-7 cells, downregulate the expression of hexokinase II, and inhibit the energy metabolism. In addition, studies have reported that matrine (**246**) has a therapeutic effect on Alzheimer's disease, encephalomyelitis, asthma, myocardial ischemia, rheumatoid arthritis, osteoporosis, and its mechanism is mainly related to the inhibition of inflammatory response and apoptosis (Liu et al. 2020a, b; Yang et al.2020a, b, c; Zhang et al. 2020a).

Matrine (**246**) has recorded to alleviate *Staph. aureus* lipoteichoic acid-induced endometritis via suppression of TLR2-mediated NF-κB activation (Jiang et al. 2019b).

The combination of *S. japonica* L. and *Scutellaria baicalensis* Georgi improved the intestinal barrier function, reduced inflammation, increased short-chain fatty acids, decreased indoxyl sulfate, and inhibited oxidative stress reactions (Guan et al. 2021). Both plants have anti-hypertensive effects with clinical benefits against kidney injury.

The pretreatment with aloperine (**284**) protected mice against ischemia reperfusion-induced acute renal injury as manifested by reducing tubular apoptosis, attenuating inflammatory infiltration, and/or improving renal function (Wang et al. 2019a; Boozari et al. 2019a). By inhibiting inflammation and infiltration of macrophages, Psf exhibited a protection against mycobacterial trehalose dimycolate-induced lung granuloma (Liu et al. 2018a). Mechanistic studies revealed that QA (**284**) selectively repressed IFN-γ and IL-1β expression by NFκB transcriptional activity and regulating PI3K/Akt/mTOR signaling (Yin et al. 2018; Ye et al. 2020). Matrine (**246**) prevented adriamycin-induced nephropathy (AIN) through the modification of disordered plasma lipids and recovery of renal function, and this bioactivity is partly attributed to the suppression of renal inflammation and Treg/Th17 imbalance regulation (Aly et al. 2017; Wang et al. 2019a). This compound (**246**) also protected PC12 cells from lipopolysaccharide-evoked inflammatory injury via upregulation of miR-9 (Jiang et al. 2020a), and normalized regulatory T cells (Treg)/T-helper17 cells (Th17) ratio in peripheral blood mononuclear cells of AIN rats (Wang et al. 2019d; Zhang et al. 2020a, 2021a, b, c).

Besides, alkaloids (Table 11) are one of the main effective substances of *Sophora* species with anti-inflammatory activity. The total alkaloids of phytoextract of *S. alopecuroides* (TASa) protected against colitis, probably due to the downstream pro-inflammatory mediators and the inhibition of nuclear transcription factor κB (NF-κB) activation (Halim et al. 2019; Chen et al. 2020b). The TASa increase the expression of $CD4^+$ $CD25^+$Tregs and IL-10 in experimental colitis (Fan et al. 2019; Li et al. 2020d).

Compound scopoletin **216**, isolated from *S. mollis* (Royle) Graham Ex Baker, showed a significant anti-inflammatory effect as it reduced edema of the paw (83.98%), which was more potent than the standard drug (ibuprofen, showed an inhibition percentage of 73.22%). A docking study on a phenolic acid derivative into the binding site of cyclooxygenase isoform showed a better protective effect against COX-1 than the COX-2 isoform (Quradha et al. 2021).

The ability of *S. flavescens* containing Chinese formula to elicit anti-inflammatory and anti-oxidative stress response in vitro has been reported. The formula blocked cellular transformation and protected against dextran sulfate sodium-induced colitis in a mouse model (Fang et al. 2018). Sophocarpine (**235**) was reported to ameliorate dextran sodium sulfate-induced colitis by regulating cytokine balance (Chen et al. 2020b). This compound has prevented cigarette smoke-induced restenosis in rat carotid arteries after angioplasty (Yang et al. 2020a). The compound can play the anti-inflammatory role in cells. The alkaloid (**249**) has an anti-inflammatory effect by interfering with the IκB-α protein expression and inhibiting NF-κB activity in colitis cells (Chen et al. 2020b).

Among QA from *S. tonkinensis*, sophocarpine (**235**), (−)-anagyrine (**273**), 14β-hydroxymatrine (**301**), and 7β-sophoramine (**302**) had high anti-inflammatory activities (*in-vitro*). While sophocarpine (**235**), 5α-hydroxymatrine

(**284**) (−)-anagyrine (**273**), and 5*α*,14*β*-dihydroxymatrine (**300**) exhibited higher anti-inflammatory effects (in vivo) (He et al. 2019). Oxymatrine (**249**) prevented synovial inflammation and migration via blocking activation in rheumatoid fibroblast-like synoviocytes (Zhou et al. 2016; Liang et al. 2018). Suppression of the activation of NF-κB and MAPK in human chondrocytes and inhibition of IL-1β-induced expression of matrix metalloproteinases were exhibited by matrine (**246**) (Fan et al. 2019; Li et al. 2020d). Aloperine (**284**) showed a suppressive effect on the swelling of hind paw inrats which induced by carrageenin, macostatin, PGE2, histamine, and 5-HT. It also increased the permeability of capillaries caused by histamine and the leukocytic migratory response (Wang et al. 2020b). Different concentrations of matrine (**246**) solution all had inhibitory effects on the growth of C6 cell lines, which showed an apparent dose- anti-glioma effect relationship (Zhang et al. 2020a, 2021a, b, c).

Recently (Li et al. 2021a), a quinolizidine alkaloid of matrine-type; sophalode K (**318**); isolated from the seeds of *S. alopecuroides* suppressed the protein levels of iNOS and COX-2, revealing its anti-inflammatory potential.

Summary of findings on the anti-inflammatory effects of compounds derived from *Sophora* species was illustrated in Table 19.

Anti-allergy activity

The anti-allergy and anti-inflammatory effects of the root of *S. flavescens* were investigated using 1-fluoro-2,4-dinitrofluorobenzene-induced contact dermatitis mouse model and in vitro using RBL-2H3 cells (Aly et al. 2019; Yoo et al. 2019). The release of histamine and β-hexosaminidase and migration was inhibited by treatment with this extract. Anti-asthma herbal medicine intervention is an aqueous extract of three herbs, including *S. flavescens* (Yoo et al. 2019). It prevented allergic asthma airway hyper-reactivity in mice and inhibited acetylcholine induced airway smooth muscle contraction in tracheal rings from allergic asthmatic mice. The methanol extract of *S. flavescens* was reported as antipruritic agent that could affect acute and chronic pruritus (Aly et al. 2019). This extract inhibited serotonin (5-HT)-induced scratching (an itch-related response) in a dose-dependent manner, without affecting the locomotor activity. Anti-allergic prenylated flavonoids from the roots of *S. flavescens* were also recorded (Boozari et al. 2019b). Sophoraflavanone G (**19**), leachianone A (**20**) and kushenol (**28**) inhibited the release of β-hexosaminidase from cultured RBL-2H3 cells (IC_{50} values ranging from 15 -30 μM). The regulatory effect of ethanolic extract of Flos *S. japonica* on allergic mediators produced by intracellular calcium ionophore activation in mast cells was reported (Peng et al. 2018).

At nontoxic concentrations, a prenylated flavonoid sophoraflavanone M **101** isolated from *S.* flavescens (as an anti-inflammatory herb), reduced LPS-induced production of inflammatory mediators IL-6, NO, TNF-α, and MCP-1 in mouse primary peritoneal macrophages. The compound inhibited two important inflammatory signaling pathways, NF-κB and JNK/AP-1 (Han et al. 2021).

Recently, the effect of sophoricoside **134** from the mature seeds of *S. japonica* on the allergic chronic inflammatory lung disorder asthma was investigated (Kim and Lee 2021). The compound **134** reduced the allergic and asthmatic symptoms by suppressing airway inflammation and antibody-antigen reaction in mouse models. It improved allergic asthma by suppressing mast cell activation and $CD4^+$ T cell differentiation. This isoflavone glycoside **134** suppressed immune cell recruitments in the airway lumens of the lungs and production of pro-inflammatory cytokines in the bronchoalveolar lavage fluid of ovalbumin (OVA)-induced mice. It also decreased the amounts of histamine and arachidonic acid metabolites released in OVA-induced mice and antibody-antigen stimulated mast cells. In addition, compound **134** decreased differentiation of naïve $CD4^+$ T cells into T helper type 1 (Th1), Th2, and Th17 cells.

The anti-allergic and anti-inflammatory actions of herbal combination four herbs including *S. flavescens* was recorded (Yoo et al. 2019). Strong anti-degranulation actions were recorded and the formation of prostaglandin D_2, interleukin-4, tumor necrosis factor-α, and leukotriene C_4 was inhibited.

The isoflavone glycoside sophoricoside **134** inhibited the bioactivities of interleukins (IL-3, 5 and 6), and granulocyte–macrophage colony-stimulating factor in BAF/BO3, Y16, MH60/BSF-2, and TF-1 cells. IL-1β and α-tumor necrosis factor in A375.S2 and WEHI-164 cells were not affected (Kim et al. 2003).

Prenylated flavonoids and 2-arylbenzofuran (**194**) could be responsible for the anti-allergic effect of *S. tonkinensis* by inhibiting IL-6 production (Boozari et al. 2019b; Zhang et al. 2021b). *S. davidii* stems and leaves affected the ear and toe swelling of the mice. They could reduce the capillary permeability of the mice and decrease the number and the duration of itching (Yoo et al. 2019). Aloperine (**284**) has been used widely in clinical settings to treat inflammatory diseases, including allergic dermatitis (Ye et al. 2020). The anti-inflammatory and anti-allergy effects of compounds derived from *Sophora* sp are summarized in Table 19.

Anti-parasite

Most of the species of genus *Sophora* (approximately 70 species) are distributed in tropical and temperate zones and serve as pesticides and/or nectariferous plants (Zhou et al. 2020). *S. flavescens* exhibited an anti-protozoal activity (in

vitro) as it inhibits *Toxoplasma gondii* proliferation at lower concentrations (Youn et al. 2003). *S. flavescens* exhibited an anti-neosporal activity to inhibit parasite proliferation, colonies containing *Neospora caninum* tachyzoites. The isoflavone was used to investigate the antileishmanial and trypanocidal compounds. Genistein (**120**) displayed a promising antileishmanial activity (IC_{50} 4.2 µM) and selectivity (IC_{50} 32.9 µM, versus Vero cells).

Many prenylated isoflavanones sophoronol (**158**), tetrapterol C-E (**148–150**), tetrapterol G-I (**151**–**153**) and tetrapterol F (**159**) were isolated from the roots of *S. mollis* and exhibited anitplasmodial activity against the CQS D10 strain of *Plasmodium falciparum* (de Andrade et al. 2020; Li et al. 2020a; Ma et al. 2020b). Sophoronol C **104** and sophoronol E **106** exhibited moderate anitplasmodial activity, with IC_{50} values of 12.9 and 12.8 µM, respectively. A fraction of PSm seeds has oxysophocarpine (**236**) and oxymatrine (**249**) as the main ingredients which showed no antiparasite effect. While the activity of another fraction has the low polarity compounds; sophocaprine (**235**) and matrine (**246**) as the main phytoconstituents, were evaluated. The fraction presented stronger protoscolicidal activity in vivo and obvious inhibiting effects against growth of *Echinococcus granulosus* cyst (Luo et al. 2018). It was suggested that the oxygen group in the alkaloid molecule might affect the activity of PSm against echinococcosis in experimentally protoscolex-infected mice.

The major phytoconstituents of phytoextracts of *S. alopecuroides* PSa and *S. flavescens* PSf are sophocarpine (**235**), matrine (**246**), and anagyrine (**273**). These alkaloids presented high mortality against the third-instar larvae of *Aedes albopictus* (Shoukat et al. 2020). Additionally, PSa extract was more effective than a single active alkaloid due to the synergism of its active ingredients, which may be effective in managing the resistant population of *Ae. albopictus*. A concentration-dependent manner was recorded, as larval mortality increased with the increase in the PSa concentration and its constituents (**235** and **246**). Maximum mortality was achieved at higher concentrations (Shoukat et al. 2020).

Sophocarpine (**235**) and matrine (**246**); isolated from *S. alopecuroides*, are the main constituents for the broad bioactivities on insect pests, especially on aphids (Ma et al. 2020b). The acaricidal bioactivity of an oxymatrine **249**-based commercial formulation was assessed against a pest in coffee cropping systems (*Oligonychus ilicis*) (de Andrade et al. 2020). QAs are widely used insecticides against citrus psyllids. Among these alkaloids, the dominant alkaloids sophocarpine (**235**) and sophoridine (**240**) were reported as the alkaloids repelled Asian citrus psyllid (Rizvi et al. 2019). The aphicidal action of sophocarpine (**235**) and matrine (**246**); isolated from *S. alopecuroides*, was reported and they have certain similarities to that of avermectin, a positive control (Ismail et al. 2020; Ma et al. 2020b). The lupin alkaloid (**246**) and its unsaturated derivatives **235** had intense nematicidal activity against nematodes. Sophoramine (**243**) had such activity, but it was less than that of **235** (Zhang et al. 2020a, 2021a, b, c; Ma et al. 2020b). Aso, cytisine-type alkaloids; N-methyl cytisine (**268**) and anagyrine (**273**) alkaloids were more active against the nematodes than the lupin-type alkaloids; sophocarpine **235**, matrine **246** (Wang et al. 2019a; de Andrade et al. 2020; Huang and Xu 2020a; Ismail et al. 2020; Ma et al. 2020b). The nematocidal effect of aqueous extract of roots and stems of *S.mollis* against root-knot nematodes (*Meloidogyne incognita*) was reported (Ismail et al. 2020).A study confirmed the inhibition effect of *S. flavescens* ethanol extract on *Phytophthora nicotianae* (a pathogen of tobacco black shank disease) which cause huge economic losses each year (Li et al. 2020b). This effect could be achieved by inhibiting the production of sporangia and the release of zoospore release.

The quinolizidine-type alkaloid **284** had significant nematocidal and insecticidal activities via binding to the nicotinic acetylcholine receptor (Zhou et al. 2020).

The cytotoxic activity of alkaloid fraction of leaves of *S. secundiflora* and *S. tomentosa* and isolated alkaloids was also studied using crystal violet assay against MCF-7 and HEPG-2 cell lines (Aly et al. 2021).

Using different concentrations and mortality rate, the insecticidal activity of 70% methanol extract of leaves of *S. tomentosa*, *S. secundiflora*, and the isolated alkaloids were assessed against 3rd instar larvae of *Culex pipiens* (Diptera: Culicidae) (Aly et al. 2021). Anagyrine (**273**) exhibited high insecticidal activity with LC_{50} value of 3.42 ppm after 24 h of exposure (Aly et al. 2021).

Antidiabetic activity

A flavonoid-rich extract of *S. davidii* (Franch.) Skeels exhibited antidiabetic activity via activation of AMP-activated protein kinase in KK-Ay mice (Huang et al. 2018b; Wang et al. 2019b; Yang et al. 2019). This extract promoted the glucose transporter 4 (GLUT-4) translocation and improved glucose uptake in L6 cells (Huang et al. 2018b). Several isoflavone glycosides isolated from the stem bark of *S. japonica* demonstrated inhibitory effects on aldose reductase in vitro (Aly et al. 2019). Among these compounds, daidzein (**108**), paratensein-7-*O*-glucoside (**113**), and puerol A **115** displayed inhibitory effects, with IC_{50} values of 3.2, 6.4, and 1.9 µM, respectively.

Flavonoid-rich extract from *S. alopecuroides* ameliorated dyslipidemia, hyperglycemia, and insulin resistance in diabetic mice (Lv et al. 2021). This was due to the activation of PKC/GLUT4 pathway and the regulation of PPARα and PPARγ expression in white adipose tissue and liver, thereby ameliorating dyslipidemia.

Flavanones were the main active principles responsible for GLUT-4 translocation activities of petroleum ether and the ethyl acetate fractions of the roots of *Sophora davidii* (Franch.) Skeels (Ma et al. 2021). The flavanones; davidones A-E **94–98** and acacetin **99** promoted GLUT-4 translocation by the range of 1.35–3.00 folds (Ma et al. 2021).

2-(2′,4′-Dihydroxyphenyl)-5,6-methylenedioxybenzofuran **192** and three 2-arylbenzofuran dimers; Shandougenine A-C (**193–195**) were obtained from the ethyl acetate fraction of *S. davidii* (Franch.) Skeels (Li et al. 2021b). These compounds were tested for their potential GLUT-4 translocation activities. L6 cell line, which stably expressed Myc-GLUT-4-mOrange, was used to evaluate these effects. The positive control was insulin (100 nM) and 2-arylbenzofurans showed weak activity. Isoluteolin (**126**), isolated from the same plant, exhibited the most potent GLUT-4 translocations with 1.60-fold enhancement (Li et al. 2021b). It is considered as an active antidiabetic constituent in the plants of genus *Sophora*.

A lavandulyl flavanone; leachianone A (**20**) from the roots of *S. davidii* had GLUT-4 translocation activities (Ma et al. 2021).

(+)-Lirioresinol-A **196** was obtained from the ethyl acetate fraction of *S. davidii* (Franch.) Skeels (Li et al. 2021b) showed moderate translocation activity, increasing GLUT-4 translocation by 1.39-fold. It could be considered as a potentially active anti-diabetic constituent in the plants of genus *Sophora*.

Isopimpinellin (**215**) isolated from *S. interrupta* has antidiabetic activity and inhibitory activity against the enzyme adenine phosphoribosyltransferase from *Leishmania* (Boozari et al. 2019b; Rammohan et al. 2020). Oxymatrine **249** reported to ameliorate diabetes-induced aortic endothelial dysfunction via the regulation of eNOS and NOX4 (Wang et al. 2019b).

Antioxidant activity

Owing to tremendous antioxidant potential (Ledoux et al. 2018; Guo et al. 2020), phytoextracts of *Sophora* are extensively used in numerous pharmaceutical formulations. Antioxidant films were prepared by mixing phytoextract of *S. japonica* (PSj) with *Artemisia sphaerocephala* gum (Guo et al. 2020). DPPH scavenging activity of the film increased significantly with PSj addition. Antioxidant activity of the edible flowers of *S. viciifolia* was reported (Lin et al. 2019a; Guo et al. 2020). Recently, Kaewdana et al. (2021) found that the ethanolic extract of *S. exigua* root could inhibit the superoxide anions, DPPH radicals, and hydroxyl radicals, with half-maximal inhibitory concentration (IC_{50}) values of 129.78 ± 0.65, 24.63 ± 1.78, and 30.58 ± 1.19 µg mL^{-1}, respectively.

