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Review

Genus *Psoralea*: A review of the traditional and modern uses, phytochemistry and pharmacology

Bhupendra Koul[a], Pooja Taak[a], Arvind Kumar[b], Anil Kumar[c], Indraneel Sanyal[c,*]

[a] School of Bioengineering and Biosciences, Lovely Professional University, Phagwara , Punjab 144411, India
[b] Chromatography and Mass Spectrometry Centre, CROM-MASS, CENIVAM, Industrial University of Santander, Carrera 27, Calle 9, Edificio 45, Bucaramanga, Colombia
[c] CSIR-National Botanical Research Institute, Plant Transgenic Laboratory, P.O. Box 436, Rana Pratap Marg, Lucknow 226001, U.P., India

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ABSTRACT

Ethnopharmacological relevance: The genus *Psoralea* (Fabaceae) harbours 105 accepted species that are extensively used by local peoples and medicinal practitioners of China, India, and other countries for treatment of tooth decay, psoriasis, leucoderma, leprosy, kidney problems, tuberculosis, indigestion, constipation and impotence. Presently, pharmacological research reports are available on only few species namely *Bituminaria bituminosa* (Syn: *P. bituminosa*), *P. canescens*, *P. corylifolia*, *P. esculenta*, *P. plicata* and *P. glandulosa* which are valued for their chemical constituents and traditional uses.

Aim of the review: This review article provides explicit information on traditional uses, phytochemistry, and pharmacological activities of selected *Psoralea* species. The possible trends and perspectives for future research on these plants are also discussed.

Materials and methods: An extensive and systematic review of the extant literature was carried out, and the data under various sections were identified using a computerized bibliographic search *via* the PubMed, Web of Science and Google Scholar, CAB Abstracts, MEDLINE, EMBASE, INMEDPLAN, NATTS as well as several websites.

Key findings: A total of 291 bioactive compounds from 06 species of genus *Psoralea* have been isolated and characterized. However, *P. bituminosa* alone possess nearly 150 compounds. These bioactive compounds belong to different chemical classes, including flavonoids, coumarins, furanocoumarins, chalcones, quinines, terpenoids and some others due to which these species exhibit significant anti-oxidant, anti-bacterial, anti-fungal, anti-viral, anti-helmintic, anti-diabetic, diuretic, hepatoprotective, anti-cancer and anti-tumor activities. *P. corylifolia* L. (Babchi), a Chinese traditional medicinal plant has been used in traditional medicine for many decades for its healing properties against numerous skin diseases such as leprosy, psoriasis and leucoderma.

Conclusions: The *in vitro* studies and *in vivo* models have provided a simple bio-scientific justification for various ethnopharmacological uses of *Psoralea* species. From the toxicological perspective, the root, leaf, and seed extracts and their preparations have been proven to be safe when consumed in the recommended doses. But, meticulous studies on the pharmaceutical standardization, mode of action of the active constituents, and sustainable conservation of *Psoralea* species are needed, to meet the growing demands of the pharmaceutical industries, and to fully exploit their preventive and therapeutic potentials.

1. Introduction

The medicinal herbs have been a major source of biodynamic compounds of therapeutic value in Ayurveda, Unani, Homeopathy, Traditional Chinese medicine (TCM) and other traditional system of medicines. Several dreadful diseases including cancer, AIDS, kidney

Abbreviations: ABA, Abscisic acid; BAP, 6-benzyl aminopurine; BVN, Bavistin; CH, Casein hydrolysate; 2, 4-D, 2, 4-dichlorophenoxyacetic acid; DPPH, 2,2-Diphenyl-1-picrylhydrazyl; FRAP, Ferric reducing antioxidant power; HPLC, High performance liquid chromatography; HPTLC, High performance thin layer chromatography; IAA, Indole 3-acetic acid; IBA, Indole 3-butyric acid; 2ip, N^6-(2-isopentenyl) adenine; KIN, Kinetin; MS, Murashige and Skoog; NAA, α-naphthalene acetic acid; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NO, Nitric oxide; PG, Phloroglucinol; ROS, Reactive oxygen species; PGR, Plant growth regulator; TDZ, Thidiazuron; TLC, Thin-layer chromatography; TRAP, Total reactive anti-oxidant properties; TNF-alpha, Tumor necrosis factor alpha; TRAIL, Tumor necrosis factor-related apoptosis-inducing ligand

* Corresponding author.
E-mail addresses: bhupendra.18673@lpu.co.in (B. Koul), arvindtomer81@gmail.com (A. Kumar), i.sanyal@nbri.res.in (I. Sanyal).

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damage, cardiovascular diseases and many more, can be cured by the use of medicinal herbs (Ceylan-Isik et al., 2008; Duke, 2009; Kolasani et al., 2011; Turchi et al., 2009). Owing to the global trend towards improved 'quality of life', the demands for herbal medicines have tremendously grown. Therefore, due to overexploitation, a large number of medicinal plant species are under the threat of extinction (Sidhu, 2010).

There are several plant genera which are reputedly known for their contribution to traditional as well as modern medicine(s). The genus *Psoralea* of the legume family (*Fabaceae*) is one among them, which was first established by Linnaeus in 1742. Till 1753, only one species, *Psoralea americana* (native to America), was recognized and described by Linnaeus. According to The Plant List (2013), *Psoralea* is a cosmopolitan genus encompassing 105 accepted species, with 23 species reported in Australia and 14 species in the Northern Territory. Two widespread species occur in the Dominican Republic. The name '*Psoralea*' is derived from the Greek term '*Psoraleos*', which means "affected with itch or with leprosy" (Chopra et al., 2013a, 2013b).

This genus is a source of several bioactive compounds which belong to the chemical class of flavonoids, coumarins, furanocoumarins, chalcones, terpenoids, and meroterpenes. Some of the medicinally important compounds obtained from *Psoralea* species are 'psoralen', 'isopsoralen' (angelicin), 'bakuchiol', 'corylifol', 'psoralidin', 'bavachinin', 'corylifolinin', 'caryophyllene', 'β-farnesene', 'α-pinene', 'camphene' and 'germacrene D' (Bertoli et al., 2004; Li et al., 2016; Tava et al., 2007). Although, some species are poisonous, the starchy roots of *P. hypogaea* Torr. & A. Gray, *P. esculenta* Pursh and *P. macrostachya* DC. are edible. At present, there are pharmacological research reports available on only few species namely *P. bituminosa* (accepted name: *Bituminaria bituminosa*), *P. canescens* Michx. [synonym: *Pediomelum canescens* (Michx.) Rydb.], *P. corylifolia* L. [accepted name: *Cullen corylifolium* (L.) Medik.], *P. esculenta* Pursh, *P. plicata* Delile [accepted name: *Cullen plicatum* (Delile) C.H.Stirt.] and *P. glandulosa* L. *P. corylifolia* is one among these medicinal herbs which is commonly known as 'babachi', 'bakuchi', 'bavachi', 'Indian bread root', 'fountain-bush' or 'scurf pea' (Alam et al., 2017; Shilandra et al., 2010; Zhang et al., 2016). It is a highly valued, endangered medicinal herb that is grown in tropical and subtropical areas of the world (China, Japan, Burma and India) due to its folkloric medicinal properties (Sehrawat et al., 2013). The dried ripe fruit of *P. corylifolia* is commonly known as 'BuguZhi' or 'Poguzhi' in traditional Chinese medicine (TCM) (Oudhiya, 2001).

The pharmacological activities of *Psoralea* species have been scientifically proven and well-documented (Alam et al., 2017; Li et al., 2016; Zhang et al., 2016). Psoralen and isopsoralen compounds obtained from *Psoralea* species are also under trials against syndromes like AIDS (Anis et al., 2005; Bhattacharjee, 1998; Duke, 2009). In a nut-shell, *Psoralea* species have served humanity as valuable medicinal herbs and are an unmatched remedy for treating leprosy, leucoderma, psoriasis and several other diseases (Ali et al., 2008; Khushboo et al., 2010; Newton et al., 2002; Wong et al., 2013; Zhang et al., 2016). But, it is unfortunate that several *Psoralea* species are vulnerable to extinction due to climate change, overexploitation and interspecific competition. Therefore, meticulous studies on the pharmacological-potential, pharmaceutical-standardization, mode of action of the active constituents, and sustainable conservation of several *Psoralea* species, are required (Li et al., 2016). In the past few decades, some reports have been published regarding its traditional uses but, a compendious review of its traditional and modern uses, phytochemistry, pharmacology and conservation has not been published so far. This review aims to bridge the gap and provides explicit information on the aforementioned parameters by studying six highly exploited species of this genus (*Bituminaria bituminosa* (L.) C.H.Stirt, *Psoralea canescens* Michx., *Cullen corylifolium* (L.) Medik., *Psoralea esculenta* Pursh, *Cullen plicatum* (Delile) C.H.Stirt., *Psoralea glandulosa* L.) which are important from ethnobotanical, chemical and pharmacological point of view. This shall create awareness among the environmentalists, botanists and pharmacists, for sustainable utilization and conservation of *Psoralea* species.

2. Methodology

An extensive and systematic review of the extant literature was carried out, and the data under various sections on distribution, traditional and modern uses, phytochemistry and biological activities of *Psolaea* species were identified using various databases including PubMed, Web of Science and Google Scholar, CAB Abstracts, MEDLINE, EMBASE, INMEDPLAN, NATTS, as well as websites such as www.jstor.org, www.sciencedirect.com, www.eflora.org and www.pfaf.org. The names of the species mentioned in this review have been validated taxonomically using the medicinal plants repositories available at http://mpns.kew.org/mpns-portal/ and www.theplantlist.org/. The chemical structures of the bioactive compounds were searched in ChemSpider and PubChem databases and redrawn using the ChemDraw® software (version 8.0). The literature reviewed consists of several abstracts, full-text articles, books, Ph.D. theses and blogs. The most relevant literature contained in 396 references was selected for further examination and inclusion in this review.

3. Distribution

As already mentioned, 105 species have been reported so far in genus *Psoralea* (*Fabaceae*) (Supplemental information 1, Table S1). *Bituminaria bituminosa* (L.) C.H.Stirt. is widely distributed in Africa; *Psoralea canescens* Michx. [synonym: *Pediomelum canescens* (Michx.) Rydb.] is native of Florida and eastern parts of South America; *Psoralea esculenta* Pursh is found in United States; *Psoralea plicata* Delile is native of Pakistan and Arabian countries; *Psoralea pinnata* L. is a native of South Africa; *Psoralea argophylla* Pursh is native of the central United States, as well as the three Canadian prairie provinces, Alberta, Saskatchewan, and Manitoba, and *Psoralea arborea* Sims is native of South Africa. *Psoralea corylifolia* L., though native of Asia, is cultivated in other continents as well (Australia, North America, and Africa). It is extensively grown in the plains, in tropical and sub-tropical areas of the world (Krishnamurthi et al., 1969). In Asia, its distribution is vast ranging from China, Japan Pakistan and India (Fig. 1). In India, it is found in Uttar Pradesh, Rajasthan, and eastern parts of Punjab. It is also reported in the Himalayan regions (up to 1000 m above sea level), Dehra Dun, Bundelkhand, West Bengal, Mumbai, Bihar, Deccan, and Karnataka. In Pakistan, it is well distributed along Baluchistan coast and Peshawar area (Saif et al., 2007; Sharma et al., 2001).

4. Traditional and modern uses

Psoralea species have been used in folklore and indigenous system of medicine for a long time. Several *Psoralea* products are successfully commercialized and available in the markets (Supplemental information 2, Table S2). The roots of *P. argophylla* Pursh (Silver leaf scurf pea, Silver leaf Indian breadroot) are eaten raw or cooked (Tanaka, 1976; Yanovsky, 1936). The dried roots may be ground into a powder and used an ingredient of soups and bread (Yanovsky, 1936). A tea prepared from the leaf and stem powder possess anti-pyretic properties (Weiner, 1990). A decoction of the plant is used as a wash for wounds (Moerman, 1998). The root extract is used as a remedy for chronic constipation (Moerman, 1998). *Bituminaria bituminosa* (L.) C.H.Stirt. (Arabian pea or pitch trefoil) is used as a forage crop. *Psoralea canescens* Michx. (Buckroot) roots are eaten raw or cooked (Hedrick, 1972; Tanaka, 1976; Yanovsky, 1936). The powdered roots are used in preparation of soups or breads (Yanovsky, 1936). As the plant has analgesic properties, a poultice prepared from roots is applied on painful areas of the body (Moerman, 1998). An infusion of the roots and its steam is used for the treatment of cold, cough, headache and sore throat (Moerman, 1998). *Psoralea castorea* S. Watson (Beaver Indian breadroot) roots are also eaten raw or cooked and the root-powder can be used in soups or breads

