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A comprehensive review on the phytochemistry, pharmacological, ethnobotany, and traditional uses of *Paeonia* species

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ABSTRACT

Since ancient times, people have used medicinal plants as a source of medications to treat and prevent diseases. *Paeonia* species are important therapeutic plants in Ayurvedic, Unani, and Traditional Chinese Medicine. This study aims to provide updated information on the ethnobotany, phytochemistry, and pharmacological activities of *Paeonia* species discovered until now. Using the keywords "Paeonia", "geographical distribution", "ethnopharmacology and traditional values", "phytochemistry", "antioxidant", "anti-inflammatory", "antimicrobial", "cardiovascular diseases", and "anticancerous properties", the published reports from 2001 to 2022 were retrieved using Google Scholar, Science Direct, PubMed, and Scopus databases. A total of 156 published articles were studied after meeting the qualifying criteria. Out of these, 52 articles were studied for phytochemistry, ethnopharmacological and traditional uses. *Paeonia emodi* is used to treat hypertension, asthma, convulsions, epilepsy, bronchitis, ascites, uterine abnormalities, and a variety of skin ailments. Bioactive compounds like triterpenes, monoterpene glucosides, phenols, tannins, emodinol, benzoic acid, paeonin A and B, steroids, several secondary metabolites like paeoniflorin and paeonol, and several minerals are abundant in the Paeonia species. In recent studies, *Paeonia emodi* has been shown to possess pharmacological properties like antioxidant, antibacterial, anti-inflammatory, insecticidal, and anti-tumor activities. Convincing data supports the traditional ethnomedicinal claims of the plant; the abundant phytocompounds of the plant are attributed to its broad spectrum of pharmacological activities. In order to understand the molecular mechanisms underlying the action of the bioactive ingredients in drug development processes and to investigate their potential at the clinical level, more research is required.

Implication for health policy/practice/research/medical education:
A literature review was constructed in this contribution to examine the significance of different *Paeonia* species across the country. As a result of this article, a new understanding of the phytochemistry, traditional medicine, ethnobotany, and potent pharmaceutical properties of the plant is revealed, which may be taken into account in future clinical studies and therapies involving this plant.

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Introduction

Human and animal diseases are treated with the naturally extracted products of medicinal plants (1). *Paeonia emodi* Royle has historically been used to treat conditions like dysmenorrhea, uterine disorders, blood pressure, palpitations, congestive heart failure, asthma, paralysis, epilepsy, convulsions, schizophrenia, cough, bronchitis, jaundice, hepatitis, abdominal colic, ascites, renal colic, calculous, and leprosy (2,3). *Paeonia emodi,* also called hemicryptophytes (family Paeoniaceae), is a vigorous herbaceous perennial plant with the features of large white flowers and deeply incised leaves. It is the tallest species compared to other peony species. The warm temperate condition is suitable for its growth (4). Generally, it

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occurs in Afghanistan, Southern Tibet, and the western Himalayan region, which is why in English, it is known as Himalayan peony (5).

The primary chemical constituents of *P. emodi* are 1b, 3b, 5a, 23, 24-pentahydroxy-30-12, 20 (29)-dien-28-oic acid, oleanolic acid, betulinic acid, ethyl gallate, methyl grevillate, 1,5-dihydroxy-3-methyl anthraquinone, wurdin, benzoylwurdin, paeoniflorin, lactiflorin, oxypaeoniflorin (6), emodinol, benzoic acid, 3-hydroxybenzoic acid (7), and paeonins A and B (8). It is also a rich source of triterpenes, monoterpene glucosides, phenols, and tannins that are important in treating inflammation, skin lesions, and neurodegenerative diseases (9,10). The phenolic compounds are effective anti-inflammatory, antibacterial, and cardioprotective agents reducing mortality rates (11,12). The root and rhizome of *P. emodi* are using to treat several disorders like epileptic disorder, or used as a nerve tonic and blood purifier, while the seeds have purgative properties (13). *P. emodi* has different elements such as calcium, magnesium, zinc, iron, cobalt, that play both curative and preventive roles in disease control (14). The different leaf extracts have shown antioxidant and antimicrobial activities (8). *Paeonia ludlowii* (Stern & G. Taylor) D.Y.Hong is renowned as a medicinal plant that reduces inflammation (15), and is confined to a tiny region of southern Tibet in western China (16). Several previous studies reported that paeony seed oil (PSO) has α-linolenic acid in an abundant concentration, which shows anti-inflammation, anti-thrombosis, and anti-tumor properties (17,18). PSO is used as a new resource of food in China (19). The present work intended to compile the recent advances made in the field of research on the Paeonia species, sporadically mentioned in literature for its various attributes, and to reveal the unexplored part of the plant to stimulate further investigation on it.

Methods

Database search

In accordance with PRISMA standards, we searched the words and terms of "Paeonia", "geographical distribution", "ethnopharmacology and traditional values", "phytochemistry", "pharmacology", "antioxidant", "anti-inflammatory", "antimicrobial", "cardiovascular diseases", and "anticancerous properties". To prepare a comprehensive review of the pharmacological ethnobotany and traditional uses of *Paeonia* species a literature search was done in English databases such as Scopus, PubMed, Web of Science, EMBASE, and Google Scholar without a time limit.

Quality assessment and article selection

Following the review of the titles and summaries of articles, a list of related papers was included for further review. After reviewing the papers, nominated papers were selected that met reasonable inclusion criteria.

Data extraction

The inclusion criteria of the present review were the research papers assessing the complete study of the phytochemical, pharmacological, and medicinal uses of *Paeonia* spp. As exclusion criteria, papers with inadequate data, abstracts only, mismatches between the process and outcome of the study, and studies with irrational results and interpretations were excluded. A study's type, control group, disease type, measurement scale, dosage, intervention process, results, and references were obtained from each selected paper (Figure 1).

Results

Geographical distribution

Paeonia is the only genus in the Paeoniaceae family, with 33 species separated into five geographical regions: Mediterranean, Central Asia, Western Himalayas, Eastern

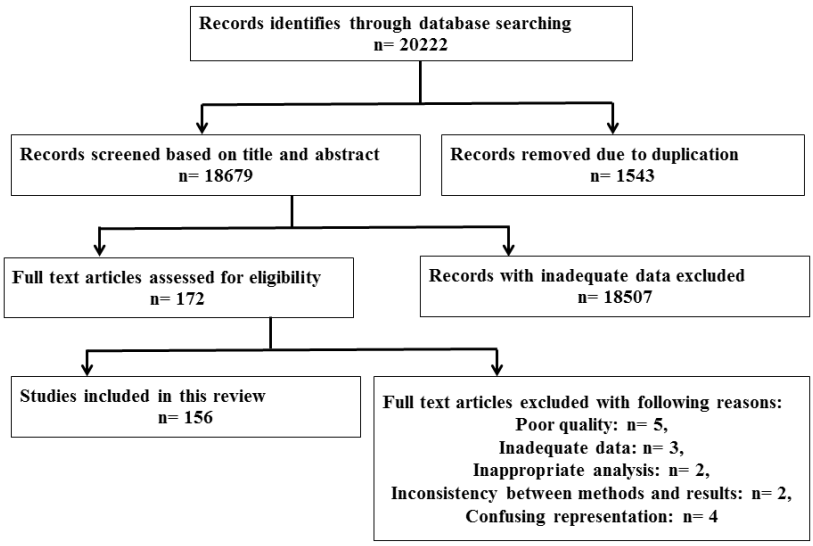

Figure 1. A flowchart representing the study based on PRISMA guidelines.

Figure 2. The natural picture of *P. emodi*, including its habitat, captured by the author from Joshimath (Uttrakhand), India.

Asia, and Pacific North America (20). It is situated in the Northern Himalaya of India, between Kashmir and the Garhwal-Kumaon regions of Uttarakhand (Figure 2) (21), at elevations ranging from 1800 m to 3000 m. *P. emodi* is most commonly observed on south-facing slopes of deciduous forests that contain various oak species and *Quercus floribunda* (22). *P. lactiflora* and *P. mairei* most likely became sympatric during their retreat, giving rise to the Himalayan species *P. emodi* and *P. sterniana*.

