Review Article

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PHYTOCHEMICAL AND BIOLOGICAL PROPERTIES OF GENUS PLEUROSPERMUM: A REVIEW

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ABSTRACT

Pleurospermum genus (family Apiaceae) comprises about 80 species native to India, Yunnan, China and Nepal. The plants of this species have long been used in traditional medicine systems to treat various illnesses. Different species are rich in coumarins, saponins, flavonoid glycosides, fatty acids and terpenoids. The extract of this genus and pure compounds isolated from it have been demonstrated to possess multiple pharmacological activities such as analgesic, anti-inflammatory, anticancer, antihyperlipidemic, immunomodulatory, neuroprotective, antimicrobial, antioxidant, etc. The present literature survey was performed exhaustively using databases such as SciFinder, Google Scholar, PubMed, Web of Science, ScienceDirect, and other resources. By corroborating the traditional uses and biological activities of Pleurospermum species, we hope to support new research on these plants, especially on those species whose biological properties have not been studied.

Keywords: Antipyretic, Apiaceae, Coumarin, Pharmaceuticals, Pleurospermum, Saponin

INTRODUCTION

Pleurospermum genus belonging to Apiaceae consists of perennial and rarely biennial herbs. There are more than 80 species of this genus found worldwide. Almost 50 species are confined to north Asia and East Europe and spread over the Himalayan region and west China.[1,2] They are distributed in Kashmir, Sikkim, Uttarakhand and Andhra Pradesh forest regions.[3] The genus Pleurospermum is well-known but is rarely explored.[4,5] The plants are traditionally used to treat cold, arthritis, arrhythmia, typhoid, hypertension, hepatitis, febrifuge, and smooth muscle relaxant.[6-12] Various species contain phytoconstituents such as coumarins, saponins, flavonoid glycosides, fatty acids and terpenoids.[13] The genus Pleurospermum is rich in essential oils like germacrene, eugenol, *β*-caryophyllene, *δ*-cadinene, (E)-*β*-farnesene, etc. obtained from different parts of the plant.[14] The plants of this genus possess several pharmacological activities such as analgesic[15], anti-inflammatory[16], anticancer[17], antihypertensive[18], antihyperlipidemic[19], antimicrobial[20], anti-oxidant[21], antiparasite[22], immunomodulatory[12], neuroprotective[23], etc. Besides their pharmacological actions, these plants are employed as metallic stearates, pharmaceuticals, soaps, cosmetics, nutraceuticals, perfumes and food packaging.[24-27] This review will mainly compile all the traditional uses, phytochemical contents, and biological activities of the Pleurospermum genus, encouraging new research on other species.

For this narrative review, the keywords used in the database search were “Pleurospermum”, “Apiaceae”, “essential oil”, “buddlejasaponin”, and “biological activities”. The information was fetched from SciFinder, PubMed, ScienceDirect, Wikipedia, Google Scholar and Wiley Online Library. Articles published from 1980 onwards were reviewed since there were limited recent articles on species of this genus. The title and abstract of articles with keywords were considered for review. Moreover, references to the cited papers were also studied to archive the literature.

Distribution and Habitat

Pleurospermum is a 10-20 cm tall perennial or biennial herb. Species of this genus are growing in the alpine zone at an altitude of 4500-5000 m above sea level. These plants are indigenous to India, Yunnan, China and Nepal.[1,2] The leaves are 2-4 pinnate with linear segments, 4-6 involucral bracts, margin entire or lobate at apex having broad white lines and 5-10 rays.[1] Flowers are in the form of umbels, and fruits are oblong-ovoid shaped. The plant flowers in June-September (Figure 1).[6]

Pleurospermum has been a problematic genus of both monophyly and species composition. Morphological examination of available species of Pleurospermum and closely related genera Aulacospermum, Hymenidium, Hymenolaena, Physospermopsis, Pseudotrachydium, Pterocyclus, and Trachydium demonstrated heterogeneity in this genus depending on the distribution of their identifying characters. Only Aulacospermum (including Pseudotrachydium) and Hymenolaena were supported as monophyletic groups based on molecular phylogenetic analysis of nuclear (nrITS) and cpDNA (psbA-trnH and trnL-trnF) sequences of representative species, indicating Pleurospermum and most of the other genera polyphyletic in nature.[4]

