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Review

A systematic review on traditional medicine *Toddalia asiatica* (L.) Lam.: Chemistry and medicinal potential

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ABSTRACT

Toddalia asiatica (L.) Lam., belonging to *Toddalia* genus of Rutaceae family, is a folk medicine in China used for hundreds of years. The whole plant can be used as medicine, especially the root that used to be applied in the folk. In recent decades, with the in-depth research from domestic and foreign researchers, it has gradually been discovered that the chemical components in *T. asiatica* are mainly coumarins and alkaloids. Its pharmacological effects are manifested in anti-inflammatory and analgesic, hemostatic coagulation, anti-tumor, treatment of cardiovascular diseases, etc. It has a wide range of clinical applications and significant effects on rheumatism, pain, wound bleeding, and bruises. Due to its important research value, in this article, the chemical compositions and pharmacological effects of *T. asiatica* are comprehensively expounded in recent years in order to provide a reference for the related research and application of this medicinal material, which were carried out through a bibliometric search using the Science Citation Index- Expanded (SCIE) database, web of science, Google scholar and Chinese National Knowledge Infrastructure (CNKI) and all that.

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1. Introduction

Toddalia asiatica Lam., a plant of the genus *Toddalia* of the family Rutaceae, earliestly recorded in "Plant name and real picture ", is a woody vine, and also the only plant in the genus (Xia and Liu, 2007). There are many aliases for *T. asiatica*, such as Jian xue fei, San bai bang, Fei long zhuang xue, Da jiu jia and so forth (Shi et al., 2011). The plant generally grows in secondary forests of roadsides, mountain forests, thickets and small trees, mainly distributed in tropical Africa and southeastern Asia, especially in the south of Wuling Mountainous areas in China (Tsai et al., 1998, Watanabe et al., 2014, Zhang et al., 2017). The old stem is brown with longitudinally lobed and protruding yellow-gray lenticels owning a thick cork layer, however, the young shoots have small round lenticels. In addition, there are many downward curved sharp thorns on the stem branches and leaf axes. The leaflets have no near stalk, while dense transparent oil spots can be seen in the light. After kneading, the aroma is similar to that of citrus leaves. The male inflorescences are panicles and umbellate but the female inflorescences are thyrses, which can blossom all the year round (Xia and Liu, 2007). Its fruit is scarlet or orange-red, 8–10 mm in diameter or slightly larger, with multiple longitudinal shallow grooves which becomes more pronounced after being dehydrated. Seeds are about 5–6 mm long on the brownish black seed coat with tiny pits (Xia and Liu, 2007).

T. asiatica has played a very important role in traditional medicine, and the whole plant can be used as medicine, especially its root often used in the folk (Yang et al., 2013, Li et al., 2018). The studies of chemical composition showed that the main chemical components were alkaloids and coumarins in *T. asiatica* (Wang et al., 2009, Hu et al., 2014, Sukieum et al., 2018, Lin and Chen, 2020). Otherwise, there were also some triterpenes (Huang et al., 2005), flavonoids (Shi et al., 2014), phenolic acids (Phatchana and Yenjai, 2014), lignans (Tsai et al., 1998) and what not. Modern pharmacological studies have suggested that *T. asiatica* shows anti-inflammatory and analgesic (Hao et al., 2004, Yang et al., 2013, Lu et al., 2015), antioxidant (Tian et al., 2011, Stephen Irudayaraj et al., 2012, Chen and Long, 2013, Tian et al., 2013), antibacterial (Ding et al., 2007, Hu et al., 2014), cardiovascular protection (Ren et al., 1993, He and Ren, 1998, Ren and He, 1998, He and Ren, 1999), anti-tumor (Iwasaki et al., 2006, Iwasaki et al., 2010, Li et al., 2018) and other pharmacological effects. According to our literature researches, this paper would review the studies on the chemical constituents and pharmacological effects of *T. asiatica* systematically in the following sections.

In this study, we employed the database such as Science Citation Index- Expanded (SCIE) database, web of science, Google scholar and Chinese National Knowledge Infrastructure (CNKI) et al., searching for researches that have been reported by scholars both at home and abroad during 1976–2020, in which '*T. asiatica*' including 'San bai bang' and 'Fei long zhuang xue' was used as the main key words. Otherwise, folk medicine, chemical composition and pharmacological effect were also used for assisting us in looking for more valuable information in all directions, the aim of which is to make the review more detailed and systematic to help researchers for their studies. The detail research procedure was shown in Fig. 1.

2. Chemical composition

So far, a total of more than 165 compounds have been reported from *T. asiatica*, including 69 coumarins, 69 alkaloids, 8 terpenoids, 5 flavonoids, and 14 other compositions such as lipids, alcohols, phenolic acids, lignans, steroids and fatty acids. Among them, the most characteristic compounds for *T. asiatica* are coumarins and alkaloids.

2.1. Coumarins and its glycosides

T. asiatica is rich in coumarins, including some simple coumarins, furanocoumarins, pyrancoumarins, and dicoumarin, summarized in Table 1. The structure of each corresponding chemical component were shown in Fig. 2. Coumarins are one of the important active ingredients in *T. asiatica*.

Japanese scholar Ishii *et al.,* (Ishii et al., 1991a,b) isolated 12 known simple coumarins from methanol extracts of *T. asiatica* root collected from Taiwan, China, which are toddaculin, coumurrayin, toddalenol, 6-(2-hydroxy-3-methoxy-3-methylbutyl)-5, 7-dimethoxycoumarin, toddalolactone, 5,7,8-trimethoxycoumarin, 5-methoxysuberenon, 8-(3,3-Dimethylallyl)-6, 7-dimethoxycoumarin, 8-formyllimettin), 6-(3-chloro-2-hydroxy-3-methylbutyl)7-dimethoxycoumarin, 6-formyllimettin, toddalenone. Oketch-Rabah *et al.,* (Oketch-Rabah et al., 2000) isolated a new coumarin compound (5,7-dimethoxy-(8-(3′-hydroxy-3′-methyl-1′-butenyl)-coumarin) from the ethyl acetate extract of *T. asiatica* root using a separation method guided by biological activity. Wang *et al.,* (Wang et al., 2009) isolated two simple coumarin compounds from the 95% ethanol extract of *T. asiatica* grown in Yunnan province, China, which are 8-geranyloxy-5,7-dimethoxycoumarin and 7-geranyloxy-5-methoxycoumarin. Qiu *et al.,* (Qiu et al., 2012) using microwave-assisted extraction isolated three furanocoumarins that were pimpinellin, isopimpinellin, and phellopterin, from *T. asiatica* root purchased from the Chinese herbal wholesale market in Hebei province, China. Phatchana and Chavi (Phatchana and Yenjai, 2014) identified three new coumarins that were 8-(3′,7′-dimethyl-7′-hydroxy-2′E,5′E-octadienyl)oxy-5,7-dimethoxycoumarin, 8-(3′,7′-dimethyl-7′-hydroxy-2′E,5′Z-octadienyl)oxy-5,7-dimethoxycoumarin, and 6-(3-Methyl-1,3-butadienyl)-5, 7-dimethoxycoumarin, and 13 known compounds. Tsai *et al.,* (Tsai et al., 1998) isolated 30 compounds from the wood of Formosan *T. asiatica*, including a new coumarin identified as toddanin. By bioassay-guided fractionation of the ethanol extract of *T. asiatica* roots, Lin *et al.,* (Lin et al., 2014) isolated 21 coumarins, including seven new prenylated coumarins, that were toddalin A, 3‴-O-demethyltoddalin A, toddalin B, toddalin C, toddalin D, ent-toddalolactone, and (−)-toddalolactone 3′-O-β-D-glucopyranoside. Ishii *et al.,* (Ishii et al., 1983) isolated a new coumarin toddalenone, and ten known coumarins that were toddalolactone, isopimpinellin, coumarrayin, toddanone, toddaculin, toddanol, 5,7,8-trimethoxycoumarin, toddasin, 5,7-Dimethoxy-6-(3′-chloro-2′-hydroxy-3′-methylbutyl) coumarin, and 8-(3,3-Dimethylallyl)-6,7-dimethoxycoumarin. Nyahanga *et al.,* (Nyahanga et al., 2013) obtained 8 compounds including 6 coumarins characterized as aculeatin, toddaculin, isopimpinellin, suberosin, toddalenol, and toddalolactone from chromatographic fractionation of n-hexane,

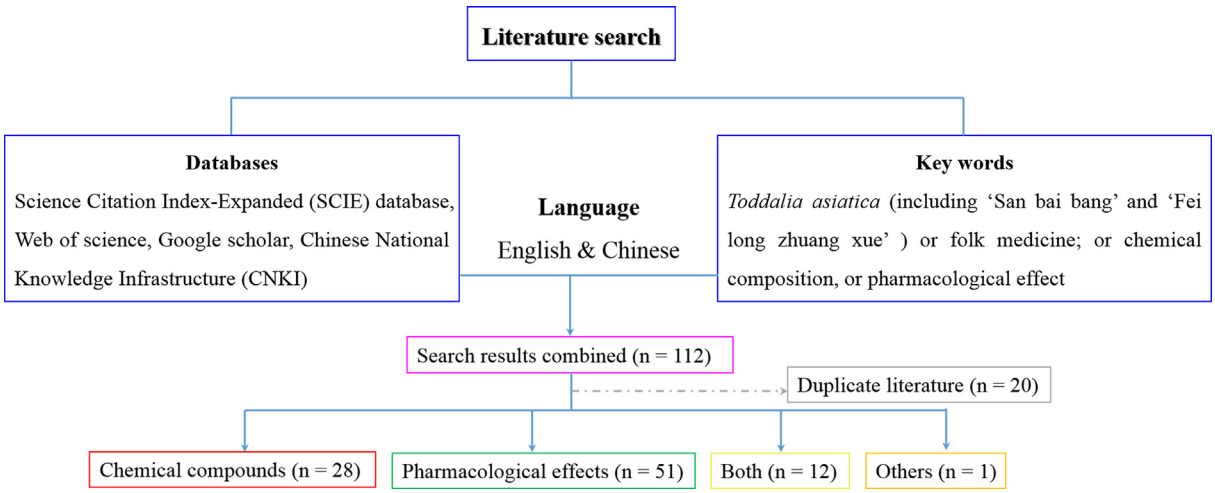

Fig. 1. Flow diagram of study selection.

ethyl acetate and methanol extracts of *T. asiatica* root bark. Moreover, two coumarin glycosides, (−)-toddalolactone 2′-*O*-*β*-D-glucopyranoside and (+) –toddalolactone-3′-*O*-*β*-D-glucopyranoside, were firstly separated using two-dimensional HPLC (Li et al., 2020). There were also some other coumarins reported in the literature, quoted in Table 1, and would not be described in detail.