Shandougenine B (**194**) is the first naturally occurring dimeric 2-arylbenzofuran with a novel C-3—C-3″ bond linkage and shandougenine A (**193**) is a unique dimeric 2-arylbenzofuran with a C-3-C5‴ bond linkage. The 2-arylbenzofuran (**194**) had a higher ABTS cation radical scavenging capacity and DPPH free radical than compound **174** (Boozari et al. 2019b).

Data suggested that the inhibition of macrophage NO production by these isoflavanones may, at least in part, be explained by their radical scavenging or reduction activity (Boozari et al. 2019b; Lin et al. 2019a). The prenylated chalcone, kuraridin (**184**) and prenylated flavonol kushenol (**28**), have more potent scavenging/inhibitory activities than the prenylated flavanones, sophoraflavanone G (**19**) and kurarinone (**23**) (Chen et al. 2019a). These prenylated flavonoids, isolated from *S. flavescens*, demonstrated significant inhibitory activities against intracellular ROS levels as well as nuclear factor-kappaB activation by tert-butylhydroperoxide (Farhadi et al. 2019). A study pointed out that flavonols have the high scavenging activity compared to flavanones and this can be related to the presence the C2=C3 double bond and the 3-OH group in the flavonol skeleton. The flavonol kushenol (**28**) presented the highest scavenging activity like that of the positive control, L-ascorbic acid followed by kuraridin (**184**) (Chen et al. 2019a). The flavanones sophoraflavanone G (**19**), leachianone A (**20**), kurarinone (**23**), and kurarinol (**29**) were moderately effective scavengers, with inhibition percentages less than 50 (at 200 µg/mL). Also, sophoraflavanone G (**19**), kurarinone (**23**) exhibited IC_{50} values of 5.26 and 7.73 µg/mL, respectively, in DPPH· scavenging assay (Boozari et al. 2019b; Cho et al. 2020).

2-Propenoic acid, 3-(3,4-dihydroxyphenyl)-octacosyl ester **320**, isolated from *S. mollis* (Royle) Graham Ex Baker, demonstrated significant free-radical scavenging activity using the 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) free-radical assay. The recorded inhibition percentage of DPPH was 95.646 ± 0.003, 94.766 ± 0.014, and 94.516 ± 0.011% at concentrations of 400, 200, and 100 µg mL^{-1}, respectively (Quradha et al. 2021).

Miscellaneous activities

Malaria is a disease caused by *Plasmodium* parasites, which infect humans and female *Anopheles* mosquitoes. The lavandulyl flavanones; sophoraflavanone G (**19**), leachianone A (**20**), and methoxykurarinone (**24**), isolated from the roots of *S. flavescens*, showed moderate antimalarial activities (in vitro) against *P. falciparum* (Li et al. 2020a; Ma et al. 2020b; Kaewdana et al. 2021). Their -half-maximal inhibitory concentration (IC50) values were 2.6, 2.1, and 2.4 µM, respectively. Recently, the aqueous extract of *S. exigua* root at doses of 200, 400, and 600 mg/kg had a stronger antimalarial

activity than the ethanolic extract (Kaewdana et al. 2021). The aqueous extract at 600 mg/kg exhibited 60.46% suppression of parasitemia (Uzor 2020).

The phytoextract of *S. tonkinensis* rhizoma (PSt) exhibited antidiarrheal activity. The extract (0.01–10 mg mL^{-1}) has spasmolytic effect and inhibited the spontaneous contraction of rabbit jejunum in a concentration-dependent manner like verapamil (Li et al. 2019c). The relationship between PSt and L-type calcium channel, concentration–response relationship curves of cumulative calcium chloride were determined. The phytoconstituents of *Sophora* species contained terpenes, sterols, flavonoids, and alkaloids, and these substances are linked to the antidiarrheal activity (Boozari et al. 2019b; Li et al. 2019c). A combination of PSf extract and a compound from *Stevia rebaudiana*, stevioside improved the small intestinal lesion score in piglets, alleviate diarrhea and decrease rotaviral shedding in feces (Boozari et al. 2019b; Wang et al. 2019a).

The lipoidal matters were reported with in vitro cytotoxic activity towards HCT-116 carcinoma cell line (IC_{50}-value of 97.00 and 38.76 µg mL^{-1} for *S. secundiflora* and *S. tomentosa,* respectively) using the MTT assay (Aly et al. 2020a). Palmitic acid **346** is the major saturated fatty acid in both lipoidal matters; it showed anti-inflammatory and selective cytotoxic activity towards the human leukemia cell line MOLT-4. Linolenic **349** bioactive lipophilic compounds in *S. secundiflora* acid in the lipoidal matter decreased the growth of transplanted prostate, colon, and breast cancer cells in vivo. Regarding the in vitro studies, compound **349** was able to inhibit growth and promote apoptosis of transplanted prostate, colon, and breast cancer cells. Linolenic acid **349**-induced apoptosis of colon and breast cancer cells via a mitochondrial-mediated pathway.

The dominant compounds in the unsaponifiable matter of *S. secundiflora* were *α*-amyrin (**230**, 9.73%) and *β*-amyrin acetate (**231**, 55.20%). While *n*-nonacosane (**362**, 43.80%) and 2-methyltriacontane (**364**, 11.94% were the main components in *S. tomentosa*. In the saponifiable fraction, the content of saturated fatty acids identified in *S. tomentosa* (58.37%) was higher than *S. secundiflora* (29.0%). The percentage of unsaturated fatty acids identified in *S. secundiflora* (62.67%) was higher than *S. tomentosa* (34.51%). Methyl linolenate **349**, 36.62%) and methyl palmitate (**346**, 40.02%) are the major compounds in S. secundiflora and S. tomentosa. The dominant compounds in the unsaponifiable matter of *S. tomentosa* were *n*-nonacosane (**362**, 43.80%) and 2-methyltriacontane (**364,** 11.94%). *α*-Amyrin (**230**, 9.73%) and *β*-amyrin acetate (**231**, 55.20%) were the main components in *S. secundiflora* (Aly et al. 2020a).

Phytol (**347**) is a cyclic diterpene and a member of branched-chain unsaturated alcohols with antioxidant activity related to antinociceptive activities (Aly et al. 2020a). *α*- and *β*-Amyrins are pentacyclic triterpenes with anti-inflammatory, antimicrobial, antioxidant, and anticancer properties. Linolenic acid (**349**, C18:3) is a polyunsaturated fatty acid called omega-3 fatty acid relative to its three double bonds (Boozari et al. 2019b; Aly et al. 2020a).

Many isoprenoid flavonoids, with particularly an isoprenyl and a lavandulyl group in backbone structures were isolated from *S. flavescens* and *S. pachycarpa* and *S. japonica* (Boozari et al. 2019a, b; Li et al. 2020a). The anti-ulcer activities of many phytoextracts of *Sophora* species (*e.g. S. subprostrata*, *S. japonica* and *S. interrupta*) were reported due to the presence of phytochemical constituents such as saponins and isoflavonoids (Boozari et al. 2019b; Farhadi et al. 2019; Chen et al. 2020b; Yang et al. 2020b, c). Genistein (**120**) and biochanin A (**130**) showed about 2.5–6.5 folds greater inhibitory effects on arachidonic acid and U46619 induced platelet aggregation. Irisolidone (**132**) was ~22–40 folds stronger inhibitor than acetylsalicylic acid on arachidonic acid and U46619 induced aggregation (Kim and Yun-Choi, 2008; Chen et al. 2020d).

Three isoflavones: genistein (**120**), biochanin A (**130**) and irisolidone (**132**); and four were identified as isoflavone-glycosides: sissotrin (**117**), tectoridin **118**, genistin (**119**), and sophorabioside (**134**) from the stems, fruits and leaves of *S. japonica* (Kim and Yun-Choi 2008; Chen et al. 2020d). The isoflavone-glycoside tectoridin **118** showed inhibitory activity on U46619 and arachidonic acid-induced aggregation (IC_{50} of 123.4 and 25.9 µM, respectively) which had an activity similar to that of genistein (**120**) and biochanin A (**130**), but less than that of irisolidone (**132**) (Kim and Yun-Choi 2008; Chen et al. 2020d).

The extract of *S. alopecuroides* reduced the acute opioid withdrawal symptoms (Kianbakht et al. 2020). It decreased the clinical opiate withdrawal scale score (at days 3 and 8 significantly) compared with the placebo and had good safety and tolerability. The activity may be attributed to its major alkaloids; sophoramine (**243**), sophocarpine (**235**) and matrine (**246**). Through regulating TGF-β/Smad signaling in rats, matrine (**246**) suppressed the pancreatic fibrosis (Liu et al. 2019b). The mechanisms of protective effects of oxymatrine (**249**), on damaged organs and tissues are mainly related to its anti-inflammatory, anti-oxidative stress, anti- or pro-apoptotic, anti-fibrotic, metabolism-regulation, and anti-nociceptive functions (Lan et al. 2020).

Accumulating evidence indicates that sophocarpine (**235**) and oxymatrine (**249**) may protect against myocardial ischemic damage. The protective effect of **235** on the cardiovascular system was reported. This compound ameliorates cardiac hypertrophy through the activation of autophagic responses (Lin et al. 2020).

The total alkaloids extract derived from *S.alopecuroides* L improved depression-like behaviors and depression-related indicators in mice (Zhang et al. 2021a). A recent study indicated that *S. alopecuroides* L.-derived alkaloids improved

Table 19 Summary of findings on the anti-inflammatory and anti-allergy effects of compounds derived from *Sophora* species

Compound	Activity	Action	References
Kushenol (**28**)	Inhibits autophagy and impairs lysosomal positioning	via VCP/p97 inhibition	Kwon et al. (2020)
	Macrophages and oxidative stress in HaCaT cells	In lipopolysaccharide-stimulated RAW264.7 and tert-butyl hydroperoxide, respectively	Cho et al. (2020)
	Skin whitener	Inhibitor of tyrosinase	Boozari et al. (2019a, b), Cho et al. (2020)
Maackiain (**172**)	Potent inflammasome-activating effect - Exerts an immunostimulatory effect by promoting IL-1β production	Promoting IL-1β production via activation of the inflammasome/caspase-1 pathway	Huh et al. (2020)
Kushenol (**28**) and sophoraflavanone B (**48**)	Wound healing		Chen et al. (2019a)
Lonchocarpol A (**56**)	Effect on expression of inflammatory mediators	downregulate PCSK9 mRNA expression in HepG2 cells	Ahn et al. (2019)
Sophoricoside (**134**)	It ameliorates the allergic chronic inflammatory lung disorder (asthma)	Preventing mast cell activation and CD4 + T cell differentiation in ovalbumin-induced mice	Kim and Lee (2021)
Sophoraflavanone M (**101**)	Alleviating inflammatory conditions	Significantly suppressed LPS-elevated inflammatory cytokinesin the serum of endotoxemia mice	Han et al. (2021)
Sophocarpine (**235**)	Colitis	Regulating cytokine balance	Chen et al. (2020b)
	Preventing restenosis after angioplasty in smokers	Inhibits the inflammatory reaction	Yang et al. (2020a)
Oxysophoridine **(242)**	Alleviation of spinal cord injury	Alleviation via anti-inflammatory, anti-oxidative stress and anti-apoptosis effects	Cao et al. (2018)
Matrine (**246**)	Alleviate *Staphylococcus aureus* lipoteichoic acid-induced endometritis	This via suppression of TLR2-mediated NF-κB activation	Jiang et al. (2019b)
	Protection from evoked inflammatory injury	protect PC12 cells via upregulation of miR-9	Jiang et al. (2020a)
	Osteoarthritis	A suppression of the activation of NF-κB and MAPK in human chondrocytes	Fan et al. (2019), Li et al. (2020d)
	Anti-glioma effect	Inhibitory effects on growth of C6 cell lines	Zhang et al. (2020a, 2021a, b, c)
Oxymatrine (**249**)	Prevents synovial inflammation and migration	This via blocking activation in rheumatoid fibroblast-like synoviocytes	Zhou et al. (2016), Liang et al. (2018)
	Colitis	interfering with the IκB-α protein expression and inhibiting NF-κB activity in colitis cells	Chen et al. (2020b)
	Suppression of renal inflammation	Modification of disordered plasma lipids and recovery of renal function	Aly et al. (2017), Wang et al. (2019a)
Aloperine (**284**)	Protection against ischemia reperfusion-induced acute renal injury	Reduce tubular apoptosis and attenuated inflammatory infiltration	Boozari et al. (2019a), Wang et al. (2019a)
	NFκB transcriptional activity	Selectively repressed IFN-γ and IL-1β expression and regulating PI3K/Akt/mTOR signaling	Yin et al. (2018), Ye et al. (2020)
	Edema in hind paw	Suppres the effect on the swelling of a rat's hind paw Increases the permeability of capillaries	Wang et al. (2020b)

Table 19 (continued)

Compound	Activity	Action	References
Sophocarpine (**235**), anagyrine (**273**), 14β-hydroxymatrine (**301**), and 7β-sophoramine (**302**)	Showed more potent in vitro anti-inflammatory activities	could contribute to the chondro-protective effect	He et al. (2019)
Sophocarpine (**235**), 5α-hydroxymatrine = (−)-anagyrine (**273**), 5α,14β-dihydroxymatrine (**300**)	Exhibited better in vivo anti-inflammatory activities	Suppression of the activation of NF-κB and MAPK	He et al. (2019)
Sophalode K (**318**)	Anti-inflammatory properties	Suppressed the protein levels of iNOS and COX-2	Li et al. (2021a)

depression in mice through modulating gut microbiota (Zhang et al. 2021a). The results of HPLC–MS (positive ionization) for total alkaloids from the seeds of *S. alopecuroides* confirmed the presence of six main alkaloids. They were identified as, sophocarpine **235**, sophoridine (**240**), oxysophoridine **242**, matrine (**246**), oxymatrine (**249**), and lupanine **253**. The role of the hippocampal PI3K/Akt/mTOR signaling of matrine **246** was reported (Wu et al. 2019a, b). Matrine **246** exerts antidepressant-like effects on mice. It ameliorates anxiety and depression-like behaviour by targeting hyperammonemia-induced neuroinflammation and oxidative stress in CCl_4 model of liver injury (Li et al. 2019a; Zhang et al. 2020a).

Many therapeutics isolated from PSf are considered as alternative anti-caries agents such as quercetin (**1**), kaempferol (**2**) and sophoraflavanone G (**19**) due to their inhibitory activities against *Streptococcus mutans* biofilms and antibacterial properties against several strains of mutans *streptococci* (Farhadi et al. 2019; Wang et al. 2019a). The application of deep eutectic solvent on the extraction of rutin from *S. japonica* bud was reported (Peng et al. 2018). Another styudy ivestigatedusing a combination of near-infrared spectroscopy and chemometrics as a rapid, quantitative analysis of the rutin (**3**) proportion in differently processed products of *S. japonica* L (Chen et al. 2018d).

Phytoextracts: a structure–activity relationship

The structure elucidation and characterization of bioactive compounds supposed that the functionality is based on structural chemistry (Boozari et al. 2019b). Previous structural modification and structure–activity relationship (SAR) studies revealed that presence of lavandulyl or isoprenyl substitution in C-8 position of flavanone structure increased the cytotoxic and antibacterial effect (Farhadi et al. 2019). Prenylated flavonoids with hydroxyl (OH) groups at the C3 and C6 and prenyl moieties at C8 site can inhibit human carboxylesterase 2 that promote the metabolic activation of ester drugs and lipid metabolism (Mukai, 2018). Also, the relationship between their structure and antibacterial activity indicates the importance of OH group on the B ring. This group can control hydrophilicity (Farhadi et al. 2019). While the presence of prenyl or lavandulyl, as an aliphatic group, could contribute to the hydrophobicity at the A ring (Boozari et al. 2019b).

Most prenylated flavonoids with lavandulyl or isoprenyl moieties at C8 displayed potent antibacterial activity. However, the position of methoxyl groups in the skeletons of compounds **19**, **20** and **24** contribute to the antimalarial activity as they did not show selective toxicity (Li et al. 2020a; Ma et al. 2020b). The isoflavone skeleton has been deserved to investigate antileishmanial and trypanocidal compounds (Boozari et al. 2019b).

Sophoraflavanone G (**19**), kurarinone (**23**), and kurarinol (**29**), are other flavanones from the phytoextract of *S. flavescens* roots have a strong tyrosinase inhibitory activity. The results of molecular modeling study have suggested that the terminal hydroxy function within the lavandulyl group was important for optimal binding. This group within kurarinol (**29**) is instrumental in the interaction with the enzyme (Farhadi et al. 2019). The presence of lavandulyl groups also attributed to the trypanocidal activity of prenylated flavonoids. Alopecurone G (**18**), sophoraflavanone G (**19**), leachianone A (**20**), kurarinone (**23**), and methoxykurarinone (**24**) showed a stronger activity compared to other prenylated flavonoids (Boozari et al. 2019b; Chang et al. 2019a). The presence of lavandulyl groups also attributed to the antibacterial activity (Farhadi et al. 2019). The additional active group of 8-lavandulyl facilitated the interaction between compound **19** (sophoraflavanone G) and bacterial cellular membranes, resulting in an enhancement of the membrane effect. Compound **19** equally reduced the fluidity of outer and inner layers of membranes compared with naringenin (worked on outer layers more than inner ones) (Farhadi et al. 2019). The isogeranyl at C-8 and OH at 3, 2′, and 4′ on the A and B rings of prenylated flavonoid improved the effects of ampicillin or oxacillin against MRSA infection (Farhadi et al. 2019).

Sophoraflavanone G (**19**) and sophoraflavanone I (**67**) (stilbene residue on B ring of flavonoid structure) showed

a cytotoxic activity against tumor cells (HSC-2 and HSG). Also, alopecurones (stilbene residue on A ring of flavonoid structure) exhibited an inhibitory activity against multi-drug resistance associated protein 1 (Boozari et al. 2019b). The lavandulyl flavanones (**19**) and (**24**) suppressed glutamate-induced neurotoxicity and ROS generation in HT22 cells via the induction of the expression of heme oxygenase (HO)-1 and increased HO activity dose- and time-dependently. Despite structural similarities, other lavandulyl flavanones (**20**) and (**23**) did not stimulate HO-1 expression, ROS scavenging, or cytoprotection and thus they did not show protection (Chang et al. 2019a).

The flavonostilbenes alopecurone A (**57**), B (**65**), and D (**59**) are considered as therapeutic reversal agents against multidrug resistance-associated protein 1 (MDRP1). They had an inhibitory activity and dramatically increased the accumulation of 6-carboxyfluorescein diacetate and doxorubicin in MDRP1-transfected U-2 OS cells (Boozari et al. 2019a,b; Yang et al. 2019; Wang et al. 2020b). The beneficial protective effects of HO-1 in inflammation were mediated not only via enzymatic degradation of pro-inflammatory free heme but also via production of the anti-inflammatory compound's bilirubin and carbon monoxide (Wang et al. 2018a).