Phytochemistry

Previous studies have reported that the leaves of *P. emodi* contain sucrose, starch, malic acid, tannins, flavonoids, polyphenols, sterol, monoterpenes, triterpenes, polyterpenes, steroids, and many organic acid alkaloids. These compounds showed antimicrobial and antioxidant activities (8). Lipoxygenases are iron-containing compounds that play an essential role in asthma, cancer, aging, and angiogenesis (23). Oleanolic acid was reported in *P. emodi* along with phenolic compounds, betulinic acid, ethyl gallate, methyl grevillate, emodinol, benzoic acid, 3-hydroxybenzoic acid, paeonin A and B, steroids, and aldehydes (24). The most abundant compounds in the fruits of *P. rockii* and *P. ostii* are polyphenols (flavonoids, tannins, stilbenes, phenolic acids, and other phenols), as well as terpenoids (monoterpenes, diterpenes, and triterpenes) (Figure 3). Phenolic compounds have antioxidant and antibacterial properties and are also beneficial in treating cancer, cardiovascular diseases, diabetes, and epilepsy (25). Previous studies reported that monoterpenes have antipyretic, anti-inflammatory, analgesic, anesthetic, and anticonvulsant effects (26). Emodinol, a new triterpene identified in *P. emodi* (7), inhibits the β-glucuronidase activity. The overexpression of β-glucuronidase may cause liver cancer and damage the liver (27). The *Paeonia* root contains secondary metabolites with 17 monoterpenoid glucosides, 11 galloyl glucose, 5 flavonoids, 6 phenolic compounds (Figure 3) (28). Thirteen secondary metabolites with Paeoniflorin and Paeonol have been identified from the 15 species and 2 sub-species of *Paeonia* root; these compounds show potent bio-activity. It also showed the antioxidant activities and antibacterial properties against gram (+ve) bacteria (29) (Figure 4).

Ethnopharmacological and traditional uses

Danpi, the cortex of the plant, is used as herbal medicine to treat blood stasis in the Eastern Han dynasty (30). The two main populations of medicinal peonies are *Paeonia suffruticosa* and *P. ostii* (31). *P. suffruticosa* is mainly grown in Dianjiang, Chongqing, where its cortex is known as "Chuan Danpi", while *P. ostii* is primarily grown in Tongling, Nanling, Bozhou, and Heze, where its cortex is known as "Feng Danpi". Shuan Danpi and Feng Danpi are both regarded as authentic herbs of the Danpi family. In the history of Chinese medicine, authentic herbs are of higher quality (32). Traditional healers use the roots of *P. emodi* to treat diarrhea, high blood pressure, heart failure,

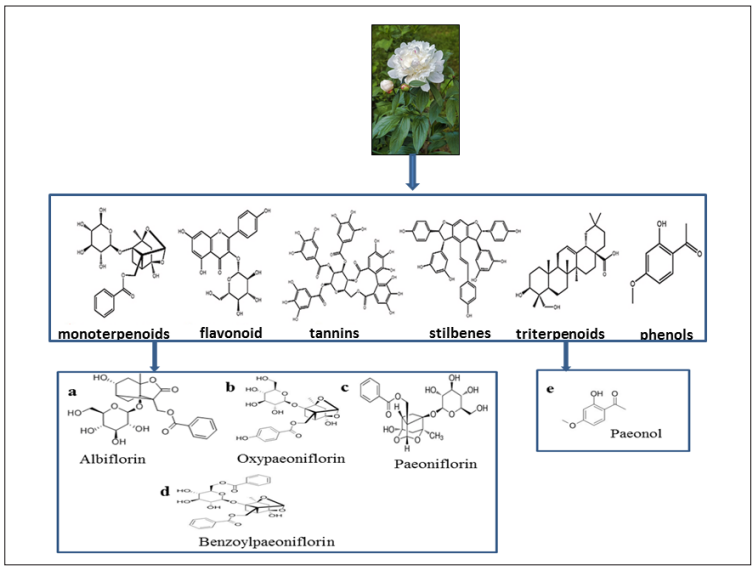

Figure 3. Phytochemical constituents from *Paeonia* spp. In the above figure, albiflorin, benzoylpaeoniflorin, oxypaeoniflorin, and paeoniflorin belong to the Monoterpenes group and paeonol belongs to the phenol group.

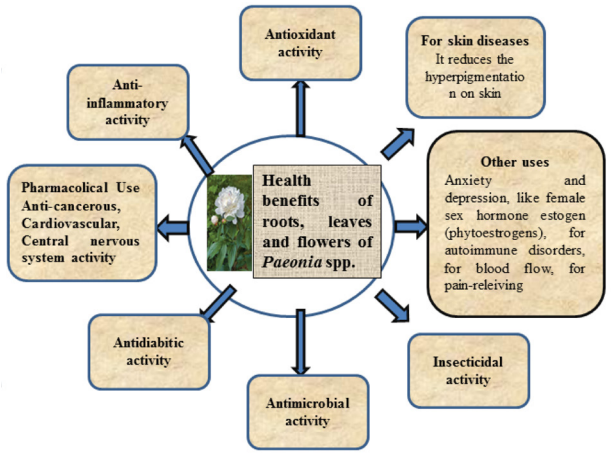

Figure 4. Ethnomedicinal and pharmacological properties of *Paeonia* spp (2).

palpitations, asthma, and arteriosclerosis. The extract of the roots lowers heartbeat rates, relaxes airways, and reduces blood clotting (33). The dry root of *P. lactiflora* or *P. veitchii*), Radix Paeoniae Alba (dry roots of *P. lactiflora*) and Cortex Moutan (dry roots of *P. ostii* or *P. suffruticosa*) are essential Chinese herbal medicine, included in Chinese Pharmacopoeia (34). The plant *P. emodi* grows in the Western Himalayan region, where locals and scientists use it to prevent epileptic attacks and treat whooping cough and cholera (35). Its tubers treat uterine infections, blood disorders, colic, bilious problems, headaches, dizziness, vomiting, dropsy, epilepsy, and hysteria, while its seeds are purgatives (Figure 4) (36). For the treatment of diarrhoea, whooping cough, haemorrhoids, and abdominal pain, dried flower infusions are effective (37).

Folk recipes are made from the whole plant or its different components, such as leaves, stems, barks, roots, flowers, seeds, and roots of props, or from secondary yields like gums, resins, and latex (38). The rhizome is used as a tonic and is used for increasing milk production in livestock (38). Dried leaves purify the blood. They are fried in Cow ghee and used for dysentery and abdominal colic (39). Most Asian women are obsessed with whitening their skin (40). Several tyrosine inhibitors and antioxidants have been isolated from the root of *P. lactiflora*. (41).

P. suffruticosa root bark has traditionally been used in treating cancer, extravasation of blood, cardiovascular diseases, inflammatory conditions, and female genital diseases (42). *P. suffruticosa* contains phenols, monoterpene glycosides, tannins, and stilbenes (43). Paeoniflorigenone (Paeo), a monoterpene, exhibits numerous biologically active properties (Table 1). Paeo inhibits lipopolysaccharide-stimulated microglia function to prevent H_2O_2-induced cytotoxicity in neuronal cells (44). Paeo also has anticoagulant and antiplatelet properties, improving blood circulation (45). Recent research suggested that Paeo had antiproliferative and cytotoxic effects on cancer cells (42).