2.2. Alkaloids

Alkaloids, second only to coumarins, are another mainly kind components in *T. asiatica*, such as quinoline alkaloids, phenanthroline alkaloids, and other alkaloids (summarized in Table 2 and Fig. 3). In recent years, with the continuous researches reported at home and abroad, scholars have found that alkaloids in *T. asiatica* played an important role in anti-inflammatory, analgesic, and anti-tumor effects (Hao et al., 2004, Hu et al., 2014). A rapid method using ultrafiltration liquid chromatography combined with stepwise flow rate counter-current chromatography was developed to screen and purify alkaloid that could be used as neuraminidase inhibitors (Cao et al., 2019). Quinoline alkaloids in the plant are primarily N-methylflindersine, toddacoumalone, skimmianine, integriquinolone, dictamnine, hannine, and oxyterihannine, etc. (Tsai et al., 1997, Tsai et al., 1998). Benzophenanthridine alkaloids in the plant are principally oxychelerythrine, des-N-methylchelerythrine, oxyavicine, oxyavicine, avicine, chelerythrine, chelerythrine-φ-cyanide, dihydroavicine, dihydrochelerythrine, 8-acetonyldihydrochelerythrin, 8-methoxydihydrochelerythrine, dihydronitidine, nitidine, oxynitidine, 8-hydroxydihydrochelerythrine, toddalidimerine and 6-methylnitidine etc. (Sharma et al., 1981a,b, Ishii et al., 1991a,b, Tsai et al., 1997, Tsai et al., 1998). The other ones are chiefly γ-fagarine, toddaquinoline, arnottianaide, methyltoddaliamide, isocoreximine, protopine, toddaliamide, N,N′-dicyclohexylurea, N, N'-dicyclohexyloxamide, methyltoddaliamide, toddaliamide, flindersine, etc. (Tsai et al., 1997, Tsai et al., 1998, Duraipandiyan and Ignacimuthu, 2009). In addition, three known alkaloids, 8-acetonyldihydronitidine, 8-acetonyldihydroavicine and decarine, were firstly discovered from the genus *Toddalia* and 8-acetonyldihydronitidine has showed strong inhibitory effect against phosphodiesterase-4 with an IC_{50} value of 5.14 μM (Lin and Chen, 2020).

2.3. Terpenoids

Except alkaloids and coumarins in *T. asiatica*, terpenoids, an important source of bioactive ingredients of natural medicines, are another important natural monomeric component in this medicinal material, summarized in Table 3 and Fig. 4. Huang *et al* (Huang et al., 2005) collected six triterpenoids that were 2α,3α,19α-trihydroxy-11-oxo-urs-12-en-28-oic acid, 2α,3α-dihydroxy-19-oxo-18,19-seco-urs-11,13(18)-diene-28-oic acid, 2α,3β,19α-trihydroxy-olean-11, 13(18)-dien-28-oic acid, 2α,3α,1lα,19α-tetrahydroxy-urs-12-en-28-oic acid, euscaphic acid, and arjunic acid from the ethanol extract of *T. asiatica* stem from Baiji Township, Nanning City, Guangxi Zhuang Autonomous Region, China. Moreover, another triterpene compound, β-amyrin (Ishii et al., 1983), was isolated from *T. asiatica*. Recently, a new sesquiterpene, (3S,4aR, 5S,8R)-8-Hydroxy-3-((R)-2-(hydroxymethyl) oxiran-2-yl) −4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one, was firstly separated from *T. asiatica* (Lin and Chen, 2020).

2.4. Flavonoids

Flavonoids are an important member in natural products. It also existed in *T. asiatica*, including hesperidin, hesperetin, neohesperidin, diosmin and hesperetin-7-O-β-D-glucopyranoside, seen in Table 4 and Fig. 5. (Chen et al., 2013, Shi et al., 2014).

2.5. Other compounds

Except the above-mentioned major components, *T. asiatica* also contains phenolic compounds such as chlorogenic acid, benzoic acid, and nelumol A; Lignin compounds: dl-lyoniresinol, and dl-syringaresinol; Quinones: 2,6-dimethoxy-p-benzoquinone; Steroids: β-sitosterol, daucosterol and stigmasterol; Fatty acids: octadecanoic acid, oleic acid, linoleic acid, and hexacosanoic acid. These compounds were summarized in Table 5 and Fig. 6.

3. Pharmacological effects of *T. asiatica*

At present, researches on the pharmacological activities of *T. asiatica* show that extracts and chemical components of *T. asiatica* have some biological activities including anti-inflammatory and analgesic, hemostatic coagulation, antibacterial, anti-oxidant and

Table 1
Coumarins reported from *T. asiatica*.

Num.	Compound name	Molecular formula	Molecular weight	Reference
1	Toddasin	$C_{32}C_{32}O_5$	544.210	(Sharma et al., 1980)
2	Dihydrotoddasin	$C_{32}H_{32}O_8$	544.601	(Sharma et al., 1980)
3	5,7-Dimethoxy-6-(3′-chloro-2′-hydroxy-3′-methylbutyl) coumarin	$C_{16}H_{19}ClO_5$	326.777	(Sharma et al., 1981a,b)
4	Toddaculin	$C_{16}H_{18}O_4$	274.317	(Ishii et al., 1983)
5	Toddalenone	$C_{15}H_{14}O_5$	274.273	(Ishii et al., 1983)
6	8-(3,3-Dimethylallyl)-6,7-dimethoxycoumarin	$C_{16}H_{20}O_4$	276.328	(Ishii et al., 1983)
7	6-Formyllimettin	$C_{12}H_{10}O_5$	234.205	(Ishii et al., 1983)
8	Toddacoumalone	$C_{31}H_{31}NO_6$	513.590	(Ishii et al., 1991a,b)
9	Toddanone	$C_{16}H_{18}O_5$	290.316	(Chen et al., 1993)
10	Toddanol	$C_{16}H_{18}O_5$	290.316	(Chen et al., 1993)
11	Toddalolactone methyl ether	$C_{17}H_{22}O_6$	322.358	(Chen et al., 1993)
12	Toddasiatin	$C_{30}H_{26}O_8$	514.532	(Tsai et al., 1997)
13	(+)-Toddanol	$C_{16}H_{18}O_5$	290.316	(Tsai et al., 1998)
14	5,7,8-Trimethoxycoumarin	$C_{12}H_{12}O_5$	236.224	(Tsai et al., 1998)
15	6-Methoxyseselin	$C_{15}H_{14}O_4$	258.274	(Tsai et al., 1998)
16	Toddalolactone	$C_{16}H_{20}O_6$	308.331	(Tsai et al., 1998)
17	Ulopterol	$C_{15}H_{18}O_5$	278.305	(Tsai et al., 1998)
18	Toddanin	$C_{15}H_{16}O_5$	276.289	(Tsai et al., 1998)
19	Phellopterin	$C_{17}H_{16}O_5$	300.311	(Tsai et al., 1998, Zhang et al., 2017)
20	5,7-Dimethoxy-(8-(3′-hydroxy-3′-methyl-1′-butenyl)-coumarin	$C_{16}H_{18}O_5$	290.30	(Oketch-Rabah et al., 2000)
21	8-(Geranyloxy)-5,7-dimethyloxycoumarin	$C_{21}H_{26}O_5$	358.434	(Wang et al., 2009)
22	7-Geranyloxy-5-methoxycoumarin	$C_{20}H_{26}O$	330.418	(Wang et al., 2009)
23	Norbraylin	$C_{14}H_{12}O_4$	244.247	(Shi et al., 2013)
24	Suberosin	$C_{15}H_{16}O_3$	244.286	(Nyahanga et al., 2013)
25	Toddalenol	$C_{16}H_{18}O_5$	290.31	(Nyahanga et al., 2013)
26	Isopimpinellin	$C_{13}H_{10}O_5$	246.219	(Liu et al., 2014)
27	Coumarrayin	$C_{16}H_{18}O_4$	274.317	(Lin et al., 2014)
28	5-Methoxyseselin	$C_{15}H_{14}O_4$	258.274	(Lin et al., 2014)
29	*cis*-Dehydrocoumurrayin	$C_{16}H_{16}O_4$	272.301	(Lin et al., 2014)
30	Gleinadiene	$C_{16}H_{16}O_4$	272.301	(Lin et al., 2014)
31	Toddacoumaquinone	$C_{23}H_{18}O_7$	406.392	(Lin et al., 2014)
32	Toddalin B	$C_{32}H_{38}O_{10}$	582.648	(Lin et al., 2014)
33	3‴ -O-Demethyltoddalin A	$C_{32}H_{36}O_{14}$	644.629	(Lin et al., 2014)
34	Toddalin A	$C_{33}H_{38}O_{14}$	658.656	(Lin et al., 2014)
35	Toddalin C	$C_{32}H_{40}O_{12}$	616.662	(Lin et al., 2014)
36	Toddalin D	$C_{32}H_{38}O_{11}$	598.647	(Lin et al., 2014)
37	ent-Toddalolactone	$C_{16}H_{20}O_6$	308.331	(Lin et al., 2014)
38	(−)-Toddalolactone 3′-O-β-D-glucopyranoside	$C_{22}H_{30}O_{11}$	470.474	(Lin et al., 2014)
39	5-Methoxy-8-hydroxy psoralen	$C_{12}H_8O_5$	232.193	(Phatchana and Yenjai, 2014)
40	5-Methoxy-8-geranyloxypsoralen	$C_{22}H_{24}O_5$	368.430	(Phatchana and Yenjai, 2014)
41	8-Hydroxy-5,7-dimethoxycoumari	$C_{11}H_{10}O_5$	222.197	(Phatchana and Yenjai, 2014)
42	Artanin	$C_{16}H_{18}O_5$	290.316	(Phatchana and Yenjai, 2014)
43	Toddalosin	$C_{32}H_{34}O_9$	562.617	(Phatchana and Yenjai, 2014)
44	8-(3′,7′-dimethyl-7′-hydroxy-2′E,5′E-octadienyl)oxy-5,7-dimethoxycoumarin	$C_{21}H_{26}O_6$	374.434	(Phatchana and Yenjai, 2014)
45	8-(3′,7′-dimethyl-7′-hydroxy-2′E,5′Z-octadienyl)oxy-5,7-dimethoxycoumarin	$C_{21}H_{26}O_6$	374.434	(Phatchana and Yenjai, 2014)
46	6-(3-Methyl-1,3-butadienyl)-5,7-dimethoxycoumarin	$C_{16}H_{16}O_4$	272.301	(Phatchana and Yenjai, 2014)
47	Omphalocarpin	$C_{17}H_{22}O_6$	332.350	(Tong et al., 2014)
48	Aculeatin	$C_{16}H_{18}O_5$	290.316	(Watanabe et al., 2014)
49	Toddayanin	$C_{16}H_{18}O_5$	290.316	(Hirunwong et al., 2016)
50	7-Methoxy-2H-1-benzopyran-2-one	$C_{10}H_{10}O_3$	170.185	(Hirunwong et al., 2016)
51	5,7-Dimethoxy-2H-1-benzopyran-2-one	$C_{13}H_{16}O_4$	236.264	(Hirunwong et al., 2016)
52	7-Geranyloxy-coumarin	$C_{10}H_{10}O_3$	170.185	(Hirunwong et al., 2016)
53	Luvangetin	$C_{15}H_{14}O_4$	258.269	(Tang et al., 2016)
54	(+)-Spirotriscoumarin A	$C_{47}H_{46}O_{12}$	802.306	(Tang et al., 2016)
55	(−)-Spirotriscoumarin A	$C_{47}H_{46}O_{12}$	802.306	(Tang et al., 2016)
56	(−)-Spirotriscoumarin B	$C_{47}H_{46}O_{12}$	802.307	(Tang et al., 2016)
57	(+)-Spirotriscoumarin B	$C_{47}H_{46}O_{12}$	802.307	(Tang et al., 2016)
58	(+)-Toddalin E	$C_{16}H_{16}O_6$	304.086	(Li et al., 2017)
59	(−)-Toddalin E	$C_{16}H_{16}O_6$	304.086	(Li et al., 2017)
60	(+)-Toddalin F	$C_{16}H_{18}O_7$	311.11	(Li et al., 2017)
61	(−)-Toddalin F	$C_{16}H_{18}O_7$	311.11	(Li et al., 2017)
62	(±)-Toddalin G	$C_{16}H_{16}O_6$	304.085	(Li et al., 2017)
63	Toddalin H	$C_{17}H_{20}O_5$	304.13	(Li et al., 2017)
64	7-Geranyloxy-5-hydroxycoumarin	$C_{19}H_{22}O_4$	314.144	(Li et al., 2017)
65	2′O-((Z,Z)-Octadeca-9,12-dienoyl)-ent-toddalolactone	$C_{34}H_{50}O_7$	570.36	(Li et al., 2017)
66	Pimpinellin	$C_{13}H_{10}O_5$	246.219	(Zhang et al., 2017)
67	2′R-acetoxytoddanol	$C_{18}H_{20}O_6$	332.14	(Sukieum et al., 2018)
68	(−)-Toddalolactone 2′-O-β-D-glucopyranoside	$C_{22}H_{30}O_{11}$	470.47	(Li et al., 2020)
69	(+)-Toddalolactone 3′-O-β-D-glucopyranoside	$C_{22}H_{30}O_{11}$	470.47	(Li et al., 2020)

