COMPRESSIVE REVIEW ON PLANT PROFILE, ETHNOMEDICINAL USES, PHYTOCHEMISTRY AND PHARMACOLOGY OF *PAEONIA EMODI* ROYLE (HIMALAYAN PAEONY)

Abstract

Members of the genus Paeonia, which consists of globally renowned ornamentals and traditional medicinal plants with a rich history spanning over 1500 years, are widely distributed throughout the Northern Hemisphere. Since 1900, over 2200 new horticultural Paeonia cultivars have been created by the discovery and breeding of wild species *Paeonia emodi* Royle (*P. emodi*, Himalayan Paeony) is a well known Himalayan medicinal plant used in the treatment of hypertension, palpitations, asthma, uterine diseases, colic, bilious obstructions and has also been used as an anticoagulant. Many of these ethnomedicinal properties have been experimentally proven in different animal models. It is categorized as critically endangered plant species. *P. emodi* is reported for diverse medicinal uses with pharmacological properties like antioxidant, nephroprotective, lipoxygenase inhibitory, cognition and oxidative stress release, cytotoxic, anti-inflammatory, antiepileptic, anticonvulsant, haemaglutination, alphachymotrypsin inhibitory, hepatoprotective, hepatic chromes and pharmacokinetics of carbamazepine expression, spasmolytic and spasmogenic, and airway relaxant. The data was extracted from unpublished theses (India, China, Pakistan, and Nepal) and different published research articles confined to pharmacology, phytochemistry and various activities using different databases through specific keywords. The relevant information regarding medicinal uses, taxonomic/common names, part used, collection and identification source, authentication, voucher specimen number, plant extracts and their characterization, isolation and identification of phytochemicals, methods of study *in silico*, *in vivo or in vitro*), model organism used, dose and duration, minimal active concentration, bioactive compound(s), mechanism of action on single or multiple targets, and toxicological information. Different classes of natural products like triterpenoids, monoterpenoids, phenolics and tannins have been isolated from the species. This study aimed to compile the detailed traditional medicinal uses, phytochemistry, pharmacology and toxicological investigations on *P. emodi*. This study also highlights taxonomic validity, quality of experimental designs and shortcomings in previously reported information on Himalayan paeony, which may help the researchers to set their minds for approaching the utility, efficacy and potency of the plant.

Keywords: *Paeonia emodi* Royle, Traditional medicinal plants, Pharmacology, Phytochemistry, Toxicological.

Introduction

Since the prehistoric times, medicinal plants have been used to treat and cure different diseases. Due to the safety and security, these medicinal plants are given the first preference in the Indian healthcare system like Ayurveda, Siddha and Unani. The literature from Rigveda, 1500-400 BC is providing the attestable evidence of curative used of these therapeutic plants [1]. From ancient time, India has been the rich repository of medicinal plants, and from ages, these plants are being used for healthcare purpose. Worldwide 4, 80,000 plants species have been discovered out of which 28,187 species are used for the therapeutic purpose [2, 3]. About 9,500 plant species are found in India which has medicinal significance [4]. Himalaya is well known for its rich biodiversity in medicinal and aromatic plants. Owing to its unique geographical setup, topography and undulant landscape the climatic conditions varied along with altitudinal gradients which attribute diversified ecological habitat ranging from tropical forest, grassland to alpine meadows with vast and diverse natural resources. Unfortunately, some of the natural resources are unscientifically exploited for various purposes particularly medicinal plants. Interest in the exploitation of medicinal and aromatic plants as pharmaceutical, herbal remedies, flavouring, perfumes and cosmetics and other natural products has greatly increased in the recent years [5, 6]. Medicinal plants of the western Himalayan region offer alternative remedies with tremendous opportunities. It not only provides access and affordable medicine to the poor people; besides they can also generate income and employment for the developing countries [7]. *Paeonia* is a single genus in the family Paeoniaceae and consists of ca. 35 species distributed mainly in warm-temperate regions of Europe and Asia [8]. *Paeonia* species are rich source of monoterpene compounds possessing a cage-like pinane skeleton [9, 10]. Many bioactive compounds including monoterpene glycosides, triterpenoids, phenols and tannins have been identified from different species [11]. The underground tubers are used in nervous diseases, uterine diseases, colic, bilious obstructions, dropsy, epilepsy, convulsions and hysteria [12]. The dried flowers are used for stomach complaints [13]. The whole plant is used for the treatment of vomiting, cholera, tuberculosis and eye diseases and as anticoagulant and emenagogue. The seeds are purgative and emetic [14]. The tender shoots of *P. emodi* are cooked and eaten as vegetable. Various constituents isolated from *Paeonia* species have shown sedative and anti-inflammatory activities and are used for blocking effect on neuromuscular junction [15]. The Himalayan paeony (*Paeonia emodi* Royle, Paeoniaceae) is