Table 1. The ethnopharmacological properties of Paeonia extracts

Paeonia species	Part used	Dosage form/Recipe	Medicinal use and disease treated	References
P. emodi	Leaves	A dried leaf is cooked and used as a vegetable. It is also fried in ghee.	Blood purifier, dysentery, colic, piles.	(46)
P. emodi	Root	Roots are fried and taken orally as a dietary supplement.	Diarrhea, rheumatic pain, gynecological disorders, vomiting, skin diseases, dyspepsia, sciatica, muscle cramps, rheumatism, epilepsy, general weakness, body and bone pain.	(38, 47)
P. emodi	Whole Plant	Extracts of roots and flowers are ingested orally. An extract of the whole plant is prepared by mixing powder with water.	Vomiting, diarrhea, blood purifier, whooping cough, diarrhea, intestinal spasm, cuts, eczema, ulcers, nervous disorders, diarrhea, headache, pain killer, vomiting, epilepsy, and dysentery.	(48)
P. emodi	Rhizome	Dried ground rhizomes are cooked.	Body pain, body weaknesses, sexual tonic, general body tonic, abdominal pain.	(49)
P. emodi	Flower	The infusion of dried flowers is used.	Abdominal pain, vomiting, hemorrhoid, antidiarrheal, antispasmodic, diarrhea, nervous system, cardiovascular, and respiratory diseases.	(38, 50)
P. emodi Wall ex Royle	Whole Plant		Whooping cough, diarrhea, intestinal spasm, cuts	(51)
P. suffruticosa Andrews	Root bark	Not mentioned	Taking care of heat, stimulating blood flow, cooling blood, and removing blood clots. It is also used to treat warmth, spotting, vomiting blood, night heat, early cooling, amenorrhea, dysmenorrhea, bruises, carbuncle swelling, tumors, fevers, carbuncle swelling, tumor, and fever.	(52).
P. veitchii var. *uuiflora*	Roots		Disperse blood stasis, cool the blood, and relieve pain by clearing heat.	(53)
P. peregrina Mill.	Roots and seeds		The roots of the plant are used as anticoagulants, analgesics, and sedatives. The seeds were used in the treatment of epilepsy.	(54)

Pharmacological study

Antioxidant properties

Radiation from the sun or excessive free radical production by the body may induce cancer, diabetes, and heart disease. Free radicals and reactive oxygen species can also damage cells. Several compounds and phenolic compounds are derived from Paeonia that contain antioxidant activity scavenging free radicals. Some phenolic compounds (gallic acid, quinic acid, dihexose, paeoniflorin derivative, etc), tannins, Monoterpenes glycosides, and flavonoids are the major antioxidant phytochemicals present in the root and leave extract of *Peonia*. As tested chemically, the leaf extracts proved more effective antioxidants than root extracts, while methanol proved more effective as a solvent than water (55). For chronic inflammatory diseases, the inflammatory pathways need to be blocked. A hotspot in medical research has been the discovery of new anti-inflammatory molecules from crude materials (Table 2).

Anti-inflammatory activity

There are many ways in which inflammation can be induced, including trauma, tissue damage, and infection; it occurs to various organs and tissues throughout the body (56). Pharmacologically, *Paeonia* is best known for its anti-inflammatory properties (Table 2). The Peonia extract contains paeoniflorin B, galloylpaeoniflorin, moudanpioside F, paeoniflorigenone, 4-*O*-methylbenzoylpaeoniflorin, which have shown potent inhibitory activity on nitric oxide (NO) production (57). The paeoniflorin A, benzoyloxypaeoniflorin, albiflorin, and intermedia C compounds of the plant inhibit the production of NO (58), and oxo-acetic acid 2-ethoxy-4-(3-hydroxy-2-oxopropyl) phenyl ester inhibits the production of the pro-inflammatory cytokines such as interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), and NO (59). Inhibition of cyclooxygenase-I and II (COX-I and II) expression is caused by paeonidanins (F, G, H), paeoniside (A, B) and paeoniflorin, benzoylpaeoniflorin, and 4-O-methyl-paeoniflorin (42). Suffruticosol A significantly inhibits the expression of NO, inducible nitric oxide (iNO), and pro-inflammatory factors (60).

Anti-microbial activity

Several pathogenic fungi, including *Trichophyton longifusus, Candida albicans, Aspergillus flavus, Microsporum canis*, and *Fusarium solani*, were completely inhibited by peony root extract (83). A natural antibacterial preservative or additive made from plant extracts has become popular because of its resistance to bacteria (84). Despite this, many studies have been conducted on wild peony root antibacterial properties (85). The root section of *Peonia* spp. contains several phenolic acids, tannins, monoterpenes glycosides, and flavonoids (Table 2). These extracts showed potent antibacterial activity on *Listeria monocytogenes* (gram-positive), *B. cereus, Bacillus subtilis, Pseudomonas aeruginosa* (gram-positive), *Salmonella typhimurium* and *Proteus vulgaris* (Gram-negative), and potent antifungal activity on *Microsporum gypsum* and *C. albicans* (8,29). Many reports have shown the antibacterial properties of phenolic compound (benzoic acid) by penetrating the bacterial cell membrane, destroying the cellular wall, and disturbing the relative conductivity of the cell membrane. Also, some enzymes within the bacterial cell membrane are inhibited, resulting in denaturation of the protein inside the cell (81). Tannins (1,2,3,4,6-penta-O-galloyl-β-D-glucopyranose; PGG) and benzoic acid are present in large amounts in peony roots, which synergistically have substantial antibacterial properties (86). The fruit and seed extracts of *P. rockii* and *P. ostii* have potent antibacterial activities against *P. vulgaris, E. coli, P. aeruginosa, S. enterica,* and *S. aureus* (82).

Insecticidal property

Tribolium castaneum, Bruchus pisorum, and *Rhyzopartha dominica* have also been found to be susceptible to paeonol (2'-hydroxy-4'-methoxyacetophenone) extract. *Permethrin* present in the aerial parts of the plant shows the ability to kill insect and pests. A sodium channel current regulates the polarization of the nerve cell membrane that is disrupted by it (21).

Cardiovascular activity

As an anti-atherosclerosis agent, paeonols (Pae) regulate lipids, inhibit lipid peroxidation, are anti-inflammatory, and protect vascular endothelium, which is an important function of paeonols (87). As a result of the drug, the total cholesterol content of the aorta and liver was significantly reduced, the plaque area narrowed, and aortic lipid plaque was inhibited from forming (88). The researchers found that paeonols inhibited the uptake of calcium by neonatal rat cardiomyocytes and significantly decreased their beating frequency. paeonols may block slow calcium channels, resulting in this effect (89). Isolated myocardium can be inhibited from self-regulating, depolarized, triggered, and antiarrhythmic by paeonols (90).

Central nervous system activity

Paeonols have sedative properties, reduce spontaneous activity, and prolong sleep, which is induced by cyclohexobarbital. In mice, it can produce anticonvulsant effects (91). Paeonols also have antidepressant and antianxiety effects (92). It is possible to treat postoperative pain, muscular discomfort, neuralgia, joint pain, dysmenorrhea, wind chill, and arthralgia with the injection of paeonols into muscles or acupuncture points (93). Through opioid receptor mediation, paeoniflorin can produce analgesia against various "phenotypes" of nociception and hypersensitivity (94). Paeoniflorin can provide analgesia for a variety of nociception and hypersensitivity phenotypes (95). It may be effective in treating stroke (Table 2). Additionally, paeoniflorin may reduce the toxicity caused by 1-methyl-4-phenyl-1,2,3,6-