Traditional uses

P. kamtschaticum is traditionally used to treat cold, arthritis, fatigue, atherosclerosis and impotence.[6] *P. rivulorum* is a Chinese traditional medicine employed as an antipyretic, analgesic, antiarrhythmic and diaphoretic agent in local villages of China.[7] *P. angelicoides* is given to treat typhoid, dysentery and fever in rural areas of China.[8,9] Traditionally, *P. govanianum* is regarded as an antiasthmatic, expectorant and smooth muscle relaxant.[10] *P. lindleyanum* is used for hypertension, other heart-related problems, high altitude sickness and hepatitis.[10,11] *P. amabile* is used as an antidote for febrifuge and dyspepsia.[12] *P. candollei* is valued in the traditional system of medicine to treat diarrhoea,

respiratory and gastric disorders, and joint and back pain. It is also being used for both male and female infertility.[28]

Other uses

The dried herbs of this genus are utilised to protect woollen cloths from the attack of moths and silverfish. The plant is also used as metallic stearates, pharmaceuticals, soaps, cosmetics and food packaging.[24,25] *P. kamtschaticum* is consumed as an edible mountain vegetable, functional food or nutraceuticals.[26] *P. densiflorum* is one of the best herbal perfumes by Himalayan people and is known for its long-lasting pleasant smell.[27]

Phytochemistry

Pleurospermum species contain various phytoconstituents such as coumarins, saponins, flavonoid glycosides, fatty acids and terpenoids.[13] *P. angelicoides* contains angelicoidenols, isocoumarins, 1-prophenyl-2,3,4-trimethoxybenzene, nathoapiole, *α*-asarone, essential oils and many monoterpenes.[3,8,9,21,29,30] Two isocoumarins, angelicoins A and B, were isolated from the roots of *P. angelicoides.*[28] *P. rivulorum* contains glycosides and a number of coumarins such as 8-geranyloxy psoralen, imperatorin, isopimpinellin, pabularinone, bergapten, xanthotoxin, isogosferol, marmesin, heraclenol, xanthotoxol and 8-(3-chloro-2- hydroxy-3-methylbutyloxy)-psoralen and bicoumarins rivulobirins A and B.[7,31] Two spirotricoumarins, rivulotririns A and B; two spirobicoumarins, rivulobirins C and D; two furanocoumarins, rivulobirin E and rivulotririn C; and three cyclospirobicoumarins, cyclorivulobirins A, B and C were also isolated from *P. rivulorum*.[32-35] *P. amabile* showed the presence of phenylpropanoids such as isoimpatorin and methyl eugenol; furanocoumarins such as bergapten and oxypeucedanin hydrate; essential oils, and many terpenoids.[36] *P. kamtschaticum* contains several triterpene saponins, flavonoids, phenols, essential oils and buddlejasaponin IV.[6,12,37] *P. austriacum* was found to have sesquiterpenes, germacranes and a vast number of essential oils.[14] Furocoumarin glycosides, flavonoids, ferulic acid and angelicin are present in *P. brunonis*.[13] Study of *P. lindleyanum* showed lignin, furocoumarinylsulfate, flavonoids, lindleyanin, bergapten and many coumarins. From aerial parts of *P. densiflorum,* esters of fatty acids were isolated.[40] *P. franchetianum* consist of a number of glycosides, octadecylcaprate, *β*-sitosterol, (22E,20S,24R)-5*α*,8*α*-epidioxy-ergosta-6,22-dien-3-*β*-ol, daucosterol, *α*-spinasterol-3-O-*β*-D-glucopyranoside, quercetin-3,7-di-O-*β*-D-glucopyranoside and kaempferol.[10] Two flavonoid glycosides, quercetin-3-O-*α*-Larabinopyranoside and quercetin 3-O-*β*-galactopyranosid,e were isolated from the butanol extract of aerial parts of *P. brunonis*.[1] (Figure 2 A-T).

The genus Pleurospermum is rich in essential oils like germacrene, eugenol, *β*-caryophyllene, *δ*-cadinene, (E)-*β*-farnesene, etc. obtained from different parts of the plant. Figure 3 shows several compounds isolated from the essential oil of various species.[14,20,39–45]

Pharmacological activities

Reports of the pharmacological studies on the genus Pleurospermum indicate the potential of extracts and pure compounds to exhibit specific therapeutic properties. Some of them are mentioned in Table 1.