A decoction of a Chinese herbal formula has been reported as a botanical remedy for treatment of skin inflammation (Chang et al. 2018). A resveratrol glucoside is considered as one of the core anti-C–C motif chemokine ligand 17 (CCL17) bioactive ingredients in a Chinese formula, comprises the rootstock of *S. flavescens* (Chang et al. 2018).

The prenyl/or lavandulyl group at the C-8 position, along with a 3,4′-dihydroxyl group, could play a predominant role in antidiabetic complications and anti-Alzheimer activities (Boozari et al. 2019b; Chang et al. 2019a). A previous review analyzed the SAR of prenylated flavonoid and clarified that the substitution of the flavonoid ring system with prenylated groups increased the lipophilicity and confers upon the molecule a strong affinity to biological membranes (Boozari et al. 2019b).

A study suggested that the β-D-glucose substitute at C-3, in the structure of flavonoids isolated from *S. davidii*, was necessary for the anti- Tobacco Mosaic Virus (TMV) activity (Yang et al. 2019). The presence of 1,3-benzodioxole ring could lead to increasing the protective effects against TMV replication.

Recently, the effect of substitutions at isoflavone derivatives on the binding affinity against the human ACE2 (hACE2), targeting COVID-19, was investigated (Alesawy et al. 2021). It was found that the substitutions at 5-position with hydroxyl (genistein **120**) and methoxy group (glycitein) increased the binding of isoflavones against hACE2, with an increased affinity of hydroxyl derivative (Alesawy et al. 2021). Isoflavonoids can strongly bind the hACE-2 and viral main protease M^{pro} with great binding modes.

Studies show that prenylation decreases the flavonoids transportation from intestinal epithelia and reduces their absorption (Boozari et al. 2019b; Chang et al. 2019a). Despite the lower absorption of prenylated flavonoids compared with flavonoids, higher accumulation was found in the liver and kidney and exerted strong biological activity.

Previous structural modification and structure–activity relationship (SAR) studies revealed that N12 modifications on **284** scaffolds could enhance the anti-HIV activity (Lv et al. 2020). N12 substitutions improved their EC_{50}'s 1.5- to 2.5-fold compared to that of unmodified **284**. The favorable modifications for the increased anti-HIV-1 activity include a spacer of 4 carbons in length attached to N12 with the other end linked to a para-substituted phenyl group through an amide bond.

A previous study compared the SAR of flavesine J (**290**) with flavesine G (**287**) revealed that the introduction of a pyridine ring to a carboxylic acid group at C-15 might enhance the antiviral activity against HBV. Also, the structure of alopecurine A (**285**, 14.1%) and alopecurine B (**286**, 46.0%) and the HBsAg inhibitory activity relationship implied that the cleavage of the C-5–C-6 bond could produce a positive effect on antiviral activity against HBV. Whereas the cleavage of the C6–C-7 bond seems to be unfavorable for this activity (Zhang et al. 2018b, c). SAR with respect to the delta-lactam moiety of the matrine-type alkaloids and nematicidal activity was examined (Zhang et al. 2020a).

The key bioactive constituents of many *Sophora* species that exhibited sedative, depressant, analgesic, hypothermic, anti-tumor, and antipyretic activities, were the quinolizidine-type alkaloids (Aly et al. 2019, 2020a, b, c, 2021; Wang et al. 2019a; Cao and He 2020; Gao et al. 2020). Quinolizidine alkaloids (QA) were chemically divided into matrine-, sparteine-, cytisine-, and aloperine- types alkaloids (Li et al. 2021a).

QA possess extensive pharmacological effects on immune system as well as the cardiovascular and the nervous systems (Ren et al. 2019). A chloro-containing matrine-type alkaloid alopecine D (**298**) was isolated from the seeds of *S. alopecuroides.* This compound, of unusual matrine-type alkaloids featuring with additional di -chloromethyl attached on the D ring displayed immunosuppressive activity (Wang et al. 2020b, c). The compound exhibitedinhibitory effects on LPS-induced B cells or the proliferation of ConA-induced T lymphocytes with IC_{50}-value of 3.74 or 3.98 μM, respectively.

The toxicological action of sophocarpine (**235**) and matrine (**246**) is related to the regulation of glutamate and γ-aminobutyric acid systems. It has certain similarities to that of avermectin, a positive control (Ma et al. 2020b). The lupin alkaloid (**246**) and its unsaturated derivative (**235**) had

a strong nematicidal activity. Another unsaturated derivative, sophoramine (**243**), had such activity, but it was less than the activity of **235**. The degree of unsaturation in the delta-lactam ring of these lupin alkaloids was necessary to enhibit pinewood nematodes (Ismail et al. 2020; Ma et al. 2020b; Zhang et al. 2020a). The crude fraction containing cytisine-type alkaloids; N-methyl cytosine (**268**) and anagyrine (**273**) was more active against the nematodes than the lupin-type alkaloids; sophocarpine (**235**), matrine (**246**) (Wang et al. 2019a; Chen et al. 2020a; Huang and Xu 2020a; Ma et al. 2020b).

Sophora species and pandemic coronavirus disease

Coronavirus disease 2019 (COVID-19) is an illness caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Zhang et al. 2020a, b, c; Majnooni et al. 2021). The ongoing COVID-19 pandemic has created an alarming situation due to its high morbidity and mortality rates, economic losses, and the threat to global health security. When the paper was submitted, about 220 countries and territories around the world have reported more than 188,616,093 million confirmed cases of SARS-CoV-2, including more than 4,065,804 deaths (https://www.worldometers.info/coronavirus/#countries). In Egypt, the total cases were 283,320 cases and 16,412 deaths. Infections caused by viruses pose a significant challenge due to their wide spectrum of clinical presentations (Zhou et al. 2020). The critical cases of coronaviruses are linked to aberrant immune response, severe acute respiratory infection, and thrombosis. In vitro antiviral assays of extracts of some medicinal plants revealed the potential of using *S. subprostrata* as an anti-SARS-CoV2 candidate for further clinical studies (Fuzimoto and Isidoro 2020; Ghoran et al. 2021).

Most of the active natural compounds with inhibitory activity towards various types of coronaviruses could inhibit SARS-CoV-2, are belongs to polyphenols and flavonoids (*e.g.* quercetin **1** and luteolin **4**) (Orhan et al. 2020). Quercetin (**1**) was tested for its SARS-CoV-3CL^{pro} inhibitory effect. The compound has reportedly inhibited cleavage activity of the 3CL^{pro} in a cell-based assay in a dose-dependent manner (Majnooni et al. 2021).

Other medicinal plants that produce various phenolic compounds and sterols are distinguished for their beneficial effects against human coronavirus (HCoV)-229E (Alesawy et al. 2021; Ghoran et al. 2021).

The isoflavonoids are an important polyphenolic subclass of flavonoids with a skeleton based on a 3-phenylchroman structure and their antiviral activity was proved in several scientific reports (Boozari et al. 2019b; Farhadi et al. 2019). Some isoflavonoids (e.g. isoflavonoid genistein **120)** could inhibit SARS-CoV-2 which target the human ACE2 (hACE2) (Alesawy et al. 2021). This compound **(120)** is the major isoflavonoid of soybean seeds, and it could inhibit herpes simplex virus HSV-2 (333 strain), HSV-1 (29R strain), and KOS strains) replications with IC_{50}-values of 14.12, 7.76 and 14.02, respectively (Alesawy et al. 2021).

Phenols and polyphenols (flavonoids) attack viral proteins present in the viral membrane or inside the virus particle. Phenolics are active against free viral particles but not—or to a lesser degree—after a virus have entered a host cell. Another group of PSMs is directed against DNA or RNA. These are DNA intercalators such as emetine and other isoquinoline alkaloids, and quinoline alkaloids. These alkaloids can inhibit viral development and viral replication in cells, as shown for SARS-CoV and other viruses.

A coumarin isopimpinellin **215**; from the leaf ethanol extract of *Angelica keiskei* (Apiaceae), targeting the SARS-CoV 3CL^{pro} and PL^{pro} by cell-based and cell-free cleavage assays possessed a deficient inhibition against SARS-CoV 3CL^{pro} with 10% at 200 µM. While the isolated isobavachalcone (**185**) ($IC_{50} = 39.4 \pm 5.2$ µM for cell-free, $IC_{50} = 11.9 \pm 2.8$ µM for cell-based assay, selectivity index SI = 1.3) displayed competitive inhibition towards SARS-CoV 3CL^{pro} with a dose-dependent manner. The same alkylated chalcone (**185**) isolated from the extract of the seed ethanol extract of *Psoralea corylifolia* L. (Fabaceae) exhibited a high inhibitory effect ($IC_{50} = 15$ µg mL^{-1}) against SARS-CoV (papain-like) PL^{pro} (Orhan et al. 2020).

The pterocarpan derivative, maackiain (**172**) was isolated from the seeds of *S. alopecuroides* (Tsai et al. 2020; Rong et al. 2020). Concerning the activity of different pterocarpan derivatives; it was noted that the compound which contained an additional tetrahydrofuran ring attached to the chromene ring showed a better binding affinity inside the human ACE2 (hACE2) than the compounds which contained free OH groups at the chromene ring (Alesawy et al. 2021).

Generally, different tested isoflavones and pterocarpans as COVID-19 agents in a screening study decreased the affinity against hACE-2 in descending order of isoflavone derivatives > pterocarpan derivatives (Alesawy et al. 2021; Ghoran et al. 2021).

Thus, to find natural compounds with inhibitory activity against SARS-CoV, many researchers evaluated several natural compounds, including flavonoids, sterols, and fatty acids, against the activity of SARS helicase. They used colorimetry-based ATP hydrolysis assay or a fluorescence resonance energy transfer-based double-strand DNA unwinding assay to evaluate the inhibitory activity (Orhan and Deniz 2020; Ghoran et al. 2021; Remali and Aizat, 2021).

Alkaloids are a group of naturally occurring chemical compounds that contain mostly basic nitrogen atoms. Various studies showed that quinolizidine alkaloid matrine **246** exhibited antiviral activities against coxsackievirus B3 in Vero cells and influenza H3N2 virus in MDCK cells (Liu

et al. 2018b; Ma et al. 2018, 2020a, b; Ren et al. 2019; Wang et al. 2019a; Sun et al. 2020).

The mechanism of anti-coronavirus effect of *S. flavescens* Aiton could be illustrated from multiple pathways, such as matrine **246** alkaloids and type I interferon, ERK signal pathway, NF-κB signal pathway and PI3K/Akt signal pathway (Zou et al. 2019; Li and Yu 2020). It provided a reference for clinical treatment of coronavirus infection pneumonia and research and development of related drugs of *S. flavescens*. The extracts of this species inhibited coronavirus replication (in vitro) and reduced the intracellular viral RNA concentration (Remali and Aizat 2021). The profiles of *S. flavescens* were analyzed to obtain biomarkers detected in different root tissues using combining metabolomes and transcriptomes (Wei et al. 2021). The expression levels of different transcripts (AO-2 & 6, LYS-A1 & A2, PMT-1, 17, 34, and 35) were highly and positively correlated with alkaloids (*e.g.,* sophoridine (**240**), oxymatrine (**249**), and matrine (**246**) content (Wei et al. 2021).

Another extract of *S. subprostrata* Chun could inhibit RdRp activity through decreasing the protein expression in murine coronavirus (Remali and Aizat 2021). The methanol extract of *S. subprostrata* radix decreased production, the intracellular viral RNA and protein expression of some coronaviruses-single-stranded, positive-strand RNA virus with a helical nucleocapsids such as mouse hepatitis virus and porcine epidemic diarrhea virus (Sun et al. 2018; Chen et al. 2020d; Remali and Aizat 2021). Of note, *S. subprostrata* radix constituents could contribute to the race for anti-COVID-19 chemotherapeutic discovery (Fuzimoto and Isidoro 2020; Ghoran et al. 2021). This herb *Sophora* radix showed inhibition effects against mouse hepatitis virus (MHV)-59/CoV (EC_{50} = 0.8 μg mL^{-1}) than ribavirin (EC_{50} = 17.5 μg mL^{-1}).

Recent animal and clinical studies revealed a therapeutic potential of quinolizidine alkaloid matrine **246** (from *S. flavescens* Radix) on COVID-19 patients (Ren et al. 2019; Wang et al. 2019a; Sun et al. 2020). The alkaloid **246** reduced IL-16, IL-10, and TNF-α levels and the viral load in lung tissues. Consequently, **246** can significantly shorten the time to viral clearance in COVID-19 patients, leading to earlier negative SARS-CoV-2 test. Concomitantly, *S. flavescens* Radix extract can moderately inhibit anti-SARS-CoV1 3CL protease (Luo et al. 2009).

The therapeutic effect of sodium chloride salt of **246** in a mouse pneumonia model infected with HCoV-229E (Choudhry et al. 2020; Jin et al. 2020). The intraperitoneal injection of alkaloid salt significantly decreased the pathological damage to the lung tissue and reduced the lung index. The percentage of T cells of $CD4^+$ and $CD8^+$, the number of B cells in peripheral blood, the production of TNF-α, IFN-γ, IL-6, IL-10, and the viral load in the lung was significantly low compared to those in the controls. Therefore, alkaloid salts have therapeutic effect on HCoV-229E-infected mice via a mechanism related to the regulation of immune function (Choudhry et al. 2020; Sun et al. 2020).

Network pharmacology and molecular docking study simulation demonstrated that **246** could interact with the three key target proteins Mpro, ACE2, and RdRp during the SARS-CoV-2 infection (Peng et al. 2020a).

Another quinolizidine alkaloid oxysophoridine (**242**) inhibited the viral replication in Vero-E6 cells at noncytotoxic concentrations (Batalha et al. 2021). In the last decades, the applications of gemcitabine as a potent antiviral and chemotherapy agent attracted growing attention. Gemcitabine exhibited in vitro activity against SARS-CoV-2, with EC_{50} = values of 1.24 μM (Zhang et al. 2020a, b, c; Batalha et al. 2021). A combination of gemcitabine with **242** had an antiviral effect against SARS-CoV-2 (Zhang et al. 2020a, b, c).

Oxysophoridine **242** exhibited a dose-dependent inhibition of 2019-CoV replication in infected cells similar to chloroquine, the reported reference drug (Zhang et al. 2020a, b, c). The compound **242** may have a broad-spectrum antiviral activity against RNA viruses. The EC_{50} value of this compound was 0.18 μM compared with 1.36 μM for chloroquine (Zhang et al. 2020a, b, c). The 50% cytotoxic concentration (CC_{50}) value was > 40 μM. The selectivity index: SI (CC_{50}/EC_{50}), in Vero cells was higher than 222 compared with just above 30 for chloroquine (the positive control). Further studies are needed to investigate the antiviral mechanism against SARS-CoV-2, toxicological evaluation and the safety profile of compound **242**. A dose-dependent inhibition of **242** on SARS-CoV-2 infectivity in Huh-7 cells was reported (Fielding et al. 2020; Zhang et al. 2020a, b, c).

Discussion and future perspectives

The present review summarizes the research progress regarding *Sophora* species, with a particular focus on the traditional uses, the phytochemical and biological characteristics. The trend in drug discovery aimed to promote the utilization of natural and traditional resources for contemporary health care, including food/diet therapy (Tsai et al. 2020). *Sophora* has been used for a long time in different standard medicine formulas as an alternative traditional medicine in many countries, particularly in China and South Korea. More than 85% of Chinese medical material originates from plants (Yao et al. 2021).

Pharmacological studies on crude extracts and pure metabolites provided details on its traditional uses, as *Sophora* has been effectively used traditionally for treating hematochezia, asthma, allergy, sores, inflammation, gastrointestinal hemorrhage, dysentery, clear heat, cool the blood

and reduce swelling, soothing the sore throat, and cough (Boozari et al. 2019b; Li et al. 2021b).

The presented data stated that all the reported phytochemical and pharmacological studies focused mainly on some species such as *S. flavescens* and *S. japonica* (Fig. 1); however, the majority of *Sophora* species still need further investigations. The relative percentage of all published chemical and biological reports regarding *Sophora* species is shown in Fig. 1.

Additionally, the state of the art on *Sophora* chemistry provides considerable opportunities for future discoveries. Approximately 370 chemical constituents have been isolated from different *Sophora* species (Fig. 2). The distribution of the secondary metabolites among *Sophora* species is illustrated in Fig. 2. These metabolites belong to different classes, including alkaloids, flavonols and flavones, isoflavonoids**,** pterocarpans, stilbene oligomers, phenolic acids, and other phenolic compounds.

This review sheds light on the promising chemical compounds extracted from *Sophora* and their bioactivities. This could make these chemical compounds suitable candidates for further development through clinical trials. There are still scientific gaps needs to be filled regarding studying chemical compositions of different species and their therapeutic effects.

First, Alkaloids are unique to *Sophora* and showed valuable pharmacological activities. The total alkaloids of *S. alopecuroides* TASa and matrine **246** inhibited auto-inducer 2 in the biofilms of *Staphylococcus epidermidis*. Also, this TASa ameliorated murine colitis by regulating bile acid metabolism and gut microbiota and had a protective effect on colitis, associated with downstream pro-inflammatory mediators and inhibition of nuclear transcription factor κB (NF-κB) activation (Halim et al. 2019; Izdebska et al. 2019; Chen et al. 2020b). Therefore, future studies are required for precise isolation and identification of each alkaloid structure, other than the major compound **246**, using advanced characterization techniques. Also, the antimicrobial, cytotoxic, antioxidant and enzyme inhibition potentials of the methanol extract of *S.alopecuroides* seeds need to be investigated for the identification and isolation of bioactive compounds. In future studies, we recommend further in vivo toxicity assays and clinical efficacies to further evaluate different biomedical properties of the bioactive compounds (Zahra et al. 2021).

Second, prenylated isoflavonoids and matrine **246**-based alkaloids in addition to lavandulyl flavanones and phenolic acids were mainly isolated from the root and rhizome parts of *Sophora* species. However, screening other parts may provide more chances for finding new bioactive substances, such as matrine-acetophenone alkaloid **281**. This alkaloid with an unusual skeleton is mainly isolated from the seeds and roots of *Sophora* organs. While the first example of sparteine-indolizine (**282**) and the epimeric normatrine-julolidine alkaloids with uncommon skeletons (**283a** and **283b**) were isolated from the roots of *S. flavescens* and *S. alopecuroides*, respectively.