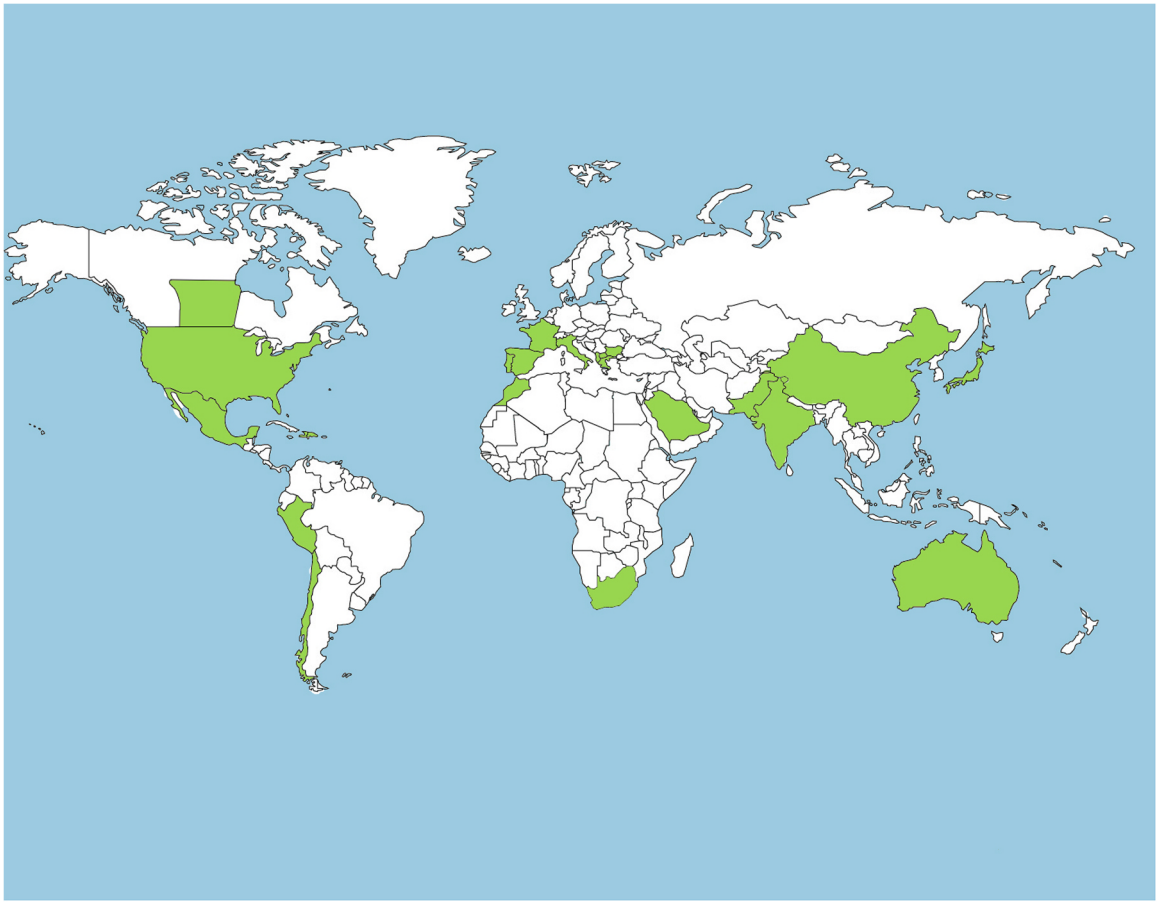

Fig. 1. World map showing the distribution of *Psoralea* species (green).

(Hedrick, 1972; Tanaka, 1976; Uphof, 1968; Yanovsky, 1936). *Psoralea corylifolia* L. (Bu Gu Zhi) is revered in Chinese traditional medicine as a tonic to improve general vitality. The name 'Buguzhi' (*Fructus psoraleae*) actually comprises of three Chinese words: 'Bu' means 'to invigorate'; 'Gu' means 'bone' and the third word 'Zhi' means 'fat'. The Chinese name of the herb suggests the function of the herb to provide fat for the invigorating bones. One of the most important features of *P. corylifolia* is that each and every part of the plant is beneficial which includes roots, stems, leaves, seeds and even blooms (Hodges, 2015). Since *P. corylifolia* is a leprosy destroyer it is revered to as "Kushtanashini" in Sanskrit. Moreove, it is an ancient remedy for leucoderma among the traditional system of medicines in India and China and also among the people in the West (Chopra and Chopra, 1958). In Unani system, the plant has been effective against fever, skin diseases and internal ulcers (Chopra and Chatterjee, 1927). It is also found to be an effective anti-helmintic and sedative (Nadkarni, 1976). For treating leprosy and leucoderma the leaves are consumed as powder and also apllied on skin in the form of paste (Anon, 1998; Nadkarni, 1976; Panda, 2000). However, some precaution should be taken when applying the herbal-paste externally, since it can cause a skin-allergic reaction when exposed to sunlight (Anderson and Voorhees, 1980). The leaves are also used to treat dermatitis, inflammation, mucomembranous disorders, oedematous conditions of the skin and to alleviate diarrhea (Rajpal, 2005; Sharma et al., 2001; Krishnamurthi et al., 1969). The plant possesses blood purifying properties and therefore used to treat boils, itching eruptions or red papules, ringworm-infection, extensive eczema, rough and discolored dermatosis with fissures, and scabies (Khare, 2004). The essential oil from plant is reported to have a strong effect on *Streptococcal* infection of the skin (Rajpal, 2005). Moreover, it is known to improve the color of skin, hair and nails.

Seeds are sweet, bitter, acrid, and astringent. The seeds are anti-pyretic and also possess alexiteric properties and therefore are given in scorpion-sting or snake bite and in bilious disorders (Agharkar, 1991; Kapoor and Boca, 2001; Nadkarni, 1976; Panda, 2000). Both the seeds and fruits contain psoralen (furocoumarin), known to regulate pigmentation (Rashid and Agarwala, 1965; Sebastian, 2006). *P. corylifolia* seed extracts have been reported to possess anti-hyperglycemic, anti-depressant, anti-tumor, anti-bacterial and anti-oxidant property (Steven and Russell, 2007; Wang et al., 1990). Seed extract and powder are beneficial as anti-helmintic, laxative, diuretic, and for healing wounds (Rajpal, 2005). They are used as stomachic, diaphoretic and aphrodisiac (Sharma et al., 2001). The major components psoralen (**92**) and isopsoralen (**2**) are known to possess anti-bacterial, anti-viral and anti-tumor properties (Liu et al., 2004). Therefore, the seeds are used for curing various disorders such as cough, asthma, nephritis, alopecia areata, menstruation, uterine disorders and haemorrhages (Qiao et al., 2007; Ruan et al., 2007). The crude extracts of seeds are used in the treatment of febrile diseases, impotence, spermatorrhea, premature ejaculation, lower back pains, incontinence, enuresis, pollakiuria, and cold symptoms in the waist and knees (Chopra et al., 1956; Lin et al., 2007; Zhao et al., 2005a, 2005b). It also possesses coronary vasodilatory activity (Ruan et al., 2007). The seeds act as deobstruent and heal ulcers, heart troubles, cure blood disorders and elephantiasis (Anonymous, 1969; Drury, 1873). The extracts also possess cytotoxic, anti-mutagenic and anti-repellant properties (Sah et al., 2006). The seeds are also used to make perfumed oil (Gupta et al., 1979; Nadkarni, 1976). In Japan, the ethanol extract of the seeds has been used as a preservative for pickles and some processed foods (Qiao et al., 2007). The seed cake is rich in nitrogen and minerals and is used as cattle feed or manure (Krishnamurthi et al., 1969).

The fruits of the *P. corylifolia* also have valuable medicinal uses. The seeds or the seed with the seed pod, possess high aphrodisiac properties

Table 1
Pharmacologically active compounds isolated from *Psoralea* species.

Plant(s)	Part used	Chemical constituents (structure number) [chemical class/sub-class]	Reference(s)
***Psoralea bituminosa* L.** [accepted name: *Bituminariabituminosa* (L.) C.H.Stirt] 	Whole plant	*Allo*-Aromadendrene **(1)**[u] Angelicin (Isopsoralen) **(2)**[n] Apiol **(3)**[s] Benzaldehyde **(4)**[d] Benzoicacid **(5)**[a] Benzyl alcohol **(6)**[b] Bergapten **(7)**[n] Bicyclogermacrene **(8)**[u] Bitucarpin A **(9)**[o] Bitucarpin B **(10)**[o] Camphene **(11)**[u] Caryophyllen-5-ol **(12)**[u] Caryophyllene oxide **(13)**[u] Chavicol **(14)**[s] (*Z*,*Z*)-Nepetalactone **(15)**[u] (*Z*,*E*)-Nepetalactone **(16)**[u] (*Z*)-γ-Cadinene **(17)**[c] Citronellylacetate **(18)**[u] Cubebol **(19)**[u] Cyclododecane **(20)**[c] Diadzin **(21)**[o] Docosanol **(22)**[b] Dodecanol **(23)**[b] Drupanin **(24)**[h] (*E*)-2-Hexenal **(25)**[d] (*E*)-2-Hexenol **(26)**[b] (*E*)-Anethole **(27)**[s] (*E*)-Phytol **(28)**[b] (*E*)-Werneriachromene **(29)**[n] (*E*)-*β*-Farnesene **(30)**[t] (*E*)-*β*-Ocimene **(31)**[u] (*E*,*E*)-Farnesol **(32)**[u] (*E*,*E*)-*α*-Farnesene **(33)**[u] (*E*,*Z*)-Farnesol **(34)**[u] Ethylbenzoate **(35)**[k] Ethyl butanoate **(36)**[k] Ethyl hexanoate **(37)**[k] Ethyl linoleate **(38)**[k] Ethyl linolenate **(39)**[k] Ethyl palmitate **(40)**[k] Ethyl salicilate **(41)**[k] Eudesma-4 (15),7-dien-1-*β*-ol **(42)**[u] Eugenol **(43)**[s] Ferulic acid ethyl ester **(44)**[r] Furanmethanol **(45)**[b] Furfural **(46)**[d] Furfuryl methyl sulphide **(47)**[x] Geraniol **(48)**[u] Germacrene D **(49)**[u] Germacrene D-4-ol **(50)**[u] Guaiacol **(51)**[r] Heptadecane **(52)**[c] Heptanal **(53)**[d]	(Azzouzi et al., 2014a, 2014b; Bertoli et al., 2004; Innocenti et al., 1998; Khatune et al., 2004; Pazos-Navarro et al., 2011; Pistelli et al., 2003;Tava et al., 2007)

(*continued on next page*)

Table 1 (*continued*)

Plant(s)	Part used	Chemical constituents (structure number) [chemical class/sub-class]	Reference(s)
		Heptane **(54)**[c]	
		Hexadecanol **(55)**[b]	
		Hexanal **(56)**[d]	
		Hexane **(57)**[c]	
		Hexanol **(58)**[b]	
		Humulene oxide II **(59)**[u]	
		Indole **(60)**[x]	
		Isoorientin **(61)**[m]	
		Isopentyl alcohol **(62)**[b]	
		Limonane **(63)**[u]	
		Limonene **(64)**[u]	
		Linalool **(65)**[u]	
		Linoleic acid **(66)**[l]	
		Linolenic acid **(67)**[l]	
		Maltol **(68)**[x]	
		Methyl benzoate **(69)**[k]	
		Methyl chavicol **(70)**[s]	
		Methyl hexadecanoate **(71)**[k]	
		Methyl linolenate **(72)**[k]	
		Methyl octadecanoate **(73)**[k]	
		Methyl tetradecanoate **(74)**[k]	
		Mint sulphide **(75)**[x]	
		n-Docosane **(76)**[c]	
		n-Eicosane **(77)**[c]	
		n-Heneicosane **(78)**[c]	
		n-Hexadecane **(79)**[c]	
		Nonanal **(80)**[d]	
		Nonane **(81)**[c]	
		Oct-1-en-3-ol **(82)**[b]	
		Octadecanoicacid **(83)**[a]	
		Octadecanol **(84)**[b]	
		Octane **(85)**[c]	
		Palmitic acid **(86)**[l]	
		Pentanol **(87)**[b]	
		Phenol **(88)**[r]	
		Phenylacetaldehyde **(89)**[d]	
		Phenylethyl alcohol **(90)**[b]	
		Plicatin B **(91)**[q]	
		Psoralen **(92)**[n]	
		p-Vinyl guaiacol **(93)**[r]	
		Sabinene **(94)**[u]	
		Spathulenol **(95)**[u]	
		Squalene **(96)**[c]	
		Terpinen-4-ol **(97)**[u]	
		Terpinolene **(98)**[u]	
		Tetradecanoicacid **(99)**[1]	
		Tetradecanol **(100)**[b]	
		Thymol **(101)**[p]	
		(*E*)-γ-Cadinene **(102)**[c]	
		Tricyclene **(103)**[u]	
		Vanillicacidethylester **(104)**[r]	
		Viridiflorol **(105)**[u]	
		Xanthotoxin **(106)**[n]	
		(*Z*)-Phytol **(107)**[b]	

(*continued on next page*)

Table 1 (*continued*)

Plant(s)	Part used	Chemical constituents (structure number) [chemical class/sub-class]	Reference(s)
		(*Z*)-2-Pentenol **(108)**[b]	
		(*Z*)-3-Hexenol **(109)**[b]	
		(*Z*)-3-Hexenyl acetate **(110)**[k]	
		(*Z,Z*)-9,12-Octadecadien-1-ol **(111)**[b]	
		(*Z,Z,Z*)-9,12,15-Octadecadien-1-ol **(112)**[b]	
		α-Bisabolol **(113)**[u]	
		α-Cadinol **(114)**[u]	
		α-Cedrene **(115)**[u]	
		α-Copaene **(116)**[u]	
		α-Cubebene **(117)**[u]	
		α-Humulene **(118)**[u]	
		α-Longipinene **(119)**[u]	
		α-Muurolene **(120)**[u]	
		α-Muurolol **(121)**[u]	
		α-Pinene **(122)**[u]	
		α-Terpineol **(123)**[b]	
		α-Ylangene **(124)**[u]	
		β-Bourbonene **(125)**[u]	
		β-Caryophyllene **(126)**[u]	
		β-Cedrene **(127)** [t]	
		β-Copaene **(128)**[u]	
		β-Cubebene **(129)**[u]	
		β-(*E*)-Damascenone **(130)**[v]	
		β-(*E*)-Ocimene **(131)**[p]	
		β-Elemene **(132)**[u]	
		β-Farnesene **(133)**[u]	
		β-Gurjunene **(134)**[u]	
		β-Myrcene **(135)**[u]	
		β-Phellandrene **(136)**[u]	
		β-Pinene **(137)**[u]	
		β-Ionone **(138)**[v]	
		γ-Muurolene **(139)**[u]	
		γ-Terpinene **(140)**[u]	
		δ-Cadinene **(141)**[u]	
		2,3-Dihydrobenzofuran **(142)**[e]	
		2-Methyl hexane **(143)** [c]	
		2-Methyl pentane **(144)**[c]	
		3-(*E*)-Hexen-1-ol **(145)**[b]	
		3-(Methylthio) propanal **(146)**[x]	
		3-Methyl-2-buten-1-ol **(147)**[b]	
		4-Allylanisole **(148)**[s]	
		4-Methoxy acetophenone **(149)**[x]	
		4-Methyl pentanol **(150)**[b]	
***Psoralea canescens*Michx.** [synonym: *Pediomelum canescens* (Michx.) Rydb.]	Rhizome	Angelicin (Isopsoralen) **(2)**[n] Drupacin **(151)**[a] Plicatin-B **(91)** [q] Psoralen **(92)** [n]	(Innocenti et al., 1997)

