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Review Article

The Therapeutic Potential of *Artemisia amygdalina* Decne, An Endemic Plant Species from Kashmir Himalaya: A Review

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Abstract

The genus *Artemisia* occupies an important place in the rich plant biodiversity of Kashmir Himalayas. Being endemic to Kashmir Himalaya, *Artemisia amygdalina* is used as medicine to treat various diseases. This plant species has been used in folk medicine in the treatment of a number of diseases, including epilepsy, piles, nervous disorders, cough, cold, fever, and pain since ages. Significant progress has been made in phytochemical and biological investigations of *Artemisia* during the past few years. However, a detailed and critical review of *A. amygdalina*, which is an important endemic medicinal plant species, is not available. It is in this backdrop that a comprehensive and critical review of this plant species has been compiled. Relevant literature regarding *Artemisia amygdalina* was retrieved from databases like Web of Science, Google Scholar, Baidu Scholar, Springer, PubMed, SciFinder, and Science Direct. Moreover, we collected data from classic books, unpublished materials and papers on this plant species. *Artemisia amygdalina* are widely utilized in the treatment of illnesses such as malaria, hepatitis, cancer, inflammation and infections by fungi, bacteria and viruses. This species is rich in bioactive compounds like alkaloids, cardiac glycosides, terpenes, p-cymene, 1, 8-cineole, phenolics, tannins (polyphenolics), steroids, etc. These secondary metabolites attribute remedial properties to the species. This review article was written to provide readers with up-to-date information on the active components, pharmacology, traditional uses, trade and difficulties in the conservation and sustainable use of this significant plant species.

Keywords: Folk medicine, Diseases, Bioactive compounds, Remedies, Conservation

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Introduction

Humans have traditionally used plants as medicine to treat various diseases, weakness and ailments. The genus *Artemisia* is one of the largest genus, and the majority of species have been used in traditional medicine since ancient times (1). The plant species of the genus has ethno-pharmacological significance due to the presence of different biological activities such as anti-hepatotoxic, antibacterial, antifungal and antioxidant activities (1). The phytoconstituent molecules of different species of the genus include

terpenoids, flavonoids, coumarins, caffeoylquinic acids, sterols and acetylenes (2).

Natural products are important in disease therapy and prevention, and more than 60% chemotherapeutic drugs used in the treatment of various diseases are of natural origin (3). Terpenoids are the largest class of natural products with biological activities and used to treat various diseases. Flavonoid has been traditionally used for a long time. These natural compounds are also used as medicine to treat diseases and have pharmacological properties (4). Keeping in view the growing interest of pharmacologists in genus *Artemisia*, a systematic review of *Artemisia amygdalina*, one of the narrow endemic species of the genus, has been compiled. This synthesis may contribute to future research towards the discovery of new formulations and its sustainable development.

Methods

The selection of relevant literature was made through electronic search using the keywords *Artemisia amygdalina*, distribution, biological activity, chemical components, traditional medicinal uses, and pharmacology in different scientific databases such as Google Scholar, PubMed, Science direct, JSTOR, Research Gate, and SciFinder. Information was also obtained from classic medicinal books, medicinal dictionaries, glossaries and reports from international and national organizations. The data from different sources were collected during 2020-2021. The scientific nomenclature of the species recognised under the genus *Artemisia* in this review follows the kew-based. The plant list is available at http://www.theplantlist.org.

Results and Discussion

1. Distribution and botanical aspects

1.1. Geographical distribution

Artemisia amygdalina Decne. (Asteraceae) occupies an important place in the rich plant biodiversity of Kashmir Himalayas and is also used as a medicine commonly known as 'Veer Teethwan' (Kashmiri). The plant species is narrow endemic to western Himalaya and distributed in sub-alpine regions of Kashmir (India) and Harara region of Pakistan (5). The species has been reported as Critically Endangered (CR) and its populations are declining therefore render it to grow only in small pockets of Kashmir Himalaya (5).