Table 2. The pharmacological properties of *Paeonia* compounds

Active components/extracts	Dose	Observed sample/assay	Effectiveness	Ref.
Antioxidant properties				
Aerial part extract of *P. lactiflora*		DPPH assay	IC50 17.08 ± 0.9 µg/mL	(61)
Ethyl acetate fraction of *P. lactiflora* extract		DPPH assay	IC50 19.75 ± 0.02 µg/mL	(61)
Chloroform and n-butanol fractions from ethanol extract of *P. emodi* rhizome		DPPH assay	IC50s of 7.05 and 6.5 µg/mL, respectively	(62)
Leaves ethanol extract of *P. anomala*		DPPH assay	IC50: 206 ± 2 µg/mL	(63)
Seeds oil of *P. suffruticosa*		DPPH assay	Effective concentration (EC50) of 29.30 mg/mL	(62)
Seeds oil of *P. suffruticosa*	1.0, 2.5 or 6.0 g/kg/d for 30 days	Diet-induced hyperlipidemia in rats	Increased levels of liver and serum MDA, AST, and ALT	(64)
Leaves extract of *P. rockii*		Fe^{2+} chelation, DPPH assay, ABTS assays	IC50s of 6.69 ± 0.00, 1.5, and 0.48 ± 0.01 µg/mL, respectively	(65)
Flowers extract of *P. rockii*		Fe^{2+} chelation, DPPH assays, ABTS assay	IC50s of 7.95 ± 0.02, 2.36, and 1.03 ± 0.01 µg/mL, respectively	(65)
Flowers extract of *P. rockii*	100 mg/kg/d, 3 weeks	A mice model triggered by D-galactose	Increased liver and brain levels of SOD and GSH	(65)
Leaf methanol extracts from *P. officinalis*		CAA assay CAA	Quercetin equivalent of 0.046 µmol/mg	(53)
Leaf water extracts from *P. officinalis*		CAA assay	Quercetin equivalent of 0.106 µmol/mg	(55)
Flower extract from *P. ludlowii*		DPPH assay	IC50 of 31 µg/mL	(66)
Methanolic extract from aerial parts of *P. arietina*		FRAP, CUPRAC, ABTS, and DPPH assays	392.96, 753.93, 659.53, and 544.72 mg TE/g extract, respectively	(67)
Methanolic extract from aerial parts of *P. kesrounansis*		FRAP, CUPRAC, ABTS, and DPPH assays	409.12, 775.09, 631.83, 540.23 mg TE/g extract, respectively	(67)
Gallic acid		DPPH assay	IC50 1.2 µg/mL	(68)
Benzoylpaeoniflorin, oxypaeonidanin		NO levels in activated macrophage-like RAW 264.7 cells were determined.	IC50 23.32 µM and IC50 40.8 µM, respectively	(69)
Paeoniflorin	1, 10 and 100 µM	Glucose-treated RSC96 cells	GST and GPX activity, as well as the nuclear protein level of Nrf2, and Nrf2-dependent ARE genes, such as HO-1 .	(70)
Paeonol	50 and 100 mg/kg for 30 days	Induction of diabetic encephalopathy by STZ in rats	GSH content in the hippocampus was significantly increased, and iNOS activity was improved	(71)
Anti-inflammation activity				
Paeoniflorin B, A		RAW 264.7 cells stimulated by LPS and macrophages activated by LPS	NO production is inhibited.	(58)
Paeonidanins F		LPS induced RAW 264.7 cells	IC50 22.7 µM	(72)
Paeonidanins G			IC50 19.4 µM	
Paeonidanins H			IC50 29.1 µM	
Paeonenoides D			IC50 9.6 µM	
Paeoniflorin		COX-I and COX-II expression was inhibited	IC50 11.9, and 10.8 µM	(42)
Benzoylpaeoniflorin			IC50 13.2, and 12.6 µM	
4-O-methyl-paeoniflorin			IC50 9.8, and 11.3 µM	
Suffruticosol A	20 mg/kg and 40 mg/kg	Mice with acute inflammation of their airways	NO, iNO, and pro-inflammatory factors (TNF-α, IL-6, and IL-1β) were inhibited	(60)

Table 2. Continued

Active components/extracts	Dose	Observed sample/assay	Effectiveness	Ref.
Central-nervous-system activities				
Extracts of *P. lactiflora*	150, 300, 600 mg/kg, 14 days	Depression SD rat model	Rat immobility was reduced in a dose-dependent manner	(73)
Extracts of Cortex Moutan	50 mg/kg, 12 days	MPTP-induced Parkinson's disease mouse model	Improved mitochondrial dysfunction, improved dopaminergic cell survival, and promoted dopaminergic neuron recovery	(18)
Paeoniflorin	30 μM	PC12 cells induced by 6-OHDA	Inhibition of the PKCd upregulation was achieved through increased GSH levels, dramatically attenuating the 6-OHDA-induced NF-κB translocation.	(74)
Albiflorin	20, 40 mg/kg, 4 weeks	CUMS-induced depression rats	Improvement in dopamine levels and serum and hypothalamic 5-HT levels	(75)
Anti-tumor activity				
Paeoniflorin	400 μg/mL	Cell line RL95-2 for human endometrial cancer	Proliferation of RL95-2 cells was significantly and dose- and time-dependently inhibited	(76)
Paeonol	100, 150 μM	Pancreatic cancer in humans Capan-1 and Panc-1 cells	An increase in E-cadherin expression and a decrease in N-cadherin, vimentin, TGF-β1, protein mother against decapentaplegic homolog2 p-Smad2/Smad2, and p-Smad3/Smad3 expression were observed	(77)
Suffruticosol A		HepG2 cancer cells	IC50 208.66 ± 17.15 μg/mL	(78)
Suffruticosol B		HepG2 cancer cells	IC50 98.19 ± 16.23 μg/mL	(78)
Suffruticosol C		HepG2 cancer cells	IC50 125.29 ± 13.12 μg/mL	(78)
Paeoniflorigenone	30 μM	Cancer cells Jurkat, lymphoma cells HL60, and T-cell leukemia cells HeLa were cultured in vitro	Decreased tumor cell line proliferation	(42)
Antibacterial activity				
Gallic acid		Fungal	MIC50 30 μg/mL	(68)
Cortex Moutan extracts in organic solvent		*Escherichia coli*	MIC50 100 μg/mL	(79)
Roots ethanolic extract from *P. lactiflora*		Influenza virus WSN (H1N1)	IC50 16 μg/mL	(80)
Peonial root extract		*Listeria monocytogenes, Pseudomonas aeruginosa, Salmonella Typhimurium*	Strong Inhibitors	(8)
Peonial root extract		*Candida albicans*and *Microsporum gypseum*		(29)
Phenolic compound		Antibacterial	Altering cell membrane permeability by destroying the cellular wall	(81)
The fruit extract and seed extract of *P. rockii* and *P. ostii*		*P. vulgaris*, *E. coli*, *P. aeruginosa,S. enterica,* and *S. aureus*	Strong antimicrobial properties	(82).

DPPH, 2,2-Diphenyl-1-picrylhydrazyl; MDA, malondialdehyde; AST, aspartate transaminase; ALT, alanine transaminase; IC50, Inhibitory concentration 50; SOD, superoxide dismutase; GSH, glutathione; TE, trolox equivalents; GST, Glutathione S-transferase; GPX, guaiacol peroxidase; Nrf2, nuclear respiratory factor-2; ARE, antioxidant response element; iNOS, inducible nitric oxide synthases; ABTS, 2,2′-azino bis (3-ethyl benzothiazoline-6 sulfonate); CAA, Cellular antioxidant activity; NO, Nitric oxide; STZ, streptozotocin; LPS, lipopolysaccharide; COX-I, cyclooxygenase-1; OX-II, cyclooxygenase-2; SD, stress disorder; MPTP, 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; 6-OHDA, 6-hydroxydopamine; CUMS, Chronic unpredictable mild stress; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; PKCd, protein kinase Cd; NF-κB, nuclear factor-kappa B; 5-HT, 5-hydroxytryptamine; TGF-β1, transforming growth factor-beta1.

tetrahydropyridine (MPTP), opening up the possibility of a nondopaminergic treatment for Parkinson's disease (96).

Anticancerous activity

Paeonols have shown strong effects on HePA tumour growth (97). Paeoniflorin has shown strong anti-cancerous properties and strong cytotoxic properties against lung cancer A549 cells (42). Overall, cell apoptosis, cell cycle arrest, EMT suppression, and MDR reversal are associated with the anticancer impact of paeoniflorin (98). Anti-cancer abilities, protection from Parkinson's syndrome, as well as other properties are detected in Paeonia seeds (99). The most commonly cancer-related mortality in the world is colon cancer (100). Surgery is still the most common method of CRC treatment; however, alternative treatments, such as traditional medicine are increasing in popularity (Table 2). Many research reports that *Paeonia* radix alba showed anti-cancerous activity in different cancers by inhibiting growth in the cancerous cells (101).

Clinical studies

When given for 8 weeks to 125 patients with IBS-C in a placebo-controlled experiment, *P. lactiflora* root, a component of a CHM formulation, an improvement was seen in CHM group in bowel habits and reduction in straining and hard lumpy stools (102).