Analgesic and Anti-inflammatory activity

Saponins and sapogenins obtained from butanol fraction of methanol extract of aerial parts of *P. kamtschaticum* showed good anti-inflammatory, analgesic and anti-nociceptive effects when subjected to nitrite assay using macrophage RAW 264.7 cells.[18] Buddlejasaponin IV from above inhibited the Lipopolysaccharide-induced activation of nuclear factor-κB (NFκB), a transcription factor necessary for proinflammatory mediators, iNOS, COX-2, TNF-*α*, IL-1*β* and IL-6 expression. This effect was accompanied by a parallel reduction in IκB-*α* degradation and phosphorylation and the nuclear translocation of the NF-κB p65 subunit. Its impact on acute phase inflammation was studied on serotonin and carrageenan-induced paw oedema compared with 10 mg/kg of indomethacin. Maximum inhibitions of 26% and 41% were noted at a 20 mg/kg dose for serotonin and carrageenan-induced paw oedema, respectively.[6,15,18] Trans-asarone and *α*-linolenic acid isolated from methanol extract of the whole plant of *P. candollei* effectively inhibited nitric oxide production, with IC_{50} values of 28.44 μM and 53.18 μM, respectively, showing significant anti-inflammatory activity.[28] Isomyricetin isolated from methanolic extract of aerial parts of *P. amabile* was studied for anti-inflammatory properties against TNBS (trinitrobenzenesulfonic acid)-induced colitis in mice. Still, it did not confer any protection against weight loss compared with weight loss in mice given TNBS.[16,46]

Anticancer activity

The methanol extract of *P. kamtschaticum* aerial parts was found to induce apoptosis via mitochondrial-dependent apoptotic signalling and the induction of the NAG-1 (nonsteroidal anti-inflammatory drug-activated gene-1), apoptotic protein in colon cancer cells and prevents colon cancer.[17] The triterpene saponins isolated from the methanol extract of aerial parts of the above species were tested for their cytotoxicity against four human tumour cell lines A549 (non-small cell lung adenocarcinoma), SK-OV-3 (ovarian cancer cells), SK-MEL-2(skin melanoma) and HCT15 (colon cancer cells) *in vitro* using the sulforhodamine B (SRB) bioassay. All compounds showed little cytotoxicity against tested cell lines (IC_{50} >30μM).[37] Buddlejasaponin IV obtained from *P. kamtschaticum* aerial parts blocks the progression of HPV (Human papillomaviruses)-induced oral carcinogenesis through inhibition of the growth of IHOK (immortalised human oral keratinocytes) cells via the induction of p53-dependent cell cycle arrest at the G2/ M phase and apoptosis via both mitochondrial-dependent and death receptor-mediated pathways.[47]

Antidiabetic activity

P. kamtschaticum showed antidiabetic activity in streptozotocin-induced diabetic rats. The plant decreased liver glycogen level and increased plasma insulin level.[48]

Antihypertensive activity

The methanolic extract of *P. kamtschaticum* inhibits the production of nitric oxide and pro-inflammatory molecules such as PGE_2 and TNF-*α,* which leads to a decrease in blood pressure. This activity is due to the saponins present in the plant.[18]

Antihyperlipidemic activity

Buddlejasaponin IV isolated from butanol fraction of methanol extract of aerial parts of *P. kamtschaticum* inhibits intrinsic and extrinsic hyperlipidemia and hypercholesterolemia in rats by reducing the blood thiobarbituric acid related substances and radical hydroxy levels and increasing superoxide dismutase activity.[19]

Antimicrobial activity

Phenols obtained from chloroform extract of *P. kamtschaticum* showed anti-microbial activity against *E. Coli.*[49] The crude butanol extract of *P. brunonis* aerial parts showed an inhibitory effect against *Bacillus licheniformis*, *Aspergillus niger* and *A. flavus*. The antifungal activity of the crude butanol extract of *P. brunonis* aerial parts was comparable to 100μg/ml of

ketoconazole against *A. flavus*, *A. niger*, *Fusarium graminearum* and *Nigrospora oryzae*. The extract also showed sensitivity for *B. pumilus*, *B. licheniformis* and *S. mutans.*[1] (E)-isoapiol isolated from the essential oil of *P. amabile* aerial parts exhibited mild antibacterial activity against *Bacillus subtilis.*[20] The leaf essential oil obtained from *P. angelicoides* shows prominent activity against *C. albicans* and *C. glabrata* comparable with the standard amphotericin B under identical conditions.[21]

Antioxidant activity

The leaf, root and flower essential oils of *P. angelicoide* showed a broad range of antioxidant potential by DPPH (1,1-diphenyl-2-picrylhydrazyl) scavenging, reducing power and chelating power.[21] The ethyl acetate and n-butanol fractions of *P. kamtschaticumin* showed the highest DPPH radical scavenging activity (IC_{50}=0.04 mg/mL) and ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) radical scavenging activity (98.86% at 0.5 mg/mL), which was similar to ascorbic acid.[50,51] Free radical scavenging activity in ethanol extract of *P. kamtschaticum* was 43.5% at a 100 µg/mL level, and the antioxidative index was 1.09 at a 500 µg/mL level.[26]