2.2. Morphological Description

Artemisia amygdalina is an erect, tall perennial plant that can grow up to 1.5 m. Stems primarily from the base, grooved, glabrous with hairy younger shoots. Leaves could almost be characterized as sessile, simple, lamina narrowly elliptic-lanceolate, 9 − 15(−16) × 1 − 3.5 cm, undivided, serrate, teeth incurved, gland-tipped, hoary tomentose beneath, glabrous green above, gradually attenuate and setose-auricled at the base, and apex long acuminate. Capitula numerous, heterogamous, more or less pendulous, c. 3–4 mm across, peduncles 1–1.5 mm long, in 20 − 35 × 5 − 6 cm panicle with sub-erect lateral branches up to 5 × 1 cm. Involucre 3-4-seriate, outermost phyllaries narrowly ovate, slightly hairy outside, c. 3 × 1.25 mm, ciliate on membranous margins, acute; inner- most elliptic-oblong, 3.5-4 × c. 1.5 mm, glabrous, margins broadly membranous. Receptacle is glabrous, convex, 1 mm in diameter. Florets up to 25, all fertile; marginal florets female, 8–10 with 2-toothed, c. 1 mm long corolla, style branches flat; disk-florets bisexual, 12–15, with 5-toothed urceolate, c. 1.5 mm long, pale, glabrous, basally constricted corolla, anther appendages ± obtuse, exerted. Cypsela terete or cylindrical, c. 1 mm long, smooth.

The time span for the flowering of this plant is generally July–September. This species can be easily distinguished from other species of *Artemisia* through its simple, serrate leaves, which are hoary tomentose beneath and glabrous green above, appearing like *Salix* leaves from a distance. The close allies of *A. amygdalina* Decne. are Chinese endemics, *Artemisia anomala* S. Moore and *Artemisia viridissima* Pamp. The signs that clearly show the close relationship of these two species could be observed mainly in the leaf and achene morphology. *A. anomala* varies from it in shorter and elliptic leaves, whereas *A. viridissima* is characterized by leaves which are highly similar to those of *Artemisia amygdalina* in shape and size (6).

2. Active constituents of *Artemisia amygdalina*

The main active principle components of the plant species are cardiac glycosides, alkaloids terpenes, 1, 8-

cineole, p-cymene, phenolics, tannins (polyphenolics), saponins and resins steroids, flavonoids (7, 8). Six cytotoxic constituents which, including Ergostadien, 3-ol, ludartin, 5-hydroxy-6, 7, 3, 4-tetramethoxy flavone, trans-matricaria ester, diacetylenic spiroenol ether, and cis-matricaria ester have also been isolated from different plant parts (9).

Artemisia amygdalina is rich in bioactive compounds having prodigious therapeutic and economic prominence. Crude extracts of various chemicals constitute different bio-active compounds, *e.g*. in chloroform, ethyl acetate, ethanolic, methanolic, aqueous and crude extracts- flavonoid and alkaloids have been isolated while tri-terpenoids exists only in the ethanolic extract. Tannins have been isolated in ethyl acetate extract while saponins in ethanolic and aqueous extracts, and these compounds are absent in methanolic, chloroformic and ethyl acetate extracts (10). Moreover the petroleum ether extracts contain artemisinin, while other compounds like terpenes, alkaloids, phenolics, tannins, cardiac glycosides, and steroids are also present (8).

4. Pharmacological Importance

It has been indicated that this plant has antioxidant properties (11), free radical scavenging activity (6), and also anti-inflammatory activity (12). The pharmacological properties of the plant species include the following:

4.1. Anti-Malaria Activity

In traditional medicine, the plant species is used as an insecticide taking clue from traditional knowledge. Due to the presence of anti-malarial constituents, including sesquiterpenes, coumarins, and polymethoxyflavone derivatives, this species can be effectively used in the treatment of malarial disease (13). Artemisinin, a sesquiterpene lactone, and its derivatives were adopted in early 2000's as a first line treatment in a combined therapy for *Plasmodium*. Artemisinin and its derivate are able to clear early infectious phases of malaria; however, this medicine has short span in vertebrates that necessitates its combination with other drugs like chloroquine and primaquine for effective use. It has been reported that 600 million people are at risk of infection by malaria and 1.2–2.7 million are killed per year by this dreadful disease (14). Keeping in view the magnitude of the disease, natural products from plant species with the claim of antimalarial properties should be screened for antiplasmodial activities and as potential sources of new antimalarial drugs (15).