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Table 1 (*continued*)

Plant(s)	Part used	Chemical constituents (structure number) [chemical class/sub-class]	Reference(s)
			
***Psoralea corylifolia* L.** [accepted name: *Cullen corylifolium* (L.) Medik.]	Whole plant	Angelicin (Isopsoralen) **(2)**[n] Astragalin **(152)**[m] Bakuchalcone **(153)**[g] Bakuchicin **(154)**[n] Bakuchiol **(155)**[p] Bakuflavonone **(156)**[m] Bakuisoflavone **(157)**[o] Bavachalcone **(158)**[g] Bavachin/Corlifolin **(159)**[m] Bavachinin **(160)**[m] Bavachinone A **(161)**[m] Bavachinone B **(162)**[m] Bavachromanol **(163)**[g] Bavachromene **(164)**[g] Bavacoumestan A **(165)**[h] Bavacoumestan B **(166)**[h] Bavacoumestan C **(167)**[h] Bavadin **(168)**[m] Bavarigenin **(169)**[m] Biochanin A **(170)**[m] Bisbakuchiols A **(171)**[p] Bisbakuchiols B **(172)**[p] Brosimacutin G **(173)**[m] Broussochalcone B **(174)**[g] Chalcone **(175)**[g] Chromenoflavanone **(176)**[m] Coryaurone A **(177)**[j] Coryfolia D **(178)**[m] Corylidin **(179)**[i] Corylifol A (Corylinin) **(180)**[m] Corylifol B **(181)**[g] Corylifol C **(182)**[m] Corylifol D **(183)**[o] Corylifol E **(184)**[o] Corylifolin **(185)**[m] Corylifonol **(186)**[e]	(Agarwal et al., 2006; Alam et al., 2017) Anwar et al., 2011; Bajwa et al., 1972; Behloul and Wu, 2013; Bhalla et al., 1968; Bourgaud et al., 2008; Chen et al., 2010; Chen et al., 2010; Chen et al., 2011; Chen et al., 2013; Chen et al., 2014; Choi et al., 2008a, b; Chopra and Chopra, 1958; Damodaran and Dev, 1973; Farahani et al., 2015; Gupta et al., 1977; Gupta et al., 1980; Gupta et al., 2005; Gupta et al., 2013a, 2013b; Hao et al., 2014; Hsu et al., 2001; Huang et al., 2014; Iwamura et al., 1989; Jeong et al., 2013; Ji and Xu, 1995; Kapoor and Raton, 2001; Katsura et al., 2001; Kawl, 1976; Khatune et al., 2002; Khatune et al., 2004; Kim et al., 2016; Kondo et al., 1990; Krishnamurthi et al., 1969; Lau et al., 2010; Lau et al., 2014; Lee et al., 2015; Li et al., 2014; Li et al., 2015; Li et al., 2016; Lim et al., 2011; Limper et al., 2013; Lin and Kuo, 1992; Lin et al., 2007; Liu et al., 2014; Manohar and UdayaSankar, 2012; Mar et al., 2001; Matsuda et al., 2007; Newton et al., 2002; Peng et al., 1995; Prakasarao et al., 1973; Prasad et al., 2004; Qiao et al., 2006; Rajpal, 2005; Rajput et al., 2008; Rastogi and Mehrotra, 1998; Rastogi and Mehrotra, 1999; Nordin et al., 2015; Rastogi and Mehrotra, 2001; Rastogi and Mehrotra, 2004; Ruan et al., 2007; Sah et al., 2006; Sardari et al., 1999; Seo et al., 2013; Shah et al., 1997; Shan et al., 2014; Sharma et al., 2001; Sheng et al. 2004; Shirwaikar et al., 2010; Siddapa et al., 1956; Siddapa et al., 1957; Siva et al., 2015; Somani et al., 2015; Song et al., 2013; Song et al., 2015; Srinivasan and Sarada, 2012; Sun et al., 2016; Teschke et al., 2014; Tewari and Bhakuni, 2010; Wang et al., 2014; Won et al., 2015; Wu et al., 2007 a, b; Wu et al., 2008; Xiao et al., 2012; Xu et al., 2012; Yadava and Verma, 2003; Yadava and Verma, 2005; Yang et al., 2006; Yang et al., 2009; Yin et al., 2004; Yu et al., 2005; Zhang et al., 2016; Zhao et al., 2005a)
			

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Table 1 (*continued*)

Plant(s)	Part used	Chemical constituents (structure number) [chemical class/sub-class]	Reference(s)
		Corylin **(187)**[m]	
		Corylinal **(188)**[o]	
		Coumestan **(189)**[o]	
		Coumesterol **(190)**[i]	
		Cyclobakuchiol C **(191)**[p]	
		Daucosterol **(192)**[r]	
		Dehydroisopsoralidin **(193)**[h]	
		Delta(10)-12,13-dihydro-12-(*R*)-methoxyisobakuchiol **(194)**[p]	
		Delta(10)-12,13-dihydro-12-(*S*)-methoxyisobakuchiol **(195)**[p]	
		Diadzein **(196)**[o]	
		Diadzin **(21)**[o]	
		Erythrinin A **(197)**[m]	
		Genistein **(198)**[o]	
		Geranylacetate **(199)**[p]	
		Hydroquinone **(200)**[r]	
		Hydroxypsoralenol A **(201)**[o]	
		Hydroxypsoralenol B **(202)**[o]	
		Isobavachalcone (corylifolinin) **(203)**[g]	
		Isobavachin **(204)**[m]	
		Isocorylifonol **(205)**[e]	
		Isoneobavachalcone **(206)**[g]	
		Isoneobavaisoflavone **(207)**[m]	
		Isopsoralenoside **(208)**[e]	
		Isopsoralidin **(209)**[n]	
		Isowighteone **(210)**[m]	
		Neobavachalcone **(211)**[g]	
		Neobavaisoflavone **(212)**[o]	
		Neocorylin **(213)**[m]	
		Neopsoralen **(214)**[h]	
		p-Hydroxybenzoicacid **(215)**[a]	
		Protocatechualdehyde **(216)**[d]	
		Psorachromene **(217)**[g]	
		Psoracorylifol A **(218)**[p]	
		Psoracorylifol B **(219)**[p]	
		Psoracorylifol C **(220)**[p]	
		Psoracorylifol D **(221)**[p]	
		Psoracorylifol E **(222)**[p]	
		Psoracorylifol F **(223)**[p]	
		Psoracoumestan **(224)**[h]	
		Psoralen **(92)**[n]	
		Psoralenol **(225)**[o]	
		Psoralenoside **(226)**[e]	
		Psoralester **(227)**[k]	
		Psoralidin **(228)**[n]	
		Psoralidin-2',3'-oxide **(229)**[i]	
		Pyranocoumarin **(230)**[h]	
		Sophoracoumestan A **(231)**[o]	
		Stigmasterol **(232)**[t]	
		Terpinen-4-ol **(97)**[u]	
		Triacontane **(233)**[c]	
		Trilaurin **(234)**[l]	
		Wighteone **(235)**[m]	

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Table 1 (*continued*)

Plant(s)	Part used	Chemical constituents (structure number) [chemical class/sub-class]	Reference(s)
		Xanthoangelol **(236)**[m] *α*-Elemene **(237)**[u] *β*-Caryophyllene **(126)**[u] *β*-Caryophyllenoxide **(238)**[u] *β*-D-Glucosyl-*cis*-*O*-hydroxycinnamicacid **(239)**[a] *β*-Sitosterol-D-glucoside **(240)**[t] γ-elemene **(241)**[u] (12′S)-Bisbakuchiol C **(242)**[p] 1-[2,4-Dihydroxy-3-(2-hydroxy-3-methyl-3-butenyl) phenyl]-3-(4-hydroxyphenyl-2-propen-1-one (Psorachalcone A) **(243)**[m] 12,13-Dihydro-12,13-epoxybakuchiol) **(244)**[p] 12,13-Diolbakuchiol **(245)**[p] 12,13-Dihydro-12,13-dihydroxybakuchiol C **(246)**[p] 12,13-Dihydro-13-hydroxybakuchiol **(247)**[p] 12,13-Epoxybakuchiol **(248)**[p] 12-Oxoisobakuchiol **(249)**[p] 13-Ethoxyisobakuchiol **(250)**[p] 12-Hydroxyisobakuchiol / 3-Hydroxy-Δ^1-bakuchiol **(251)**[p] 13-Hydroxyisobakuchiol / 2-Hydroxy-Δ^3-bakuchiol **(252)**[p] 13-Methoxyisobakuchiol **(253)**[p] 15-Demetyl-12,13-dihydro-13-ketobakuchiol **(254)**[p] 3,5,3′,4′-tetrahydroxy-7-methoxyflavone-3′-*O*-*α*-L-xylopyranosyl (1→3)-*O*-*α*-L-arabinopyranosyl(1→4)-*O*-*β*-D-galactopyranoside **(255)**[m] 3-Hydroxybenzaldehyde **(256)**[d] 4,2′-Dihydroxy-4′-methoxy-5′-(3″,3‴-dimethyl allyl)-chalkone **(257)**[m] 4-Hydroxylonchocarpin (Isobavachromene) **(258)**[m] 4,2′-dihydroxy-2″-(1‴-methylethyl)-2″-3″-dihydro-(4″,5″,3′,4′) furanochalkone **(259)**[m] 4-*O*-Methylbavachalcone **(260)**[g] 6-(-3-Methylbut-2-enyl)-6′-7-dihydroxycoumestan **(261)**[m] 6-Prenylnaringenin **(262)**[m] 7,2′,4′-Trihydroxy-3-arylcoumarin **(263)**[h] 7-Methoxybavachin **(264)**[m] 7-*O*-Isoprenylcorylifol A **(265)**[m] 7-*O*-Methylbavachin**(266)**[m] 7-*O*-Methylcorylifol A **(267)**[m] 8-Methoxypsoralen **(268)**[n] 8-Oxo-8H-furo [2, 3-f][l]benzopyran **(269)**[f] 8-Prenyldaidzin **(270)**[m]	
***Psoralea esculenta* Pursh** [synonym: *Pediomelum esculentum* (Pursh) Rydb.]	Root	Diadzin **(21)**[o] Genistein **(198)**[o]	(Christensen et al., 2008; Kaye and Moodie, 1978; Perara, Reese, 2002; Stahnke et al., 2008)

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Table 1 (*continued*)

Plant(s)	Part used	Chemical constituents (structure number) [chemical class/sub-class]	Reference(s)
			
***Psoralea plicata* Delile** [accepted name: *Cullen plicatum* (Delile) C.H.Stirt.]	Leaf, Flower, Seed	Angelicin (Isopsoralen) **(2)**[n] Bakuchicin **(154)**[n] Corylifonol **(186)**[e] Coumestan **(189)**[o] Diadzin **(21)**[o] (*E*)-Werneriachromene **(29)**[n] Isocorylifonol **(205)**[e] Isopsoralicacid **(271)**[h] Isopsoralicacid-*O*-glucopyranosyl **(272)**[w] Isovitexin **(273)**[m] Lupeol **(274)**[u] *p*-Dimethyl coumaric acid **(275)**[a] Plicadin **(276)**[i] Plicatin A **(277)**[q] Plicatin B **(91)**[q] Psoracinol **(278)**[p] Psoralen **(92)**[n] Psoralic acid **(279)**[h] Roseoside A **(280)**[w] Stigmasterol **(232)**[t] (*Z*)-Werneriachromene **(281)**[n] *α*-Diplicatin-B **(282)**[q] *α*-Tocopherol **(283)**[t] *β*-Caryophyllene **(126)**[u] *β*-Caryophyllenoxide **(238)**[u] *β*-Duplicatin-B **(284)**[q] 3-(-3-Methyl-2,3-epoxybutyl)-*p*-coumaric acid methyl ester **(285)**[q]	(Arfaoui et al., 2013; Cheikh et al., 2015; El-Abgy et al., 2012; Hamed et al., 1997, 1999; Khatune et al., 2004; Menon et al., 1999; Rasool et al., 1989, 1990;1991; Youssef et al., 2013)
			
***Psoralea glandulosa* L.**	Resinous exudate, young shoots, leaves	Angelicin **(2)**[n] Bakuchiol **(155)**[p] Bakuchiol acetate **(286)**[p] Bakuchiol methyl ether **(287)**[p] Cyclobakuchiol A **(288)**[p] Cyclobakuchiol B **(289)**[p] Drupanin**(24)**[h] Drupanin methyl ester **(290)**[h]	(Backhouse et al., 2001;Labbe et al., 1996; Li et al., 2016; Madrid et al., 2012, 2013, 2015a, 2015b)

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Table 1 (*continued*)

Plant(s)	Part used	Chemical constituents (structure number) [chemical class/sub-class]	Reference(s)
		Psoralen **(92)**[n] 3-Hydroxybakuchiol **(291)**[p] 12,13-Dihydro-12,13-epoxybakuchiol **(244)**[p] 12-Hydroxyisobakuchiol **(251)**[p] 13-Hydroxyisobakuchiol **(252)**[p]	

[a] Acids
[b] Alcohols
[c] Aliphatichydrocarbons
[d] Alkylaldehyde
[e] Benzofuran
[f] Benzopyran
[g] Chalcone
[h] Coumarins
[i] Coumesterol
[j] Dihydrofuran
[k] Esters
[l] Fattyacids
[m] Flavonoids
[n] Furanocoumarin
[o] Isoflavone
[p] Meroterpene
[q] Phenoliccinnamate
[r] Phenols
[s] Phenylpropene
[t] Sterols
[u] Terpenes
[v] Rose-ketones
[w] Glycoside
[x] Miscellaneous.

and are used as a tonic to strengthen the genital organs (Ven, 1987). The fruits are bitter in taste, can prevent vomiting, cure difficulty in micturition, cure piles, bronchitis and anaemia and are known to improve complexion (Joshi, 2000). Moreover, fruit extract inhibits the growth of *Mycobacterium tuberculosis* (Yeung, 1985). The roots and seeds of *P. corylifolia* are used for preventing tooth decay (Duke, 2009). They also promote bone calcification, and hence are beneficial for treating bone fractures and osteoporosis (Joshi, 2000; Krishnamurthi et al., 1969; Wong and Rabie, 2010a, 2010b).