Antiparasitic activity

Isomyristicin and bergapten obtained from crude methanol extract of *P. amabile* showed significant anthelmintic activity against *Schistosoma mansoni* and *Trichuris muris,* with bergapten being the most efficacious compound against both parasites (*S. mansoni* IC_{50} = 8.6 µg/mL and *T. muris* IC_{50} = 10.6 µg/mL) and also against the schistosomulum stage of *S. mansoni*.[22]

Immunomodulatory activity

Bergapten from crude methanol extract of *P. amabile* aerial parts displayed immunosuppressive properties by strongly downregulating gene and protein expression of MHC-I (major histocompatibility complex-I) and other co-stimulatory molecules.[12]

Neuroprotective activity

The ethanolic extract of *P. kamtschaticum* showed effective DPPH radical scavenging and solid cytotoxic activity, and it inhibited SK-N-SH neuronal cells and phosphorylation of P38 in brain neural cells to show neuroprotective activity.[23]

Table 1: Pharmacological activities of different species of Pleurospermum

Species	Component responsible	Activity
P. kamtschaticum	Buddlejasaponin IV	Analgesic and anti-inflammatory[18]
P. candollei	Trans-asarone and α-linolenic acid	Anti-inflammatory[28]
P. kamtschaticum	Buddlejasaponin IV and triterpene saponins	Anti-cancerous[47]
P. kamtschaticum	-	Anti-diabetic[49]
P. kamtschaticum	Saponins	Anti-hypertensive[18]
P. kamtschaticum	Buddlejasaponin IV	Anti-hyperlipidemic[19]
P. kamtschaticum *P. brunonis* *P. amabile*	Phenol Flavonoid glycosides Volatile oil	Anti-microbial[49,1,20]
P. angelicoides *P. kamtschaticum*	Essential oils Phenols and flavonoids	Anti-oxidant[24,49]
P. amabile	Isomyristicin and bergepten	Anti-parasitic[22]
P. amabile	Bergapten	Immunomodulatory[12]
P. kamtschaticum	Flavanoids, vitamins and buddlejasaponin IV	Neuroprotective[23]

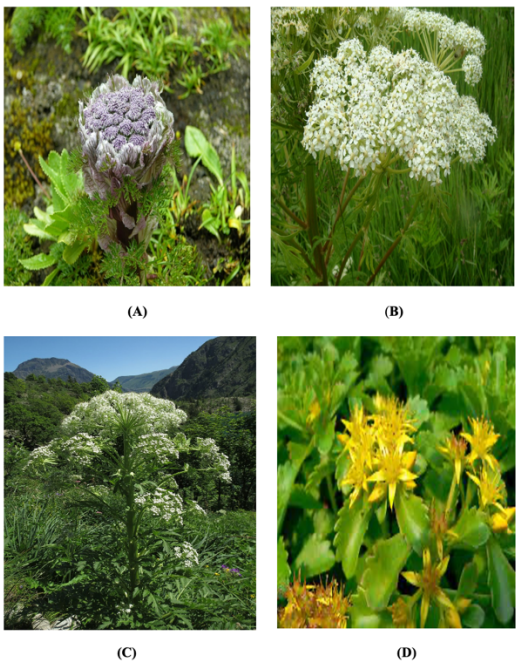

Figure 1: Various species of Pleurospermum
(A) *P. amabile,* (B) *P. angelicoides,* (C) *P. austricum,* (D) *P. kamtschaticum*