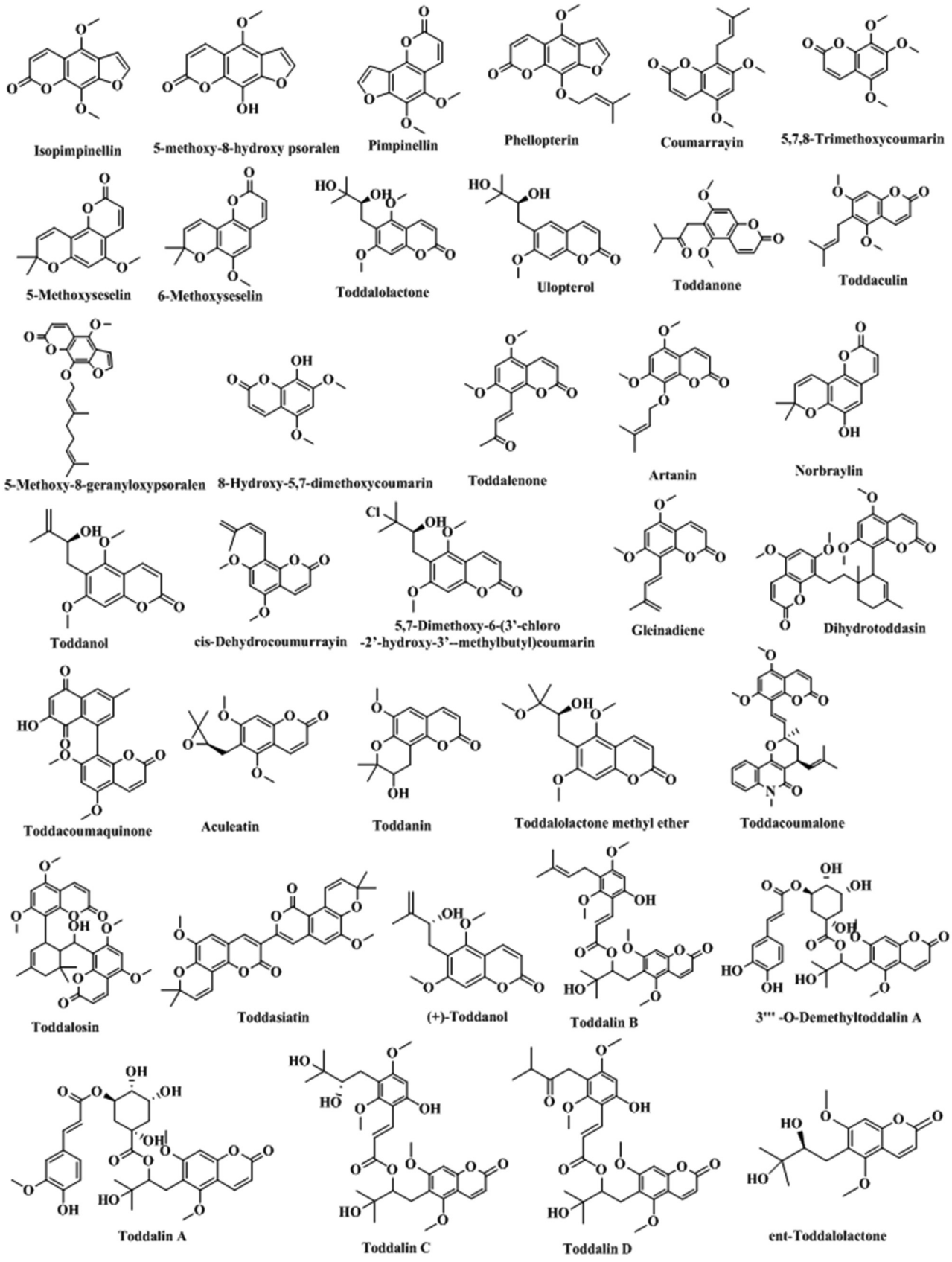

Fig. 2. Structure and corresponding chemical name of coumarins and its derivants from *Toddalia asiatica.*

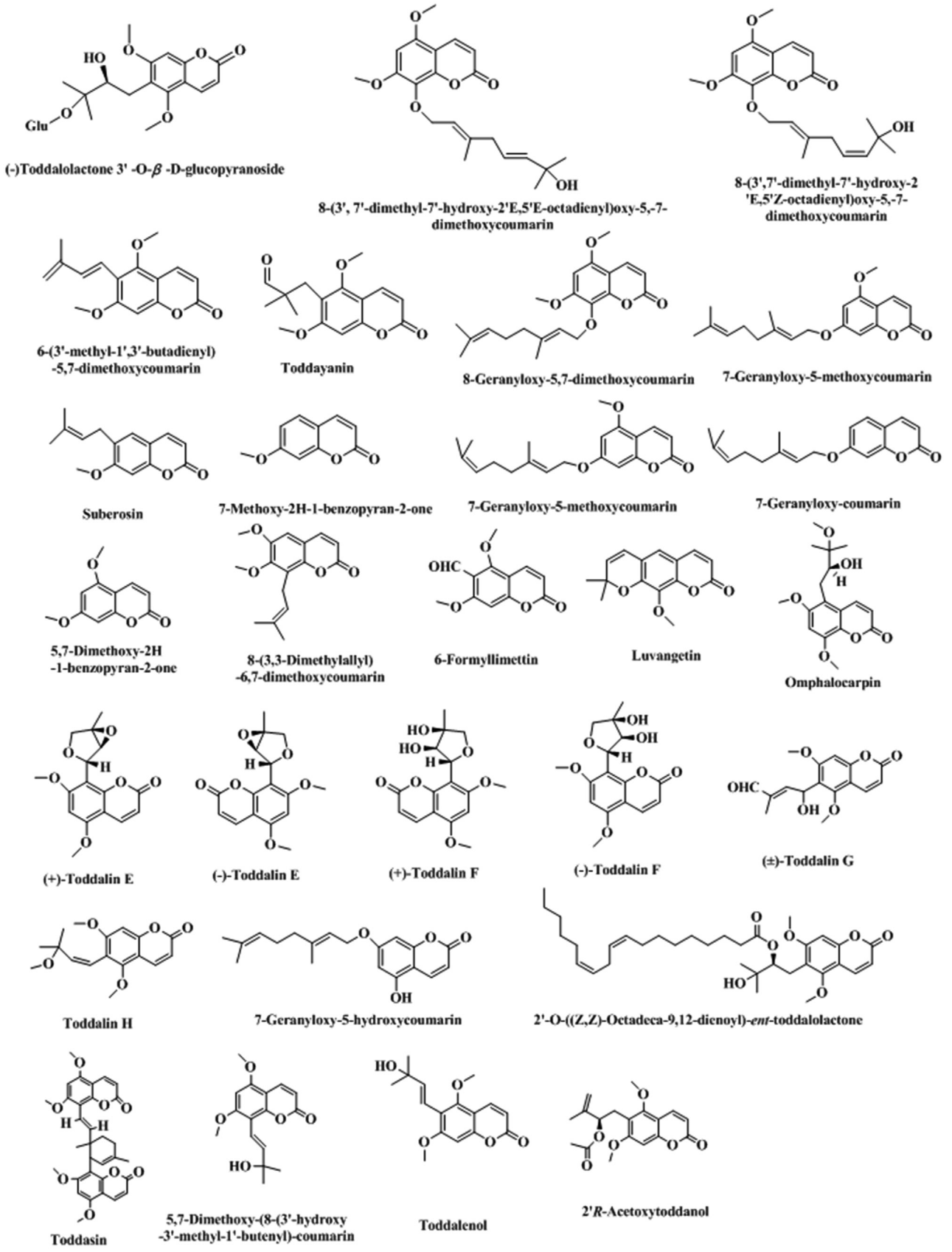

Fig. 2 (*continued*)

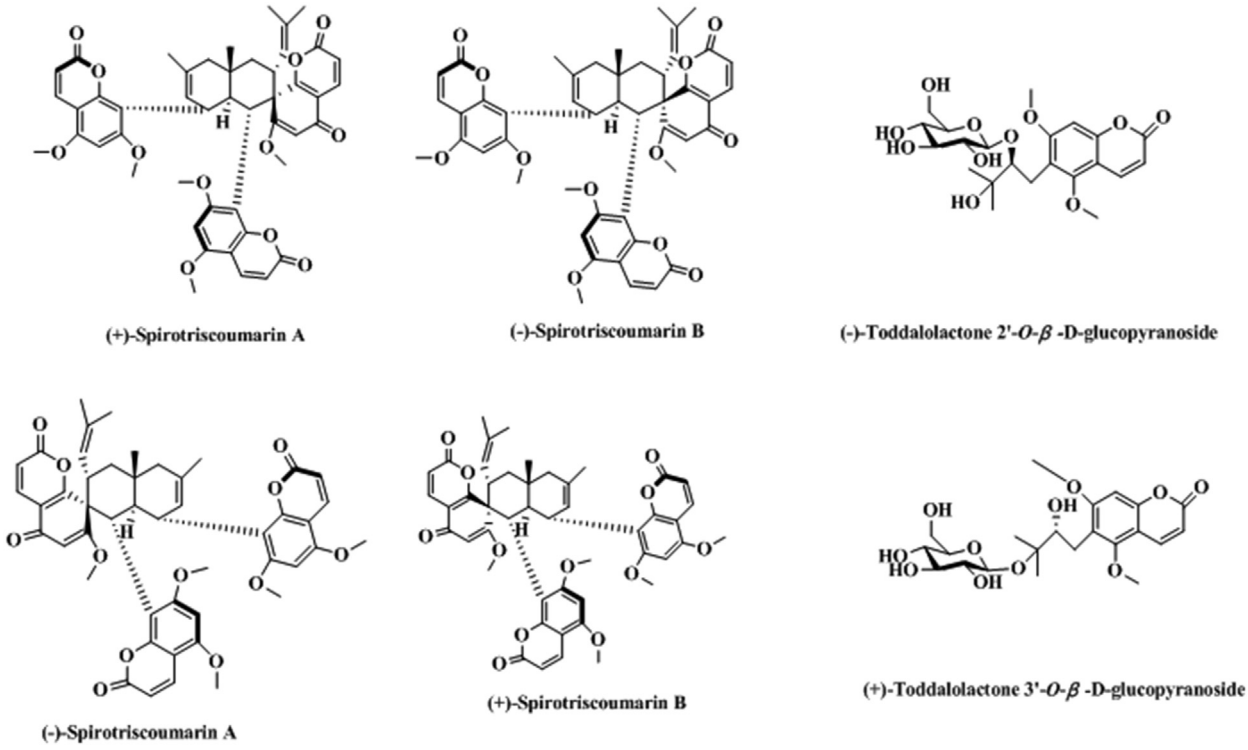

Fig. 2 (*continued*)

anti-tumor effects and so forth. To the best of our knowledge, pharmacological effects were mainly focused on the extracts of alcohol, water and methanol and so on. Just few monomeric compounds on their pharmacological effects were reported summarized in Fig. 7. The following will elaborate on these activities in turn.