Psoralea esculenta Pursh. (Breadroot, Large Indian breadroot) roots are starchy (70% starch), glutinous (9% protein) with a sweetish turnip-like taste (5% sugars) and are eaten raw or cooked (Hedrick, 1972; Saunders, 2011; Tanaka, 1976; Uphof, 1968; Yanovsky, 1936). The dried roots are pulverized and used with cereals in making cakes and porridge (Facciola, 1983). A poultice prepared from the crushed roots is applied to sprains and fractures. An infusion of the dried roots is used in the treatment of sore throats, gastro-enteritis and chest problems. The roots are chewed by children as a treatment for bowel complaints (Moerman, 1998).

Psoralea glandulosa L. is cultivated in Chile for its leaves and young shoots, which are used to make a refreshing cold drink. The leaves are anti-helmintic. *Psoralea hypogaea* Torr. & A. Gray (Small Indian breadroot) roots are eaten raw or cooked (Elias and Dykeman, 2009; Harrington, 1974; Hedrick, 1972; Moerman, 1998; Yanovsky, 1936). The roots are rich in starch and can be ground into a powder and used in soups or with cereals for making bread (Yanovsky, 1936). The roots were used an important source of food for the native North American Indians (Diggs et al., 1999). *Psoralea macrostachya* DC. (Large Leather Root) roots are eaten raw or cooked and may be dried for winter use. Moreover, the plant has been used in the treatment of ulcers and sores (Moerman, 1998). A strong fibre is obtained from the inner bark of the stem (Saunders, 2011; Usher, 1974). A fibre is also obtained from the roots, which is used to make ropes and bags (Moerman, 1998; Uphof, 1968). Roots are aromatic and the perfume persists for several months (Saunders, 2011). A yellow dye is also obtained from the roots (Moerman, 1998). *Psoralea orbicularis* Lindl. (Roundleaf leather root) leaves are cooked and eaten (Moerman, 1998; Tanaka, 1976; Yanovsky, 1936). A decoction of the root is used to purify blood and to treat prexia (Moerman, 1998). The plant is a good soil stabilizer (Huxley, 1992). *Psoralea pedunculata* (Mill.) Vail (Sampson's snakeroot) is used as a bitter tonic.

5. Phytochemistry

Psoralea species have been investigated since 1890s (Dymock et al., 1893). Leaf, rhizome, root, seeds, fruit and resinous extracts of *Psoralea* species have been subjected to HPLC and HPTLC followed by pharmacological analyses (Pandey et al., 2012; Shailajan et al., 2012; Uikey et al., 2010; Won et al., 2015; Yin et al., 2015; Zhao et al., 2005a). Detailed and extensive chemical investigation of six *Psoralea* species viz: *P. bituminosa* L. (Syn: *Bituminaria bituminosa*), *P. canescens* Michx., *P. corylifolia* L., *P. esculenta* Pursh, *P. plicata* Delile and *P. glandulosa* L. led to the characterization of a large number of bioactive constituents. Review of literature reveals the presence of altogether 291 chemical constituents including volatile compounds in the aforementioned species (Table 1). These chemical compounds have been categorized into coumarins, furanocoumarins, flavonoids (polyphenols), isoflavones, meroterpenes, chalcones, phenols, phenolic cinnamates, phenylpropene, sterols, terpenes, tocopherols, benzofurans, sesquiterpenes, acids, fatty acids, alkyl aldehydes, alcohols and esters (Agarwal et al., 2006; Bertoli et al., 2004; Hsu et al., 2001; Qiao et al., 2006; Ruan et al., 2007; Tava et al., 2007; Yin et al., 2006, 2007; Yu et al., 2005). The chemical structures of 1–291 compounds are shown in the supplemental information (Supplemental information 3, Fig. S1). Their chemical names, chemical class and the corresponding plant sources are compiled in Table 1. The structures of those bioactive compounds which are representative of the genus and with reported pharmacological activities are presented in the main text (Fig. 2).

Recently, an isoflavone synthase (IFS) gene has been isolated and functionally characterized from *P. corylifolia* (Misra et al., 2010). The active principle found in *P. corylifolia* is bakuchiol (**155**) and psoralen (**92**) (Dev, 1999; Wang et al., 2009). Psoralen is linear in structure and may be called as a derivative of umbelliferone (Jois et al., 1933; Rangari and Agrawal, 1992). The production of psoralen enhances when the plant is exposed low dose of gamma radiation (Jan et al., 2011). Isopsoralen (**2**) is a structural isomer of psoralen (**92**), and it was found to be identical to angelicin (**2**) (Jois et al., 1933; Jois and Manjunath, 1934; Seshadri and Venkata Rao, 1937). Angelicin (isopsoralen) (**2**) is a photosensitizing agent and used for determination of DNA and RNA structures in cells and microorganisms (Kittler et al., 1980). Angelicin (**2**) and its derivatives occur in a number of plants belonging to the family Umbelliferae. The active compound, bakuchiol (**155**) is a monoterpene phenol, has been obtained in a pure state and named after Sanskrit name of the plant (Mehta et al., 1973) and possess the potent anti-bacterial property (Satyavati et al., 1987).

The seed contains volatile oils, monoterpenes, flavones, coumarins, stigmasteroids, resins, lipid compounds and phenols. The volatile oils include limonene (**64**), linalool (**65**), β-caryophyllene (**126**), geranyl acetate (**199**) and terpinen-4-ol (**97**), coumarin derivatives include psoralen (**92**), isopsoralen (**2**), isopsoralidin (**209**), corylidin (**179**), psoralidin (**228**), bavacoumestan A (**165**), bavacoumestan B (**166**), 8-methoxypsoralen (**268**) and sophoracoumestan A (**231**). Flavones include corylifolinin (**203**), bavachin/corlifolin (**159**), neobavaisoflavone (**212**), bavachromene (**164**), isobavachin (**204**), bavachalcone (**158**), corylin (**187**), and neobavachalcone (**211**). Lipids include triglycerides, diglycerides and monoglycerides. Monoterpene phenol includes bakuchiol (**155**). Others include free fatty acids, stigmasterol (**232**), triacontane (**233**), daucosterol (**192**), glucose and saponin. The fatty acids obtained from oil were found to be primarily palmitic acid (**86**) and linoleic acid (**66**) together with small fraction of linolenic acid (**67**). The pharmacologically active oil is identical with the unsaponifiable oil isolated by earlier workers (Gaind et al., 1965; Gupta et al., 1962). More that 188 chemical constituents (belonging to furanocoumarins, coumestrol group, chalcones and flavones) have been reported from the seeds (Bhalla et al., 1968; Chakrovarti et al., 1948; Chen et al., 2005; Satyavati et al., 1987; Tsai et al., 1996).

6. Pharmacological activities

Psoralea species have received tremendous attention because of their bioactive principles possessing remarkable pharmaceutical properties (Fig. 3; Supplemental information 4, Table S3).

6.1. Anti-oxidant activity

Several protocols have been followed to analyse the anti-oxidant property of seeds and leaf extracts of *P. bituminosa*, *P. glandulosa*, *P. corylifolia*, *P. plicata*, *P. esculenta* and *P. glandulosa.* The phenolic compounds obtained from different extracts were found to protect the biological membranes from oxidative stresses (Haraguchi et al., 2002; Guo et al., 2005; Borchardt et al., 2008; Kim et al., 2013; Madrid et al., 2013; Huang et al., 2014). The antioxidant activity of fruit extracts of *Psoralea plicata* was evaluated by DPPH assay. The study indicated that the methanol extract shows an anti-oxidant activity (288.32 micromol Trolox equivalent/100 g dry material) which is slightly higher as compare to aqueous extract (258,65μmol Trolox equivalent/100 g dry material) (Cheikh et al., 2015). In a study on *P. corylifolia*, several bioactive compounds such as bakuchiol (**155**), psoralen (**92**), isopsoralen (**2**), corylin (**187**), corylifolin (**185**) and psoralidin (**228**) were screened for their anti-oxidant potential. Their antioxidant activities were investigated individually and compared with butylated hydroxytoluene (BHT) and α-tocopherol by the oxidative stability instrument

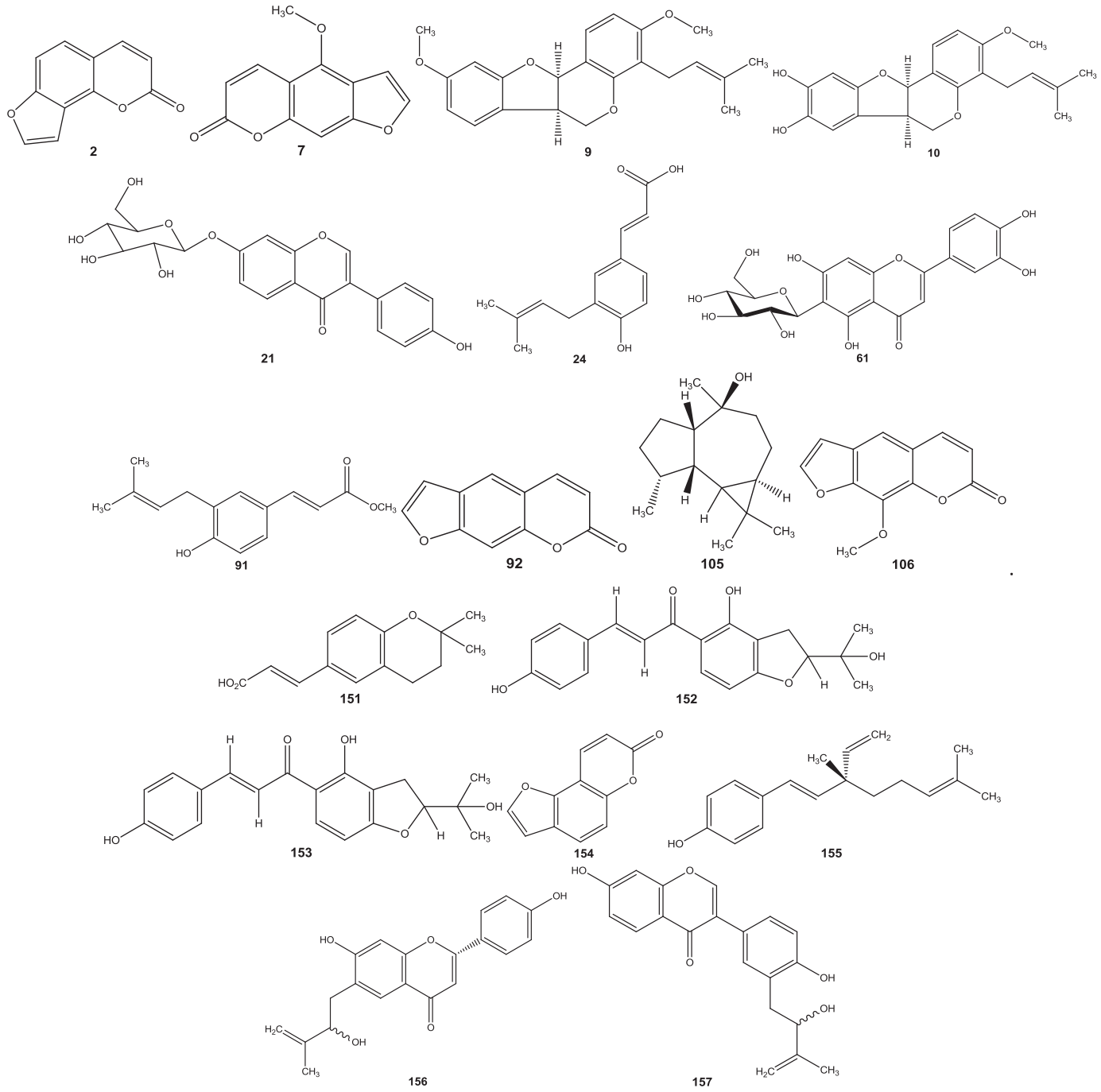

Fig. 2. Chemical structures of selected phytochemicals isolated and characterized from *Psorelea* species.

(OSI) at 100ºC Among these compounds psoralidin exhibited highest anti-oxidant activity (5.23) than that of standard compounds (Psoralidin > BHT > α-tocopherol > bakuchiol > corylifolin > corylin > isopsoralen~psoralen) (Jiangning et al., 2005). However, antioxidant activity alone cannot be of any pharmacological significance. It is accompanied by other specific pharmacological activities to claim any therapeutic benefit.