commonly called the queen of herbs. It is commonly distributed in Himalayan regions of Northern Pakistan, China, North- West India and West Nepal with altitudinal range of 2200 to 3200 meters [16]. It naturally grows in loamy-moist soil with cool climatic conditions and cultivated in temperate parts of the world. Flowering occurs during the months of April and May. This species is one of the most useful medicinal plants reported for treatment of various diseases [17]. Its roots (rhizomes) are frequently traded in herbal markets of various countries. Due to its high medicinal value and illegal trade, this species is facing severe threats towards its sustainability [18]. It is well known wild edible plant with diverse traditional medicinal uses as reported in previous studies. Different parts of this species are used to treat various ailments [19]. The family Paeoniaceae is also known by the name of Ranunculaceae consisting of 33 genera distributed mainly in warm temperate region of Europe, Asia, and North-Western America. They are perennial herbs or sometime shrubby plants up to 2 m tall and grow from stout rootstocks [20].Different authors have cited Himalayan peony under different scientific names but according to the recent guidelines [21, 22] there can be only one accepted scientific name for a particular plant and the rest shall be treated as synonyms. The Synonym of the plant is *P. emodi* Wall, *P. anomala* var. *emodi*, *P. emodi* f. *glabrata*, *P. emodi* var. *glabrata*, *P. emodi* subs. *Sterniana.* The taxonomical classification of *P. emodi* consists of Kingdom: Plantae, Division: Magnoliophyta, Subdivision: spermatophytina, Class: Magnoliopsida, Order: Saxifragales, Family: Paeoniaceae, Genus: *Paeonia,* Species: *Paeonia emodi* or *P. emodi.* Biological name: *Paeonia emodi* Wall. ex Royle. The *P. emodi* is known with different names like paeony rose, himalayan paeony (English), undsalib, pamekh, ood-salib (Urdu), pawin, chandayra, ud-salap (Hindi), mamekh, mamaikh (Pashto, Hindko, Gojri and Kalasha), chandra (Sanskrit), bhoi (Marathi), dhandharu (Garhwali) [23]. Therefore, in this study, the ethno pharmacological review of *P. emodi* was carried out aimed at providing a detailed précis of the botany, ethnomedicinal uses, pharmacological activities and chemical composition of the species.

Figure 1 Photographs of the *P. emodi* in the field

Research methodology

Data on *P. emodi* was compiled using various search engines i-e, PubMed, Scopus, Google Scholar, Medline, Web of Science, Google scholar, Science Direct. Indicators like *Paeonia emodi*, Himalayan paeony, ethnopharmacology, ethnobotany, traditional uses, phytochemistry and toxicology were applied for searching the literature. However, the correct taxonomic names and synonyms were verified using databases; (www.theplantlist.org). Ethnomedicinal uses were downloaded and cross checked from accessible unpublished theses of different universities and research institutes of India (http://shodhganga.inflibnet.ac.in), China (http://www.cnki.net), Pakistan (http://eprints.hec.gov.pk/), and Nepal (http://tribhuvan-university.edu.np/tu-central-library-tucl). In addition to this, 1200 research articles published on ethnopharmacological /ethnobotanical uses in various journals of repute cross the world were also reviewed. Chemical structures of bioactive compounds were drawn using scientifically accepted program Chem Draw. The above mentioned databases were used to compile detailed information on *P. emodi* about its taxonomic validity (correct taxonomic names, common names, distribution, identification, Herbarium etc.), ethnopharmacology (part used, traditional uses, preparation and administration etc), pharmacology (extract preparation, dosage, duration, model organism, clinical trials etc), phytochemistry (bioactive compounds, extraction, separation, isolation, structural elucidation etc), various biological activities (strain used, dosage, zone of inhibition, positive and negative control etc), clinical trials (*in vitro*, *in vivo* etc).