3.1. Anti-inflammatory analgesic effect

Researches (Lu et al., 2015, Zhang et al., 2019) found that the alcohol, water and n-butanol extracts of *T. asiatica* root had analgesic effects and the former had better analgesic effects than the two latter. Its mechanism may be related to increasing the content of serum β-endor endorphin (β-EP), decreasing the content of prostaglandin E2 (PGE2) and nitric oxide (NO), up-regulating the expression of β-EP receptor and down-regulating the expression of PGE2 receptor. Yang *et al.,* (Yang et al., 2013) found that feeding arthritis mice with type II bovine collagen injected with ethanol and ethyl acetate extracts of *T. asiatica* could relieve swelling of paws and joints. Histopathological examination showed that the extracts could protect the knee joint from the erosion and deformation of bone and cartilage, significantly decrease the concentration of tumor necrosis factor-α (TNF- α), interleukin-1-1 β (IL-1 β) and interleukin-6 (IL-6), and increase the concentration of interleukin-10 (IL-10), compared with the control group, which showed similar results according with the consequence obtained by Tian *et al.,* (Tian et al., 2018). The anti-inflammation mechanism of *T. asiatica* extract maybe involve the balance between Th17 and Treg in the rat model with wind-chill and dampness adjuvant arthritis (Wang et al., 2016, Liu et al., 2018a,b).

Tong *et al.,* (Tong et al., 2014) used RAW264.7 as the test cell to study the anti-inflammatory activity of coumarin omphalocarpin. The consequences suggested that omphalocarpin could reduce the release of NO induced by lipopolysaccharide and the secretion of TNF- α and IL-6 inflammatory factors, strongly inhibit the expression and activity of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), and inhibit the transfer of NF- κ B to the nucleus. Kumagai *et al.,* (Kumagai et al., 2018) also found that aculeatin and toddaculin isolated from *T. asiatica* could also play important roles in anti-inflammation in LPS-stimulated RAW264 macrophages via different mechanisms, which further demonstrated that extracts from *T. asiatica* own significant anti-inflammatory effect.

Hao *et al.,* (Hao et al., 2004) found that the total alkaloids from the root bark of *T. asiatica* can significantly inhibit xylene-induced ear swelling and agar-induced foot swelling in mice, and significantly inhibit the migration of hemameba in abdominal cavity induced by sodium carboxymethyl cellulose and the writhing reaction induced by acetic acid in mice, which showed no damage to the liver when given for a long time. Wang *et al.,* (Wang et al., 2007) found that the water extract from the rhizome of *T. asiatica* had anti-inflammatory and analgesic effects, and could also reduce the number of writhing induced by glacial acetic acid in mice and prolong the latent period of licking hind feet in mice through hot plate test. It could significantly inhibit the foot swelling induced by carrageenan and the ear swelling induced by xylene in mice. Liu *et al.,* (Liu et al., 2007) investigated the analgesic and anti-inflammatory effects of alcohol extract and water extract of *T. asiatica*. The results showed that both alcohol extract and water extract had certain analgesic and anti-inflammatory effects, but the analgesic and anti-inflammatory effect of alcohol extract was stronger than that of water extract. Balasubramaniam *et al.,* (Balasubramaniam et al., 2012) found that 50% ethanol extract from *T. asiatica* had good analgesic and anti-inflammatory effects through carrageenan-induced foot swelling and cotton ball-induced granuloma in rats. Kariuki *et al.,* (Kariuki et al., 2013) using formalin-induced pain test and carrageenan-induced foot swelling test investigated the analgesic and anti-inflammatory effects of methane/methanol (1:1) extract from *T. asiatica*. The results showed that the methane/methanol (1:1) extract from *T. asiatica* had good analgesic and anti-inflammatory effects under 100 mg/

Table 2
Alkaloids reported from *T. asiatica*.

Num.	Compound name	Molecular formula	Molecular weight	Reference
1	Robustine	$C_{12}H_9NO_3$	215.06	(Deshmukh et al., 1976)
2	8-Acetonyldihydrochelerythrine	$C_{24}H_{23}NO_5$	405.44	(Sharma et al., 1981a,b)
3	Toddalidimerine	$C_{44}H_{38}N_2O_9$	738.79	(Sharma et al., 1981a,b)
4	8-Methoxydihydrochelerythrine	$C_{22}H_{21}NO_5$	379.41	(Sharma et al., 1982)
5	2,3-Dimethoxy-6-(5-(N-methylformamido)naphtho[2,3-d][1,3]dioxol-6-yl)phenyl acetate	$C_{23}H_{21}NO_7$	423.42	(Sharma et al., 1982)
6	8-Acetoxydihydrochelerythrine	$C_{23}H_{21}NO_6$	407.42	(Sharma et al., 1982)
7	Chelerythrine-φ-cyanide	$C_{22}H_{18}N_2O_4$	374.39	(Ishii et al., 1983)
8	Chelerythrine	$C_{21}H_{18}NO_4$	348.38	(Ishii et al., 1983)
9	4-Methoxy-1-methylquinolin-2-one	$C_{11}H_{11}NO_2$	189.21	(Ishii et al., 1983)
10	Oxychelerythrine	$C_{21}H_{17}NO_5$	363.37	(Ishii et al., 1983)
11	Integriquinolone	$C_{11}H_{13}NO_3$	207.27	(Ishii et al., 1983)
12	N-methylflindersine	$C_{15}H_{15}NO_2$	241.11	(Ishii et al., 1983)
13	Oxyavicine	$C_{20}H_{13}NO_5$	347.32	(Ishii et al., 1991a,b)
14	Avicine	$C_{20}H_{14}NO_4Cl$	367.79	(Chen et al., 1993)
15	Toddaquinoline	$C_{14}H_9NO_3$	239.23	(Chen et al., 1993)
16	Dicyclohexylurea	$C_{13}H_{24}N_2O$	224.35	(Tsai et al., 1997)
17	Norchelerythrine	$C_{20}H_{15}NO$	333.34	(Tsai et al., 1997)
18	N,N' -dicyclohexyloxamide	$C_{14}H_{24}N_2O_2$	252.36	(Tsai et al., 1997)
19	Toddaliamide	$C_{22}H_{33}NO_6$	407.51	(Tsai et al., 1997)
20	Methyltoddaliamide	$C_{23}H_{35}NO_6$	421.53	(Tsai et al., 1997)
21	Toddayanis	$C_{36}H_{43}NO_5$	569.74	(Tsai et al., 1997)
22	Cyclohexylamine	$C_6H_{13}N$	99.18	(Tsai et al., 1998)
23	Haplopine	$C_{13}H_{11}NO_4$	245.24	(Tsai et al., 1998)
24	Isocoreximine	$C_{19}H_{21}NO_4$	327.38	(Tsai et al., 1998)
25	8-Hydroxy-9-methoxy-5-methyl-2,3-methylenedioxybenzo[c]phenanthridin-6 (5H)-one	$C_{20}H_{15}NO_5$	349.34	(Tsai et al., 1998)
26	N-[6-(6-hydroxy-benzo[1,3]dioxol-5-y l)-naphtho[2,3-d][1,3]dioxol-5-yl]-N-methyl-formamide	$C_{20}H_{15}NO_6$	365.34	(Tsai et al., 1998)
27	Nitidine CHCLl3 adduct	$C_{22}H_{18}Cl_3NO_4$	466.75	(Tsai et al., 1998)
28	Oxyterihannine	$C_{20}H_{15}NO_5$	349.34	(Tsai et al., 1998)
29	Chelerythrine chloride	$C_{21}H_{18}ClNO_4$	383.83	(Jain et al., 2006)
30	Nitidine chloride	$C_{21}H_{18}NO_4Cl$	383.83	(Jain et al., 2006)
31	3-(2,3-Dihydroxy-3-methylbutyl)-4,7-dimethoxy-1-methyl-1H-quinolin-2-one	$C_{17}H_{23}NO_5$	321.37	(Jain et al., 2006)
32	N-methyl-4-hydroxy-7-methoxy-3-(2,3-epoxy-3-methylbutyl)-1H-quinolin-2-one	$C_{16}H_{19}NO_4$	289.33	(Jain et al., 2006)
33	Flindersine	$C_{14}H_{13}NO_2$	227.26	(Duraipandiyan and Ignacimuthu, 2009)
34	Demethylnitidine	$C_{20}H_{16}NO_4$	334.35	(Iwasaki et al., 2010)
35	Dihydroavicine	$C_{20}H_{15}NO_4$	333.34	(Shi et al., 2011)
36	Skimmianine	$C_{14}H_{13}NO_4$	259.26	(Shi et al., 2013)
37	γ-Fagarine	$C_{13}H_{11}NO_3$	229.24	(Shi et al., 2013)
38	Dihydrochelerythrine	$C_{21}H_{19}NO_4$	349.38	(Shi et al., 2013)
39	Dihydronitidine	$C_{21}H_{19}NO_4$	349.39	(Nyahanga et al., 2013)
40	Zanthocadinanine A	$C_{37}H_{45}NO_5$	583.76	(Liu et al., 2014)
41	Protopine	$C_{20}H_{19}NO_5$	353.37	(Liu et al., 2014)
42	Oxynitidine	$C_{21}H_{17}NO_5$	363.37	(Hu et al., 2014)
43	Arnottianamide	$C_{21}H_{19}NO_6$	381.39	(Hu et al., 2014)
44	5-Methoxydictamnine	$C_{13}H_{11}NO_3$	229.23	(Hu et al., 2014)
45	8-Methoxychelerythrine	$C_{22}H_{20}NO_5$	378.40	(Hu et al., 2014)
46	Methoxynitidine	$C_{22}H_{20}NO_5$	378.40	(Hu et al., 2014)
47	11-Demethylrhoifolin B	$C_{20}H_{15}NO_5$	349.34	(Hu et al., 2014)
48	Rhoifoline B	$C_{21}H_{17}NO_5$	363.36	(Hu et al., 2014)
49	8-Methoxynorchelerythrine	$C_{21}H_{17}NO_5$	363.36	(Hu et al., 2014)
50	8,9,10,12-tetramethoxynorchelerythrine	$C_{22}H_{19}NO_6$	393.39	(Hu et al., 2014)
51	8-Acetylnorchelerythrine	$C_{22}H_{17}NO_5$	375.37	(Hu et al., 2014)
52	1-Demethyl dicentrinone	$C_{18}H_{13}NO_5$	323.30	(Hu et al., 2014)
53	Dicentrinone	$C_{18}H_{11}NO_5$	321.28	(Hu et al., 2014)
54	(2,3,10,11)-dimethylenedioxytetrahydroprotob-erberine	$C_{19}H_{17}NO_4$	323.34	(Hu et al., 2014)
55	11-hydroxy-10-methoxy-(2,3)-methylenedioxytetrahydroprotoberberine	$C_{20}H_{19}NO_5$	353.13	(Hu et al., 2014)
56	4-Hydroxy-N-methylproline	$C_6H_{11}NO_3$	145.16	(Shi et al., 2014)
57	Dictamnine	$C_{12}H_9NO_2$	199.21	(Shi et al., 2014)
58	8-hydroxy-dihydrochelerythrine	$C_{21}H_{19}NO_5$	365.38	(Shi et al., 2014)
59	Nitidine	$C_{21}H_{18}NO_4$	348.38	(Rashid et al., 2014)
60	Magnoflorine	$C_{20}H_{24}NO_4$	342.41	(Rashid et al., 2014)
61	Pioglitazone	$C_{19}H_{20}N_2O_3S$	356.45	(Watanabe et al., 2014)
62	N-*cis*-feruloyltyramide	$C_{18}H_{19}NO_4$	313.35	(Hu et al., 2015)
63	(7E)-N-(4′ -hydroxyphenethyl)-3,4,5-trihydroxycinnamamide	$C_{17}H_{17}NO_5$	315.33	(Hu et al., 2015)
64	(7Z)-N-(4′ -hydroxyphenethyl)-3-methoxy-4,5-dihydroxycinnamamide	$C_{18}H_{19}NO_5$	329.35	(Hu et al., 2015)
65	(7Z)-N-(4′ -methoxyphenethyl)-3-methoxy-4-hydroxycinnamamide	$C_{19}H_{21}NO_4$	327.38	(Hu et al., 2015)
66	8S-10-O-demethylbocconoline	$C_{21}H_{19}NO_5$	365.38	(Sukieum et al., 2018)
67	8-Acetonyldihydronitidine	$C_{24}H_{23}NO_5$	405.45	(Lin and Chen, 2020)
68	8-Acetonyldihydroavicine	$C_{23}H_{19}NO_5$	389.41	(Lin and Chen, 2020)
69	Decarine	$C_{19}H_{13}NO_4$	319.32	(Lin and Chen, 2020)