6.2. Anti-bacterial activity

There are several reports on the anti-bacterial activitiy of *P. bituminosa* and *P. corylifolia*. The ethanol and methanol extracts obtained from the aerial parts of *P. bituminosa* contain flavones and isoflavones, while the seed extracts of *P. corylifolia* contain psoralidin (**228**), bakuchicin (**154**), psoralen (**92**) and angelicin (**2**), which have shown significant anti-bacterial activities. Techniques such as disc-diffusion method, UV (ultraviolet), H NMR (proton nuclear magnetic resonance), C NMR (carbon nuclear magnetic resonance), anti-bacterial assay, broth-dilution method, column chromatography, HPLC (high performance liquid chromatography) and TLC (thin layer chromatography) were used to quantitate and analyse the anti-bacterial property of these natural compounds (Azzouzi et al., 2014a, 2014b; Bhawna et al., 2013; Cui et al., 2015). Bakuchiol obtained from seed extract of *P. corylifolia* has been reported to inhibit the growth of *Staphylococcus mutans* and *Actinomyces viscosus* and hence possess strong anti-bacterial activity and MIC value of bakuchiol was found to be 9.76–19.5 μg/mL (Khushboo et al., 2010; Rao et al., 2011). In a study, the compounds psoralidin (**228**), bakuchicin (**154**), psoralen (**92**) and angelicin (**2**)

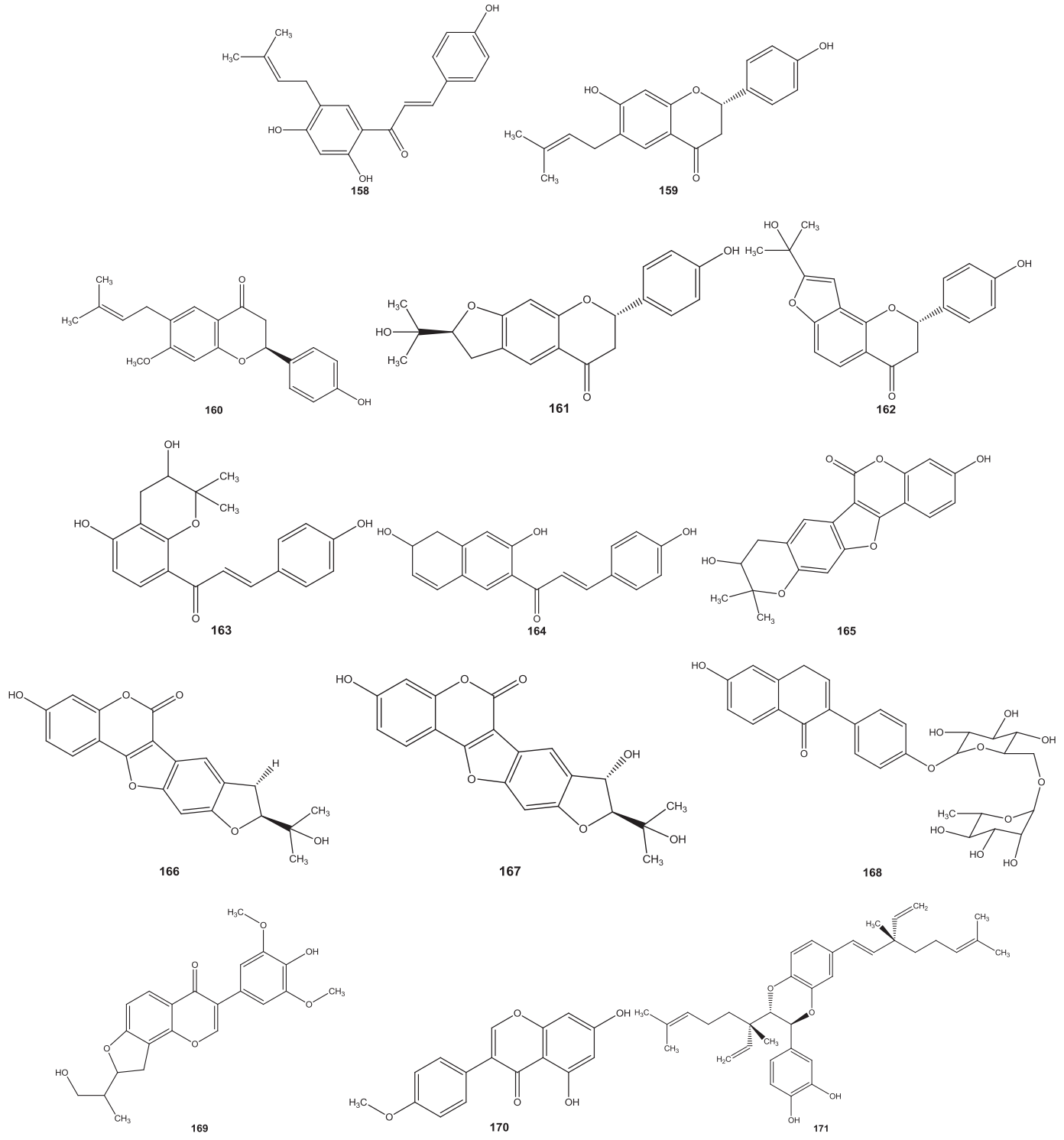

Fig. 2. (*continued*)

obtained from different extracts of the plant were found to show anti-bacterial activity against different gram-positive and gram-negative bacteria. Among them, psoralidin (**228**) showed highest anti-bacterial activity against *Shigella sonnei* and *S. flexneri* as depicted by disc diffusion assay (Khatune et al., 2004).

6.3. Anti-fungal activity

P. corylifolia and *P. glandulosa* are known to possess significant anti-fungal activity. Aqueous and methanol extract of seeds and petroleum ether extract of the aerial parts *P. corylifolia* have been tested against various seed borne fungi such as (*Alternaria*, *Cladosporium*, *Dreschslera* and *Rhizophus* spp.) of maize. In aqueous extract, maximum inhibition (95.4% inhibition at 50% concentration) was observed against *A. alternata* followed by *C. lunata* (86.0%), *Rhizopus sp.* (82.3%), *D. halodes* (68.0%) and *C. cladosporioides* (57.7%). Among the solvents used for the preparation of extracts, maximum inhibition was observed with petroleum ether extract and moderate activity was observed with methanol extract (Kiran et al., 2011). In an anti-fungal assay, the essential oil extracted from *P. corylifolia*, was studied against three

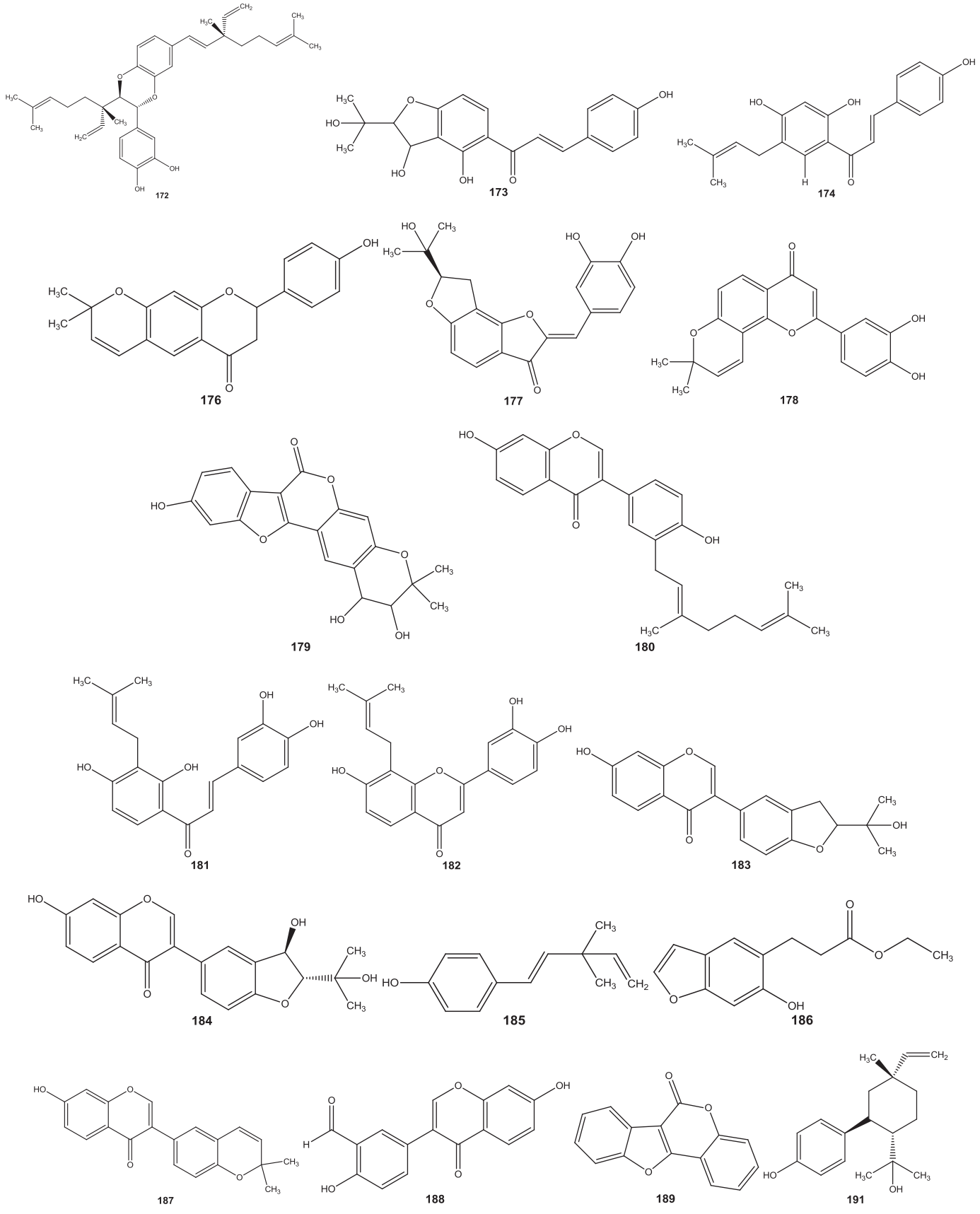

Fig. 2. (*continued*)

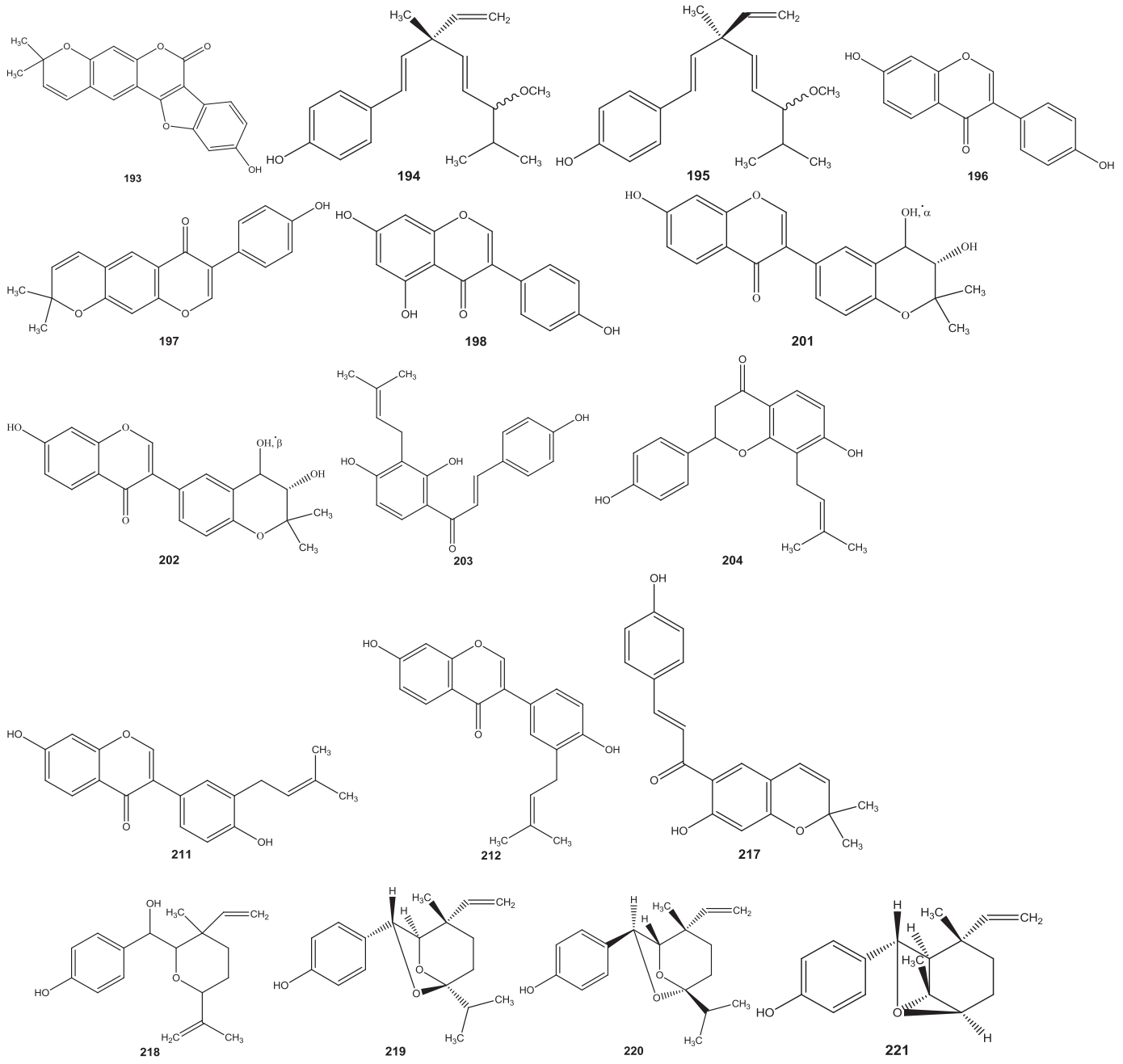

Fig. 2. (*continued*)

dermatophytic fungi *Microsporum canis*, *Trichophyton rubrum* and *Trichophyton mentagrophytes*. The zone of inhibition (by disc-diffusion assay) for *M. canis*, *T. rubrum* and *T. mentagrophytes* was found to be 20, 35 and 37 mm respectively, while the minimum inhibitory concentration was reported to be 1.4, 0.4 and 0.5 µl/mL, respectively (Sharma and Tiwari, 2012). In another study, methanol extract of *P. corylifolia* seeds was found to be most effective against tomato late blight (*Phytophthora infestans*) and wheat leaf rust (*Puccinia recondite*) (Shim et al., 2009). The crude extract of *P. corylifolia* exhibited significant antifungal activity against *Candida albicans* (Anwar et al., 2011). In a study by Borate et al. (2014), methanol extract of *P. corylifolia* seeds was reported to exhibit a maximum zone of inhibition against *C. albicans* (16.25 mm) followed by *Malassezia furfur* (14.25 mm) and *A. niger* (12.22 mm). Two active compounds bakuchiol (**155**) and 3-hydroxybakuchiol (**291**) obtained from resinous exudate of aerial plant parts of *P. glandulosa* were reported to show MIC 80 ranging from 4 to 416 and 0.125–16 mg/mL, respectively against various strains of *Candida* (Madrid et al., 2012).