Botany and taxonomy

The Himalayan peony is a diploid nothospecies with tenchromosomes (2n=10), that results from hybridisation between *P. lactiflora* and *P. mairei* [24]. The life cycle of plant *P. emodi* starts from mid-February and completed in month of August-September. This large species of

perennial herbaceous peony with hairless stems of 60-150 cm high, has large deep-cut leaves of 30-60 cm long, with up to fifteen hairless, lanceolate pointed leaflets or lobesof up to 14 cm. The stems may carry two to four buds, not all of which always develop into flowers of 8-12cm in diameter in May or June. Three to six bracts which look like leaflets subtend each flower. The mostly three persistent sepals are approximately circular and convex-concave with a pointed tip. Five to ten white elliptical petals are inverted egg-shaped, 4½×2½ cm, encircle many stamens consisting of filaments of 1½–2 cm long and topped by yolk yellow anthers. There is a short ring-shaped disc which encircles the very base of only one, sometimes two, pale yellow carpels, mostly covered in felty hairs. This develops into a densely hairy or hairless follicle of 2–3½ cm, which contains several roundish seeds which are scarlet at first but turn brownish black if fertile in Augustor September [25]. In microscopy, the foliar epidermis consists of irregular shaped epidermal cell with undulating walls. The size of adaxial epidermal cell is 71.5µm (length) and 73.5µm (width) while abaxial epidermal cell is 88.5 µm (length) and 76µm (width). The stomata are mostly anomocytic type with varying size in length and width [26]. Fruit is ovoid follicle with lobose black colored seeds. Pollens are tricolporate, monad and circular shape in polar view while perprolate in equatorial view. Polar diameter is 38.14µm (polar view), 30.87µm (equatorial view), P/E ratio 1.23µm, colpi length 12.3µm, width 15.83µm and exine thickness 2.5µm [27].

Phytochemistry

In literature, major phytochemicals reported in *P. emodi* includes phenolics, monoterpenes, triterpenes, steroids and variety of organic acids. Phenolics were considered to be beneficial in treating cancers, cardiovascular diseases, diabetes, and epilepsy [28-30]. Monoterpenes were reported to be used as antipruritic, anti-inflammatory, analgesic and anesthetic [31-33]. About 4000 known triterpenes reported in *P. emodi* were used in different drugs [34, 35], while steroids were known for bronchodilation and act as anticancer [36]. In previous studies different types of **phenolics** were reported including paeonol, eugenol, carvacrol, thymol, trans-myrtanol, *cis*-myrtanol, carvacrol methyl ether, hydroxybenzoic acid, gallic acid, methyl grevillate, ethyl gallate, methyl gallate, benzoic acid, 4-hydroxy benzoic acid, oligostilbene, benzenol and baicalein; **monoterpenes** includes paeonin A, B, C, wurdin (Boron nitride), benzoyl wurdin (Dibenzoyl peroxide), oxypaeoniflorin, paeoniflorin, lactiflorin, tricyclene, α-thujene, α-pinene, sabinene, β-pinene, myrcene, p-cymene, limonene, 1,8-cineole, %-terpinene, terpinolene, terpnen-4-ol, myrtenal; reported **triterpenes** were emodinol, suberoretisteroid, syringic acid, oxamic acid, trans aconitic acid, oleanolic acid,

betulinic acid, b-amyrin, lupeol, 24-methylenecycloartanol, β-amyrin, butyrospermol, 24-methylenecycloartanol; **organic compounds include** benzoylwurdin, anthraquinones, tannins, carbohydrate, alkaloids, vitamin A, C and E; **steroids include** campesterol, sitosterol, terpenoids; **aldehydes include** salicylaldehyde, *trans*-myrtanal, *cis*-myrtanal, nopinone and various other compounds including monosaccharide sugar, metabolites, glycosides [23]. In previous studies, it is stated that the quality and quantity of plant-based phytochemicals may vary to some extent depending upon environmental conditions where the medicinal plant grow, cultivation condition, harvesting and extraction techniques as well as processing methods [37].

Occurrence and distribution

It is largely distributed in North West India, Northern Pakistan, Eastern Afghanistan, China and West Nepal [38]. It is known from a single locality in China [39]. In India it is located in North-west Himalayas from Kashmir to Garhwal- Kumaon regions of Uttarakhand [40, 41] at altitude of 1800m asl to 3000 m asl [42]. *P. emodi* is found in deciduous forests of several oak species and *Quercus floribunda*, most often on south facing slopes. Generally, plant grows on moist place of deciduous mixed forest with *Quercus* species.