4.2. Antitumor Activities

Antitumor natural products characterized from Artemisia genus include mono- and sesquiterpenes and phenolic compounds. These phenolic compounds have been considered as powerful antioxidants and are more effective antioxidants than vitamin C, E and carotenoids (8, 16). These natural compounds are also able to scavenge free radicals, and decrease the risk of cancer in living organisms (17). Antioxidant compounds like anthocyanins, kaempferol, quercetin, esters of coumaric acid and ellagic acid obtained from plants are used to treat various human diseases such as cancer and cardiovascular diseases (18). Experimental studies have shown that extracts of some plant parts (fruits) can be used against different human related cancers (19). These natural compounds also inhibit various pathways to reduce the risk of diseases in living organisms (18).

Phenolic compounds have potential physiological impacts with regard to the protection and treatment of cancer and cardiovascular diseases due to their antioxidant activity. According to (Zhang et al. (20), phenolic compounds are capable of blocking carcinogenesis initiation through the inactivation of exogenous or endogenous molecules and reactive oxygen species. Another mechanism involves the hindering of activity and synthesis of carcinogen metabolizing enzymes and detoxifies molecules of procancérogènes (21)

4.3. Antiviral Activity

The antiviral constituents from this species include sterols, acetylenes, and flavonoids. Flavonoids are hydroxylated phenolic substances synthesized by plants in response to microbial infection (22). It has been shown that these compounds are efficient antimicrobial substances against many microorganisms (23). Flavonoid compounds have inhibitory impacts against several viruses (24). World Health Organization (WHO) advocates that medicinal herbs such as *Artemisia annua* are being regarded as potential remedies for COVID-19 and should be examined for effectiveness and negative side effects (25). Therefore, plant species like *A. amygdalina* are

the natural repository to treat various viral diseases in the scenario of global climate change and the pandemic like Covid-19.

4.4. *Antioxidant Activity*

Antioxidant components characterized from *Artemisia* species were mainly phenolic compounds and flavonoids. It has been reported that methanol extract of callus of *A. amygdalina* by DPPH assay showed high antioxidant activity followed by aqueous extract. When the extracts of callus were compared with tocopherol, BHT (Butylated hydroxy toulene) and ascorbic acid, it was found that the methanolic extract of callus could exhibit the highest percentage inhibition value (11). Similarly, the petroleum extract of callus showed free radical scavenging activity by Riboflavin photooxidation assay (11). The Deoxyribose assay revealed that methanolic soluble fraction could have the highest percentage inhibition in scavenging hydroxyl radicals when compared with synthetic antioxidant tocopherol. The experimental studied revealed that the activity of these extracts is intensified with increase in concentration of extracts (11). Antioxidant activity has been reported in the essential oils of *A. absinthium* as well (26). The naturally occurring antioxidant substances are recently preferred because these are non-toxic, relatively inexpensive, and effective (27). Therefore, *Artemisia* is a potential source of naturally occurring antioxidant substances.

The phenolic hydroxyl group of phenolic group can bind easily to the macromolecules such as proteins in the extract. The amount of total phenolic compounds and flavonoids play an important role in anti-oxidant activity (28, 29). Leopoldini et al (30) conducted a theoretical study to determine the dissociation energy of OH bonds and the adiabatic ionization potentials of various phenolic compounds of varied structure and polarity as well.

4.5. Antihepatitis and Hepatoprotective Activities

Liver diseases are one of the global problems with high mortality rates. Presently, liver patients are treated with available practices and liver transplantation. These treatments are not so effective and also accompanied by numerous risky side effects (31). These concerns have forced the mankind to look for some safe and efficient alternative drugs, particularly drugs produced from natural resources (32). The target species may also prove one of the natural resourcs for discovery of hepatoprotective drugs. The antihepatitis and hepatoprotective components from *Artemisia* species included monoterpenes, flavonoids, and coumarins. These compounds are hepatoprotective mainly due to hepatotoxicity-alleviating or by antioxidative traits (32).

4.6. Anti-Fungal Activity

Constituents from *Artemisia* species, including flavonoids, polyacetylenes, and sesquiterpenes, can be used as antifungal substances because of the presence these compounds in the genius (33). Existence of these components in the target species makes it a candidate for antifungal activities.

4.7. Antibacterial Activity

Antibacterial substances characterized from *Artemisia* species were monoterpenes, flavonoids, and sesquiterpene lactones. In the Asteraceae, particularly, sesquiterpene lactones are one of the main compounds with antibacterial properties. Sesquiterpenes attack by disrupting the cell wall of the microbes (33). Due to the presence of these compounds, the species may be exploited for the discovery of new formulations to treat various bacterial diseases.