Discussion

Paeonia spp. belongs to the genus *Paeonia*, the only genus of the Paeoniaceae family. As of currently, 33 *Paeonia* species have been recorded across the World. They are mostly found in temperate regions of Asia, southern Europe, and western North America (103). Many species of *Paeonia* plants have been used in traditional medicine for thousands of years, and their roots and bark are primarily used in medicine. The seeds and flowers are eaten as food or used for aesthetic reasons, while the bark and leaves are used in medicine (38). This study gathered information on the traditional usage, medical applications, toxic effects, pharmacological properties, and phytoconstituents of the *Paeonia* species. Most of the *Paeonia* spp have been investigated for their medicinal and nutritional aspects throughout the World. Among the Paeony species, *P. emodi, P. suffruticosa, P. veitchii* var. *uuiflora,* and *P. peregrine* have ethnomedicinal benefits (34). Paeony spp., *P. lactiflora, P. emodi, P. anomala, P. suffruticosa, P. rockii, P. officinalis, P. ludlowii, P. Cristina, P. kesrounansis,* and *P. ostii* have exhibited modern pharmacological qualities such as antioxidant, anti-inflammatory, anti-tumor and CNS activities. *P. emodi* has been used in traditional and folk medicine apart from its use as foodstuff. The antioxidant property exhibited due to the presence of phenolic compounds in the plant are absorbed from intestines and reacts with a large number of free radicals. Due to its high quantity of carbohydrates, amino acids, minerals, and other bioactive substances, *P. lactiflora* is said to be very nutritive (66). The central nervous system's kappa-opioid receptors and beta (2)-adrenoceptors may act as mediators of the analgesic effect (92,96). The paeonidanins of paeonis' exhibit inflammatory activities by blocking major inflammatory pathways and inhibiting expressions of proinflammatory markers (42). Benzoic acid and the betanin are the major compounds of the plant responsible for antimicrobial activities (81). The antitumour activity is exhibited through the cytotoxicity to the cancerous cells, which attributes due to the polyphenol and flavonoid contents in the Paeonis (42). Esculetin, methyl eugenol, isovanillic acid present in the plant attribute to the cardioprotective activity against myocardial injury (94,96). Several monoterpenes of the Paeonia are responsible for neuroprotection due to oxidative stress and fatty acids components of the plant (9,10). Traditional medicine's claims require more phytochemical testing; their usage must be validated through reverse pharmacology and clinical research. The plant preceding to widespread clinical use deserve in vivo study to establish its efficacy and safety.

Future prospects

Paeonia spp. are in the practice of traditional and indigenous healers, which is culturally acceptable, inexpensive, and compatible with minimal adverse effects. The plant is a source of numerous valuable ingredients that can be used to develop pharmaceuticals, non-pharmacopoeial, and synthetic medicines. The current review has anticipated its therapeutic extension and expansion of nanomedicines besides its routine use based on its chemical composition. It also provokes the researchers to conduct more rigorous scientific clinical studies on the therapeutic efficacy and safety of the plant. Revalidating the current claims by the indigenous system is also a vital thrust area of research.

Moreover, studies are required to develop the agro technology of the plant in proper climatic conditions. Mass cultivation of the plant can strengthen the economic state of the farmers and its industrial attributes. A unique conservation strategy requires for the sustainable utilization of the plant.

Conclusion

Paeonia spp. are valuable medicinal plants found in the Himalayan region of India. Studies have revealed that many secondary metabolites in these plants attribute a wide range of pharmacological activities. The plant exhibits antioxidant, antimicrobial, anti-inflammatory, antitumour, and numerous CNS activities. However, the claims mentioned in traditional medicines for *Paeonia* require rigorous scientific validation to support them. The pharmacological activities, particularly gastrointestinal, reproductive, and hemopoietic systems, need further exploration. Since *P. emodi* is mostly available in sizeable location, it is urgent to propagate in various agroclimatic zones before it becomes extinct from the wild. The

discovery of other bioactive molecules from this plant and the novel targets are yet to be discovered.

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Authors' contribution

SK: Collection of articles, drafting and writing the review article. KK R: The outline, design, and directing the study. MMR, and RNA: Study supervision, manuscript revision, manuscript review, and editing. All authors read, reviewed, and approved the manuscript and English language.

Conflict of interests

The authors declare that they have no competing interests.

Ethical considerations

Authors have carefully monitored ethical issues such as text plagiarism, duplicated publication, misconduct, data fabrication, and falsification.

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References

1. Chandra S, Saklani S. Phytochemical Investigation, antioxidant activity and nutraceutical potential of *Angelica archangelica*. European J Biomed Pharm Sci. 2017;4(10):418-22.
2. Kumari P, Ujala, Bhargava B. Phytochemicals from edible flowers: opening a new arena for healthy lifestyle. J Funct Foods. 2021;78:104375. doi: 10.1016/j.jff.2021.104375.
3. Joshi P, Prakash P, Purohit VK, Bahuguna V. *Paeonia emodi*: a review of multipurpose wild edible medicinal plant of Western Himalaya. Int J Adv Sci. 2017;5(12):480-6. doi: 10.21474/ijar01/5982.
4. Zargar BA, Masoodi MH, Khan BA, Akbar S. *Paeonia emodi* Royle: ethnomedicinal uses, phytochemistry and pharmacology. Phytochem Lett. 2013;6(2):261-6. doi: 10.1016/j.phytol.2013.03.003.
5. Sang T, Crawford DJ, Stuessy TF. Documentation of reticulate evolution in peonies (*Paeonia*) using internal transcribed spacer sequences of nuclear ribosomal DNA: implications for biogeography and concerted evolution. Proc Natl Acad Sci U S A. 1995;92(15):6813-7. doi: 10.1073/pnas.92.15.6813.
6. Riaz N, Anis I, Aziz-ur-Rehman, Malik A, Ahmed Z, Muhammad P, et al. Emodinol, ß-glucuronidase inhibiting triterpene from *Paeonia emodi*. Nat Prod Res. 2003;17(4):247-51. doi: 10.1080/1057563021000060103.
7. Riaz N, Anis I, Malik A, Ahmed Z, Aziz-ur-Rehman, Muhammad P, et al. Paeonins A and B, lipoxygenase inhibiting monoterpene galactosides from *Paeonia emodi*. Chem Pharm Bull (Tokyo). 2003;51(3):252-4. doi: 10.1248/cpb.51.252.
8. Saklani S, Chandra S, Joshi A. In Vitro antimicrobial, antioxidant activity and phytochemical screening of *Paeonia emodi*. Appl Innov Res. 2020;2:152-5.
9. Tu J, Guo Y, Hong W, Fang Y, Han D, Zhang P, et al. The regulatory effects of paeoniflorin and its derivative paeoniflorin-6'-O-benzene sulfonate CP-25 on inflammation and immune diseases. Front Pharmacol. 2019;10:57. doi: 10.3389/fphar.2019.00057.
10. Zhong X, Li G, Qiu F, Huang Z. Paeoniflorin ameliorates chronic stress-induced depression-like behaviors and neuronal damages in rats via activation of the ERK-CREB pathway. Front Psychiatry. 2018;9:772. doi: 10.3389/fpsyt.2018.00772.
11. Blando F, Russo R, Negro C, De Bellis L, Frassinetti S. Antimicrobial and antibiofilm activity against *Staphylococcus aureus* of *Opuntia ficus-indica* (L.) Mill. cladode polyphenolic extracts. Antioxidants (Basel). 2019;8(5):117. doi: 10.3390/antiox8050117.
12. Bondonno NP, Dalgaard F, Kyrø C, Murray K, Bondonno CP, Lewis JR, et al. Flavonoid intake is associated with lower mortality in the Danish Diet Cancer and Health Cohort. Nat Commun. 2019;10(1):3651. doi: 10.1038/s41467-019-11622-x.
13. Zaidi SM, Path S, Singh S, Ahmad F, Jamil SS, Khar R. Effect of repeated administration of *Paeonia emodi* wall root extract in experimental models of epilepsy and behavior. J Pharmacol Toxicol. 2012;7(2):64-77. doi: 10.3923/jpt.2012.64.77.
14. Haq F, Ahmad H, Ullah R, Iqbal Z. Species diversity and ethno botanical classes of the flora of Allai Valley district Battagram Pakistan. Int J Plant Res. 2012;2(4):111-23. doi: 10.5923/j.plant.20120204.03.
15. Liu MH, Lin AH, Ko HK, Perng DW, Lee TS, Kou YR. Prevention of bleomycin-induced pulmonary inflammation and fibrosis in mice by paeonol. Front Physiol. 2017;8:193. doi: 10.3389/fphys.2017.00193.
16. Hao HP, He Z, Li H, Shi L, Tang YD. Effect of root length on epicotyl dormancy release in seeds of *Paeonia ludlowii*, Tibetan peony. Ann Bot. 2014;113(3):443-52. doi: 10.1093/aob/mct273.
17. Kim HG, Park G, Piao Y, Kang MS, Pak YK, Hong SP, et al. Effects of the root bark of *Paeonia suffruticosa* on mitochondria-mediated neuroprotection in an MPTP-induced model of Parkinson's disease. Food Chem Toxicol. 2014;65:293-300. doi: 10.1016/j.fct.2013.12.037.
18. Li SS, Yuan RY, Chen LG, Wang LS, Hao XH, Wang LJ, et al. Systematic qualitative and quantitative assessment of fatty acids in the seeds of 60 tree peony (*Paeonia* section *Moutan* DC.) cultivars by GC–MS. Food Chem. 2015;173:133-40. doi: 10.1016/j.foodchem.2014.10.017.
19. McGeorge P, McGeorge R. Peonies. 1st ed. Albany: Firefly Books; 2006.
20. Liu P, Zhang Y, Gao JY, Du MZ, Zhang K, Zhang JL, et al. HPLC-DAD analysis of 15 monoterpene glycosides in oil peony seed cakes sourced from different cultivation areas in China. Ind Crops Prod. 2018;118:259-70. doi: 10.1016/j.indcrop.2018.03.033.
21. Ismail M, Iqbal Z, Ahmad B, Zakir S, Niaz U. Biological and pharmacological properties of two indigenous medicinal plants, *Rheum emodi* and *Paeonia emodi*. Pak J Biol Sci.