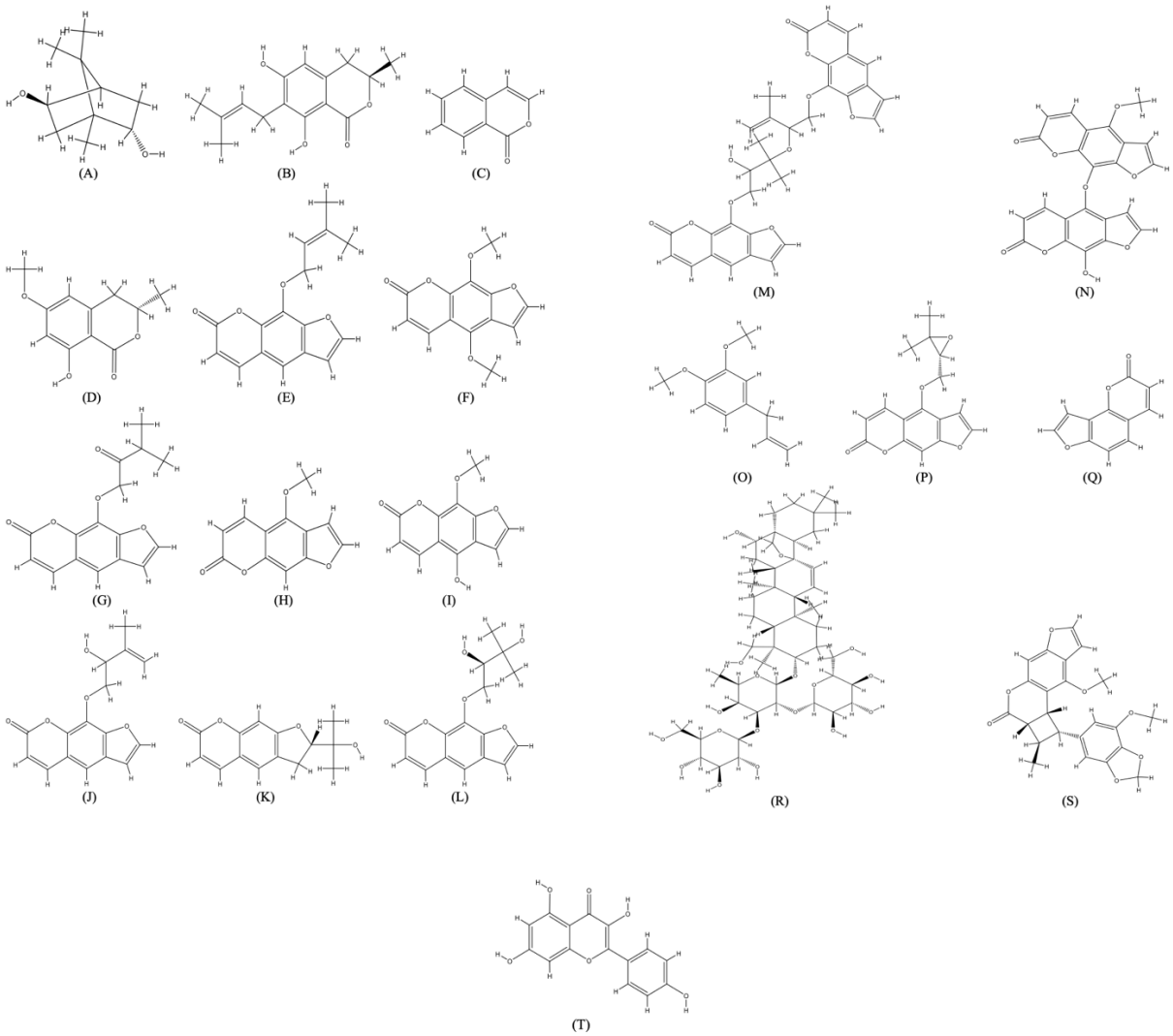

Figure 2: Phytochemicals obtained from Pleurospermum

(A) Angelicoidenol (B) Angelicoin A (C) Isocoumarin (D) Angelicoin B (E) Imperatorin (F) Isopimpinellin (G) Pabularinone (H) Bergepten (I) Xanthotoxin (J) Isogosferol (K) Marmesin (L) Heraclenol (M) Rivulobirin A (N) Rivulobirin B (O) Eugenol (P) Oxypeucedanin (Q) Angelicin (R) Buddlejasaponin IV (S) Lindlevanin (T) Kaempferol

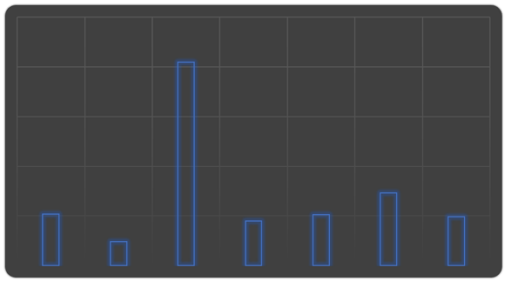

Figure 3: Number of compounds obtained from essential oils of various Pleurospermum species

CONCLUSION

This review summarises the current status, distribution, chemical value and biological studies on the genus Pleurospermum. Although there are 80 species in this genus, only a few species have been investigated. Phytochemical investigations of Pleurospermum species have revealed that many components from this genus exhibit significant biological and pharmacological activities. Further phytochemical and biological studies should be carried out on this genus to elucidate the active principles and mechanisms of action of the active constituents.

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