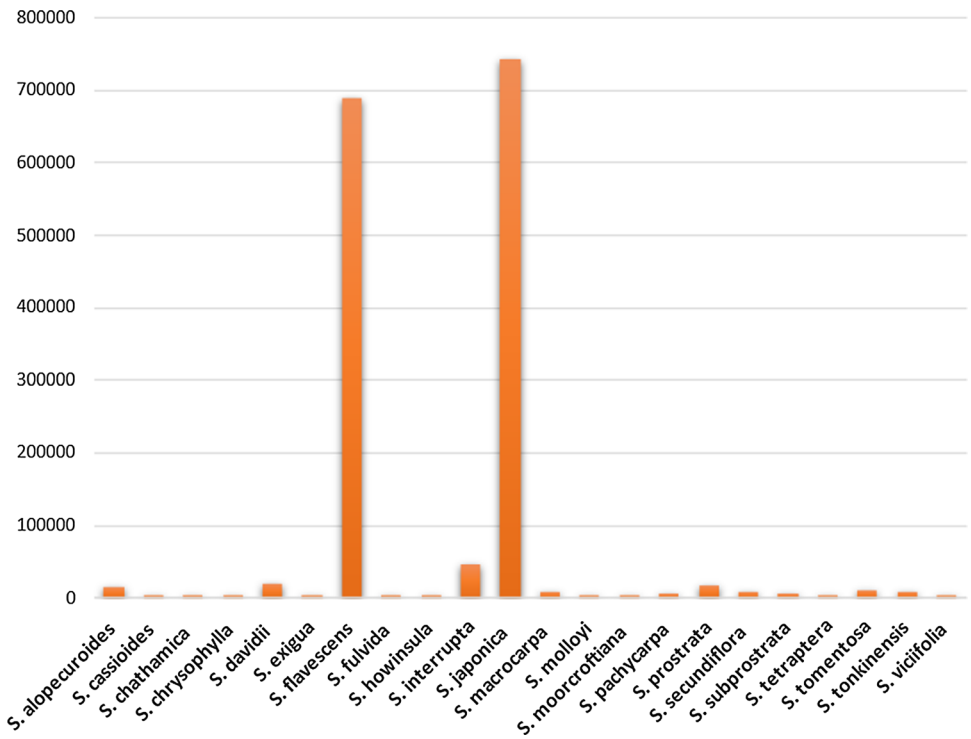


Fig. 1 The relative percentage of all published chemical and biological reports regarding *Sophora* species

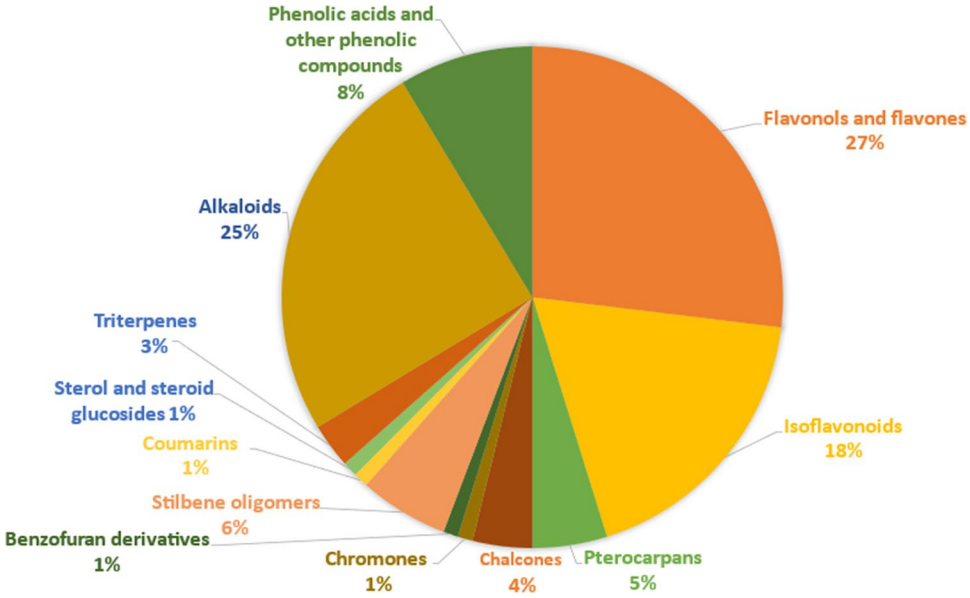


Fig. 2 Approximate distribution of the secondary metabolites among *Sophora* species

The class of isoflavonoids could prevent and cure some diseases. The various therapeutic effects of prenylated isoflavonoids were described in other reviews primarily through several biochemical, cellular, and molecular mechanisms (Ahn et al. 2019). However, more standardization and documentation are needed for the isolation and identification of the prenylated isoflavonoids to validate their health benefit claims. Moreover, Prenylated isoflavonoids exhibited various pharmacological properties, including anticancer, anti-inflammatory, and antioxidant activities (Boozari et al. 2019b; Cho et al. 2020). Further studies could contribute to a new era of prenylated isoflavonoids (isolated from genus *Sophora*)-based medicinal and nutraceutical agents for the treatment of oxidative stress mediated diseases.

Third, in the last two decades, prenylated coumarins displayed promising and effective pharmacological properties, including antimicrobial, anti-inflammatory, and antioxidant activities (Lin et al. 2014; Hassanein et al. 2020). However, more research is needed to isolate and identify the prenylated coumarins from other *Sophora* species other than *S. interrupta* (the species characterized by the presence of di-*C*-prenylated coumarin **214)** (Rammohan et al. 2015).

Fourth, the studies on oligostilbenes, pterocarpans and triterpenes are scarce when compared with the studies conducted on the isoflavonoids, flavonols, flavones and alkaloids. While the investigation of benzofuran derivatives, steroids, phenolic acids and chalcones compounds is still in the initial stage. Thus, more bioactive components could be identified using bioactivity guided isolation strategies.

Fifth, Fig. 3 illustrates the relative percentage of the secondary metabolites isolated from each *Sophora* species under investigation.

Figure 4 illustrates the type and the relative percentage of each chemical class isolated from *Sophora* species as a guide for further in-depth phytochemical scanning. In the current review, we discussed the structure–activity relationships SAR (Huang and Xu 2020a; Li et al. 2020d).

These results indicated that *S. flavescens* and *S. alopecuroides* are the main biologically explored species ((Boozari et al. 2019b; Wang et al. 2020b), while other species such as; *S. mollis*, *S. tomentosa*, *S. interrupta*, and *S. moorcroftiana* are insufficiently chemically studied. Therefore, more studies are needed for better understanding their chemical structures and properties to explain their biological activities.

Furthermore, there are still several gaps in our understanding of the applications of different *Sophora* species, despite many performed pharmacological studies on their medicinal importance. Although a large dose compound *S. flavescens* Ait injection is safe and effective to treat the advanced malignant tumors (recommended dose of 20 mL/day), some in vitro and in vivo studies were conducted at high doses for a clinical study (Ao et al. 2019; Kianbakht et al. 2020). For example, doses of *Sophora* extracts that were applied to evaluate antipruritic, anti-inflammatory effects (administrated personally at 200 mg kg^{-1} of extract in mice) were too high for the application in clinical studies (Aly et al. 2019; Yoo et al. 2019). The methanol extracts of *S. flavescens* significantly inhibited a serotonin-induced itch-related response (scratching), a mouse model of atopic dermatitis. The plant and its constituents affected acute and chronic pruritus and could be considered as new antipruritic agents.

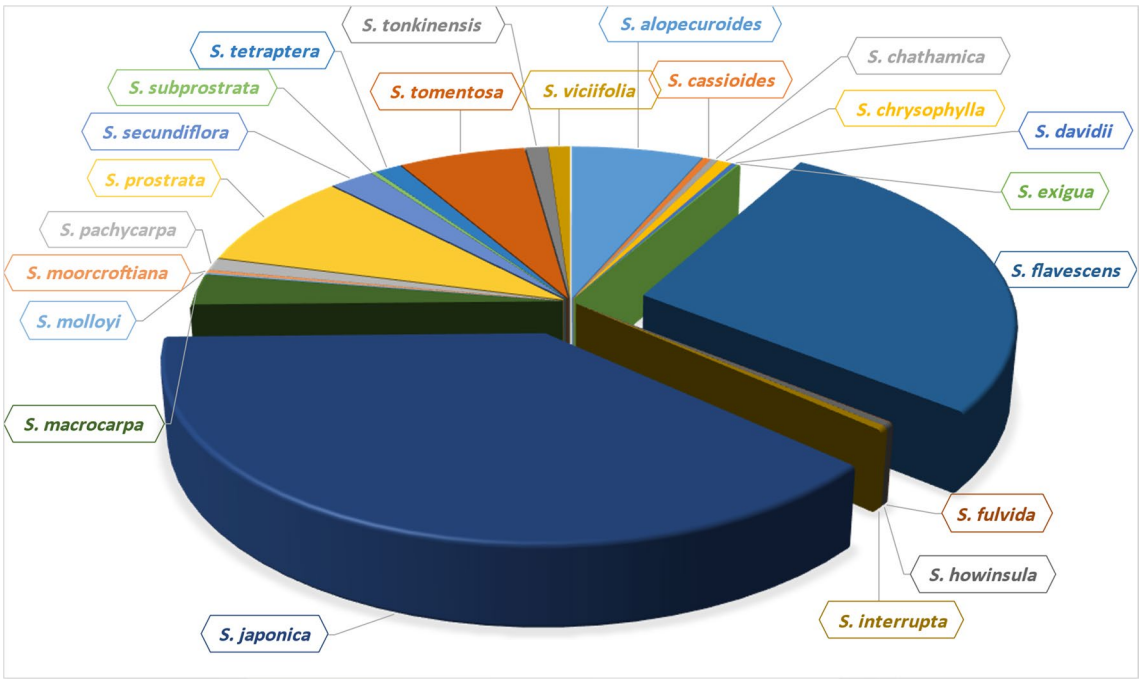


Fig. 3 The relative percentage of major secondary metabolites isolated from each *Sophora* species

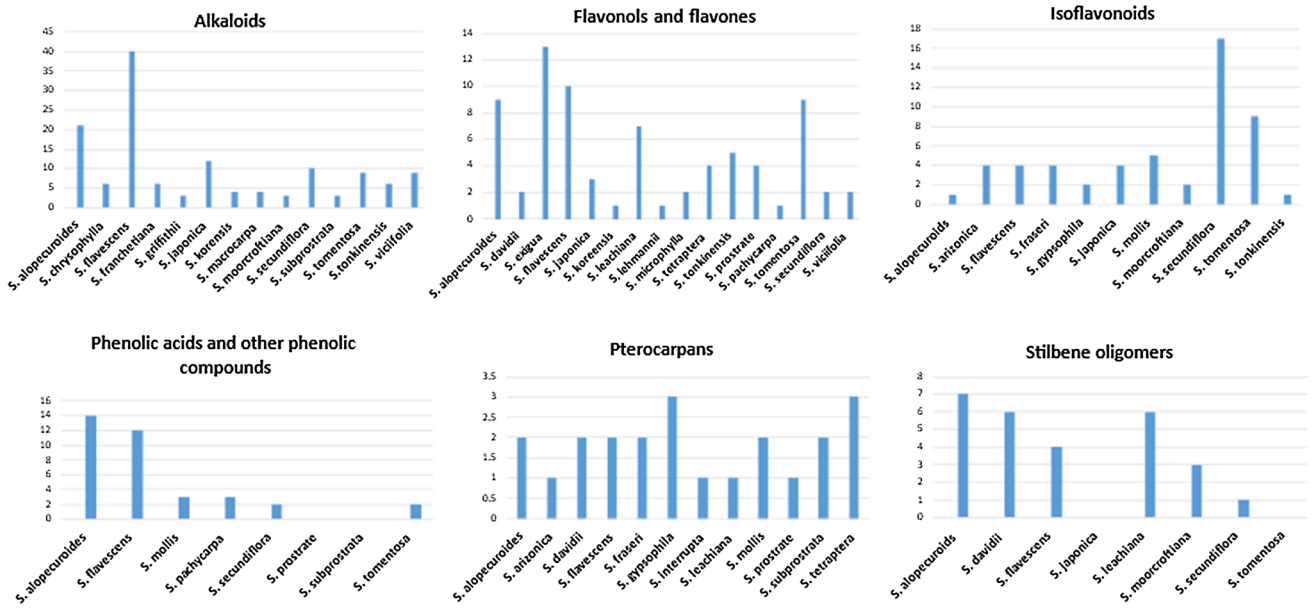


Fig. 4 The relative percentage of each chemical class among different *Sophora* species

The different pharmacological activities performed on *Sophora* species are illustrated in Fig. 5. The collected data indicated extensive pharmacological studies of some species *e.g. S.alopecuroides,* S. *flavescens* and *S. tomentosa*, while other species such as *S. chrysophylla*, *S. exigua* and *S. viciifolia* remain insufficiently studied. Other species *e.g. S. franchetiana S. griffithii*, *S. korensis* and *S. macrocarpa,* were pharmacologically not reported till now.

Sixth, many species of *Sophora* were tested as anti- herpesviruses (Zhou et al. 2010; Hassan, 2020). Herpesviruses are one of the most important viruses that infect humans and animals. The correlation between herpesviruses and coronaviruses is limited to the induced complications following the

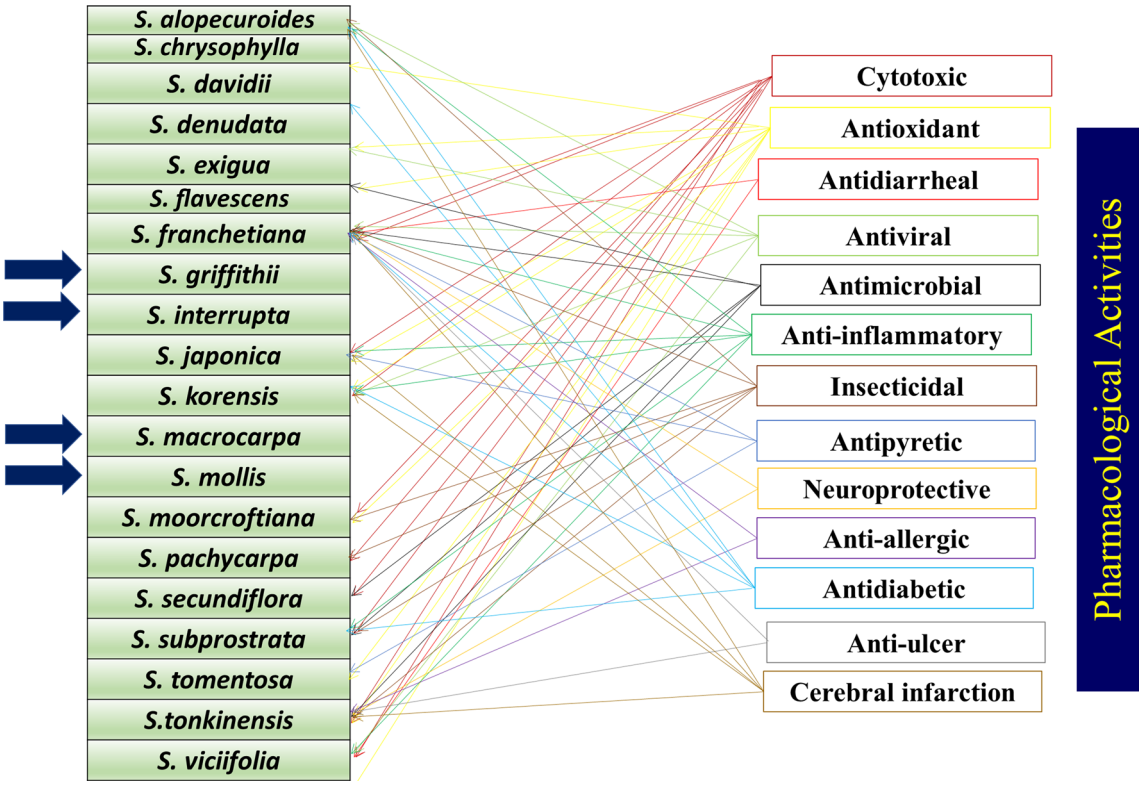


Fig. 5 The pharmacological activities of different *Sophora* species

infections (Hassan 2020). An attention to some natural anti-herpesvirus alkaloid compounds, which have recently been proven to have excellent inhibitory efficacy against SARS-CoV-2 replication, was drawn by Hassan (2020). This was an attempt to explore various treatment options to combat COVID-19 based on available drugs with antiviral properties. Total alkaloids extracted from *S. alopecuroides* (TASa) were useful in the treatment of oral herpes catarrhalis, dental ulcer and herpes zoster (Zhou et al. 2010). To obtain the best performance, several factors affecting the encapsulation efficiency of TASa binary ethosome were investigated. A transmembrane pH gradient active loading method to prepare TASa binary ethosomes was developed (Zhou et al. 2010). The external preparation is limited by its low percutaneous penetration and bitter taste.

A combination of gemcitabine with oxysophoridine **242** had an additive antiviral effect against SARS-CoV-2 (Zhang et al. 2020a, b, c). Gemcitabine has been reported to block infection of diverse DNA and RNA viruses. Its activity against SARS-CoV-2 has been recently reported in Vero E6 and Huh7 cells. Gemcitabine as an antiviral drug, is not yet extensively investigated, particularly in terms of SAR or combination with other alkaloids (Zhang et al. 2020a, b, c). Overall, little is known about the antiviral mode of action of oxysophoridine **242**; thus, future studies are needed to determine how this alkaloid interferes with coronaviral replication (Fielding et al. 2020).

A plant gel containing *S. alopecuroides* extracts (as an antiviral agent) was prepared. A patent has described the use of this gel as the external preparation for treating herpes zoster (Google patents CN102100734A). The gel can relieve the pain and has less side effects.

The gut microbes are closely related to depression as recently suggested (Zhang et al. 2021a). The depression in both patients and model animals significantly altered the gut microbiota. A recent study indicated that *S. alopecuroides* L.-derived alkaloids improved depression in mice through modulating gut microbiota (Zhang et al. 2021a). Therefore, further studies are needed to illustrate the activity of other *Sophora* species.

Seventh, a study was conducted to develop and evaluate chitosan/gelatin-based *S. gibbosa* extract-loaded microemulsion as a wound dressing (Shalaby et al. 2021). The dressing displayed superior wound repair compared to the control in terms of histological examination, proliferating cell nuclear antigen determination and alpha-smooth muscle actin (Shalaby et al. 2021). Thus, this natural product-loaded microemulsion-impregnated gelatin/chitosan could be a potential candidate for wound healing preparations.