2003;6(9):984-6.
22. Rawat B, Gairola S, Bhatt A. Habitat characteristics and ecological status of Paeonia emodi Wallich ex Royle: A high value medicinal plant of West Himalaya. Medicinal Plants. 2010;2(2):139-43.
23. Riaz N, Malik A, Aziz-ur-Rehman, Ahmed Z, Muhammad P, Nawaz SA, et al. Lipoxygenase inhibiting and antioxidant oligostilbene and monoterpene galactoside from *Paeonia emodi*. Phytochemistry. 2004;65(8):1129-35. doi: 10.1016/j.phytochem.2003.10.012.
24. Ahmad M, Malik K, Tariq A, Zhang G, Yaseen G, Rashid N, et al. Botany, ethnomedicines, phytochemistry and pharmacology of Himalayan paeony (*Paeonia emodi* Royle.). J Ethnopharmacol. 2018;220:197-219. doi: 10.1016/j.jep.2018.04.004.
25. Helal A, Tagliazucchi D, Verzelloni E, Conte A. Gastro-pancreatic release of phenolic compounds incorporated in a polyphenols-enriched cheese-curd. LWT Food Sci Technol. 2015;60(2 Pt 1):957-63. doi: 10.1016/j.lwt.2014.10.037.
26. Teerapattarakan N. The presence of monoterpenes in *Rhynchanthus longiflorus* Hook.f. confirms the value of its use in Akha folk medicine. Greater Mekong Sub-region Medical Journal. 2021;1(2):65-70.
27. Levvy GA, Marsh CA. Preparation and properties of beta-glucuronidase. Adv Carbohydr Chem. 1959;14:381-428. doi: 10.1016/s0096-5332(08)60227-1.
28. Yang Y, Li SS, Teixeira da Silva JA, Yu XN, Wang LS. Characterization of phytochemicals in the roots of wild herbaceous peonies from China and screening for medicinal resources. Phytochemistry. 2020;174:112331. doi: 10.1016/j.phytochem.2020.112331.
29. Yan Z, Xie L, Li M, Yuan M, Tian Y, Sun D, et al. Phytochemical components and bioactivities of novel medicinal food–peony roots. Food Res Int. 2021;140:109902. doi: 10.1016/j.foodres.2020.109902.
30. Shuangxi Y. Study on the history of Chinese Peony. Agricult Hist China. 1987;92-100.
31. Huasheng P, Dequn W, Dayin P, Luqi H. Germplasm interfluve of medicinal and ornamental Peony: Advise Chinese Pharmacopoeia to revise the original plants ofmedicinal Peony. National Pharmacy History and Herbal Academic Symposium; 2015.
32. Xiaolong L, Rongbin W, Xueyi L, Feng Q, Duan L, Cunqin W, et al. Research on the varieties of Anhui Fengdan. J Chin Med Mater. 2009;32:1316-8.
33. Prakash P, Joshi P, Purohit VK. Impact on Density of *Paeonia emodi* along altitudinal gradient in Garhwal Himalaya, India. ESSENCE Int J Env Rehab Conserv. 2020;98-106.
34. Li P, Shen J, Wang Z, Liu S, Liu Q, Li Y, et al. Genus *Paeonia*: a comprehensive review on traditional uses, phytochemistry, pharmacological activities, clinical application, and toxicology. J Ethnopharmacol. 2021;269:113708. doi: 10.1016/j.jep.2020.113708.
35. Watt G. A Dictionary of the Economic Products of India. Vol 6. Superintendent of Government Printing; 1893.
36. Ibrar M, Khan MA, Nisar M, Khan M. Evaluation of *Paeonia emodi* for its cardioprotective potentials: An investigative study towards possible mechanism. J Ethnopharmacol. 2019;231:57-65.
37. Gaur RD. Flora of the District Garhwal, North West Himalaya. Transmedia; 1999.
38. Haq F, Rehman S, Ahmad H, Iqbal Z, Ullah R. Elemental analysis of *Paeonia emodi* and *Punica granatum* by atomic absorption spectroscopy. Am J Biochem. 2012;2(4):47-50. doi: 10.5923/j.ajb.20120204.02.
39. Negi VS, Maikhuri RK. Forest resources consumption pattern in Govind Wildlife Sanctuary, Western Himalaya, India. J Environ Plan Manag. 2017;60(7):1235-52. doi: 10.1080/09640568.2016.1213707.
40. Pillaiyar T, Manickam M, Namasivayam V. Skin whitening agents: medicinal chemistry perspective of tyrosinase inhibitors. J Enzyme Inhib Med Chem. 2017;32(1):403-25. doi: 10.1080/14756366.2016.1256882.
41. Nie R, Zhang Y, Zhang H, Jin Q, Wu G, Wang X. Effect of different processing methods on physicochemical properties, chemical compositions and in vitro antioxidant activities of *Paeonia lactiflora* Pall seed oils. Food Chem. 2020;332:127408. doi: 10.1016/j.foodchem.2020.127408.
42. Huang Y, Ohno O, Suenaga K, Miyamoto K. Apoptosis-inducing activity and antiproliferative effect of paeoniflorigenone from Moutan Cortex. Biosci Biotechnol Biochem. 2017;81(6):1106-13. doi: 10.1080/09168451.2017.1300517.
43. Lin HC, Ding HY, Wu YC. Two novel compounds from *Paeonia suffruticosa*. J Nat Prod. 1998;61(3):343-6. doi: 10.1021/np9704258.
44. Kim SH, Lee MK, Lee KY, Sung SH, Kim J, Kim YC. Chemical constituents isolated from *Paeonia lactiflora* roots and their neuroprotective activity against oxidative stress in vitro. J Enzyme Inhib Med Chem. 2009;24(5):1138-40. doi: 10.1080/14756360802667977.
45. Koo YK, Kim JM, Koo JY, Kang SS, Bae K, Kim YS, et al. Platelet anti-aggregatory and blood anti-coagulant effects of compounds isolated from *Paeonia lactiflora* and *Paeonia suffruticosa*. Pharmazie. 2010;65(8):624-8.
46. Pandey NC, Bhatt D, Arya D, Chopra N, Upreti BM, Joshi GC, et al. Diversity of ethno-medicinal plant: a case study of Bageshwar district Uttarakhand. J Med Plants Stud. 2017;5(2):11-24.
47. Shah SA, Shah NA, Ullah S, Alam MM, Badshah H, Ullah S, et al. Documenting the indigenous knowledge on medicinal flora from communities residing near Swat River (Suvastu) and in high mountainous areas in Swat-Pakistan. J Ethnopharmacol. 2016;182:67-79. doi: 10.1016/j.jep.2016.02.008.
48. Gilani SN, Bhat BA, Rafiqi FA, Rahi S, Nusrat, Khan S, et al. Awareness among university students on forests and traditional use of medicinal plants in Kashmir Valley: a sample survey. Int J Innov Res Rev. 2017;5(2):11-27.
49. Khalid M, Bilal M, Hassani D, Zaman S, Huang D. Characterization of ethno-medicinal plant resources of karamar valley Swabi, Pakistan. J Radiat Res Appl.Sci. 2017;10(2):152-63. doi: 10.1016/j.jrras.2017.03.005.
50. Malik ZA, Bhat JA, Ballabha R, Bussmann RW, Bhatt AB. Ethnomedicinal plants traditionally used in health care practices by inhabitants of Western Himalaya. J Ethnopharmacol. 2015;172:133-44. doi: 10.1016/j.jep.2015.06.002.
51. Chandra R, Uniyal VP. An ethnobotanical study of wild medicinal plants among the mountain community of Western Himalayas: a case study of Govind Wildlife Sanctuary & National Park. Med Plants. 2021;13(2):251-65.