Ethnopharmacology

P. emodi has widely been used in the indigenous and traditional systems of medicine because of its wide therapeutic profile. The fleshy roots are used in uterine diseases, biliousness, dropsy and nervous affections; they are also prescribed as a blood purifier for children. Excessive doses cause headache, confused vision and vomiting. The seeds are emetic and cathartic. An infusion of the dried flowers is given to control diarrhea [43]. The rhizome of *P. emodi* has been indicated for the treatment of headache, abdominal spasms, hysteria and is also used as nervine tonic. It is one of the constituents of important formulation in Unani pharmacopoeia which is widely prescribed for the treatment of urinary incontinence [44]. Peony has also been used in different cardiovascular and respiratory illnesses including palpitations, high blood pressure, congestive heart failure and atherosclerosis [45].

Reported pharmacological activities of *P. emodi*

The crude extracts as well as pure compounds obtained from *P. emodi* have been used to establish the local and traditional claims and to search for novel activities. The different compounds obtained from *P. emodi* possess a number of biological activities which have been reported from time to time.

Anti-inflammatory activity

Ahmad et al., 2015 studied the root extract of *P. emodi* containing polysaccharides showed significant anti-inflammatory activity during *in vivo* experiments in male albino rats. It is suggested that *P. emodi* should be checked to determine the anti-inflammatory potential during *in vitro* studies [46].

Lipoxygenase inhibitory activity

Lipoxygenase enzymes are responsible to produce compounds like leukotrienes, hepoxylines and lipoxins in human and other animals. While such compounds may cause number of disorders like bronchial asthma, inflammation and tumor angiogenesis. However, the lipoxygenase could be inhibited using plant based extracts. In literature [47, 48], the leaves and fruit extracts of *P. emodi* inhibit the synthesis of lipoxygenase. **Riaz et al., 2003** identified the paeoninol and paeonin C in Himalayan Paeony and considered to be the natural agents to inhibit the synthesis of lipoxygenase. However, in above mentioned studies, plant based extracts were neither characterized analytically nor tested for *in vivo* studies [49].

Nephroprotective and Antihyperlipidimic activity

Nephropathy is one of the common complications in major diseases like diabetes which may leads to morbidity and mortality, while hyperlipidemia is one of the major causes of oxidative stress, weak oxidant defense, diabetes and nephropathy. Some of the workers in past studied the fruit extracts to treat nephropathy and it was found that this plant considerably reduce the glucose level up to normal range [50]. While above mentioned studies were deficient in screening of specific or active compounds and without the information regarding their action of mechanism [51-54].

Hepatoprotective and α- chymotrypsin inhibitory activities

Liver is an important organ responsible for various functions in digestive system and detoxification of xenobiotic products produced in the body. Methanolic and ethanolic extracts of *P. emodi* have been studied for hepatoprotective potential [55, 56]. Raish et al., 2017 stated that the extract of *P. emodi* significantly reduced the expression of hepatic cytochrome P450 (CYP3A2 and CYP2C11) [57]. Riaz et al., 2003 studied the inhibitory activity of emodinol in β-glucuronidase [49] while Nawaz et al., 2000 reported that the triterpenoids extracted from the root of Himalayan paeony can also inhibit the β- glucuronidase [58]. It is observed that the inhibition of β-glucuronidase can prevent enlargement of liver and spleen disorders. Alpha- chymotrypsin is an enzyme responsible for synthesis of proteins such as serine which is involved in replication of HCV. The ethyl acetate extract of *P. emodi* containing alpha-chymotrypsin having inhibition capability up to 91% [59].

Antiepileptic and anticonvulsant activities

Epilepsy is one of the neurological disorders mainly caused by psychological, physical and social behaviors. Regarding the traditional uses of *P. emodi*, number of authors documented this species to be used for treatment of epilepsy due to its antiepileptic and anticonvulsant activity [60-62].

Gastrointestinal activities

It is well known in previous studies that various parts of *P. emodi* are used to treat various gastrointestinal disorders. In some studies it is stated that the aerial parts of Himalayan Paeony have potential significance for spasmolytic and spasmogenic activities [63].

Cardioprotective and mutagenic potentials

In literature *P. emodi* was also studied for cardiovascular and airway relaxant activities [45], cardioprotective and antihyperlipidemic potentials [64, 65], cardioprotective potential [66], anti-mutagenic potential [67].

Antimicrobial properties

It is obvious from previous studies that various plant parts of *P. emodi* have following antimicrobial activities, antibacterial and antifungal [68-75].