6.4. Anti-viral activity

The crude ethanol extract of the seeds of *P. corylifolia* exhibited significant anti-viral activity against the severe acute respiratory syndrome corona virus (SARS-CoV) papain-like protease (PLpro). The IC50 value for the same was 15 µg/mL. SARS-CoV-PLpro is the enzyme that is crucial for replication of SARS virus (Kim et al., 2014). In a recent study, it was reported that bakuchiol (**155**) present in seeds of *P. corylifolia* inhibited the influenza A viral infection and growth and activated the nuclear factor erythroid 2-related factor (Nrf2) pathway. This pathway is responsible for cellular defense against electrophilic or oxidative stress (Shoji et al., 2015).

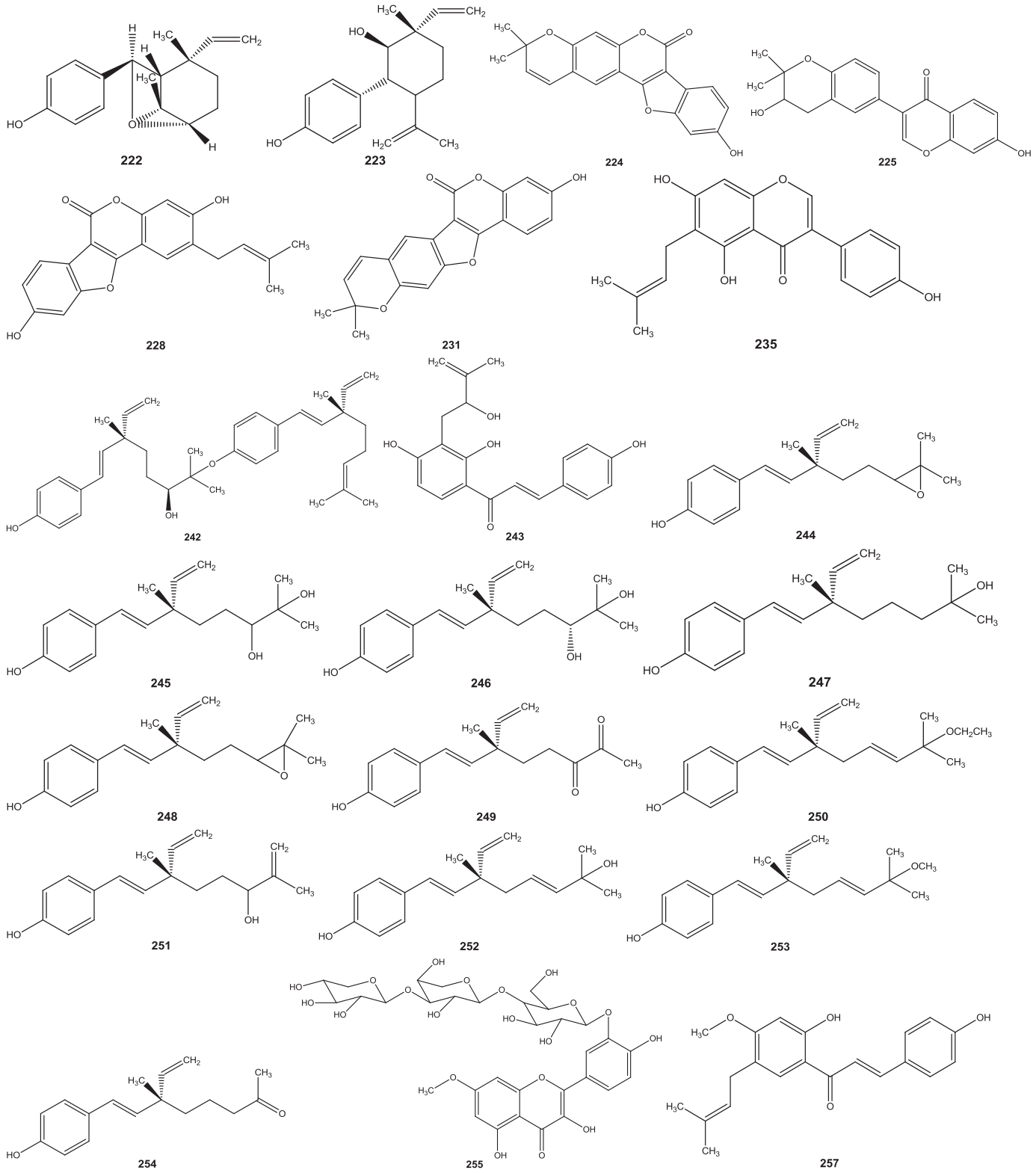

Fig. 2. (*continued*)

6.5. Anti-inflammatory activity

Bakuchiol (**155**) extracted (petroleum ether extract, dichloromethane extract, and methanol extract) from the aerial parts of *P. glandulosa* inhibits degranulation in human neutrophils and decreases the cell migration, eicosanoid levels and myeloperoxidase activity in mice thus, confirming its anti-inflammatory potential (Ferrándiz et al., 1996; Backhouse et al., 2001). In another study, bakuchiol (**155**) from *P. corylifolia* was reported to inhibit the expression of inducible nitric oxide synthase (NOS) gene through the inactivation of nuclear transcription factor-B in RAW 264.7 macrophages (Pae et al., 2001). The bioactive compounds obtained from leaves, fruits and seeds of *P. corylifolia* inhibit the functioning of tumor necrosis factor-alpha (TNF-α) and exhibt anti-inflammatory activity (Mueller et al., 2010). The

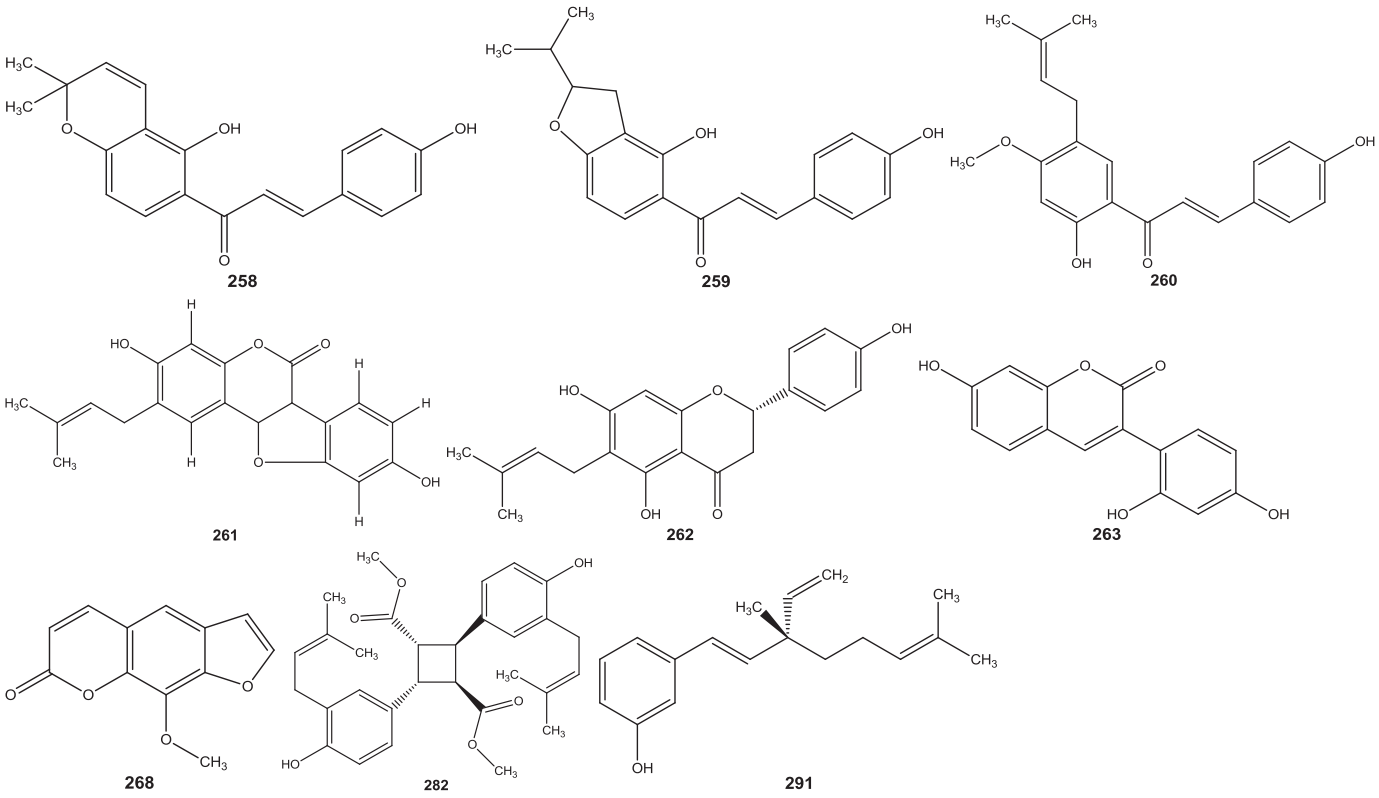

Fig. 2. (*continued*)

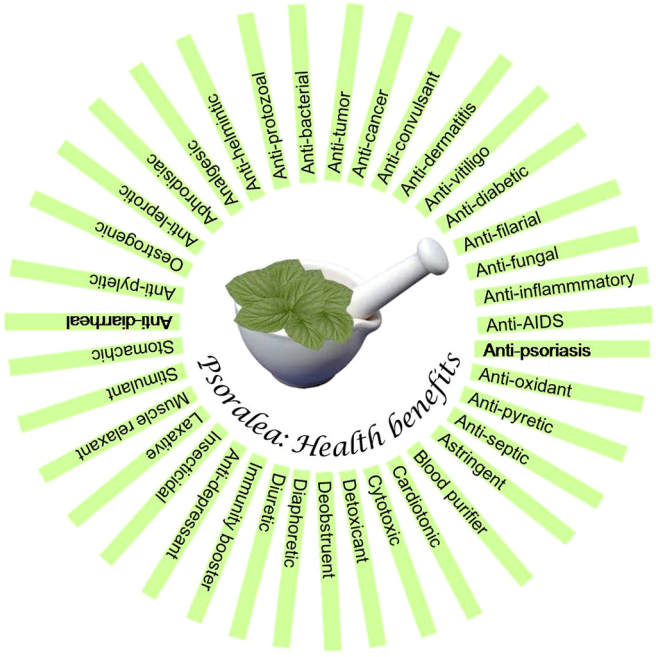

Fig. 3. Medicinal properties of *Psoralea* specie(s).

production of inflammatory mediators such as, reactive oxygen species (ROS), reactive nitrogen species (RNS), and cytokines such as IL-1β, IL-6 and TNF-α (tumor necrosis factor) in PMA (phorbol 12-myristate 13-acetate)/LPS (lipopolysaccharide), in IFN-stimulated murine peritoneal macrophage cell line (RAW 264.7) was inhibited by neobavaisoflavone (**212**) (Szliszka et al., 2011a). Cytotoxicity of neobavaisoflavone (**212**) was tested by using LDH assay (lactate dehydrogenase assay). Psoralidin (**228**) suppresses the activity of pro-inflammatory cytokines which regulate pulmonary inflammation in human lung-fibroblasts and in mice, by ionizing radiation, has been reported (Yang et al., 2011). In a recent study the activity of IL-6-induced STAT3 (Signal transducer and activator of transcription 3) was found to be inhibited by bavachin (**159**), bakuchiol, bavachinin (**160**), corylin (**187**), corylifol A (**180**), neobavaisoflavone (**212**), and isobavachalcone (**203**). Hence, these bioactive compounds hold promise to cure inflammatory diseases (Lee et al., 2012).

6.6. Anti-leprotic activity

In a study by Newton et al. (2002), forty-three plant species were screened for their anti-mycobacterial activities. Among them, bakuchiol (**155**) extracted from *P. corylifolia* hexane seed-extract exhibited significant anti-bacterial activity (MIC = 31.25 g/mL) against *Mycobacterium aurum* and *M. smegmatis* thus, confirming its potential for treatment of leprosy. However, these studies further require *in vitro* and *in vivo* analyses for their large-scale utilization (Newton et al., 2002).