doi: 10.5958/0975-6892.2021.00028.9.
52. Song WH, Cheng ZH, Chen DF. Anticomplement monoterpenoid glucosides from the root bark of *Paeonia suffruticosa*. J Nat Prod. 2014;77(1):42-8. doi: 10.1021/np400571x.
53. He X, Han L, Huang X. A new phenolic glucoside from *Paeonia lactiflora*. Chin Herb Med. 2011;3(2):84-6.
54. Rainer B, Revoltella S, Mayr F, Moesslacher J, Scalfari V, Kohl R, et al. From bench to counter: discovery and validation of a peony extract as tyrosinase inhibiting cosmeceutical. Eur J Med Chem. 2019;184:111738. doi: 10.1016/j.ejmech.2019.111738.
55. Dienaitė L, Pukalskienė M, Pukalskas A, Pereira CV, Matias AA, Venskutonis PR. Isolation of strong antioxidants from *Paeonia officinalis* roots and leaves and evaluation of their bioactivities. Antioxidants (Basel). 2019;8(8):249. doi: 10.3390/antiox8080249.
56. Medzhitov R, Horng T. Transcriptional control of the inflammatory response. Nat Rev Immunol. 2009;9(10):692-703. doi: 10.1038/nri2634.
57. Ding L, Zhao F, Chen L, Jiang Z, Liu Y, Li Z, et al. New monoterpene glycosides from *Paeonia suffruticosa* Andrews and their inhibition on NO production in LPS-induced RAW 264.7 cells. Bioorg Med Chem Lett. 2012;22(23):7243-7. doi: 10.1016/j.bmcl.2012.09.034.
58. Wang QS, Gao T, Cui YL, Gao LN, Jiang HL. Comparative studies of paeoniflorin and albiflorin from *Paeonia lactiflora* on anti-inflammatory activities. Pharm Biol. 2014;52(9):1189-95. doi: 10.3109/13880209.2014.880490.
59. Choi YH, Yoo HJ, Noh IC, Lee JM, Park JW, Choi WS, et al. Bioassay-guided isolation of novel compound from *Paeonia suffruticosa* Andrews roots as an IL-1β inhibitor. Arch Pharm Res. 2012;35(5):801-5. doi: 10.1007/s12272-012-0506-z.
60. Ryu HW, Song HH, Shin IS, Cho BO, Jeong SH, Kim DY, et al. Suffruticosol A isolated from *Paeonia lactiflora* seedcases attenuates airway inflammation in mice induced by cigarette smoke and LPS exposure. J Funct Foods. 2015;17:774-84. doi: 10.1016/j.jff.2015.06.036.
61. Gendaram O, Lai D, Erdenetsogt P, Proksch P. Pancreatic lipase inhibitory and antioxidative constituents from the aerial parts of *Paeonia lactiflora* Pall. (Ranunculaceae). Phytochem Lett. 2017;21:240-6. doi: 10.1016/j.phytol.2017.07.009.
62. Ilahi I, Khan J, Ghaffar R, Hussain A, Rahman K, Wahab S, et al. In vitro antioxidant and hepatoprotective activities of *Paeonia emodi* (Wall.) rhizome methanol extract and its phenolic compounds rich fractions. Pak J Pharm Sci. 2016;29(5 Suppl):1787-94.
63. Enkhtuya E, Shimamura T, Kashiwagi T, Ukeda H. Antioxidative constituents in the leaves of *Paeonia anomala* grown in Mongolia. Food Sci Technol Res. 2017;23(1):63-70.
64. Yang X, Zhang D, Song LM, Xu Q, Li H, Xu H. Chemical profile and antioxidant activity of the oil from peony seeds (*Paeonia suffruticosa* Andr.). Oxid Med Cell Longev. 2017;2017:9164905. doi: 10.1155/2017/9164905.
65. Bao Y, Qu Y, Li J, Li Y, Ren X, Maffucci KG, et al. In vitro and in vivo antioxidant activities of the flowers and leaves from *Paeonia rockii* and identification of their antioxidant constituents by UHPLC-ESI-HRMSn via pre-column DPPH reaction. Molecules. 2018;23(2):392. doi: 10.3390/molecules23020392.
66. Li J, Wang ZH. Nutrients, fatty acid composition and antioxidant activity of the flowers and seed oils in wild populations of *Paeonia ludlowii*. Emir J Food Agric. 2019;31(3):206-13. doi: 10.9755/ejfa.2019.v31.i3.1922.
67. Sut S, Zengin G, Dall'Acqua S, Gazdová M, Šmejkal K, Bulut G, et al. *Paeonia arietina* and *Paeonia kesrounansis* bioactive constituents: NMR, LC-DAD-MS fingerprinting and in vitro assays. J Pharm Biomed Anal. 2019;165:1-11. doi: 10.1016/j.jpba.2018.11.040.
68. Picerno P, Mencherini T, Sansone F, Del Gaudio P, Granata I, Porta A, et al. Screening of a polar extract of *Paeonia rockii*: composition and antioxidant and antifungal activities. J Ethnopharmacol. 2011;138(3):705-12. doi: 10.1016/j.jep.2011.09.056.
69. Liu P. Herbal textural research on *Paeonia lactiflora*, *Radix Paeoniae Alba* and *Radix Paeoniae Rubra*. J Tradit Chin Med. 2018;33(12):5662-5.
70. Yang X, Yao W, Shi H, Liu H, Li Y, Gao Y, et al. Paeoniflorin protects Schwann cells against high glucose induced oxidative injury by activating Nrf2/ARE pathway and inhibiting apoptosis. J Ethnopharmacol. 2016;185:361-9. doi: 10.1016/j.jep.2016.03.031.
71. Liu J, Wang S, Feng L, Ma D, Fu Q, Song Y, et al. Hypoglycemic and antioxidant activities of paeonol and its beneficial effect on diabetic encephalopathy in streptozotocin-induced diabetic rats. J Med Food. 2013;16(7):577-86. doi: 10.1089/jmf.2012.2654.
72. Fu Q, Yu T, Yuan H-M, Song Y, Zou L. Paeonidanins F-H: three new dimeric monoterpene glycosides from *Paeonia lactiflora* and their anti-inflammatory activity. Phytochem Lett. 2015;13:386-9. doi: https://doi.org/10.1016/j.phytol.2015.08.003.
73. Yu XH, Song T, Hou XL, Sui Y, Li YL, Hu D, et al. Anti-depressant effect of *Paeonia lactiflora* Pall extract in rats. Trop J Pharm Res. 2017;16(3):577-80. doi: 10.4314/tjpr.v16i3.11.
74. Dong H, Li R, Yu C, Xu T, Zhang X, Dong M. Paeoniflorin inhibition of 6-hydroxydopamine-induced apoptosis in PC12 cells via suppressing reactive oxygen species-mediated PKCδ/NF-κB pathway. Neuroscience. 2015;285:70-80. doi: 10.1016/j.neuroscience.2014.11.008.
75. Song J, Hou X, Hu X, Lu C, Liu C, Wang J, et al. Not only serotonergic system, but also dopaminergic system involved in albiflorin against chronic unpredictable mild stress-induced depression-like behavior in rats. Chem Biol Interact. 2015;242:211-7. doi: 10.1016/j.cbi.2015.10.001.
76. Zhang J, Wang F, Wang H, Wang Y, Wu Y, Xu H, et al. Paeoniflorin inhibits proliferation of endometrial cancer cells via activating MAPK and NF-κB signaling pathways. Exp Ther Med. 2017;14(6):5445-51. doi: 10.3892/etm.2017.5250.
77. Cheng CS, Chen JX, Tang J, Geng YW, Zheng L, Lv LL, et al. Paeonol inhibits pancreatic cancer cell migration and invasion through the inhibition of TGF-β1/smad signaling and epithelial-mesenchymal-transition. Cancer Manag Res. 2020;12:641-51. doi: 10.2147/cmar.s224416.
78. Yang X, Deng R, Liu P, Hu J, Niu W, Gao J. Secondary metabolite mapping identifies peony episperm inhibitors of human hepatoma cells. Nat Prod