Eighth, the potential economic use of *Sophora* species for the enhance crop yield and quality was suggested. In an

effort to find growth-promoting strains that could be applied to enhance crop yield and quality, the fungal endophytes isolated from *S. flavescens* is gaining attention (Turbat et al. 2020). The symbiotic effects of endophytic fungi in association with their host plant can improve plant growth and reduce the adverse effects of both biotic and abiotic stresses. The plant growth-promoting activities of endophytic fungi isolated from various parts of *S. flavescens* have been revealed.

Nineth, a study demonstrated the use of *S. flavescens* in antimicrobial nanoparticles coated onto carbon fiber (CF) filters (Sim et al. 2014). Recent studies are now focusing on nanosized materials and their antimicrobial activities; this could facilitate the preparation of CF with reduced biocontamination (Haroun et al. 2017; Rizk et al. 2018). This may be a scientific basis for controlling both gaseous and bioaerosol pollutants using antimicrobial CF filters coated with *S. flavescens* nanoparticles. The efficiency of *Staphylococcus epidermidis* inactivation increased with the concentration of *S. flavescens* nanoparticles in the activated CF filter coating. Reported information focused on the use of other species nanoparticles and their pharmacological aspects are scarce.

Tenth, the promising results confirmed by animal models should be further investigated by clinical studies. For example, SKI3301 (a purified herbal extract from *S. tonkinensis*), inhibited airway inflammation and bronchospasm in allergic asthma animal models (in vivo) (Yoo et al. 2017). The novel herbal cocktail (F-PASA) with anti-allergic properties which was also proved by investigating the IgE/antigen-mediated allergic responses in RBL-2H3 cells and passive cutaneous anaphylaxis in mice (Yoo et al. 2019). Other preparation like compound Kushen injection has combined with chemotherapy on postoperative patients with breast cancer as plant-derived anticancer agents (Ao et al. 2019). The extract of *S. alopecuroides* also reduced acute opioid withdrawal symptoms (Kianbakht et al. 2020). It decreased the clinical opiate withdrawal scale score and seems to be safe and tolerable.

Conclusions and further needs

Sophora species (family Fabaceae) are intriguing medicinal plants and rich sources of diverse and chemical structures especially in terms of the alkaloids and prenylated flavonoids. The claimed health benefits of these classes of compounds include anti-inflammatory, antiviral, anti-cancer, and other promising effects that were thoroughly summarized. However, although the current evidence is promising, further clinical studies are needed to evaluate the role of these compounds to support human health. Besides, the mechanisms by which they confer the health benefits, the bioavailability studies on *Sophora*'s alkaloids and prenylated flavonoids are also scarce. Furthermore, *Sophora* species are characterized by rare and unique skeletons of matrine-acetophenone and normatrine-julolidine alkaloids type and the 2-arylbenzofuran dimers. Biologically, *Sophora* species naturally synthesize secondary metabolites with outstanding biological potential, especially anti-inflammatory and anti-cancer activities. *Sophora* species are widely used in folk medicine, but they still deserve to be investigated for their clinical and medicinal properties. The current review provides details on some *Sophora* species that need further phytochemical and/ or pharmacological investigations. Further studies on this genus are recommended to study other *Sophora* species and to better correlate the bioactivity and chemical properties of these species. Moreover, *S. subprostrata* constituents could be considered as a candidate for future clinical trials to develop effective chemical drugs against SARS-CoV-2.

Acknowledgements The authors wish to thank the facilities support of the National Research Centre, Egypt. The authors acknowledge the help of Marwa Mostafa, Bab El Shaariya University Hospital, Cairo (Egypt) for drawing the chemical structures of some compounds. Mohamed O. Radwan would like to express heartfelt gratitude to Omnia Fouad for her ongoing and unwavering support. Thank you of being a part of my story.

Declarations

Conflict of interest The authors declare no conflict of interest.

References

Abd-Alla HI, Moharram FA, Gaara AH, El-Safty MM (2009) Phytoconstituents of *Jatropha curcas* L. leaves and their immunomodulatory activity on humoral and cell-mediated immune response in chicks. Z Naturforsch 64C:495–501. https://doi.org/10.1515/znc-2009-7-805

Ahn DK (1998) Illustrated Book of Korean Medicinal Herbs. Kyo-Hak Publisher, Seoul, p 199

Ahn J, Kim YM, Chae HS, Choi YH, Ahn HC, Yoo H, Kang M, Kim J, Chin YW (2019) Prenylated flavonoids from the roots and rhizomes of *Sophora tonkinensis* and their effects on the expression of inflammatory mediators and proprotein convertase subtilisin/kexin type 9. J Nat Prod 82(2):309–317. https://doi.org/10.1021/acs.jnatprod.8b00748

Alesawy MS, Abdallah AE, Taghour MS, Elkaeed EB, Eissa H, Metwaly AM (2021) In silico studies of some isoflavonoids as potential candidates against covid-19 targeting human ACE2 (hACE2) and viral main protease (Mpro). Molecules 26(9):2806. https://doi.org/10.3390/molecules26092806

Aly HF, Abd-Alla HI, Ali SA, Alez RA, Abu-Krisha T, Mamdouh MM (2017) Bioinformatics: inflammatory cytokines and attenuation of diabetes hypercholesterolemia-induced renal injury using morning glory and necklace pod extracts. Asian J Pharm Clin Res 10:347–355. https://doi.org/10.22159/ajpcr.2017.v10i11.20119

Aly SH, Elissawy AM, Eldahshan OA, Elshanawany MA, Efferth T, Singab AN (2019) The pharmacology of the genus *Sophora* (Fabaceae): an updated review. Phytomedicine 64:153070. https://doi.org/10.1016/j.phymed.2019.153070

Aly HS, Elissawy AM, Eldahshan OA, Elshanawany MM, Singab AN (2020a) Phytochemical investigation using GC/MS analysis and evaluation of antimicrobial and cytotoxic activities of the lipoidal matter of leaves of *Sophora secundiflora* and *Sophora tomentosa*. Arch Pharm Sci Ain Shams Univ. 4(2):207–214. https://doi.org/10.21608/APS.2020.38371.1039

Aly SH, Elissawy AM, Eldahshan OA, Elshanawany MA, Singab AN (2020b) Variability of the chemical composition of the essential oils of flowers and the alkaloid contents of leaves of *Sophora secundiflora* and *Sophora tomentosa*. J Essent Oil-Bear Plants 23(3):442–452. https://doi.org/10.1080/0972060X.2020.1750489

Aly SH, Elissawy AM, Fayez AM, Eldahshan OA, Elshanawany MA, Singab AN (2020c) Neuroprotective effects of *Sophora secundiflora*, *Sophora tomentosa* leaves and formononetin on scopolamine-induced dementia. Nat Prod Res. https://doi.org/10.1080/14786419.2020.1795853

Aly SH, Elissawy AM, Allam AE, Farag SM, Eldahshan OA, Elshanawany MA, Singab AN (2021) New quinolizidine alkaloid and insecticidal activity of *Sophora secundiflora* and *Sophora tomentosa* against *Culex pipiens* (Diptera: Culicidae). Nat Prod Res. https://doi.org/10.1080/14786419.2021.1919108

Ao M, Xiao X, Li Q (2019) Efficacy and safety of compound Kushen injection combined with chemotherapy on postoperative patients with breast cancer: a meta-analysis of randomized controlled trials. Medicine 98:e14024. https://doi.org/10.1097/MD.0000000000014024

Awad HM, Abd-Alla HI, Mahmoud KH, El-Toumy SA (2014) In vitro anti-nitrosative, antioxidant, and cytotoxicity activities of plant flavonoids: a comparative study. Med Chem Res 23:3298–3307. https://doi.org/10.1007/s00044-014-0915-2

Awad HM, Abd-Alla HI, Ibrahim MA, El-Sawy ER, Abdalla MM (2018) Flavones from Heavenly Blue as modulators of Alzheimer's amyloid-beta peptide (Aβ) production. Med Chem Res 27:768–776. https://doi.org/10.1007/s00044-017-2100-x

Batalha PN, Forezi LSM, Lima CGS, Pauli FP, Boechat FCS, de Souza MCBV, Cunha AC, Ferreira VF, da Silva FDC (2021) Drug repurposing for the treatment of COVID-19: Pharmacological aspects and synthetic approaches. Bioorg Chem 106:104488. https://doi.org/10.1016/j.bioorg.2020.104488

Bisby FA, Buckingham J, Harborne JB (eds) (1994) Phytochemical dictionary of the Leguminosae. CRC Press, Boca Raton

Boozari M, Ebrahimi SN, Soltani S, Tayarani-Najaran Z, Emami SA, Asili J, Iranshahi M (2019a) Absolute configuration and anticancer effect of prenylated flavonoids and flavonostilbenes from *Sophora pachycarpa*: possible involvement of Wnt signaling pathway. Bioorg Chem 85:498–504. https://doi.org/10.1016/j.bioorg.2019.01.051

Boozari M, Soltani S, Iranshahi M (2019b) Biologically active prenylated flavonoids from the genus *Sophora* and their structure–activity relationship—a review. Phytother Res 33:546–560. https://doi.org/10.1002/ptr.6265

Borges L, Bruneau A, Cardoso D, Crisp M, Delgado-Salinas A, Doyle JJ, Egan A, Herendeen PS, Hughes C, Kenicer G, Klitgaard B (2013) Towards a new classification system for legumes: progress report from the 6th International Legume Conference. S Afr J Bot 89:3–9. https://doi.org/10.1016/j.sajb.2013.07.022

Cai XH, Zhang HY, Xie B (2020) Matrine-family alkaloids: versatile precursors for bioactive modifications. Med Chem 16(4):431–453. https://doi.org/10.2174/1573406415666190507121744

Cao X, He Q (2020) Anti-tumor activities of bioactive phytochemicals in *Sophora flavescens* for breast cancer. Cancer Manag Res 12:1457–1467. https://doi.org/10.2147/CMAR.S243127

Cao Z, Chen L, Liu Y, Peng T (2018) Oxysophoridine rescues spinal cord injury via antiinflammatory, antioxidative stress and antiapoptosis effects. Mol Med Rep 17:2523–2528. https://doi.org/10.3892/mmr.2017.8170

Chang JB, Lane ME, Yang M, Heinrich M (2018) Disentangling the complexity of a hexa-herbal Chinese medicine used for inflammatory skin conditions—predicting the active components by combining lc-ms-based metabolite profiles and in vitro pharmacology. Front Pharmacol 9:1091. https://doi.org/10.3389/fphar.2018.01091

Chang HC, Liu KF, Teng CJ, Lai SC, Yang SE, Ching H, Wu CR (2019a) *Sophora tomentosa* extract prevents MPTP-induced parkinsonism in C57BL/6 mice via the inhibition of GSK-3β phosphorylation and oxidative stress. Nutrients 11:252. https://doi.org/10.3390/nu11020252

Chang Z, Zhang P, Zhang M, Jun F, Hu Z, Yang J, Wu Y, Zhou R (2019b) Aloperine suppresses human pulmonary vascular smooth muscle cell proliferation via inhibiting inflammatory response. Chin J Physiol 62(4):157–165. https://doi.org/10.4103/CJP.CJP_27_19

Chen Y, Yang Y, Wang F, Yang X, Yao F, Ming K, Yuan W, Zeng L, Liu J (2018a) Antiviral effect of baicalin phospholipid complex against duck hepatitis A virus type 1. Poult Sci 97(8):2722–2732. https://doi.org/10.3382/ps/pey155

Chen Y, Yang Y, Yuan W, Wang Z, Ming K, Zeng L, Liu J (2018b) Effects of Bush Sophora Root polysaccharide and its sulfate on DHAV-1 replication. Carbohydr Polym 197:508–514. https://doi.org/10.1016/j.carbpol.2018.06.039

Chen Y, Yuan W, Yang Y, Yao F, Ming K, Liu J (2018c) Inhibition mechanisms of baicalin and its phospholipid complex against DHAV-1 replication. Poult Sci 97(11):3816–3825. https://doi.org/10.3382/ps/pey255

Chen Y, Zhong Y, Qi Y, Qiu Y, Yang L, Liang S (2018d) Near-infrared spectroscopy for rapid evaluation of different processing products of *Sophora japonica* L. Spectr Lett 51(1):37–44. https://doi.org/10.1080/00387010.2017.1416478

Chen H, Yang J, Hao J, Lv Y, Chen L, Lin Q, Yuan J, Yang X (2019a) A novel flavonoid kushenol Z from *Sophora flavescens* mediates mTOR pathway by inhibiting phosphodiesterase and Akt activity to induce apoptosis in non-small-cell lung cancer cells. Molecules 24(24):4425. https://doi.org/10.3390/molecules24244425

Chen L, Chen L, Wan L, Huo Y, Huang J, Li J, Lu J, Xin B, Yang Q, Guo C (2019b) Matrine improves skeletal muscle atrophy by inhibiting E3 ubiquitin ligases and activating the Akt/mTOR/FoxO3α signaling pathway in C2C12 myotubes and mice. Oncol Rep 42(2):479–494. https://doi.org/10.3892/or.2019.7205

Chen Y, Chen L, Zhang JY, Chen ZY, Liu TT, Zhang YY, Fu LY, Fan SQ, Zhang MQ, Gan SQ, Zhang NL (2019c) Oxymatrine reverses epithelial-mesenchymal transition in breast cancer cells by depressing αVβ3 integrin/FAK/PI3K/Akt signaling activation. OncoTargets Ther 12:6253. https://doi.org/10.2147/OTT.S209056

Chen Z, Nishimura N, Okamoto T, Wada K, Naora K (2019d) Molecular mechanism of matrine from *Sophora alopecuroides* in the reversing effect of multi-anticancer drug resistance in K562/ADR cells. BioMed Res Int. https://doi.org/10.1155/2019/1269532

Chen F, Yin X, Wang Y, Lv Y, Sheng S, Ouyang S, Zhong Y (2020a) Pharmacokinetics, tissue distribution, and druggability prediction of the natural anticancer active compound cytisine n-isoflavones combined with computer simulation. Biol Pharm Bull. https://doi.org/10.1248/bpb.b20-00004

Chen L, Shao J, Luo Y, Zhao L, Zhao K, Gao Y, Wang S, Liu Y (2020b) An integrated metabolism in vivo analysis and network pharmacology in UC rats reveal anti-ulcerative colitis effects from *Sophora flavescens* EtOAc extract. J Pharm Biomed Anal 186:113306. https://doi.org/10.1016/j.jpba.2020.113306

Chen N, Qiao Z, Xu J, Wei K, Li M (2020c) Physiological mechanism and developmental events in differentiating floral buds of *Sophora tonkinensis* gagnep. Pharmacogn Mag 16(67):83. https://doi.org/10.4103/pm.pm_174_19

Chen Y, Luo Q, Li S, Li C, Liao S, Yang X, Zhou R, Zhu Y, Teng L, Chen H, Yang Y (2020d) Antiviral activity against porcine epidemic diarrhea virus of Pogostemon cablin polysaccharide. J Ethnopharmacol 259:113009. https://doi.org/10.1016/j.jep.2020.113009

Cho YR, Lee JH, Kim JH, Lee SY, Yoo S, Jung MK, Kim SJ, Yoo HJ, Pack CG, Rho JK, Son J (2018) Matrine suppresses KRAS-driven pancreatic cancer growth by inhibiting autophagy-mediated energy metabolism. Mol Oncol 12(7):1203–1215. https://doi.org/10.1002/1878-0261.12324

Cho BO, Che DN, Kim JS, Kim JH, Shin JY, Kang HJ, Jang SI (2020) In vitro anti-inflammatory and anti-oxidative stress activities of kushenol C isolated from the roots of *Sophora flavescens*. Molecules 25:1768. https://doi.org/10.3390/molecules25081768

Choudhry N, Zhao X, Xu D, Zanin M, Chen W, Yang Z, Chen J (2020) Chinese therapeutic strategy for fighting COVID-19 and potential small-molecule inhibitors against severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). J Med Chem 63(22):13205–13227. https://doi.org/10.1021/acs.jmedchem.0c00626

Chung TW, Lin CC, Lin SC, Chan HL, Yang CC (2019) Antitumor effect of kurarinone and underlying mechanism in small cell lung carcinoma cells. OncoTarg Ther 12:6119. https://doi.org/10.2147/OTT.S214964

Dai M, Chen N, Li J, Tan L, Li X, Wen J, Lei L, Guo D (2021) In vitro and in vivo anti-metastatic effect of the alkaloid matrine from *Sophora flavescens* on hepatocellular carcinoma and its mechanisms. Phytomedicine 87:153580. https://doi.org/10.1016/j.phymed.2021.153580

Dang Z, Zhu L, Lai W, Bogerd H, Lee KH, Huang L, Chen CH (2016) Aloperine and its derivatives as a new class of HIV-1 entry inhibitors. ACS Med Chem Lett 7(3):240–2444. https://doi.org/10.1021/acsmedchemlett.5b00339

de Andrade DJ, da Rocha CM, de Matos ST, Zanardi OZ (2020) Oxymatrine-based bioacaricide as a management tool against *Oligonychus ilicis* (McGregor)(Acari: Tetranychidae) in coffee. Crop Protec 134:105182. https://doi.org/10.1016/j.cropro.2020.105182

Elberry A, Mufti S, Al-Maghrabi J, Ghareib S, Mosli H, El-Halawany A, Abdel-Sattar E (2020) The protective effect of *Sophora japonica* on prostatic hypertrophy and inflammation in rat. Inflammopharmacology. https://doi.org/10.1007/s10787-020-00723-5

Fan CL, Zhang YB, Chen Y, Xie P, Wang GC, Tian HY, Li YL, Huang XJ, Zhang XQ, Li ZY, Liu JS (2019) Alopecuroides A-E, matrine-type alkaloid dimers from the aerial parts of *Sophora alopecuroides*. J Nat Prod 82:3227–3232. https://doi.org/10.1021/acs.jnatprod.8b01081

Fang R, Wu R, Zuo Q, Yin R, Zhang C, Wang C, Guo Y, Yang AY, Li W, Lin L, Kong AN (2018) *Sophora flavescens* containing-QYJD formula activates Nrf2 anti-oxidant response, blocks cellular transformation and protects against DSS-induced colitis in mouse model. Am J Chin Med 46(07):1609–1623. https://doi.org/10.1142/S0192415X18500829

Fang H, Bo T, Zi X, Tan D, Liu X, Jiang C, Lei G, Deng Y, Cui L (2020) Sophocarpine exert protective effect against ox-LDL-induced endothelial damage via regulating NF-κB signaling pathway. Biosci Biotechnol Biochem 84(10):2104–2112. https://doi.org/10.1080/09168451.2020.1787813

Farhadi F, Khameneh B, Iranshahi M, Iranshahy M (2019) Antibacterial activity of flavonoids and their structure–activity relationship: an update review. Phytother Res 33:13–40. https://doi.org/10.1002/ptr.6208

Fielding BC, da Silva Maia Bezerra Filho C, Ismail NS, Sousa DP (2020) Alkaloids: therapeutic potential against human coronaviruses. Molecules 25(23):5496. https://doi.org/10.3390/molecules25235496

Fu S, Zhao N, Jing G, Yang X, Liu J, Zhen D, Tang X (2020) Matrine induces papillary thyroid cancer cell apoptosis in vitro and suppresses tumor growth in vivo by downregulating miR-182–5p. Biomed Pharmacother 128:110327. https://doi.org/10.1016/j.biopha.2020.110327

Fuzimoto AD, Isidoro C (2020) The antiviral and coronavirus-host protein pathways inhibiting properties of herbs and natural compounds—additional weapons in the fight against the COVID-19 pandemic? J Trad Compl Med 10(4):405–419. https://doi.org/10.1016/j.jtcme.2020.05.003

Gao DD, Zhang ZJ, Li HM, Chen XQ, Liu D, Li RT (2020) Four new quinolizidine alkaloids from the flowers of *Sophora viciifolia*. Phytochem Lett 36:91–94. https://doi.org/10.1016/j.phytol.2020.01.007

Ghoran SH, El-Shazly M, Sekeroglu N, Kijjoa A (2021) Natural products from medicinal plants with anti-human coronavirus activities. Molecules 26(6):1754. https://doi.org/10.3390/molecules26061754

Google patents (2011) Sophora alopecuroide total alkali medicine for treating herpes zoster Publication number CN102100734A, priority date 22.6.2011.