6.7. Anti-psoriatic activity

In a study by Dwarampudi et al. (2012), the ethanolic seed extract of *P. corylifolia* showed an IC50 value of 255 μg/mL and a considerable anti-psoriatic activity (75.87%), using the mouse tail model. The seed extract converted parakeratosis stage (keratinization) to orthokeratosis (formation of anuclear keratin layer) stage of the cell, thus confirming its anti-psoriatic potential (Dwarampudi et al., 2012). In a recent report, different micro-emulsions containing single and both *Commiphora mukul* powder and babchi-oil from *P. corylifolia* were used to assess the anti-psoriatic efficacy on diseased rat paw. The synergistic effect of both the natural products gave better results, hence this herbal combination could be a cheap and effective source of anti-psoriatic agent (Marwaha, 2013). In a study involving human subjects, *P. corylifolia* hexane-seeds extract was prepared into a cream using stearic acid followed by an open clinical trial on thirty patients suffering from eczema, for a period

of one month. The placebo preparation, for this experiment contained all the ingredients except the seed extract. The parameters studied were length of the lesion, exudation rate and rate of itching. The symptoms score reduced after two weeks of cream application. Finally, the length of the lesion reduced from 6.367 ± 1.098–0.333 ± .279, exudation rate reduced from 1.333 ± .994–0.165 ± .087 and the rate of itching reduced from 2.567 ± .504–0.165 ± .132. This study concluded that *P. corylifolia* seed extracts could be used effectively used for the treatment of eczema (Gidwani et al., 2010a).

6.8. Anti-vitiligo/anti-leucoderma activity

The compounds obtained from the *P. corylifolia* extract have played an influential role for the treatment of vitiligo. The furocoumarins, psoralen (**92**) and isopsoralen (**2**) present in *Psoralea* species assists the skin to produce new pigment. They initiate the transformation of dihydroxyphenylalanine (DOPA) to melanin when exposed to sunlight and are therefore being used for treating vitiligo, psoriasis and leprosy (Fitzpatrick and Pathak, 1959; Hussain et al., 2016; Song et al., 2004; Yin et al., 2004). Psoralen (**92**) alone can effectively treat psoriasis and alopecia areata (Ji and Xu, 1995; Wang and Wang, 2007). In a report by Abu Tahir et al. (2010), human melanocytes were used to test the anti-vitiligo activity of the oleo-resinous extracts of the seeds. The seed extract acted as an effective anti-vitiligo agent by restoring the melanocytes of the affected area (Abu Tahir et al., 2010).

6.9. Anti-diabetic activity

Ethanol seed extract of *P. corylifolia* when administrated orally to streptozotocin-nicotinamide (STZ) induced diabetic rats lead to an increase in glycogen content of liver and insulin level in plasma with a decrease in plasma cholesterol and blood glucose level (Kamboj et al., 2011). In a report by Bera et al. (2013), the aqueous seed extract of *P. corylifolia* was found to regulate the functioning of insulin sensitive enzyme activities in Wistar strain male albino rats. The seed extract tends to increase the activity of liver hexokinase, glucose-6-phosphate and decrease the level of glucose-6-phosphatase (Bera et al., 2013).

6.10. Anti-depressant activity

The furanocoumarins psoralen (**92**) and isopsoralen (**2**) obtained from the seed extract of *P. corylifolia* have showed anti-depressant activity in mice by hindering the MAO (monoamine oxidase) activity, hypothalamic-pituitary-adrenal axis action and oxidative stress (Chen et al., 2005, 2007, 2008). Another compound, psoralidin (**228**) inhibits the transcription of CRF (corticotrophin releasing factor) gene, which is responsible for stress response (Chen et al., 2007). The anti-depressant activity of psoralidin (**228**) was evaluated by applying the forced swimming test on rats (Yi et al., 2008). Psoralen was reported to successfully change the level of 5-hydroxyindoleacetic acid (5-HIAA) and serotonin (5-HT) in Hippocampus and frontal cortex of mice (Xu et al., 2008). Bakuchiol (**155**) decreases the immobilization time in behavioral despair mouse and plasma epinephrine and norepinephrine (neurotransmitter) levels in bovine adrenal medullary cells hence, exhibits anti-depressant activity (Hao et al., 2014). These results depict the anti-depressant activity of psoralen and bakuchiol.

6.11. Anti-cancer activity

Psoralea species possess unique bioactive compounds with anti-cancer properties. *P. corylifolia* leaves contain remarkably high concentrations (more than 2 g per Kg dry weight) of genistein (**198**), the anti-cancer metabolite. Bioactivity of two furocoumarins psoralen (**92**) and isopsoralen (**2**) was determined for their cytotoxicity on carcinoma lines KB, KBv200 (vincristine resistance subline of KB), human erythroleukemia cell K562 and K562/ADM (doxorubicin resistance subline of K562). Both the compounds induced apoptosis in these cells thus, confirming their anti-cancer potential. The IC50 values of psoralen were 88.1, 86.6, 24.4 and 62.6, which of isopsoralen were 61.9, 49.4, 49.6 and 72.0, respectively (Wang et al., 2011). Psolaren (**92**) when subjected to human hepatocarcinoma cells, showed its inhibitory activity by inducing the mechanism of apoptosis. Psoralen (92) was able to inhibit the growth of SMMC-7721 cells in a dose- and time-dependent manner and had a strong proapoptotic effect on these cells (Jiang and Xiong, 2014; Khan et al., 2015). The bioactive compounds 7,2′,4′-trihydroxy-3-arylcoumarin (**263**), psoracoumestan (**224**) and corylifol C (**182**) from *P. corylifolia* showed strong anti-cancer potential by inhibiting the enzyme MAPK/ERK kinase phosphorylation and inducing aptotic cell death (Limper et al., 2013). In a study, psoralidin (**228**) showed its activity in MCF-7 cancer cells (isolated from human breast) by induction of pS2 gene activity, with an EC50 value of ERE-reporter gene transcription activity of 1.85 μM (Liu et al., 2014). The seed extract of *P. corylifolia* induced apoptosis in the human breast cancer (MCF-7) cells followed by mitochondrial cell death (Rajan et al., 2014). In another study, psoralidin (**228**) was reported to generate reactive oxygen species and also inhibited A549 cell proliferation. The method adopted was MTT assay and the IC50 values obtained after 24-, 48- and 72-h treatment were 19.2, 15.4, and 11.8 μM, respectively (Hao et al., 2014). Psoralidin (**228**) and neobavaisoflavone (**212**) in combination with TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) have showed their anti-cancer property by inducing apoptosis in LNCaP (human adinocarcinoma prostate cancer cells) (Szliszka et al., 2011a). In another report, psoralidin (**228**) in combination with TRAIL influenced apoptosis in HeLa cells by increasing the expression of death receptor (TRAIL-R2) (Bronikowska et al., 2012). In a similar report, psoralidin (**228**) compound obtained from different extracts of *P. corylifolia* exhibited the anti-cancer activitiy against human lung cancer (A549) cells. Psoralidin dramatically decreased the cell viabilities in dose and time-dependent manner (Hao et al., 2014). *Psoralea fructus* suppressed the proliferation of human colorectal cancer cell lines, such as LoVo (IC50: 23.3 ± 1.9 μg/mL), SW480 (IC50: 37.9 ± 1.6 μg/mL), HT-29 (IC50 value: 40.7 ± 1.5 μg/mL), and HCT116 (IC50: 45.3 ± 1.2 μg/mL) by decreasing the protein expression of cyclin D1 and CDK4. Succeeding experiments with many kinase inhibitors revealed that *P. fructus*-mediated degradation of cyclin D1 and CDK4 is dependent on GSK3β and/or ERK1/2 (Park et al., 2016). Psoralen (**92**), isoporalen (**2**) and bakuchiol (**155**) identified in *P. corylifolia* extracts (chloroform and ethanol) have shown their cytotoxic property against HEp-2 cell line (Whelan and Ryan, 2003), BGC-823 cancer cell (Guo et al., 2003) and cultured human cancer cells (SK-OV-3, A549, XF498 and SK-MEL-2HCT15) (Ryu et al., 1992). Bakuchiol (**155**) is one of the active ingredients of the dried ripe fruit of *P. corylifolia*. In a study by Miao et al., 2013, bakuchiol (**155**) suppressed the testosterone induced cell proliferation and gene expression in androgen-dependent prostate cancer (PCa) cell line (LNCaP). The IC50 of bakuchiol (**155**) to androgen receptor was 8.87×10^4, which was similar to the standard flutamide (10.00×10^4). Bakuchiol (**155**) has also showed a strong anti-cancer action against human lung adenocarcinoma cell line A549 and showed better results than its analogue resveratrol. IC50 of bakuchiol (**155**) at 72 h was 9.58 ± 1.12 μmol/L, much lower than that of resveratrol (33.02 ± 2.35 μmol/L). Compared to resveratrol, bakuchiol (**155**) triggered the process of apoptosis to a higher level. It was also observed that oxygen species mediated apoptosis contributes to the cytotoxic properties of bakuchiol (**155**) and can therefore be used against non-small-cell lung cancer (Chen et al., 2010). Invitro experiments with A2058 melanoma cells using *P. glandulosa* resinous exudates revealed that it can inhibit the growth of cancer cells after 48 h of treatment. These experiments confirmed the anti-cancer potential of *P. glandulosa* which can be attributed to the presence of bakuchiol, 3-hydroxy-bakuchiol and 12-hydroxy-isobakuchiol (Madrid et al., 2015b).

Ethanol, methanol, chloroform and aqueous seed extracts of *P. corylifolia* were tested against the tumor cells of mice and were found to stimulate the antibody complement-mediated cytotoxicity during tumor development (Latha et al., 2000). Anti-tumor property of bakuchiol (**155**) was also compared with resveratrol and it was observed that bakuchiol was more efficient in inhibiting the growth of tumor cells, when tested against human lung adeno-carcinoma A549 cell line (Chen et al., 2010). In a similar study on tumor cells of murine origin, radioiodinated bakuchiol showed greater cytotoxic effect than bakuchiol (Bapat et al., 2005). Bakuchiol (**155**) also induced ERβ expression and suppressed the ERα expression in MCF-7 cells (breast cancer cells). It also caused the arrest of S-phase in MCF-7 and MDA-MB 231 cells and showed a stronger anti-proliferative effect than resveratrol. Additionally, bakuchiol (**155**) caused the apoptotic cell induction and interrupted membrane potential in mitochondria of MCF-7 cells *via* an intrinsic apoptotic pathway. The same compound when tested for *in vivo* anti-breast cancer effect in Zebrafish xenografts showed a significant reduction in MCF-7 cell mass (Li et al., 2017). Similarly, two more compounds from the same species identified as isobavachalcone (**203**) and bavachinin (**160**) attenuate Aβ42-induced cell toxicity. The investigation was carried out on yeast two-hybrid system. During this study, eight compounds were tested, and among them IBC (3 μM) and BCN (30 μM) proved to be active at non-toxic concentrations (Chen et al., 2013).

6.12. Osteogenic activity

This is a significant property which is associated with the *P. corylifolia* fruit extract, the osteoblastic proliferation in cultured UMR106 (osteosarcoma) cell line and enhancing the formation of bones (Wang et al., 2001). In several studies, *P. corylifolia* extracts showed significant inhibitory effect on osteoclasts (Yang et al., 2007; Zhang et al., 1995). Corylin (**187**) and bavachin/coryfilolin (**159**) were reported to promote the proliferation of osteoblasts and inhibit bone resorption (Wang et al., 2001). Bakuchiol (**155**) compound in the extracts showed inhibitory effect on osteoporosis, mediated through estrogen deficiency (Lim et al., 2009; Tsai et al., 2007). In a report by Tsai et al. (2007), it was observed that *P. corylifolia* extract lead to a decrease in calcium and osteocalcin through urinary excretion in ovariectomized (OVX) rat model and thus, maintained the bone density (Tsai et al., 2007). In a similar report, ethanolic bakuchiol present in seed extract of *P. corylifolia* reduced the bone loss in OVX rat model thus, showed promising anti-osteoporosis activity (Lim et al., 2009).

6.13. Estrogenic activity

The ethanolic fruit extract of *P. corylifolia* showed estrogenic activity, which was demonstrated by transcription of *lac*Z in recombinant yeast system (Zhang et al., 2005). In another report by Zhao et al. (2007), proliferation rates of MCF-7 cells increased significantly when treated with the *P. corylifolia* extract (Zhao et al., 2007). In a study by Lim et al. (2011) Bakuchiol (**155**) showed a higher estrogenic activity and estrogen receptor (ER) binding affinity than genistein, both *in vitro* and *in vivo* (Lim et al., 2009, 2011). Among the seven bioactive components of *P. corylifolia* extract exhibited isobavachalcone (**203**), bavachin (**159**), corylifol A (**180**), neobavaisoflavone (**212**), bakuchiol (**155**), and two coumarins psoralen (**92**) and isopsoralen (**2**) compounds selectively activated ER-α while the other compounds activated both ER-α and ER-β (Xin et al., 2010). Park et al. (2012), reported that bavachin (**159**) could bind and activate the estrogen receptor (Park et al., 2012). In addition to it, psoralidin (**228**) was reported as aganist for both ER-α and ER-β (Liu et al., 2014). In a similar study by Xin et al. (2010), seed extract of *P. corylifolia* containing psoralen (**92**) and isopsoralen (**2**) enhanced the MCF7 cell prolification by enhancing the activity of ERα (estrogen receptors), hence showed significant estrogenic activity.

6.14. Hepatoprotective activity

P. corylifolia is revered for its hepatoprotective potential (Dai et al., 2009; Ye et al., 1999). Three compounds psoralen (**92**), bakuchicin (**153**) and bakuchiol (**155**) (EC50 values of 1.0, 47.0, and 50.0 μg/mL, respectively) have shown hepatoprotective activity towards the liver cells (Hep G2 cells) in which the cytotoxicity was induced by tacrine (cholinesterase inhibitor) (Cho et al., 2001). In a similar study, bakuchiol (**155**) reduced the toxic activity of carbon tetrachloride (CCl_4), D-galactosamine (D-GaIN), and tert-butylhydroperoxide (tBH) in primary rat hepatocytes (Park et al., 2005). The activity of hepatic stellate cells (involved in liver fibrosis) was reduced by bakuchiol in liver injured rats thus, confirming its hepatoprotective activity (Park et al., 2007). In a recent report, bakuchiol (**155**) obtained from the seed extract of the *P. corylifolia* exhibited hepatoprotective activity by inhibiting the production of reactive oxygen species (ROS) and malfunctioning of the mitochondria in human diploid fibroblast (HDF) (Seo et al., 2013).