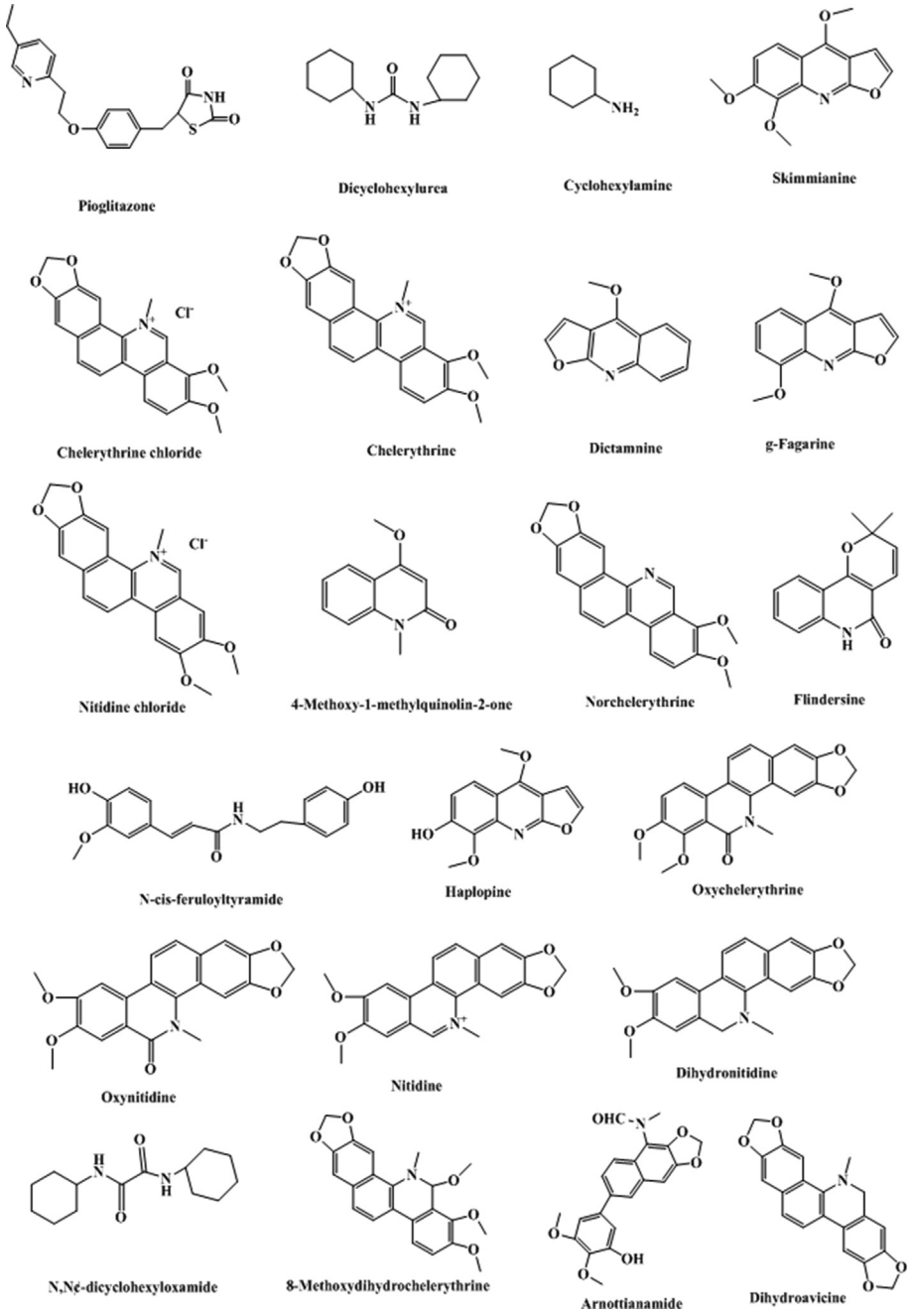

Fig. 3. Structure and corresponding chemical name of alkaloids from *T. asiatica.*

kg. Hu *et al.,* (Hu et al., 2000) found that the ethanol extract from *T. asiatica* could reduce the writhing times of mice induced by acetic acid and alleviate the foot swelling induced by agar, both of which were dose-dependent. Besides, investigation performed by Qin *et al.,* (Qin et al., 2020) found that 60% ethanol extract from *T. asiatica* could inhibit macrophage migration through high throughput screening. Those consequences showed that compounds from *T. asiatica* had played an important role in anti-inflammatory effect.

3.2. Bacteriostatic effect

Ding *et al.,* (Ding et al., 2007) selected four different polar solvents (distilled water, anhydrous ethanol, ethyl acetate, petroleum ether) and two different extraction methods (cold soaking method and heating reflux method) to extract the root of *T. asiatica*. It was found that anhydrous ethanol and ethyl acetate extracts could significantly inhibit the growth of *Bacillus subtilis*, *Shigella dysentery* and *Saccharomyces cerevisiae*. At the same time, the alkaloids isolated from the ethanol extract of *T. asiatica* root by Hu *et al.,* (Hu et al., 2014) can inhibit the growth of bacteria and fungi. Narod *et al.,* (Narod et al., 2004) found that aqueous extracts of *T. asiatica* stems and leaves could inhibit the proliferation of *Pseudomonas aeruginosa* and *Staphylococcus aureus*; the extract of methanol/chloroform (1:1) from stem can inhibit the proliferation of *P. aeruginosa*, *S. aureus* and *Aspergillus*; the extract of n-hexane from leaves can inhibit the growth of *P. aeruginosa*, *S. aureus*, *Aspergillus* and *Candida albicans*. Continuous extraction was used by Duraipandiyan *et al* (Duraipandiyan and Ignacimuthu, 2009) to extract the leaves and root of *T. asiatica*, and found that ethyl acetate extract had the best antibacterial activity. Moreover, flindersine was fur-

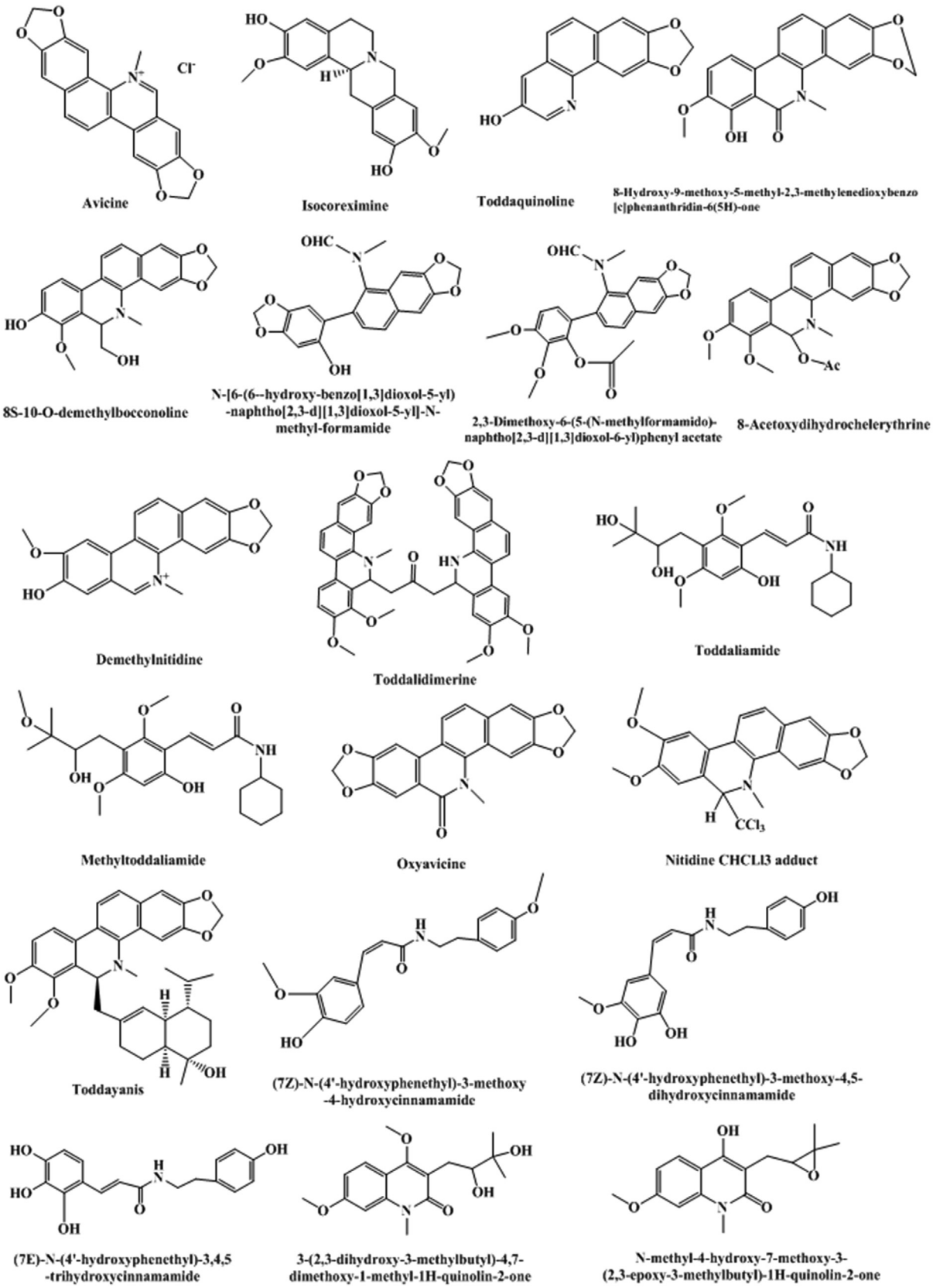

Fig. 3 (*continued*)

ther isolated from the ethyl acetate layer extract, and demonstrated to inhibit the growth of *S. aureus*, *Bacillus subtilis*, *S. epidermidis*, *Enterococcus faecalis*, *P. aeruginosa*, *Acinetobacter baumannii*, *Trichophyton rubrum*, *T. dermatophytes* and *C. albicans*. Karunau Raj *et al.*, (Karunai Raj et al., 2012) also found a coumarin compound (Ulopterol), from the ethyl acetate extract of the leaves of