Gu J, Zhang Y, Wang X, Xiang J, Deng S, Wu D, Chen J, Yu L, Zhou Y, Wang Y, Shen J (2020) Matrine inhibits the growth of natural killer/T-cell lymphoma cells by modulating CaMKIIγ-c-Myc signaling pathway. BMC Complem Med Ther 20(1):1–1. https://doi.org/10.1186/s12906-020-03006-2

Guan Y, Chen K, Quan D, Kang L, Yang D, Wu H, Yan M, Wu S, Lv L, Zhang G (2021) The combination of *Scutellaria baicalensis* Georgi and *Sophora japonica* L. ameliorate renal function by regulating gut microbiota in spontaneously hypertensive rats. Front Pharmacol 11:2322. https://doi.org/10.3389/fphar.2020.575294

Guo Z, Wu X, Zhao X, Fan J, Lu X, Wang L (2020) An edible antioxidant film of *Artemisia sphaerocephala* Krasch gum with *Sophora japonica* extract for oil packaging. Food Packag Shelf Life 24:100460. https://doi.org/10.1016/j.fpsl.2019.100460

Hadadi Z, Nematzadeh GA, Ghahari S (2020) A study on the antioxidant and antimicrobial activities in the chloroformic and methanolic extracts of 6 important medicinal plants collected from North of Iran. BMC Chem 14:1–1. https://doi.org/10.1186/s13065-020-00683-5

Halim CE, Xinjing SL, Fan L, Vitarbo JB, Arfuso F, Tan CH, Narula AS, Kumar AP, Sethi G, Ahn KS (2019) Anti-cancer effects of oxymatrine are mediated through multiple molecular mechanism (s) in tumor models. Pharmacol Res 147:104327. https://doi.org/10.1016/j.phrs.2019.104327

Han J, Lee S, Lee N, Jo HJ, Park CS (2018) Relaxation of bladder smooth muscle by flavonoids from *Sophora flavescens* via direct activation of the large-conductance calcium-activated potassium channel. FASEB J 32:533–577. https://doi.org/10.1096/fasebj.2018.32.1

Han Y, Zhang X, Kang Y, Gao Y, Li X, Qi R, Cai R, Qi Y (2021) Sophoraflavanone M, a prenylated flavonoid from Sophora flavescens Ait., suppresses pro-inflammatory mediators through both NF-κB and JNK/AP-1 signaling pathways in LPS-primed macrophages. Europ J Pharmacol 9:174246. https://doi.org/10.1016/j.ejphar.2021.174246

Haroun AA, Elnahrawy AM, Abd-Alla HI (2017) Sol-gel preparation and in vitro cytotoxic activity of nanohybrid structures based on multi-walled carbon nanotubes and silicate. Inorg Nano-Metal Chem 47(7):1023–1027. https://doi.org/10.1080/24701556.2017.1284087

Hassan ST (2020) Shedding light on the effect of natural anti-herpesvirus alkaloids on SARS-CoV-2: a treatment option for COVID-19. Viruses 12(4):476. https://doi.org/10.3390/v12040476

Hassanein EH, Sayed AM, Hussein OE, Mahmoud AM (2020) Coumarins as modulators of the Keap1/Nrf2/ARE signaling pathway. Oxid Med Cell Longev 2020:1675957. https://doi.org/10.1155/2020/1675957

He LJ, Liu JS, Luo D, Zheng YR, Zhang YB, Wang GC, Li YL (2019) Quinolizidine alkaloids from *Sophora tonkinensis* and their anti-inflammatory activities. Fitoterapia 139:104391. https://doi.org/10.1016/j.fitote.2019.104391

Hong X, Zhong L, Xie Y, Zheng K, Pang J, Li Y, Yang Y, Xu X, Mi P, Cao H, Zhang W (2019) Matrine reverses the Warburg effect and suppresses colon cancer cell growth via negatively regulating HIF-1α. Front Pharmacol 10:1437. https://doi.org/10.3389/fphar.2019.01437

Hou M, Hu W, Hao K, Xiu Z (2020) Flavonoids and phenolic acids from the roots of *Sophora tonkinensis* Gagnep. Biochem Syst Ecol 89:104011. https://doi.org/10.1016/j.bse.2020.104011

Huang H, Wang Q, Du T, Lin C, Lai Y, Zhu D, Wu W, Ma X, Bai S, Li Z, Liu L (2018a) Matrine inhibits the progression of prostate cancer by promoting expression of GADD45B. Prostate 78(5):327–335. https://doi.org/10.1002/pros.23469

Huang Y, Hao J, Tian D, Wen Y, Zhao P, Chen H, Lv Y, Yang X (2018b) Antidiabetic activity of a flavonoid-rich extract from *Sophora davidii* (Franch.) Skeels in KK-Ay mice via activation of AMP-activated protein kinase. Front Pharmacol 9:760. https://doi.org/10.3389/fphar.2018.00760

Huang Y, Zhang J, Wang G, Chen X, Zhang R, Liu H, Zhu J (2018c) Oxymatrine exhibits anti-tumor activity in gastric cancer through inhibition of IL-21R-mediated JAK2/STAT3 pathway. Int J Immunopathol Pharmacol 32:2058738418781634. https://doi.org/10.1177/2058738418781634

Huang WC, Gu PY, Fang LW, Huang YL, Lin CF, Liou CJ (2019) Sophoraflavanone G from *Sophora flavescens* induces apoptosis in triple-negative breast cancer cells. Phytomedicine 61:152852. https://doi.org/10.1016/j.phymed.2019.152852

Huang X, Xu H (2020) Advances on the bioactivities, total synthesis, structural modification, and structure-activity relationships of cytisine derivatives. Mini Rev Med Chem 20(5):369–395. https://doi.org/10.2174/1389557519666191104121821

Huang XB, Yuan LW, Shao J, Yang Y, Liu Y, Lu JJ, Chen L (2020) Cytotoxic effects of flavonoids from root of *Sophora flavescens* in cancer cells. Nat Prod Res 11:1–6. https://doi.org/10.1080/14786419.2020.1712382

Huh JW, Lee JH, Jeon E, Ryu HW, Oh SR, Ahn KS, Jun HS, Ha UH (2020) Maackiain, a compound derived from Sophora flavescens, increases IL-1β production by amplifying nigericin-mediated inflammasome activation. FEBS Open Bio 10(8):1482–1491. https://doi.org/10.1002/2211-5463.12899

Ismail M, Fayyaz S, Kowsar A, Javed S, Ali I, Ali S, Hussain F, Ali H (2020) Evaluation of nematocidal effects of some medicinal plant extracts against root-knot nematodes (*Meloidogyne incognita*). Ital J Agron 15(1):63–69. https://doi.org/10.4081/ija.2020.1475

Izdebska M, Zielińska W, Hałas-Wiśniewska M, Mikołajczyk K, Grzanka A (2019) The cytotoxic effect of oxymatrine on basic cellular processes of A549 non-small lung cancer cells. Acta Histochem 121(6):724–731. https://doi.org/10.1016/j.acthis.2019.06.008

Jia F, Zhou Q, Li X, Zhou X (2019) Total alkaloids of *Sophora alopecuroides* and matrine inhibit auto-inducer 2 in the biofilms of *Staphylococcus epidermidis*. Microb Pathog 136:103698. https://doi.org/10.1016/j.micpath.2019.103698

Jia YQ, Yuan ZW, Zhang XS, Dong JQ, Liu XN, Peng XT, Yao WL, Ji P, Wei YM, Hua YL (2020) Total alkaloids of *Sophora alopecuroides* L. ameliorated murine colitis by regulating bile acid metabolism and gut microbiota. J Ethnopharmacol 255:112775. https://doi.org/10.1016/j.jep.2020.112775

Jiang JH, Pi J, Jin H, Yang F, Cai JY (2018) Chinese herb medicine matrine induce apoptosis in human esophageal squamous cancer KYSE-150 cells through increasing reactive oxygen species and inhibiting mitochondrial function. Pathol-Res Pract 214(5):691–699. https://doi.org/10.1016/j.prp.2018.03.015

Jiang D, Rasul A, Batool R, Sarfraz I, Hussain G, Mateen Tahir M, Qin T, Selamoglu Z, Ali M, Li J, Li X (2019a) Potential anticancer properties and mechanisms of action of formononetin. BioMed Res Int. https://doi.org/10.1155/2019/5854315

Jiang K, Guo S, Yang J, Liu J, Shaukat A, Zhao G, Wu H, Deng G (2019b) Matrine alleviates *Staphylococcus aureus* lipoteichoic acid-induced endometritis via suppression of TLR2-mediated NF-κB activation. Int Immunopharmacol 70:201–207. https://doi.org/10.1016/j.intimp.2019.02.033

Jiang J, Wang G (2020a) Matrine protects PC12 cells from lipopolysaccharide-evoked inflammatory injury via upregulation of miR-9. Pharm Biol 58(1):314–320. https://doi.org/10.1080/13880209.2020.1719165

Jiang JS, Shen Y, Feng ZM, Yang YN, Zhang X, Yuan X, Zhang PC (2020b) New benzoic acid glycosides from *Sophora flavescens*. J Asian Nat Prod Res. https://doi.org/10.1080/10286020.2020.1801650

Jiang P, Sun Y, Cheng N (2020c) Liver metabolomic characterization of *Sophora flavescens* alcohol extract-induced hepatotoxicity in rats through UPLC/LTQ-Orbitrap mass spectrometry. Xenobiotica 50(6):670–676. https://doi.org/10.1080/00498254.2019.1687962

Jin SJ, Yang Y, Ma L, Ma BH, Ren LP, Guo LC, Wang WB, Zhang YX, Zhao ZJ, Cui M (2017) In vivo and in vitro induction of the apoptotic effects of oxysophoridine on colorectal cancer cells via the Bcl-2/Bax/caspase-3 signaling pathway. Oncol Lett 14(6):8000–8006. https://doi.org/10.3892/ol.2017.7227

Jin X, Lu Y, Chen S, Chen D (2020) UPLC-MS identification and anticomplement activity of the metabolites of *Sophora tonkinensis* flavonoids treated with human intestinal bacteFan. J Pharm Biomed Anal 184:113176. https://doi.org/10.1016/j.jpba.2020.113176

Kaewdana K, Chaniad P, Jariyapong P, Phuwajaroanpong A, Punsawad C (2021) Antioxidant and antimalarial properties of *Sophora exigua* Craib. root extract in *Plasmodium berghei*-infected mice. Trop Med Health 49(1):24. https://doi.org/10.1186/s41182-021-00314-2

Kianbakht S, Hajiaghaee R, Akhondzadeh S (2020) Efficacy and safety of *Sophora alopecuroides* var. alopecuroides seed extract for opioid detoxification: a randomized, double-blind, and placebo-controlled clinical trial. Phytother Res 34(5):1108–1113. https://doi.org/10.1002/ptr.6578

Kim JM, Yun-Choi HS (2008) Anti-platelet effects of flavonoids and flavonoid-glycosides from *Sophora japonica*. Arch Pharm Res 31:886–890. https://doi.org/10.1007/s12272-001-1242-1

Kim BH, Lee S (2021) Sophoricoside from *Sophora japonica* ameliorates allergic asthma by preventing mast cell activation and CD4+ T cell differentiation in ovalbumin-induced mice. Biomed Pharmacother 133:111029. https://doi.org/10.1016/j.biopha.2020.111029

Kim BH, Chung EY, Ryu JC, Jung SH, Min KR, Kim Y (2003) Anti-inflammatory mode of isoflavone glycoside sophoricoside by inhibition of lnterleukin-6 and cyclooxygenase-2 in inflammatory response. Arch Pharm Res 26(4):306–311. https://doi.org/10.1007/BF02976960

Kim Y, Oh Y, Lee H, Yang B, Choi CH, Jeong H, Kim H, An W (2021) Prediction of the therapeutic mechanism responsible for the effects of *Sophora japonica* flower buds on contact dermatitis by network-based pharmacological analysis. J Ethnopharmacol 271:113843. https://doi.org/10.1016/j.jep.2021.113843

Krishna PM, KNV R, Sandhya S, BanjiI D (2012) A review on phytochemical, ethnomedical and pharmacological studies on genus *Sophora*, Fabaceae. Rev Bras Farmacogn 22(5). https://doi.org/10.1590/S0102-695X2012005000043

Kwon M, Ko SK, Jang M, Kim GH, Ryoo IJ, Son S, Ryu HW, Oh SR, Lee WK, Kim BY, Jang JH (2019) Inhibitory effects of flavonoids isolated from *Sophora flavescens* on indoleamine 2, 3-dioxygenase 1 activity. J Enzyme Inhib Med Chem 34(1):1481–1488. https://doi.org/10.1080/14756366.2019.1640218

Kwon M, Jang M, Kim GH, Oh T, Ryoo IJ, Ryu HW, Oh SR, Kim BY, Jang JH, Ko SK, Ahn JS (2020) Kushenol E inhibits autophagy and impairs lysosomal positioning via VCP/p97 inhibition. Biochem Pharmacol 175:113861. https://doi.org/10.1016/j.bcp.2020.113861

Lan X, Zhao J, Zhang Y, Chen Y, Liu Y, Xu F (2020) Oxymatrine exerts organ-and tissue-protective effects by regulating inflammation, oxidative stress, apoptosis, and fibrosis: from bench to bedside. Pharmacol Res 151:104541. https://doi.org/10.1016/j.phrs.2019.104541

Ledoux A, Cao M, Jansen O, Mamede L, Campos PE, Payet B, Clerc P, Grondin I, Girard-Valenciennes E, Hermann T, Litaudon M (2018) Antiplasmodial, anti-chikungunya virus and antioxidant activities of 64 endemic plants from the Mascarene Islands. Int J Antimicrob Agents 52:622–628. https://doi.org/10.1016/j.ijantimicag.2018.07.017

Li W, Lu Y (2018) Hepatoprotective effects of sophoricoside against fructose-induced liver injury via regulating lipid metabolism, oxidation, and inflammation in mice. J Food Sci 83(2):552–558. https://doi.org/10.1111/1750-3841.14047

Li Z, Yu KX (2020) Exploration on mechanism of anti-coronavirus of *Sophora flavescens* through multi-pathway. Chin Trad Herbal Drugs 2020:888–894. https://pesquisa.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/resource/pt/covidwho-46903

Li L, Huang T, Lan C, Ding H, Yan C, Dou Y (2019a) Protective effect of polysaccharide from *Sophora japonica* L. flower buds against UVB radiation in a human keratinocyte cell line (HaCaT cells). J Photochem Photobiol B 191:135–142. https://doi.org/10.1016/j.jphotobiol.2018.12.001

Li Q, Zhang S, Wang M, Dong S, Wang Y, Liu S, Lu T, Fu Y, Wang X, Chen G (2019b) Downregulated miR-21 mediates matrine-induced apoptosis via the PTEN/Akt signaling pathway in FTC-133 human follicular thyroid cancer cells. Oncol Lett 18(4):3553–3560. https://doi.org/10.3892/ol.2019.10693

Li Y, Li J, Liu X, Zhang J, Mei X, Zheng R, Chen W, Zheng Q, Zhong S (2019c) Antidiarrheal activity of methanol extract of *Sophora tonkinensis* in mice and spasmolytic effect on smooth muscle contraction of isolated jejunum in rabbits. Pharm Biol 57:477–484. https://doi.org/10.1080/13880209.2019.1645701

Li Y, Lin H, Deng N, Xie L, Luo R (2019d) Matrine from Vietnamese *Sophora* root inhibits the growth of oral squamous cell carcinoma cells *in vitro* and *in vivo*. Food Sci Technol 39(4):855–858. https://doi.org/10.1590/fst.11518

Li JJ, Zhang X, Shen XC, Xu CY, Tan CJ, Lin Y (2020a) Phytochemistry and biological properties of isoprenoid flavonoids from *Sophora flavescens* Ait. Fitoterapia 143:104556. https://doi.org/10.1016/j.fitote.2020

Li Q, Dai ML, Xie Y, Yan CB, Liu JH, Zhang YP, Yao BF, Zhang YY (2020b) Inhibition of ethanol extracts of *Psoralea corylifolia* and *Sophora flavescens* on *Phytophthora nicotianae* and their compound effect. Int J Agric Biol 23(1):75–81. https://doi.org/10.17957/IJAB/15.1260

Li X, Liang T, Chen SS, Wang M, Wang R, Li K, Wang JC, Xu CW, Du N, Qin S, Ren H (2020c) Matrine suppression of self-renewal was dependent on regulation of LIN28A/Let-7 pathway in breast cancer stem cells. J Cell Biochem 121(3):2139–2149. https://doi.org/10.1002/jcb.29396