6.15. Neuroprotective activity

In a study, the cultured rat pheochromocytoma (PC12) cells pretreated with *P. corylifolia* L. seed extract significantly attenuated 3-NP induced cell death, reduced ATP levels, and lowered the mitochondrial membrane potential. Thus, *P. corylifolia* seed extract has the potential to treat neurodegenerative diseases (Im et al., 2014). In another study, it was revealed that isobavachalcone, a flavonoid from *P. corylifolia*, has the ability to ameliorate the neuronal injury in brain diseases related to inflammation, and this was accomplished through inhibition of the expression of lipopolysaccharide induced intercellular adhesion molecule-1 and leukocyte adhesion to brain endothelial cell, by blocking toll-like receptor 4 signaling (Lee et al., 2015).

6.16. Immunomodulatory activity

P. corylifolia extract effectively increased the proliferation rate of diploid fibroblasts (in mice) and increased the ability of non-specific immunity (Wang et al., 1990). In the study, a mixture of fruit extracts of *P. corylifolia* and *Brucea javanica* improved the immunological regulation in rats that were infected with *Pneumocystis carinii* pneumonia. As a result of the treatment, gain in body weight, decline in the number of cysts produced in the lungs and the level of T cells (CD4 + and CD8 +) and TNF-alpha in the serum also increased considerably in the immunosuppressed rats (Qin et al., 2006). In another study, the ethanol seed-extracts of *P. corylifolia* stimulated the immune system in mice by increasing both cell-mediated and humoral immune responses in mice (Latha et al., 2000).

6.17. Anti-asthma activity

P. corylifolia has long been used for its anti-asthmatic properties. Experiments have shown that coumarins isolated from *P. corylifolia* exhibits anti-asthmatic activity by markedly increasing the level of serum cAMP (Deng et al., 2001; Yu et al., 2006). In another study, a Chinese herbal decoction, which contained six herbs, along with *P. corylifolia* seeds, could prompt treatment for asthma in the convalescent stage, to prevent emphysema (Fu, 1989). In a study by Hongfen (2007), the preparations obtained from the *P. corylifolia* showed high anti-asthma activity by stabilization of mast cells and inhibition of histamine release. Thus, the natural compounds obtained from *P. corylifolia* can act as promising molecules to cure asthma.

6.18. Anti-obesity activity

Several studies on animal models showed that a trihydroxyflavone, genistein (**198**) has the potential to decrease body weight by decreasing the food intake. One such study was conducted on ovariectomised mice wherein, it reduced the fat pad weight and enhanced the apoptosis of adipose tissues. Genistein (**198**) isolated from *P. corylifolia*, exhibited a potential anti-obesity and ant-diabetic activity through multiple mechanisms and cell signaling pathways by the action on adipocyte life cycle, obesity-related low-grade inflammation, and oxidative stress (Behloul and Wu, 2013).

6.19. Anti-filarial activity

In a report, the aqueous and alcohol extracts of the leaves and seeds of *P. corylifolia* showed significant anti-filarial activity against *Setaria cervi*. Alcohol extracts of both leaves and seeds caused death of microfilariae *in vitro*. The LC50 and LC90 for alcohol extract of leaves and seed was 15, 25 ng/mL and 12, 18 ng/mL respectively (Qamaruddin et al., 2002). The extracts also caused the inhibition of spontaneous movements of the whole worm and the nerve muscle preparation of *S. cervi* (Qamaruddin et al., 2002).

6.20. Anti-platelet activity

The methanolic *P. corylifolia* seed extracts was observed to inhibit the aggregation of rabbit platelets induced by arachidonic acid, collagen, and platelet activating factors. The anti-platelet aggregation activity of isobavachalcone was found to be most effective against aggregation induced by arachidonic acid, with a 50% inhibitory concentration (IC50) of about 0.5 μM (Tsai et al., 1996).

6.21. Anti-pyretic activity

Using rabbit as an animal model, and *Escherichia coli* endotoxin (13 ng/kg) as a pyrogen, the petroleum ether, dichloromethane, and methanol extracts of the aerial parts of *P. glandulosa* have been reported to possess anti-pyretic activity. The anti-pyretic effect (21.7%) of the petroleum ether extract was reported because of bakuchiol compound present in the extract. Maximum anti-pyretic effect (68%) was observed at the dose of 17 mg/kg (Backhouse et al., 2001).

6.22. Anti-Alzheimer's activity

Isobavachalcone (**203**) and bavachinin (**160**) from *Psoralea* modulate amyloid β (Aβ) peptides, especially the peptides with 40 (Aβ40) or 42 (Aβ42) residues, which are believed to be responsible for the development of amyloid plaques in Alzheimer's disease. Isobavachalcone significantly inhibits both oligomerization and fibrillarization of Aβ42, whereas, bavachinin converts Aβ42 into large unstructured aggregates in neuroblastoma cells (Chen et al., 2013). Psoralen (**92**) isolated from *P. corylifolia* fruits was investigated as an inhibitor of AChE enzyme in an attempt to explore its potential for the management of Alzheimer's disease. The concentration of psoralen used was 25–400 μg/mL. It inhibited the AchE in a dose-dependent manner in animal models. Adult male Wistar rats, weighing 180–250 g, were used in the study. While molecular docking study was also carried out, which showed that psoralen (**92**) binds well within the binding site of the enzyme showing interactions such as hydrogen bonding and π-π stacking (Somani et al., 2015). These findings may provide valuable information for the synthesis of new drugs or for the treatment of Alzheimer's disease.

7. Side-effects and toxicity

Although having excellent bioactivities, excess intake or use of *Psoralea* is not free from side-effects. *P. fascicularis* (synonym: *Psoralea tenuifolia* Thunb.) has been reported to be toxic to horses, cattle and therefore is not recommended as a fodder. There have been reports on skin allergic reactions after the oral and injected preparations of *Psoralea* (Bensky et al., 2004). In over-dose, *Psoralea* has been associated with dizziness, general weakness, blurred vision, rapid breathing, and vomiting. Severe cases of overdose have been associated with vomiting of blood, loss of consciousness, and coma (Bensky et al., 2004; Chen and Chen, 2004).

Psoralen plus UVA (PUVA) therapy has been used to treat skin diseases, such as vitiligo and psoriasis. The reported side-effects include dermatitis, blistering, edema, renal complications, loose-motions, biliousness, malaise, sleeplessness, annoyance and mental depression. Prolonged therapy has reported to affect liver, eyes, and the immune system (Rajpal, 2005). The psoralen (**92**) treatment along with UVA can cumulatively cause extensive chromosome damage to mammalian cells and could lead to malignancy. A mixture of psoralen (**92**), isopsoralen (**2**), and imperatorin caused hypertrophy of liver, kidney, and spleen in rats at a daily dose of 2.5 mg/75 g for 60 days (Sharma, 2001). In a similar study, different concentrations of *P. corylifolia* extracts were administered to the rats for 90 days. The treatment decreased the body weight and gonad weight (testes and ovaries) thus indicating psoralen-induced reproductive toxicity (Takizawa et al., 2002). There are several reports on hepatotoxicity symptoms in mice and rats after long-term usage of psoralen or isopsoralen (Khushboo et al., 2010; Totonchy and Chiu, 2014; Wang et al., 2012). In an investigation, *P. corylifolia* and its natural compounds (bavachin, corylifol A, neobavaisoflavone, IBC, and BCN) were evaluated for their potential toxicity, and the results showed it had a potent inhibitory effect against human UDP-glucuronosyltransferase 1A1 (UGT1A1) which is considered a stimulant for *P. corylifolia* related toxicity, including hepatic injury and raised bilirubin levels (Wang et al., 2015). In another study, *P. corylifolia* extract and fractionated compounds such as psoralen (**92**) and isopsoralen (**2**) were incubated with the recombinant CYP3A4 enzyme or differentiated HuH-7 and HepaRG cells. *P. corylifolia* extract, psoralen, and isopsoralen caused the inhibition of concentration CYP3A4 activity in a dose dependent manner with different potency *in vitro*. It was also noted that none of the sample tested showed any toxicity (Liu and Flynn, 2015). Three cases of liver injury have been reported in Chinese population associated with consumption of *P. corylifolia* dried seeds (*Fructus psoraleae*) (Cheung et al., 2009). Pregnant women are discouraged from consuming *P. corylifolia* (Bensky et al., 2004; Chen et al., 2007). In a case study, a 44-year-old female ingested *P. corylifolia* seeds every 1 h for seven weeks for treating osteoporosis but, developed acute cholestatic hepatitis (Nam et al., 2005). In another case study, a 64-year-old female developed severe hepatotoxicity after administration for nine months of three kinds of herbal tablets and herbal tea for treating vitiligo. Tablets made from *P. corylifolia* leaves were identified as the most probable cause of the hepatotoxicity (Teschke and Bahre, 2009; Teschke et al., 2014). However, the underlying hepatotoxic mechanisms of *P. corylifolia* and its major components are not well elucidated. A text on traditional Chinese medicine reports that no adverse effects of *Psoralea* occur when a normal dose range (decoction of 4.5–9.0 g) is consumed (Bensky et al., 2004). In all the case-studies/experiments on psoralea induced toxicity one thing was found common and that is purposeful/deliberate and continuous/prolonged intake/application of a high dose. Going through the available literature we can conclude that there are mixed opinions about the *Psoralea* induced toxicity and therefore there is still a research gap with regard to its mode of action and its pharmaceutical standardization.

8. Conclusions

As already mentioned the genus *Psoralea* has immense potential to cure various diseases and the most important among these are psoriasis, leprosy and vitiligo. Although pre-clinical studies have shown promising results, further studies are required to explore the in-depth molecular mechanisms responsible for the afore-mentioned pharmacological activities and to test the efficacy of isolated compounds, in properly designed experiments. In addition, long term toxicity studies and data on interaction with other drugs are also required to establish the safety profile of extracts before the commencement of clinical trials.

The efficiency and efficacy of the bioactive compounds present in the *Psoralea* species has been evaluated from time to time. Now, since there is awareness complemented with scientific proof regarding the medicinal benefits, their mass cultivation/propagation and extraction of bioactive compounds should also be the objective of further research. The commercialization of pharmaceutical drugs containing *Psoralea* as a sole or a part of the ingredients shall bring relief to millions of people suffering from psoriasis, leprosy and vitiligo, in a natural way. Looking into the available literature on the genus *Psoralea*, including the discovery of the number of bioactive compounds from each species (as mentioned in Table 1) it is very clear that *P. corylifolia* is an important member of the genus from ethnobotanical, ethnopharmacological, biological, and phytochemical point of view.

Several bioactive compounds isolated from *Psoralea* are commercially available. The compounds such as Daidzin (CAS 552-66-9) is a potent inhibitor of human mitochondrial aldehyde dehydrogenase that indicates it chemopreventive property (Keung and Vallee, 1993); Angelicin (CAS 523-50-2) is an antifungal compound (Sardari et al., 2000); 8-Methoxypsoralen (CAS 298-81-7) has been known as a potent suicide inhibitor of cytochrome P-450 (Tinel et al., 1987); Corylifol C and xanthoangelol are potent protein kinase inhibitors and induce apoptotic cell death therefore, possess anti-cancer property (Limper et al., 2013); Bakuchiol (CAS 10309-37-2) is a PTP1B and DNA polymerase inhibitor (Choi et al., 2015); Genistein (CAS 446-72-0) is a highly specific inhibitor of protein tyrosine kinase (Zarmouh et al., 2016); Psoralen has been used as photochemical probe in DNA mutation and repair studies (Gasparro, 1988); and Bavachin (CAS 19879-32-4) stimulates bone formation (anti-osteoporotic activity) (Wang et al., 2001; Xin et al., 2010). These examples indicate the utility of bioactive compounds isolated from *Psoralea* species.

Psoralea species are difficult to propagate because of poor seed-germination and high seedling-mortality (Mitter et al., 1993; Saxena et al., 1997; Siva et al., 2014). To ensure sustained production and benefits of *Psoralea* products we must aim at its mass cultivation through conventional approaches as well as micropropagation (Koul and Chase, 2015). *Psoralea guenzii* Harv. has become extinct while species like *P. asarina* (P.J.Bergius) T.M.Salter, *P. fascicularis* DC. and *P. glaucina* Harv. are vulnerable to extinction. Their bioactive principles and mode of action has not been explored yet. Their conservation would also ensure an alternative source of continuous and sustainable supply of elite bioactive compounds such as bakuchiol, psoralen, angelicin and psoralidin, for the pharmaceutical industry (Supplemental information 5, Table S4). Although, reproducible or rapid regeneration protocols for all the *Psoralea* species are not yet developed, but the same can ensure the enhancement of bioactive compound(s) production in near future, through suspension culture or transgenic technology (Arya and Gothalwal, 2015). These techniques may also streamline the path for further research on the bioactive principles and for the discovery of new compounds with novel properties in future. This is the first report wherein a detailed botanical description, traditional uses, phytochemistry and conservation of *Psoralea* species has been discussed. To conclude, *Psoralea* species have immense potential to act as panacea to several health-related maladies and so its conservation before excessive exploitation should be a prerequisite.

CRediT authorship contribution statement

Bhupendra Koul: Conceptualization, Data Curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Pooja Taak:** Data Curation, Investigation, Project administration, Visualization, Writing - original draft, Writing - review & editing. **Arvind Kumar:** Data Curation, Formal analysis, Methodology, Project administration, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. **Anil Kumar:** Visualization, Writing - review & editing. **Indraneel Sanyal:** Supervision, Writing - original draft, Writing - review & editing.

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Ethical statement

There are no ethical issues related to this manuscript.

Conflict of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jep.2018.11.036

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