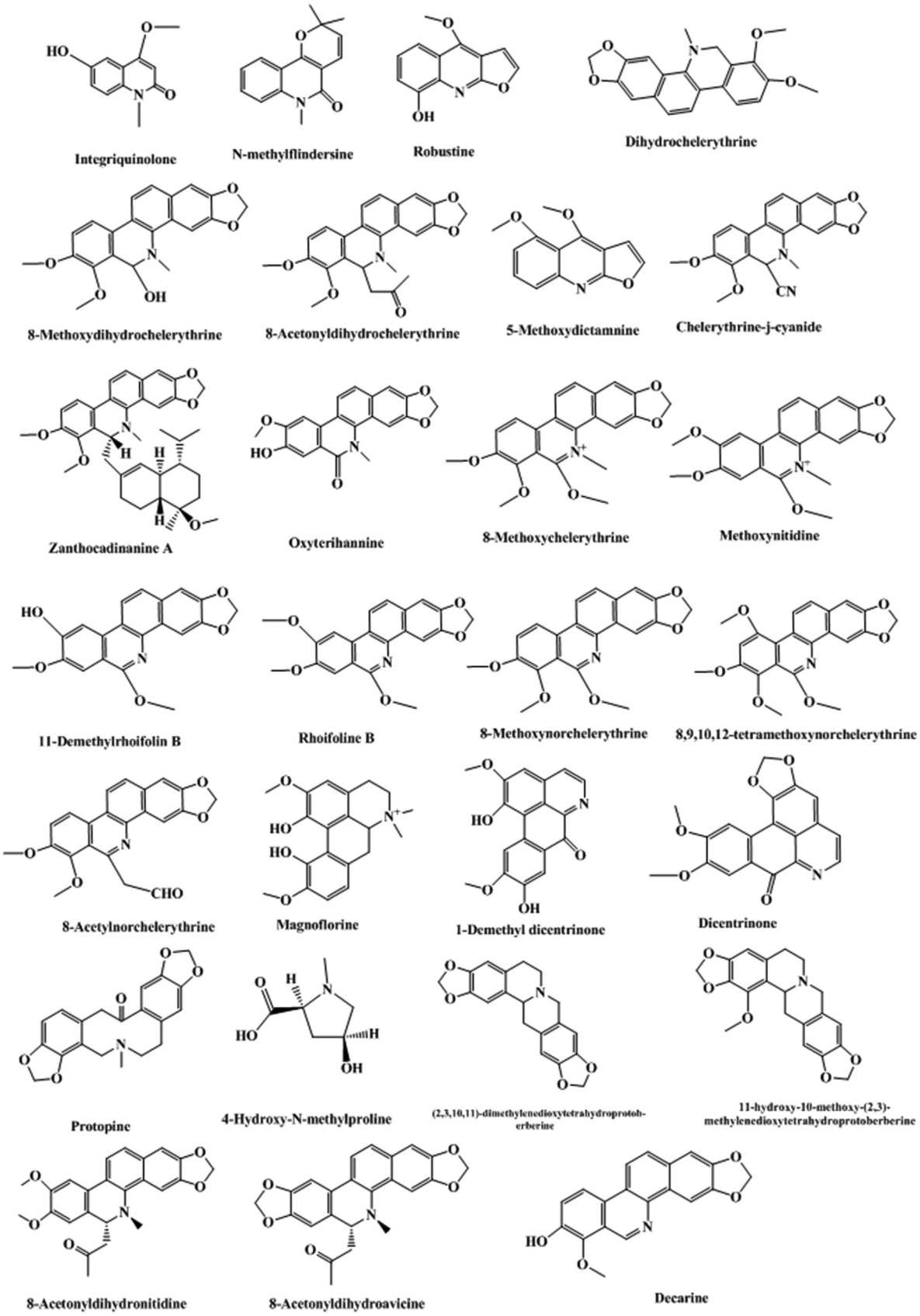

Fig. 3 (*continued*)

Table 3
Terpenoids reported from *T. asiatica.*

Num.	Compound name	Molecular formula	Molecular weight	Reference
1	β-Amyrin	$C_{30}H_{50}O$	426.72	(Ishii et al., 1983)
2	2α,3α,19α-Trihydroxy-11-oxo-urs-12-en-28-oic acid	$C_{30}H_{46}O_6$	502.68	(Huang et al., 2005)
3	2α,3α-Dihydroxy-19-oxo-18,19-seco-urs-11, 13(18)-diene-28-oicacid	$C_{30}H_{46}O_5$	486.68	(Huang et al., 2005)
4	2α, 3β,19α-Trihydroxy-olean-11, 13(18)-dien-28-oic acid	$C_{30}H_{46}O_5$	486.68	(Huang et al., 2005)
5	2α,3α,11α,19α-Tetrahydroxy-urs-12-en-28-oic acid	$C_{30}H_{48}O_6$	504.70	(Huang et al., 2005)
6	Euscaphic acid	$C_{30}H_{48}O_5$	488.70	(Huang et al., 2005)
7	Arjunic acid	$C_{30}H_{48}O_5$	488.70	(Huang et al., 2005)
8	(3S,4aR, 5S,8R)-8-Hydroxy-3-((R)-2-(hydroxymethyl) oxiran-2-yl) −4a,5-dimethyl-4,4a,5,6,7,8- hexahydronaphthalen-2(3H)-one	$C_{15}H_{22}O_4$	266.34	(Lin and Chen, 2020)

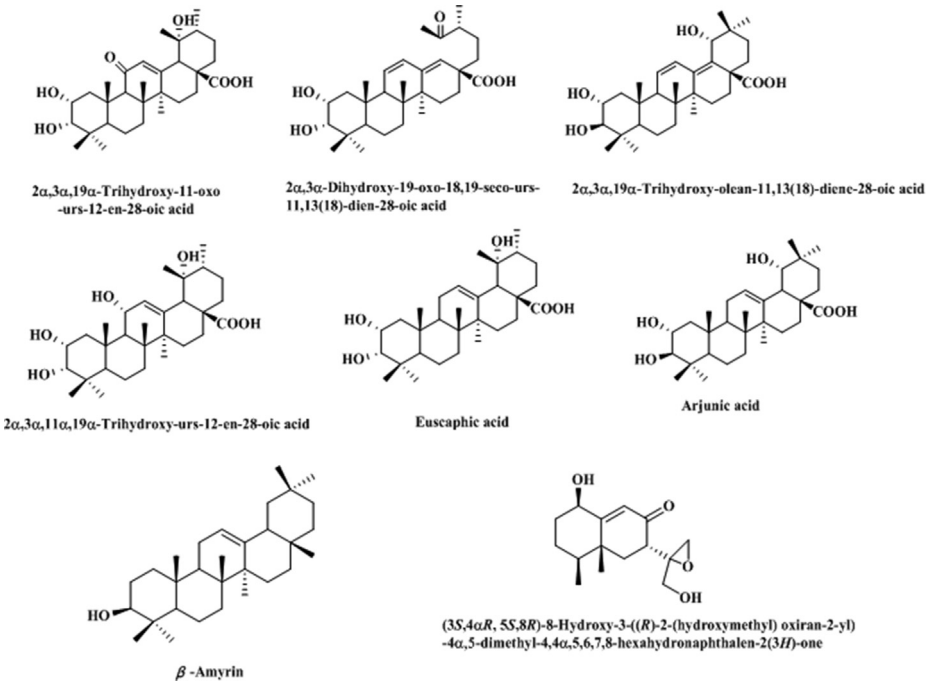

Fig. 4. Structure and corresponding chemical name of terpenoids from *T. asiatica.*

Table 4
Flavonoids reported from *T. asiatica.*

Num	Compound name	Molecular formula	Molecular weight	Reference
1	Hesperetin	$C_{16}H_{14}O_6$	302.28	(Chen et al., 2013)
2	Hesperidin	$C_{28}H_{34}O_{15}$	610.57	(Shi et al., 2014)
3	Neohesperidin	$C_{28}H_{34}O_{15}$	610.57	(Shi et al., 2014)
4	Diosmin	$C_{28}H_{32}O_{15}$	608.54	(Shi et al., 2014)
5	Hesperetin-7-O-β-D-glucopyranoside	$C_{22}H_{24}O_{11}$	464.42	(Shi et al., 2014)

T. asiatica, which could inhibit the growth of *S. epidermidis*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Escherichia coli*, *A. flavus*, *C. Cruise*, *Botrytis cinerea* etc.. Indirect immunofluorescence was used to observe the effects of different herbs on the adhesion of *C. albicans* to oral mucosal epithelial cells in vitro. It was found that *T. asiatica* had the dual effects of anti- *C. albicans* and anti- *C. albicans* adhesion (Hou and Wang, 1990). Microbroth dilution method (Xu et al., 2012) was used to investigate the inhibitory effect of ethanol extract of *T. asiatica* in vitro, the consequences of which showed that the minimum inhibitory concentration of ethanol extract against *C. albicans* was 7.5 mg/mL, while the minimum bactericidal concentration was 15.0 mg/mL. With the increase of drug concentration, the expression of virulence factors SNF2 and PDE2 decreased obviously, which inferred that the antibacterial effect is mainly due to inhibiting the formation of pathogenic mycelium and destroying the integrity of bacterial cell wall. It has also been confirmed that the metabolites of *T. asiatica* had broad-spectrum bacteriostatic activity (Guo et al., 2014). Furthermore, He *et al.*, (He et al., 2018) investigated the antibacterial mechanism of chelerythrine isolated from *T. asiatica* root and discovered that chelerythrine could play a role in antibacterial activity via destroying the bacterial cell wall and membrance, and inhibiting protein biosynthesis.