Li Y, Wang G, Liu J, Ouyang L (2020d) Quinolizidine alkaloids derivatives from *Sophora alopecuroides* Linn: Bioactivities, structure-activity relationships and preliminary molecular mechanisms. Eur J Med Chem 188:111972. https://doi.org/10.1016/j.ejmech.2019.111972

Li JC, Dai WF, Liu D, Zhang ZJ, Jiang MY, Rao KR, Li RT, Li HM (2021a) Quinolizidine alkaloids from *Sophora alopecuroides* with anti-inflammatory and anti-tumor properties. Bioorg Chem 110:104781. https://doi.org/10.1016/j.bioorg.2021.104781

Li K, Ma Y, Zhou T, Yang X, Choi HY (2021b) Chemical constituents from roots of *Sophora davidii* (Franch.) Skeels and their glucose transporter 4 translocation activities. Molecules 26(3):756. https://doi.org/10.3390/molecules26030756

Liang J, Chang B, Huang M, Huang W, Ma W, Liu Y, Tai W, Long Y, Lu Y (2018) Oxymatrine prevents synovial inflammation and migration via blocking NF-κB activation in rheumatoid fibroblast-like synoviocytes. Int Immunopharmacol 55:105–111. https://doi.org/10.1016/j.intimp.2017.12.006

Liang L, Wu J, Luo J, Wang L, Chen ZX, Han CL, Gan TQ, Huang JA, Cai ZW (2020) Oxymatrine reverses 5-fluorouracil resistance by inhibition of colon cancer cell epithelial-mesenchymal transition and NF-κB signaling in vitro. Oncol Lett 19(1):519–526. https://doi.org/10.3892/ol.2019.11090

Lin TT, Huang YY, Tang GH, Cheng ZB, Liu X, Luo HB, Yin S (2014) Prenylated coumarins: natural phosphodiesterase-4 inhibitors from *Toddalia asiatica*. J Nat Prod 77(4):955–962. https://doi.org/10.1021/np401040d

Lin BB, Liu X, Wu SQ, Zheng HX, Huo KK, Qi SS, Chen C (2019a) Phytochemicals content, antioxidant and antibacterial activities of *Sophora viciifolia*. Chem Biodivers 16(7):e1900080. https://doi.org/10.1002/cbdv.201900080

Lin G, Wu Y, Cai F, Li Z, Su S, Wang J, Cao J, Ma L (2019b) Matrine promotes human myeloid leukemia cells apoptosis through Warburg effect mediated by hexokinase 2. Front Pharmacol 10:1069. https://doi.org/10.3389/fphar.2019.01069

Lin YB, Huang DJ, Huang HL, Chen DX, Huang JH (2020) Sophocarpine ameliorates cardiac hypertrophy through activation of autophagic responses. Biosci Biotechnol Biochem 84(10):2054–2061. https://doi.org/10.1080/09168451.2020.1780111

Liu D, Chan BC, Cheng L, Tsang MS, Zhu J, Wong CW, Jiao D, Chan HY, Leung PC, Lam CW, Wong CK (2018a) *Sophora flavescens* protects against mycobacterial trehalose dimycolate-induced lung granuloma by inhibiting inflammation and infiltration of macrophages. Sci Rep 8(1):1–4. https://doi.org/10.1038/s41598-018-22286-w

Liu Y, Yao W, Si L, Hou J, Wang J, Xu Z, Li W, Chen J, Li R, Li P, Bo L (2018b) Chinese herbal extract Su-duxing had potent inhibitory effects on both wild-type and entecavir-resistant hepatitis B virus (HBV) in vitro and effectively suppressed HBV replication in mouse model. Antivir Res 155:39–47. https://doi.org/10.1016/j.antiviral.2018.04.017

Liu JS, Huo CY, Cao HH, Fan CL, Hu JY, Deng LJ, Lu ZB, Yang HY, Yu LZ, Mo ZX, Yu ZL (2019a) Aloperine induces apoptosis and G2/M cell cycle arrest in hepatocellular carcinoma cells through the PI3K/Akt signaling pathway. Phytomedicine 61:152843. https://doi.org/10.1016/j.phymed.2019.152843

Liu P, Zhu L, Zou G, Ke H (2019b) Matrine suppresses pancreatic fibrosis by regulating TGF-β/Smad signaling in rats. Yonsei Med J 60(1):79–87. https://doi.org/10.3349/ymj.2019.60.1.79

Liu J, Guo Y, Cao J (2020a) Matrine triggers colon cancer cell apoptosis and G0/G1 cell cycle arrest via mediation of microRNA-22. Phytother Res. https://doi.org/10.1002/ptr.6626

Liu ZM, Yang XL, Jiang F, Pan YC, Zhang L (2020b) Matrine involves in the progression of gastric cancer through inhibiting miR-93-5p

and upregulating the expression of target gene AHNAK. J Cell Biochem 121(3):2467–2477. https://doi.org/10.1002/jcb.29469

Long GQ, Wang DD, Wang J, Jia JM, Wang AH (2020) Chemical constituents of *Sophora flavescens* Ait. and cytotoxic activities of two new compounds. Nat Prod Res. https://doi.org/10.1080/14786419.2020.1765340

Luo W, Su X, Gong S, Qin Y, Liu W, Li J, Yu H, Xu Q (2009) Anti-SARS coronavirus 3C-like protease effects of *Rheum palmatum* L. extracts. Biosci Trends 3(4):124–126. https://www.biosciencetrends.com/downloadpdf/227

Luo Y, Zhang G, Liu X, Yuan M, Gao Q, Gao H, Ke L, Zhang X, Shi Y, Ma X, Zhang L (2018) Therapeutic and immunoregulatory effects of water-soluble alkaloids E2-a from *Sophora moorcroftiana* seeds as a novel potential agent against echinococcosis in experimentally protoscolex-infected mice. Vet Res 49:100. https://doi.org/10.1186/s13567-018-0596-9

Lv XQ, Zou LL, Tan JL, Li H, Li JR, Liu NN, Dong B, Song DQ, Peng ZG (2020) Aloperine inhibits hepatitis C virus entry into cells by disturbing internalisation from endocytosis to the membrane fusion process. Eur J Pharmacol 883:173323. https://doi.org/10.1016/j.ejphar.2020.173323

Lv Y, Zhao P, Pang K, Ma Y, Huang H, Zhou T, Yang X (2021) Anti-diabetic effect of a flavonoid-rich extract from *Sophora alopecuroides* L. in HFD-and STZ-induced diabetic mice through PKC/GLUT4 pathway and regulating PPARα and PPARγ expression. J Ethnopharmacol 268:113654. https://doi.org/10.1016/j.jep.2020.113654

Ma Q, Yu Q, Xing X, Liu S, Shi C, Luo J (2018) San Wu Huangqin decoction, a Chinese herbal formula, inhibits influenza a/PR/8/34 (H1N1) virus infection in vitro and in vivo. Viruses 10:11. https://doi.org/10.3390/v10030117

Ma QH, Ren MY, Luo JB (2020a) San Wu Huangqin decoction regulates inflammation and immune dysfunction induced by influenza virus by regulating the NF-κB signaling pathway in H1N1-infected mice. J Ethnopharmacol 264:112800. https://doi.org/10.1016/j.jep.2020.112800

Ma T, Shi X, Ma S, Ma Z, Zhang X (2020b) Evaluation of physiological and biochemical effects of two *Sophora alopecuroides* alkaloids on pea aphids Acyrthosiphon pisum. Pest Manag Sci. https://doi.org/10.1002/ps.5950

Ma Y, Zhou T, Zhao P, Choi HY, Hao J, Huang H, Wu C, Yang X, Pang K (2021) New flavonoids from the roots of *Sophora davidii* (Franch.) Skeels and their glucose transporter 4 translocation activities. Bioorgan Chem 106:104500. https://doi.org/10.1016/j.bioorg.2020.104500

Majnooni MB, Fakhri S, Bahrami G, Naseri M, Farzaei MH, Echeverría J (2021) Alkaloids as potential phytochemicals against SARS-CoV-2: approaches to the associated pivotal mechanisms. Evid Based Complement Altern Med 2021:632623. https://doi.org/10.1155/2021/6632623

Mao D, Pan X, Rui Y, Li F (2020) Matrine attenuates heterotopic ossification by suppressing TGF-β induced mesenchymal stromal cell migration and osteogenic differentiation. Biomed Pharmacother 127:110152. https://doi.org/10.1016/j.biopha.2020.110152

Mukai R (2018) Prenylation enhances the biological activity of dietary flavonoids by altering their bioavailability. Biosci Biotechnol Biochem 82(2):207–215. https://doi.org/10.1080/09168451.2017.1415750

Muhammad T, Sakhawat A, Khan AA, Huang H, Khan HR, Huang Y, Wang J (2020) Aloperine in combination with therapeutic adenoviral vector synergistically suppressed the growth of non-small cell lung cancer. J Canc Res Clin Oncol 146(4):861–874. https://doi.org/10.1007/s00432-020-03157-2

Nourmohammadi S, Aung TN, Cui J, Pei JV, De Ieso ML, Harata-Lee Y, Qu Z, Adelson DL, Yool AJ (2019) Effect of compound kushen injection, a natural compound mixture, and its identified chemical components on migration and invasion of colon, brain, and breast cancer cell lines. Front Oncol 9:314. https://doi.org/10.3389/fonc.2019.00314

Orhan IE, Deniz FS (2020) Natural products as potential leads against coronaviruses: could they be encouraging structural models against SARS-CoV-2? Nat Prod Bioprospect 10(4):171–186. https://doi.org/10.1007/s13659-020-00250-4

Pan QM, Li YH, Hua J, Huang FP, Wang HS, Liang D (2015) Antiviral matrine-type alkaloids from the rhizomes of *Sophora tonkinensis*. J Nat Prod 78(7):1683–1688. https://doi.org/10.1021/acs.jnatprod.5b00325

Parvez MK, Rehman MT, Alam P, Al-Dosari MS, Alqasoumi SI, Alajmi MF (2019) Plant-derived antiviral drugs as novel hepatitis B virus inhibitors: cell culture and molecular docking study. Saudi Pharm J 27:389–400. https://doi.org/10.1016/j.jsps.2018.12.008

Peng F, Xu P, Zhao BY, Zong MH, Lou WY (2018) The application of deep eutectic solvent on the extraction and *in vitro* antioxidant activity of rutin from *Sophora japonica* bud. J Food Sci Technol 55(6):2326–2333. https://doi.org/10.1007/s13197-018-3151-9

Peng W, Xu Y, Han D, Feng F, Wang Z, Gu C, Zhou X, Wu Q (2020a) Potential mechanism underlying the effect of matrine on COVID-19 patients revealed through network pharmacological approaches and molecular docking analysis. Arch Physiol Biochem. https://doi.org/10.1080/13813455.2020.1817944

Peng Z, Guan Q, Luo J, Deng W, Liu J, Yan R, Wang W (2020b) Sophoridine exerts tumor-suppressive activities via promoting ESRRG-mediated β-catenin degradation in gastric cancer. BMC Cancer 20(1):582. https://doi.org/10.1186/s12885-020-07067-x

Qiu M, Shi F, Dai F, Song R, Wang S, You Y, Zhao B (2018) A reactive oxygen species activation mechanism contributes to Sophoridine-induced apoptosis in rat liver BRL-3A cells. J Ethnopharmacol 213:376–383. https://doi.org/10.1016/j.jep.2017.10.030

Qiu M, Liu J, Feng P, Su Y, Guo R, Shi F, Wang S, Zhao B (2020a) Cytochrome P450s regulates aloperine-induced pathological changes in mouse liver and kidney. Res Vet Sci 132:97–100. https://doi.org/10.1016/j.rvsc.2020.06.005

Qiu M, Liu J, Su Y, Liu J, Wu C, Zhao B (2020b) Aloperine induces apoptosis by a reactive oxygen species activation mechanism in human ovarian cancer cells. Protein Pept Lett 27(9):860–869. https://doi.org/10.2174/0929866527666200320094313

Quradha MM, Khan R, Adhikari A, Rauf A, Rashid U, Bawazeer S, Al-Awthan YS, Bahattab O, Mubarak MS (2021) Isolation, biological evaluation, and molecular docking studies of compounds from *Sophora mollis* (Royle) Graham Ex Baker. ACS Omega 6(24):15911–15919. https://doi.org/10.1021/acsomega.1c01532

Rammohan A, Munikishore R, Gunasekar D, Deville A, Bodo B (2015) A new di-C-prenylated coumarin from *Sophora interrupta*. Nat Prod Res 29:82–85. https://doi.org/10.1080/14786419.2014.959010

Rammohan A, Bhaskar BV, Venkateswarlu N, Gu W, Zyryanov GV (2020) Design, synthesis, docking and biological evaluation of chalcones as promising antidiabetic agents. Bioorg Chem 95:103527. https://doi.org/10.1016/j.bioorg.2019.103527

Remali J, Aizat WM (2021) A review on plant bioactive compounds and their modes of action against coronavirus infection. Front Pharmacol. https://doi.org/10.3389/fphar.2020.589044

Ren G, Ding G, Zhang H, Wang H, Jin Z, Yang G, Han Y, Zhang X, Li G, Li W (2019) Antiviral activity of sophoridine against enterovirus 71 in vitro. J Ethnopharmacol 236:124–128. https://doi.org/10.1016/j.jep.2019.02.045

Rizk MZ, Abo-El-Matty DM, Aly HF, Abd-Alla HI, Saleh SM, Younis EA, Elnahrawy AM, Haroun AA (2018) Therapeutic activity of sour orange albedo extract and abundant flavanones loaded silica nanoparticles against acrylamide-induced hepatotoxicity. Toxicol Rep 5:929–942. https://doi.org/10.1016/j.toxrep.2018.08.021

Rizvi SA, Ling S, Tian F, Liu J, Zeng X (2019) Interference mechanism of *Sophora alopecuroides* L. alkaloids extract on host finding and selection of the Asian citrus psyllid *Diaphorina citri* Kuwayama (Hemiptera: Psyllidae). Environ Sci Pollut Res 26(2):1548–1557. https://doi.org/10.1007/s11356-018-3733-0

Rong ZJ, Hu GS, Lin SY, Yan T, Li N, Zhao Y, Jia JM, Wang AH (2020) Constituents from the seeds of *Sophora alopecuroides* L. Molecules 25(2):411. https://doi.org/10.3390/molecules25020411

Shalaby K, Mostafa EM, Musa A, Moustafa AE, Ibrahim MF, Alruwaili NK, Zafar A, Elmowafy M (2021) Enhanced full-thickness wound healing via *Sophora gibbosa* extract delivery based on a chitosan/gelatin dressing incorporating microemulsion. Drug Dev Ind Pharm 47(2):215–224. https://doi.org/10.1080/03639045.2020.1863420

Shen Y, Feng ZM, Jiang JS, Yang YN, Zhang PC (2013) Dibenzoyl and isoflavonoid glycosides from *Sophora flavescens*: inhibition of the cytotoxic effect of D-galactosamine on human hepatocyte HL-7702. J Nat Prod 76(12):2337–2345. https://doi.org/10.1021/np400784v

Shi J, Han X, Wang J, Han G, Zhao M, Duan X, Mi L, Li N, Yin X, Shi H, Li C (2019) Matrine prevents the early development of hepatocellular carcinoma like lesions in rat liver. Exp Ther Med 18(4):2583–2591. https://doi.org/10.3892/etm.2019.7875

Shim JG, Yeom SH, Kim HJ, Choi YW, Lee DI, Song KY, Kwon SH, Lee MW (2005) Bone loss preventing effect of Sophorae Fructus on ovariectomized rats. Arch Pharm Res 28(1):106–110. https://doi.org/10.1007/s12272-010-2240-8

Shoukat RF, Shakeel M, Rizvi SA, Zafar J, Zhang Y, Freed S, Xu X, Jin F (2020) Larvicidal, ovicidal, synergistic, and repellent activities of *Sophora alopecuroides* and its dominant constituents against *Aedes albopictus*. Insects 11:246. https://doi.org/10.3390/insects11040246

Sim KM, Kim KH, Hwang GB, Seo S, Bae GN, Jung JH (2014) Development and evaluation of antimicrobial activated carbon fiber filters using *Sophora flavescens* nanoparticles. Sci Total Environ 493:291–297. https://doi.org/10.1016/j.scitotenv.2014.06.002

Simpson MG (2010) 8—diversity and classification of flowering plants: eudicots. Plant Syst. https://doi.org/10.1016/B978-0-12-374380-0.50008-7

Song P, Chen H, Wen Y, Lv Y, Deng S, Yang X (2018) Cytotoxic compounds from the seeds of *Sophora alopecuroides*. Nat Prod Commun 13(8):1934578X1801300818. https://doi.org/10.1177/1934578X1801300818

Song P, Chen H, Huang Y, Wen Y, Hao J, Lv Y, Deng S, Yang X (2019) Phenolic acids from the seeds of *Sophora alopecuroides*. Chem Nat Compd 55(5):835–838. https://doi.org/10.1007/s10600-019-02826-0

Song Z, Gong X, Ou C, Zhang W, Wang J, Yao C, Qin S, Yan B, Li Q, Wei K, Hou X (2021) Chloroform extract from *Sophora tonkinensis* Gagnep. inhibits proliferation, migration, invasion and promote apoptosis of nasopharyngeal carcinoma cells by silencing the PI3K/AKT/mTOR signaling pathway. J Ethnopharmacol 271:113879. https://doi.org/10.1016/j.jep.2021.113879

Su G, Yang W, Meng W, Wu Q, Luo Y, Ma X, Zhao S, Xie X, Guo GQ (2018) Anti-proliferation effects of ethanolic extracts from *Sophora moorcroftiana* seeds on human hepatocarcinoma HepG2 cell line. Nat Prod Res 32:1472–1475. https://doi.org/10.1080/14786419.2017.1353503

Sun P, Sun N, Wang Z, Guo J, He Y, Li H (2018) Matrine inhibits replication of porcine reproductive and respiratory syndrome virus (PRRSV) by influencing the activation of Nsp9. Pak Vet J 38(4):359–364. https://doi.org/10.29261/pakvetj/2018.079

Sun J, Zhao RH, Guo SS, Shi YJ, Bao L, Geng ZH, Gao YJ, Liu J, Li Q, Cui XI (2020) Effect of matrine sodium chloride injection on a mouse model combining disease with syndrome of human coronavirus pneumonia with cold-dampness pestilence attacking the lung. Acta Pharm Sin 55(3):366–373. https://doi.org/10.16438/J.0513-4870.2020-0222

Sweelam HM, Abd-Alla HI, Abdelwahab AB, Gabr MM, Kirsch G (2018) Secondary metabolites and biological activity of *Pentas* species: a minireview. J Adv Res 10:21–30. https://doi.org/10.1016/j.jare.2017.12.003