Anticancer activity

Tantry et al., 2012 evaluated cytotoxic activities of isolated compounds from chloroform-ethyl acetate extract of the roots of *P. emodi* against human cancer cell lines A549, HL-60, HCT116 and ZR-75-30 [76].

Parkinson's disease

Jalgaonkar et al., 2018 evaluated the neuroprotective effect of *P. emodi* in 6-hydroxy dopamine induced Parkinson's disease (PD) model. The ethanolic extract showed neuroprotective activity against 6-hydroxy dopamine induced Parkinson's disease in rats because of its ability to reduce the oxidative stress. [77].

Safety and toxicology

There has been renewed interest in herbal dugs around the world for a decade while the issue of safety of herbal medicines has been continuously questioned. At present there are misunderstandings and prejudice toward the safety of herbal medicine [78-80]. Based on literature reviewed, only limited work is carried out on toxicology of *P. emodi*. Ismail et al. 2003 studied cytotoxic effect of this plant species on brine shrimps (*Artemia salina*) and found that the ethanolic extract did not show any toxicity [41]. Similarly, Zargar et al., 2014 stated that hydroalcoholic and aqueous plant extracts did not cause any mortality up to 2000mg/Kg body weight and thus considered as safe [54]. There are a number of causes of adverse events to herbal medicines, which can be divided into direct and indirect reason.

Direct reason is the intrinsic toxicity of some herb at normal therapeutic dosage or in overdose. A regularity framework for herbal medicines can provide greater assurance to consumers. However, the regulation and specification of herbal medicines vary significantly in different countries. In order to ensure the quality and safety of herbal medicines, the World Health Organization should propose global unified planning, which includes global management standards and quality standards, radical source of herbs, seeds and seedling breeding, planting, harvesting and storage, rational proceedings, manufacture and quality standards. Moreover, safety guarantee system comprised rational clinical practice and risk monitoring should be established to improve the safety of herbal medicine and to play more important role in maintaining human health.

Future perspectives

The detailed information on pharmacological activities using *P. emodi* especially antiepileptic using correct taxonomic validation, effective extraction techniques, role of synergism and mechanism of action of compounds on single or multiple targets and toxicology need further consideration in future research. In future more studies are required regarding correct plant identification, improved methodologies, systematic approach of extraction, characterization and isolation using analytical techniques such as GC-MS, NMR, LC-MS, and HPLC. Proper dose duration, mechanism of action on single or multiple target, responsible active compounds, chemical structural elucidation in relation to their pharmacological actions and link to their folk traditional usage are some of the important future perspectives. The taxonomic validity should include comprehensive information on correct taxonomic name, its validation from Herbaria, source of identification, deposition of voucher specimen in recognized herbarium, use of online databases such as The plant list:(TPL) (theplantlist.org), source of plant collection, place, time, season and morphological as well as physiological notes. Similarly regarding the trade samples of *P. emodi*, one should kept in mind about the commercial source, shop, company name, its location, brand name, postharvest treatment, quality control assurance using DNA barcoding and herbal processing may be taken in consideration. In addition to this advanced technique such as system biology coupled with metabolomics may be apply for further determination of mechanism of action on targets [81]. It is suggested that the pharmacological activities should be directly linked with folk uses mentioned in ancient literature [82, 83].

Conclusion

P. emodi is endemic to western Himalaya and has been known to be used as traditional medicine in various parts of the world. Large number of phytochemical and pharmacological

studies was carried out in the last 62 years and has confirmed the diverse medicinal properties of *P. emodi*. This is the first comprehensive and critical review about the traditional medicinal uses, phytochemical, pharmacological, toxicological and botanical authentication. There is a great scope for further screening of the plant against dropsy, Parkinson's and other neurodegenerative disorders. The plant can also be evaluated against hyperlipidemia since oxidation of LDL leads to its accumulation in the plasma and inhibits its clearance by liver. The oxidative modification of APO A-1 leads to the conversion of normal HDL to dysfunctional HDL and thus hinders reverse cholesterol transport. The phytochemical screening can also be performed to explore new chemical entities present in the plant since it is the least exploited species in the genus. In future, it is suggested that detailed clinical investigations may be carried out to scientifically prove the effectiveness of drugs prepared from the different parts of *P. emodi*. *P. emodi* should be further studied for green synthesis of nanomedicine for biotechnological and nuetro-pharmaceuticals. Potential synergetic or antagonistic effects of the extracts and isolated compounds also require validation.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

NOTE:

The study highlights the efficacy of "traditional medicine" which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.

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