Commun. 2019;14(7):1934578X19860313. doi: 10.1177/1934578x19860313.
79. Yang J, Kim JS, Sa YJ, Kim MO, Jeong HJ, Yu CY, et al. Antioxidant, antibacterial and α-glucosidase inhibitory activities of different extracts of Cortex Moutan. Afr J Biotechnol. 2011;10(46):9438-44. doi: 10.5897/ajb11.1115.
80. Ho JY, Chang HW, Lin CF, Liu CJ, Hsieh CF, Horng JT. Characterization of the anti-influenza activity of the Chinese herbal plant *Paeonia lactiflora*. Viruses. 2014;6(4):1861-75. doi: 10.3390/v6041861.
81. Dong AR, Miao JJ, Guo CH, Yang JB, Zhou Y. Antibacterial effect of benzoic acid, fumaric acid and its compound acids against common pathogenic bacteria in vitro. J Southwest Minzu University (Nat. Sci. Ed.). 2019;01:57-62.
82. Bai ZZ, Tang JM, Ni J, Zheng TT, Zhou Y, Sun DY, et al. Comprehensive metabolite profile of multi-bioactive extract from tree peony (*Paeonia ostii* and *Paeonia rockii*) fruits based on MS/MS molecular networking. Food Res Int. 2021;148:110609. doi: 10.1016/j.foodres.2021.110609.
83. Mufti FU, Ullah H, Bangash A, Khan N, Hussain S, Ullah F, Jamil M, Jabeen M. Antimicrobial activities of *Aerva javanica* and *Paeonia emodi* plants. Pak J Pharm Sci. 2012;25(3):565-9.
84. Cui H, Gabriel AA, Nakano H. Antimicrobial efficacies of plant extracts and sodium nitrite against *Clostridium botulinum*. Food Control. 2010;21(7):1030-6. doi: 10.1016/j.foodcont.2009.12.023.
85. Parker S, May B, Zhang C, Zhang AL, Lu C, Xue CC. A pharmacological review of bioactive constituents of *Paeonia lactiflora* Pallas and *Paeonia veitchii* Lynch. Phytother Res. 2016;30(9):1445-73. doi: 10.1002/ptr.5653.
86. Baljeet SY, Simmy G, Ritika Y, Roshanlal Y. Antimicrobial activity of individual and combined extracts of selected spices against some pathogenic and food spoilage microorganisms. Int Food Res J. 2015;22(6):2594-600.
87. Qiuyan L, Wenxue Z. Research advance in study of components and phamacological roles of Sect. Moutan DC. Acad Period Farm Prod Process. 2009;21-5.
88. Dai M, Zhi X, Peng D, Liu Q. [Inhibitory effect of paeonol on experimental atherosclerosis in quails]. Zhongguo Zhong Yao Za Zhi. 1999;24(8):488-90. [Chinese].
89. Jirong T, Lin S. Effect of paeonol on calcium uptake in the cultured neonatal rat myocardial cells. Chin J Pharmacol Toxicol. 1991. p. 108-10.
90. Malik ZA, Bhat JA, Ballabha R, Bussmann RW, Bhatt AB. Ethnomedicinal plants traditionally used in health care practices by inhabitants of Western Himalaya. J Ethnopharmacol. 2015;172:133-44. doi: 10.1016/j.jep.2015.06.002.
91. Jianping Z, Lianzhen L, Hongjiang Z, Xianling W. A survey of the chemical constituents, pharmacological effects and clinical application of Cortex Moutan. China Journal of Traditional Chinese Medicine and Pharmacy. 2006;21:295-7.
92. Mi XJ, Chen SW, Wang WJ, Wang R, Zhang YJ, Li WJ, et al. Anxiolytic-like effect of paeonol in mice. Pharmacol Biochem Behav. 2005;81(3):683-7. doi: 10.1016/j.pbb.2005.04.016.
93. Xiaogang W, Shuqin N, Yiqi H. A survey of studies on Paeoniaceae. Chinese Journal of Experimental Traditional Medical Formulae. 2003;9:55-9.
94. Yu HY, Liu MG, Liu DN, Shang GW, Wang Y, Qi C, et al. Antinociceptive effects of systemic paeoniflorin on bee venom-induced various 'phenotypes' of nociception and hypersensitivity. Pharmacol Biochem Behav. 2007;88(2):131-40. doi: 10.1016/j.pbb.2007.07.013.
95. Yumei W, Hanpeng X, Chunting W, Hao Y, Gong J. Protective effects of paeoniflorin on cultured cortical neurons of mice. Chin J Pharmacol Toxicol. 2002;16(3):172-5.
96. Liu HQ, Zhang WY, Luo XT, Ye Y, Zhu XZ. Paeoniflorin attenuates neuroinflammation and dopaminergic neurodegeneration in the MPTP model of Parkinson's disease by activation of adenosine A1 receptor. Br J Pharmacol. 2006;148(3):314-25. doi: 10.1038/sj.bjp.0706732.
97. Sun GP, Wang H, Xu SP, Shen YX, Wu Q, Chen ZD, et al. Anti-tumor effects of paeonol in a HepA-hepatoma bearing mouse model via induction of tumor cell apoptosis and stimulation of IL-2 and TNF-alpha production. Eur J Pharmacol. 2008;584(2-3):246-52. doi: 10.1016/j.ejphar.2008.02.016.
98. Deng LJ, Lei YH, Chiu TF, Qi M, Gan H, Zhang G, et al. The anticancer effects of paeoniflorin and its underlying mechanisms. Nat Prod Commun. 2019;14(9):1934578X19876409.
99. Liu WN, Shi J, Fu Y, Zhao XH. The stability and activity changes of apigenin and luteolin in human cervical cancer Hela cells in response to heat treatment and Fe2+/Cu2+ addition. Foods. 2019;8(8):346. doi: 10.3390/foods8080346.
100. Bazensky I, Shoobridge-Moran C, Yoder LH. Colorectal cancer: an overview of the epidemiology, risk factors, symptoms, and screening guidelines. Medsurg Nurs. 2007;16(1):46-51.
101. Zhang L, Li DC, Liu LF. Paeonol: pharmacological effects and mechanisms of action. Int Immunopharmacol. 2019;72:413-21. doi: 10.1016/j.intimp.2019.04.033.
102. Bensoussan A, Kellow JE, Bourchier SJ, Fahey P, Shim L, Malcolm A, et al. Efficacy of a Chinese herbal medicine in providing adequate relief of constipation-predominant irritable bowel syndrome: a randomized controlled trial. Clin Gastroenterol Hepatol. 2015;13(11):1946-54.e1. doi: 10.1016/j.cgh.2015.06.022.
103. Christenhusz MJ, Byng JW. The number of known plants species in the world and its annual increase. Phytotaxa. 2016;261(3):201-17. doi: 10.11646/phytotaxa.261.3.1.