Ti H, Zhuang Z, Yu Q, Wang S (2021) Progress of plant medicine derived extracts and alkaloids on modulating viral infections and inflammation. Drug Des Devel Ther 15:1385–1408. https://doi.org/10.2147/DDDT.S299120

Tsai RT, Tsai CW, Liu SP, Gao JX, Kuo YH, Chao PM, Hung HS, Shyu WC, Lin SZ, Fu RH (2020) Maackiain ameliorates 6-hydroxydopamine and SNCA pathologies by modulating the PINK1/Parkin pathway in models of Parkinson's disease in *Caenorhabditis elegans* and the SH-SY5Y cell line. Int J Mol Sci 21(12):4455. https://doi.org/10.3390/ijms21124455

Turbat A, Rakk D, Vigneshwari A, Kocsubé S, Thu H, Szepesi Á, Bakacsy L, Škrbić D, Jigjiddorj EA, Vágvölgyi C, Szekeres A (2020) Characterization of the plant growth-promoting activities of endophytic fungi isolated from *Sophora flavescens*. Microorganisms 8(5):683. https://doi.org/10.3390/microorganisms8050683

ur Rashid H, Xu Y, Muhammad Y, Wang L, Jiang J (2019) Research advances on anticancer activities of matrine and its derivatives: an updated overview. Eur J Med Chem 161:205–238. https://doi.org/10.1016/j.ejmech.2018.10.037

ur Rashid H, Rasool S, Ali Y, Khan K, Martines MA (2020) Anti-cancer potential of sophoridine and its derivatives: recent progress and future perspectives. Bioorg Chem. https://doi.org/10.1016/j.bioorg.2020.103863

Uzor PF (2020) Alkaloids from plants with antimalarial activity: a review of recent studies. Evid-Based Compl Altern Med 2020:8749083. https://doi.org/10.1155/2020/8749083

Wang H, Tong Y, Li W, Zhang X, Gao X, Yong J, Zhao J, Koike K (2018a) Enhanced ultrasound-assisted enzymatic hydrolysis extraction of quinolizidine alkaloids from *Sophora alopecuroides* L. seeds. J Nat Med 72(2):424–432. https://doi.org/10.1007/s11418-017-1165-7

Wang H, Xiao D, Li W, Zhang X, Gao X, Yong J, Zhao J, Koike K (2018b) A simple and fast quantitative analysis of quinolizidine alkaloids and their biosynthetic precursor, lysine, in *Sophora alopecuroides* by hydrophilic interaction chromatography coupled with triple-quadrupole tandem mass spectroscopy. Phytochem Anal 29(5):500–506. https://doi.org/10.1002/pca.2757

Wang M, Liu G, Li H (2018c) Extraction of matrine from *Sophora flavescens* Ait. and evaluation of its inhibitory effects on human nasopharyngeal carcinoma CNE-2 cells. Food Sci Technol 38:333–337. https://doi.org/10.1590/fst.24117

Wang R, Wang S, Pan W, Li Q, Xia Z, Guan E, Zheng M, Pang G, Yang Y, Yi Z (2018d) Strategy of tobacco plant against black shank and tobacco mosaic virus infection via induction of PR-1, PR-4 and PR-5 proteins assisted by medicinal plant extracts. Physiol Molecul Plant Pathol 101:127–145. https://doi.org/10.1016/j.pmpp.2017.07.002

Wang X, Zheng R, Huang X, Mao Z, Wang N, Li H, Wen C, Shou D (2018e) Effects of alkaloids from *Sophora flavescens* on osteoblasts infected with *Staphylococcus aureus* and osteoclasts. Phytother Res 32(7):1354–1363. https://doi.org/10.1002/ptr.6069

Wang Y, Xia Z, Liu Z, Wan C, Luo X, Zhang L (2018f) Streptomyces carminius sp. nov., a novel actinomycete isolated from *Sophora alopecuroides* in Xinjiang, China. Antonie Van Leeuwenhoek 111(10):1807–1814. https://doi.org/10.1007/s10482-018-1069-x

Wang H, Xia C, Chen L, Zhao J, Tao W, Zhang X, Wang J, Gao X, Yong J, Duan JA (2019a) Phytochemical information and biological activities of quinolizidine alkaloids in *Sophora*: a

comprehensive review. Curr Drug Targets 20(15):1572–1586. https://doi.org/10.2174/1389450120666190618125816

Wang L, Li X, Zhang Y, Huang Y, Zhang Y, Ma Q (2019b) Oxymatrine ameliorates diabetes-induced aortic endothelial dysfunction via the regulation of eNOS and NOX4. J Cell Biochem 120(5):7323–7332. https://doi.org/10.1002/jcb.28006

Wang W, Nakashima KI, Hirai T, Inoue M (2019c) Anti-inflammatory effects of naturally occurring retinoid X receptor agonists isolated from *Sophora tonkinensis* Gagnep. via retinoid X receptor/liver X receptor heterodimers. J Nat Med 73(2):419–430. https://doi.org/10.1007/s11418-018-01277-1

Wang W, Nakashima KI, Hirai T, Inoue M (2019d) Neuroprotective effect of naturally occurring RXR agonists isolated from *Sophora tonkinensis* Gagnep. on amyloid-β-induced cytotoxicity in PC12 cells. J Nat Med 73(1):154–162. https://doi.org/10.1007/s11418-018-1257-z

Wang H, Tong Y, Xiao D, Xia B (2020a) Involvement of mTOR-related signaling in antidepressant effects of Sophoraflavanone G on chronically stressed mice. Phytother Res. https://doi.org/10.1002/ptr.6675

Wang R, Deng X, Gao Q, Wu X, Han L, Gao X, Zhao S, Chen W, Zhou R, Li Z, Bai C (2020b) *Sophora alopecuroides* L.: an ethnopharmacological, phytochemical, and pharmacological review. J Ethnopharmacol 248:112172. https://doi.org/10.1016/j.jep.2019.112172

Wang XF, Zhu Z, Hao TT, Fang QQ, Jiang K, Qu SJ, Zuo JP, Zhu W, He SJ, Tan CH (2020c) Alopecines A-E, five chloro-containing matrine-type alkaloids with immunosuppressive activities from the seeds of *Sophora alopecuroides*. Bioorg Chem 99:103812. https://doi.org/10.1016/j.bioorg.2020.103812

Wei G, Chen Y, Guo X, Wei J, Dong L, Chen S (2021) Biosyntheses characterization of alkaloids and flavonoids in *Sophora flavescens* by combining metabolome and transcriptome. Sci Rep 11(1):1–2. https://doi.org/10.1038/s41598-021-86970-0

Wu B, Yue H, Zhou GH, Zhu YY, Wu TH, Wen JF, Cho KW, Jin SN (2019a) Protective effects of oxymatrine on homocysteine-induced endothelial injury: involvement of mitochondria-dependent apoptosis and Akt-eNOS-NO signaling pathways. Eur J Pharmacol 864:172717. https://doi.org/10.1016/j.ejphar.2019.172717

Wu D, Zhu X, Kang X, Huang H, Yu J, Pan J, Zhang X (2019b) The protective effect of sophocarpine in osteoarthritis: an in vitro and in vivo study. Int Immunopharmacol 67:145–151. https://doi.org/10.1016/j.intimp.2018.11.046

Yang C, Yu Y, Wu F, Wu Y, Feng J, Yan L, Han L, Ren J, Nie L, Zhou R (2018) Vasodilatory effects of aloperine in rat aorta and its possible mechanisms. Chin J Physiol 61:293–301. https://doi.org/10.4077/CJP.2018.BAH609

Yang J, Fei J, Su H, Tian H, Huang S, Yang P, Mao D, Hu S (2019) Flavonoids from the flowers of *Sophora davidii* and their anti-tobacco mosaic virus activities. Nat Prod Commun 14(6):1934578X19856786. https://doi.org/10.1177/1934578X19856786

Yang G, Zeng R, Song X, Li T, Liu C, Ni L (2020a) Sophocarpine prevents cigarette smoke-induced restenosis in rat carotid arteries after angioplasty. Ann Palliat Med 9(4):1622–1630. https://doi.org/10.21037/apm-19-568

Yang J, Cao MX, Hu WY, Wei YY, Hu TJ (2020b) *Sophora subprotsrata* polysaccharides suppress the inflammatory reaction of RAW264. 7 cells infected with PCV2 via regulation NF-κB/MAPKs/c-Jun signal pathway and histone acetylation modification. Int J Biol Macromol 159:957–965. https://doi.org/10.1016/j.ijbiomac.2020.05.128

Yang Y, Tian Y, Zhang Q, Li X, Fu Y, Pei H, Lui D (2020c) Comparative effects of flavonoids from Fructus Sophorae on rat osteoblasts in vitro. Rec Nat Prod 14(1):65–76. https://doi.org/10.25135/rnp.138.19.04.1262

Yang YN, Zhu H, Yuan X, Zhang X, Feng ZM, Jiang JS, Zhang PC (2021) Seven new prenylated flavanones from the roots of *Sophora flavescens* and their anti-proliferative activities. Bioorg Chem 109:104716. https://doi.org/10.1016/j.bioorg.2021.104716

Yao XQ, Zhang YH, Long W, Liu PX (2012) Oxysophoridine suppresses the growth of hepatocellular carcinoma in mice: in vivo and cDNA microarray studies. Chin J Integr Med 18:209–213. https://doi.org/10.1007/s11655-012-1001-6

Yao CL, Zhang JQ, Li JY, Wei WL, Wu SF, Guo DA (2021) Traditional Chinese medicine (TCM) as a source of new anticancer drugs. Nat Prod Rep. https://doi.org/10.1039/D0NP00057D

Ye Y, Wang Y, Yang Y, Tao L (2020) Aloperine suppresses LPS-induced macrophage activation through inhibiting the TLR4/NF-κB pathway. Inflamm Res 7:1–9. https://doi.org/10.1007/s00011-019-01313-0

Yin W, Han J, Zhang Z, Han Z, Wang S (2018) Aloperine protects mice against bleomycin-induced pulmonary fibrosis by attenuating fibroblast proliferation and differentiation. Sci Rep 8:6265. https://doi.org/10.1038/s41598-018-24565-y

Yoo H, Kang M, Pyo S, Chae HS, Ryu KH, Kim J, Chin YW (2017) SKI3301, a purified herbal extract from Sophora tonkinensis, inhibited airway inflammation and bronchospasm in allergic asthma animal models in vivo. J Ethnopharmacol 206:298–305. https://doi.org/10.1016/j.jep.2017.05.012

Yoo JM, Park KI, Yang JH, Cho WK, Lee B, Ma JY (2019) Anti-allergic actions of F-PASA, a novel herbal cocktail, in IgE/antigen-mediated allergic responses in RBL-2H3 cells and passive cutaneous anaphylaxis in mice. Phytomedicine 55:229–237. https://doi.org/10.1016/j.phymed.2018.06.034

Youn HJ, Lakritz J, Kim DY, Rottinghaus GE, Marsh AE (2003) Anti-protozoal efficacy of medicinal herb extracts against *Toxoplasma gondii* and *Neospora caninum*. Vet Parasitol 116:7–14. https://doi.org/10.1016/s0304-4017(03)00154-7

Zahra SA, Iqbal J, Abbasi BA, Yaseen T, Hameed A, Shahbaz A, Kanwal S, Mahmood T, Ahmad P (2021) Scanning electron microscopy of *Sophora alopecuroides* L. seeds and their cytotoxic, antimicrobial, antioxidant, and enzyme inhibition potentials. Microsc Res Tech. https://doi.org/10.1002/jemt.23740

Zhang F, Hu C, Cheng S, Wang S, Li B, Cao D, Fan H, Pan R, Yang M, Xu Y (2018a) The investigation of the effect and mechanism of *Sophora moorcroftiana* alkaloids in combination with albendazole on echinococcosis in an experimental rats model. Evid Based Compl Altern Med. https://doi.org/10.1155/2018/3523126

Zhang YB, Luo D, Yang L, Cheng W, He LJ, Kuang GK, Li MM, Li YL, Wang GC (2018b) Matrine-type alkaloids from the roots of *Sophora flavescens* and their antiviral activities against the hepatitis B virus. J Nat Prod 81:2259–2265. https://doi.org/10.1021/acs.jnatprod.8b00576

Zhang YB, Yang L, Luo D, Chen NH, Wu ZN, Ye WC, Li YL, Wang GC (2018c) Sophalines E-I, Five quinolizidine-based alkaloids with antiviral activities against the hepatitis B virus from the seeds of *Sophora alopecuroides*. Organ Lett 20(18):5942–5946. https://doi.org/10.1021/acs.orglett.8b02637

Zhang H, Chen L, Sun X, Yang Q, Wan L, Guo C (2020a) Matrine: a promising natural product with various pharmacological activities. Front Pharmacol 11:588. https://doi.org/10.3389/fphar.2020.00588

Zhang Y, Gu D, He S, Meng J, Wang J, Wang Y, Wang Y, Tian J, Yang Y (2020b) Enzyme reaction-guided identification of active components from the flowers of *Sophora japonica* var. violacea. Food Funct. https://doi.org/10.1039/d0fo00625d

Zhang YN, Zhang QY, Li XD, Xiong J, Xiao SQ, Wang Z, Zhang ZR, Deng CL, Yang XL, Wei HP, Yuan ZM, Ye HQ, Zhang B (2020c) Gemcitabine, lycorine and oxysophoridine inhibit novel coronavirus (SARS-CoV-2) in cell culture. Emerg Microb Infect

9(1):1170–1173. https://doi.org/10.1080/22221751.2020.1772676

Zhang M, Li A, Yang Q, Li J, Wang L, Liu X, Huang Y, Liu L (2021a) Beneficial effect of alkaloids from *Sophora alopecuroides* L. on CUMS-induced depression model mice via modulating gut microbiota. Front Cell Infect Microbiol 11:665159. https://doi.org/10.3389/fcimb.2021.665159

Zhang SN, Li XZ, Tan LY, Zhu KY (2021b) A review of pharmacological and toxicological effects of *Sophora tonkinensis* with bioinformatics prediction. Am J Chin Med 49(2):359–389. https://doi.org/10.1142/S0192415X21500178

Zhang ZJ, Dong SW, Gao DD, Du XY, Xie YQ, Xia XS, Li RT (2021c) Unusual matrine–adenine hybrids isolated from *Sophora davidii* and their inhibitory effects on human cytomegalovirus. Phytochemistry 190:112842. https://doi.org/10.1016/j.phytochem.2021.112842

Zhao J, Zhang G, Li M, Luo Q, Leng Y, Liu X (2018) Neuro-protective effects of aloperine in an Alzheimer's disease cellular model. Biomed Pharmacother 108:137–143. https://doi.org/10.1016/j.biopha.2018.09.008

Zhao WY, Xiao W, Hao HQ, Zheng K, Zhang DD, Jin Q, Zhu QS (2021) Comparison of activity and components of *Sophora flavescens* root and seed. IOP Conf Ser 705(1):012021. https://doi.org/10.1088/1755-1315/705/1/012021

Zhou Y, Wei Y, Liu H, Zhang G, Wu XA (2010) Preparation and in vitro evaluation of ethosomal total alkaloids of *Sophora alopecuroides* loaded by a transmembrane pH-gradient method. AAPS PharmSciTech 11(3):1350–1358. https://doi.org/10.1208/s12249-010-9509-6

Zhou R, Xu Q, Xu Y, Xiong A, Wang Y, Ma P (2016) Oxymatrine attenuated isoproterenol-induced heart failure in rats via relation of COX-2/PGI2 pathway. Biomed Pharmacother 84:1359–1366. https://doi.org/10.1016/j.biopha.2016.10.070

Zhou B, Yu Y, Yu L, Que B, Qiu R (2018a) Sipi soup inhibits cancer-associated fibroblast activation and the inflammatory process by downregulating long non-coding RNA HIPK1-AS. Mol Med Rep 18(2):1361–1368. https://doi.org/10.3892/mmr.2018.9144

Zhou BG, Wei CS, Zhang S, Zhang Z, Gao HM (2018b) Matrine reversed multidrug resistance of breast cancer MCF-7/ADR cells through PI3K/AKT signaling pathway. J Cell Biochem 119(5):3885–3891. https://doi.org/10.1002/jcb.26502

Zhou CH, Shi ZL, Meng JH, Hu B, Zhao CC, Yang YT, Yu W, Chen ZX, Heng BC, Parkman VJ, Jiang S (2018c) Sophocarpine attenuates wear particle-induced implant loosening by inhibiting osteoclastogenesis and bone resorption via suppression of the NF-κB signalling pathway in a rat model. Br J Pharmacol 175(6):859–876. https://doi.org/10.1111/bph.14092

Zhou GZ, Shi YY, Cui LS, Li A, Wang QQ, Liu M (2018d) Oxymatrine induces A549 human non-small lung cancer cell apoptosis via extrinsic and intrinsic pathways. Mol Med Rep 17(1):1071–1076. https://doi.org/10.3892/mmr.2017.7982

Zhou YJ, Guo YJ, Yang XL, Ou ZL (2018e) Anti-cervical cancer role of matrine, oxymatrine and *Sophora flavescens* alkaloid gels and its mechanism. J Cancer 9(8):1357. https://doi.org/10.7150/jca.22427

Zhou H, Li J, Sun F, Wang F, Li M, Dong Y, Fan H, Hu D (2020) A review on recent advances in aloperine research: pharmacological activities and underlying biological mechanisms. Front Pharmacol 11:538137. https://doi.org/10.3389/fphar.2020.538137

Zhu L, Huang S, Li J, Chen J, Yao Y, Li L, Guo H, Xiang X, Deng J, Xiong J (2020) Sophoridine inhibits lung cancer cell growth and enhances cisplatin sensitivity through activation of the p53 and Hippo signaling pathways. Gene. https://doi.org/10.1016/j.gene.2020.144556

Zhuang H, Dai X, Zhang X, Mao Z, Huang H (2020) Sophoridine suppresses macrophage-mediated immunosuppression through TLR4/IRF3 pathway and subsequently upregulates CD8+ T cytotoxic function against gastric cancer. Biomed Pharmacother 121:109636. https://doi.org/10.1016/j.biopha.2019.109636

Zou Y, Sarem M, Xiang S, Hu H, Xu W, Shastri VP (2019) Autophagy inhibition enhances Matrine derivative MASM induced apoptosis in cancer cells via a mechanism involving reactive oxygen species-mediated PI3K/Akt/mTOR and Erk/p38 signaling. BMC Cancer 19(1):949. https://doi.org/10.1186/s12885-019-6199-7