3.3. Antioxidant activity

Tian *et al.*, (Tian et al., 2011) using Fenton and 1,1-Diphenyl-2-picrylhydrazine (DPPH) method, found that polysaccharides from

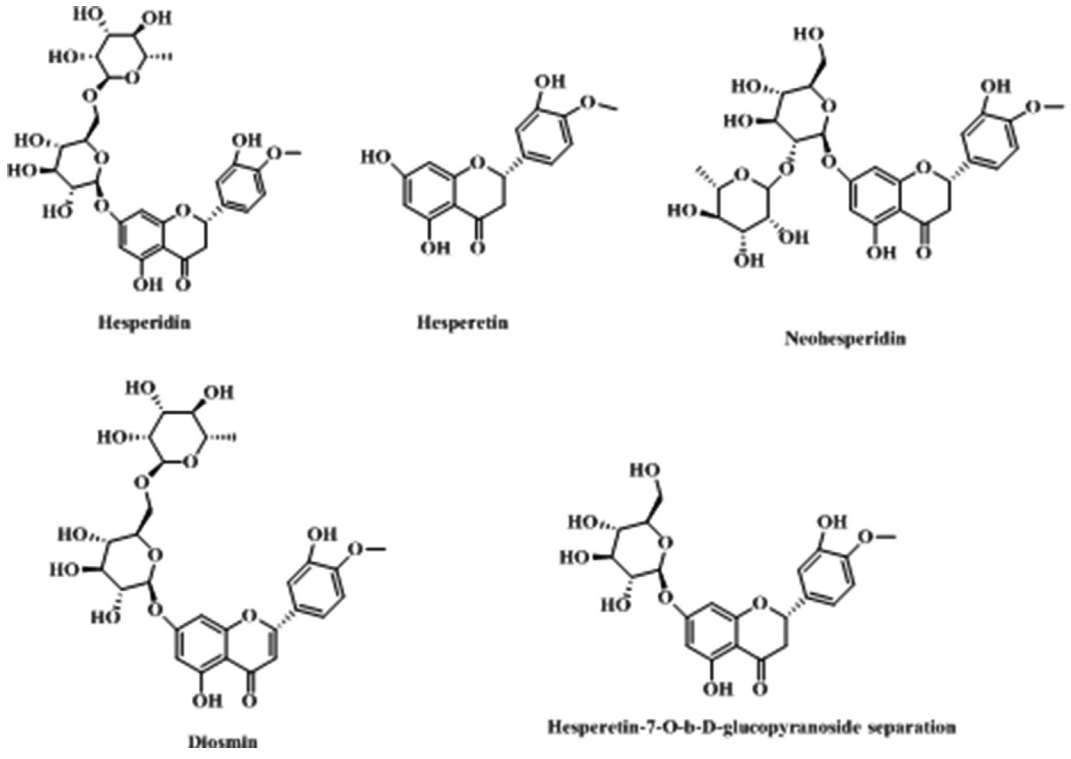

Fig. 5. Structure and corresponding chemical name of flavonoids from *T. asiatica.*

Table 5
Other compounds reported in *T. asiatica.*

Num.	Compound name	Molecular formula	Molecular weight	Reference
1	dl-Lyoniresinol	$C_{22}H_{28}O_8$	420.45	(Tsai et al., 1998)
2	dl-Syringaresinol	$C_{22}H_{26}O_8$	418.44	(Tsai et al., 1998)
3	2,6-Dimethoxy-p-benzoquinone	$C_8H_8O_4$	168.15	(Tsai et al., 1998)
4	Benzoic acid	$C_7H_6O_2$	122.12	(Jain et al., 2006)
5	Stigmasterol	$C_{29}H_{48}O$	412.70	(Jain et al., 2006)
6	β-Sitosterol	$C_{29}H_{50}O$	414.71	(Shi et al., 2012)
7	Citronellol	$C_{10}H_{20}O$	156.26	(Chen et al., 2013)
8	Chlorogenic acid	$C_{16}H_{18}O_9$	354.31	(Liu et al., 2014)
9	Daucosterol	$C_{35}H_{60}O_6$	576.90	(Shi et al., 2014)
10	Eugenol	$C_{10}H_{12}O_2$	164.20	(Shi et al., 2014)
11	Nelumol A	$C_{21}H_{30}O_4$	346.46	(Phatchana and Yenjai, 2014)
12	4-O-geranylconiferyl alde-hyde	$C_{19}H_{26}O_3$	302.41	(Phatchana and Yenjai, 2014)
13	1,2-seco-Dihydromethylumbelliferonem methyl ester	$C_{11}H_{14}O_4$	210.23	(Phatchana and Yenjai, 2014)
14	Methyl(E)-3,4-bis(4-hydroxyphenyl)-4-oxobut-2-enoate	$C_{17}H_{14}O_5$	298.08	(Li et al., 2017)

the root of *T. asiatica* could scavenge hydroxyl radical and DPPH free radical, and the scavenging ability of the two free radicals was positively correlated in the concentration range of 0.2–0.4 g/L and 5 × (10^{-3}–10^{-1}) g/L, respectively. The scavenging rate of hydroxyl radical was 73.7% when the concentration of 0.4 g/L was 0.5 g/L, and the scavenging rate of DPPH free radical was 79.5%. With vitamin C (VC) and tea polyphenols as positive controls, the ability of scavenging hydroxyl free radicals of polysaccharides from *T. asiatica* was studied by flow injection chemiluminescence method. The scavenging ability of 0.1–500 mg/L to hydroxyl radical was related to the concentration, and the IC_{50} values were 5.69, 2.19 and 0.745 mg/L, respectively. The free radical scavenging rate was as high as 94% when the concentration of polysaccharides was up to 500 mg/L, and the photostability was stronger than that of VC and tea polyphenols (Tian et al., 2011). Chen *et al.,* (Chen and Long, 2013) investigated the antioxidant activity of the extract from *T. asiatica* stem by Fenton method, DPPH method and Fe^{2+}- cysteine reaction and found that the n-butanol extraction exhibits strong hydroxyl radical scavenging ability; Ethyl acetate extract has the strongest ability of scavenging DPPH; 70% ethanol extract and n-butanol extract showed strong anti-lipid peroxidation activity, which indicated that the extracts of different polar solvents had certain antioxidant activity. Balasubramaniam *et al.,* (Balasubramaniam et al., 2012) found that 50% ethanol extract of *T. asiatica* stem can scavenge hydroxyl radical, diphenylpicryl hydrazide radical and nitric oxide radical, and also has the ability of chelating divalent iron ion, which indicates that 50% ethanol extract of *T. asiatica* stem has antioxidant activity in vitro. Stephen Irudayaraj *et al.,* (Stephen Irudayaraj et al., 2012) found that the activities of catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) were low in diabetic rats, while the activities of the three enzymes returned to the normal range in intragastric administration of ethyl acetate extract from *T. asiatica* leaves of diabetic rats, indicating that the ethyl acetate extract has antioxidant activity.

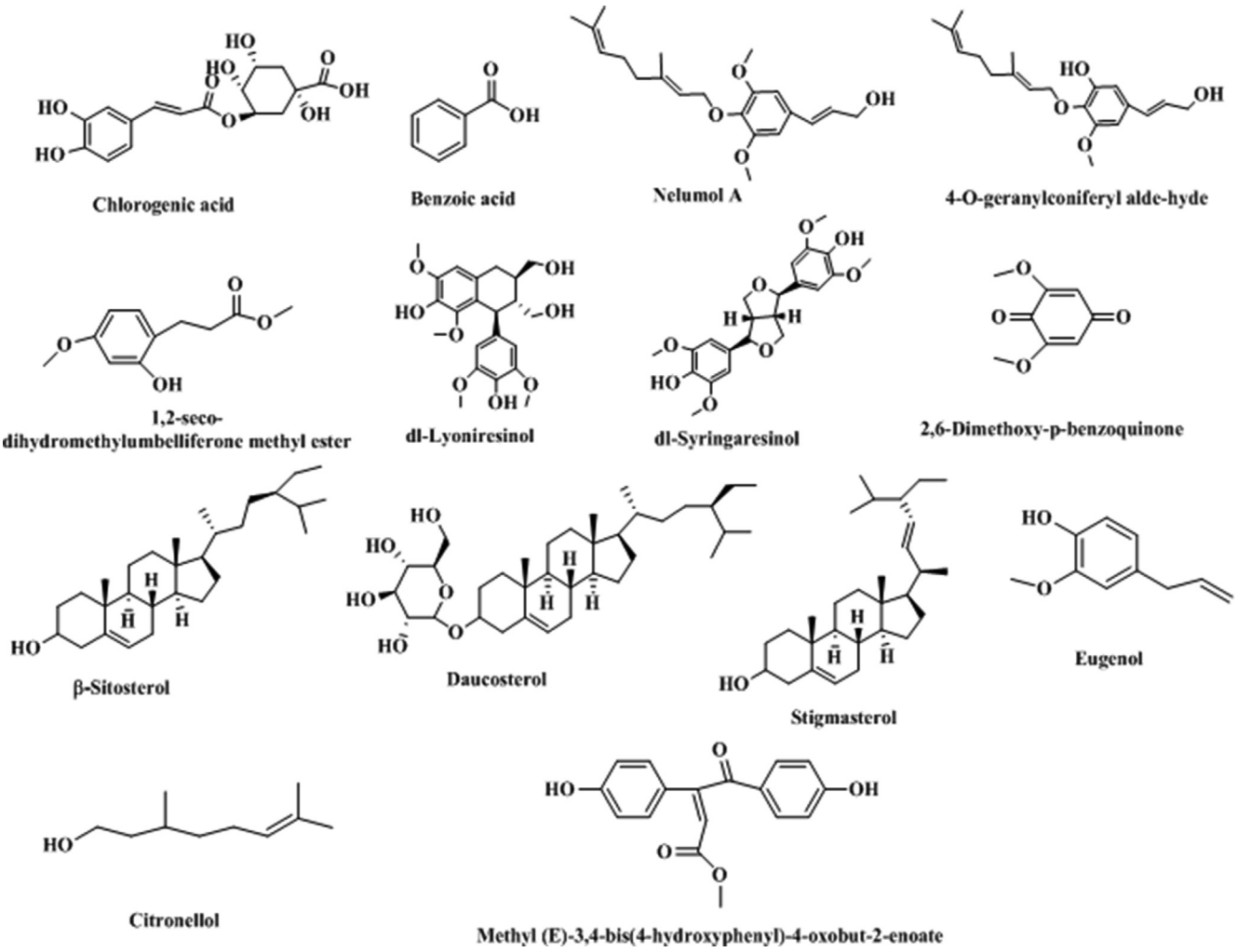

Fig. 6. Structure and corresponding chemical name of other compounds from *T. asiatica.*

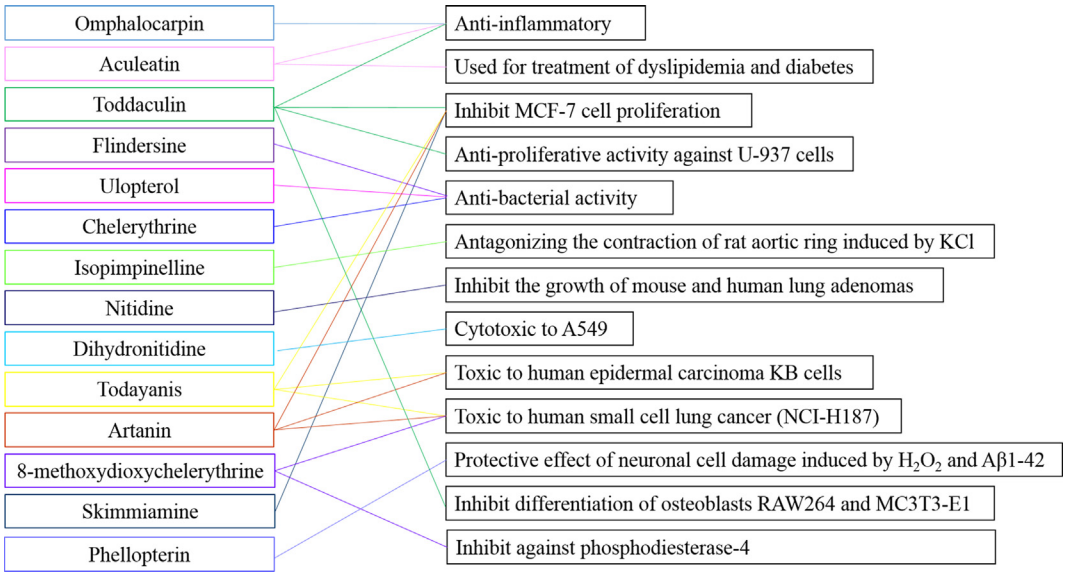

Fig. 7. Relationship between chemical compounds from *T. asiatica* and their pharmacological effects.

3.4. Cardiovascular protective effect

Ren *et al.,* (Ren et al., 1993) performed a systematic study on the cardiovascular protective effect of *T. asiatica* and found that Long Jing 1 (*L*01, extract from *T. asiatica*) could reduce the blood pressure of anesthetized rats and relax the contractile smooth muscle induced by KCl in vitro, and its mechanism might be related to inhibition of calcium influx. Iso-anise coumarin (isopimpinelline) found in ethanol extract could antagonize the contraction of rat aortic ring induced by KCl (Guo et al., 1998). In addition, Fei Long 1 (F01), aqueous extract from *T. asiatica*, has protective effects on coronary artery contraction induced by pituitrin, myocardial overexcitation caused by isoproterenol, and acute myocardial ischemia caused by coronary artery occlusion and ligation (He and Ren, 1998, Ren and He, 1998, He and Ren, 1999). F01 can significantly reduce the work and oxygen consumption of acute ischemic myocardium in New Zealand rabbits without ligation of the left anterior descending branch of pleural coronary artery, regulate the balance of oxygen supply and demand, and improve the function of pumping blood, so as to protect the ischemic myocardium (He et al., 2000). Through the study of cardiac function and hemodynamics in normal domestic cats, it is proved that F01 can inhibit the heart and dilate peripheral blood vessels, and reduce cardiac afterload as well as myocardial work and oxygen consumption, which may be another anti-myocardial ischemia mechanism (Ren et al., 2000). Rats were fed with high fat diet and injected isoprenaline hydrochloride (Iso) once a day for consecutive three days at the end of the 4-weeks treatment and the results suggested that *T. asiatica* extract could significantly improve the Iso-induced electrocardiogram changes in rats, reduce the heart, liver and fat indexes, the level of total cholesterol (TC), triglyceride (TG), low density (LDL), TNF-α, interferon-γ (INF-γ) and IL-6, increase the contents of high density lipoprotein (HDL) and IL-10, and improve the pathological damages of myocardium, which may regulate the balance of anti-inflammatory and proinflammatory cytokines in protecting rat model from cardiovascular diseases (Liu et al., 2018a,b).

3.5. Antimalarial activity

Orwa *et al.,* (Orwa et al., 2013) carried out antimalarial experiments on extracts from different parts of the *T. asiatica*, using chloroquine-sensitive D6 and chloroquine-resistant *Plasmodium falciparum* strain W2 incorporated 50% radioisotope to determine the inhibitory concentration of antimalarial parasite IC_{50} in vitro. Through the experiment of mice infected with *P. berghei*, quinine hydrochloride used as positive control, it was found that the ethyl acetate extract from *T. asiatica* fruit showed high activity against chloroquine-resistant *P. falciparum* strain with IC_{50} 1.87 ug/mL, followed by the water extract of root bark with IC_{50} 2.43 μg/mL. The inhibitory activity of ethyl acetate extract (500 mg/kg) and root bark water extract (250 mg/kg) of fruit against *P. berghei* in vivo were 81.34% and 56.8%, respectively. The root bark extracts of *T. asiatica* and the isopimpinellin, geraniol and D-limonene separated from *T. asiatica* (Liu et al., 2013) were found to have antimalarial and insecticidal effect.

3.6. Inhibitory effect on the proliferation of human cancer cells

Iwasaki *et al.,* (Iwasaki et al., 2006, Iwasaki et al., 2010) found that two alkaloids, nitidine and dihydronitidine, which were isolated from *T. asiatica* could inhibit the proliferation of mouse and human lung adenocarcinoma cells in vitro. Results have shown that nitidine can effectively inhibit the growth of mouse and human lung adenomas in subcutaneous xenograft models without any significant side effects; dihydronitidine is highly specific cytotoxic to human lung adenocarcinoma (A549) cells. It can upregulate apoptosis-related genes and regulate cell cycle gene expression, that is, inhibiting cell proliferation. Furthermore, researchers isolated 18 compounds from *T. asiatica*, named todayanin, toddayanis, artanin, coumurrayin, toddaculin, toddanol, toddalolactone, isopimpinellin, phellopterin, 5-methoxy-8-geranyloxypsoralen, 8-methoxydihydrochelerythrine, methoxynorchelerythrine, skimmiamine, norchelerythrine, chelerythrine, oplopanone, nelumol and p-isopentenoxybenzenepropanoic acid. Among them, todayanis is toxic to human epidermal carcinoma KB cells, breast cancer cell line MCF-7 cells, and human small cell lung cancer (NCI-H187) cell lines, with IC_{50} of 32.2, 5.8, and 17.6 μg/mL, respectively. Artanin is toxic to all three cancer cells, with IC_{50} ranging from 7.4 to 31.0 μg/mL. Moreover, 8-methoxydioxychelerythrine is the most toxic to NCI-H187 cells with IC_{50} of 0.8 μg/mL. In addition, toddaculin and skimmiamine can inhibit MCF-7 cell proliferation with IC_{50} of 23.4 and 8.7 μg/mL, separately, which have been suggested that the two compounds are the most likely anticancer lead compounds (Murakami et al., 2000, Hirunwong et al., 2016). Vázquez *et al.,* (Vazquez et al., 2012) isolated six isoprene-substituted coumarins from *T. asiatica*, among which toddaculin had the strongest cytotoxicity and anti-proliferative activity against U-937 cells. Further research found that toddaculin had dual effects, which could induce apoptosis of U-937 cells at a drug concentration of 250 μmol/L, and promote cell differentiation at a concentration of 50 μmol/L.

3.7. Inhibiting the pathogenesis of Alzheimer's disease (AD)

Alzheimer's disease (AD) is the most common cause of dementia and a chronic and progressive neurodegenerative disorder following with memory impairment, gradual loss of attention, emotions, mental capacity and the learning ability and what not. Takomthong *et al.,* (Takomthong et al., 2020) investigated that seven out of nine coumarins isolated from *T. asiatica* were identified as the multifunctional agents which could inhibit the pathogenesis of AD, especially the phellopterin that showed significant protective effect of neuronal cell damage induced by H_2O_2 and $A\beta_{1\text{-}42}$ toxicity. With the intensification of aging in the whole world, the number of AD patients is increasing, which aggravates the burden of families and social medical treatment, specially there are no specific medicine used in clinic. Therefore, traditional Chinese herb is another effective breach that could provide a new treatment for AD patients, which has also attracted extensive attention of scholars engaged in medical researches.

3.8. Other pharmacological effects

T. asiatica has also played an important role in other pharmacological effects other than the above six pharmacological effects. Using mouse tail amputation and capillary glass tube method, the bleeding time, bleeding volume and clotting time were used to investigate the hemostatic activity of different polar parts of blood root bark (Zhao et al., 2016). The average bleeding time, bleeding volume and clotting time of ethyl acetate in cold extract were (59.67 ± 12.31) s, (4.42 ± 1.67) mg and (79.67 ± 5.57) s, respectively. It was also found that the hemostatic activity of ethyl acetate in cold immersion was better than the other polar extracts. Ethanol extract can significantly shorten the mice's bleeding and clotting time, and the hemostatic time is similar to that of *Panax notoginseng* powder which has better hemostatic effect at present. Further studies found that the hemostatic effect of *T. asiatica* may be related to the increase of fibrinogen content ($p < 0.05$), the promotion of endogenous coagulation pathway and the change of platelet morphology (Liu et al., 2016). To observe the bleeding and

coagulation activity of different polar parts of *T. asiatica* in mice, methanol part has the best coagulation effect, which can improve the coagulation function of the body and enhance the hemostatic effect (Shi et al., 2010). Research carried out by Tsai *et al.,* (Tsai et al., 1998) showed that seven compounds had anti-platelet aggregation effect in vitro after biological activity guided the separation of chemical constituents from *T. asiatica*. Watanabe *et al.,* (Watanabe et al., 2014) found that extracted from *T. asiatica* could increase the differentiation and lipolysis of adipocytes at the same time, and be used in the treatment of dyslipidemia and diabetes. They then found that the toddaculin in *T. asiatica* acted on osteoclasts RAW264 and osteoblasts MC3T3-E1 in vitro via inhibition of osteoclast differentiation by activating NF- κ B, ERK1/2 and p38MAPK signal transduction pathways (Watanabe et al., 2015). Otherwise, *T. asiatica*. also has the effects of antiviral (Tan et al., 1991, Mao et al., 2002, Li et al., 2005), antispasmodic (Lakshmi et al., 2002), diuretic (Liu et al., 2007), anti-HIV (Rashid et al., 2014) and larvicidal (Borah et al., 2010).

4. Conclusion and future perspectives

T. asiatica is a traditional Chinese herbal medicine in China, which is a characteristic ethnic medicine in southwest China, Wuling Mountainous areas, such as Guizhou, Yunnan, Guangxi and Enshi, Hubei province and others. Its unique geographical advantages and abundant medicinal resources have laid a solid foundation for its sustainable development and utilization. However, there has been a lack of theoretical guidance for the study of modern medicine. It is of great significance for the development of new drugs with reliable efficacy to carry out the systematic pharmaceutical research on *T. asiatica*. So far, large-scale clinical application of *T. asiatica* is still relatively rare, mainly in anti-inflammation and analgesia, hemostasis and coagulation. Moreover, pharmacological research is still in the basic research stage. With the rapid development of modern medical science and technology, the active material basis, pharmacological effects and mechanisms of *T. asiatica* would be explored more deeply. A small number of unknown active natural compounds, novel pharmacology and pharmacological mechanisms will also be found. Otherwise, there are few reports on the safety of *T. asiatica*, which needs to be further strengthened and improved in the future, so as to provide a scientific basis for the development and rational application of the medicinal resources.

Based on the bioactivities and pharmacokinetics, coumarins and alkaloids are the main compounds in *T. asiatica* as there are 138 compositions isolated from the plant. On one hand, these compounds provide framework for biosynthesis; on the other hand, they play an important role in pharmacological activities in vitro, which lay a foundation for clinic application, although there is still a long way to go. As shown in Fig. 7, pharmacological mechanisms of monoclonal compounds are still defective and more work could be done in future. In addition, the resource of *T. asiatica* is abundant, but the officinal part of this plant is root and stem, which would lead to decrease the number of the wild *T. asiatica.* Therefore, more works need to be done to fill gaps in protection of the medicine resource.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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