4.8. Anti-Inflammatory Activity

The anti-inflammatory compounds present in the genius mainly include coumarins, sesquiterpene lactones, and essential oils. When severe inflammation occurs, serum proteins and leukocytes move to areas of tissue damage. Gathering of cells in inflammatory sites depends on the release of vasoactive and chemotactic determinants that raise regional blood flow and micro vascular permeability and increase the movement of leukocytes from the intravascular space into the tissues (34). *A. amygdalina* may prove an efficient resource of bioactive components, particularly flavonoids which are immune-modulatory and show anti-inflammatory activities (35). Different extracts were examined orally for anti-inflammatory activity at a dose of 250mg/kg. Methanolic extract of *A. amygdalina* showed maximum anti-inflammatory activity as compared to ethyl acetate and petroleum ether (12).

In inflammation, cells and tissue damages are caused

by the toxicity of ROS created and released from activated phagocytes (36). Free radical scavenging activity and reducing power of *Artemisia* plant extract could be central to the quenching super-oxide anions and retaining the cellular redox homeostasis against detrimental oxidants and radicals in cells. It has been indicated that the declining power exerts an antioxidant impacts through donating a hydrogen atom and breaking the free radical chain (37), it is related closely to the existence of reductones which are powerful declining agents, hence could be considered effective antioxidants.

4.9. Anti-Diabetic Potential

Given the traditional claims of the genus *Artemisia* to be used for the treatment of diabetes, Ghazanfar *et al*. (38) conducted studies on anti-diabetic and antihyperlipidemic effects of *A. amygdalina* and reported that extracts of *A. amygdalina* showed anti-diabetic potentials in experimental rats, and it was found that polyphagia, and polydipsia reduced in these experimental animals along with weight loss. Researchers have indicated that flavonoids are able to reduce the intensity of diabetes mellitus either by the inhibition of glucose absorption or by improving glucose tolerance (38) via hindering the activity of α-glucosidase in the small intestine. Diabetes mellitus is known one of the biggest health challenges throughout the world (39). A the World Health Organization (WHO) has stated, diabetes is expected to be the seventh leading cause of death worldwide by 2030 (40). Flavonoids render a better pathogenesis of diabetes and its complications through the regulation of glucose metabolism, hepatic enzymes activities, and a lipid profile (41). Therefore, plant species like *A. amygdalina* can be exploited for the new leads in drug discovery against this silent killer disease.

4.10. Essential Oils

Essential oils obtained from leaves are monoterpene hydrocarbons and oxygenated monoterpenes which constitute about 82.0 % of the total oil composition. The main components that have been found out include sabinene, p-cymen, 1, 8-cineole, and Borneol. The essential oil obtained from stem in addition to above mentioned monoterpenes also contain sesquiterpene hydrocarbons (7). The major constituents were α-pinene (6.0 %), camphene (10.4 %), β-pinene (40.2 %) and borneol (5.7 %) (7). The plants collected from wild have the highest level of the presence of oxygenated monoterpenes followed by monoterpene hydrocarbons and sesquiterpene hydrocarbons, while as the micropropagated plants are characterized by the highest level of sesquiterpene hydrocarbons followed by oxygenated monoterpenes and monoterpene hydrocarbons (7). Essential oils are used as perfumes, flavors for foods and beverages, or as therapeutic agents to treat various diseases (42).

5. Ethno-Medicinal Uses

The species of genus *Artemisia* are widespread throughout the world and are widely used in Chinese traditional preparations. The species are widely used to cure illnesses such as malaria, hepatitis, cancer, inflammation and infections by fungi, bacteria and viruses. The roots of *A. amygdalina* are traditionally used as insecticides to protect woolen clothes. In tribal areas, the upper parts of plants could be utilized as fuel and fodder. Moreover, dried leaves are smoked as tobacco. Furthermore, it is also used to make complexion better, as a hair wash to destroy lice and to turn grey hair to black. The plant extract is used locally to cure epilepsy, piles, nervous disorders, cough, cold, fever and pain (6). Native women of the valley use it against amenorrhea and dysmenorrhoea (43). It is also used as hepato-protective agent which is utilized to lower blood pressure. Moreover, it is used against fever and sedation, and also in the treatment of gastrointestinal ailments (43, 44). Various ethnomedicinal uses of this plant species have been presented in Table 1.

6. Challenges in the Conservation and Sustainable Use

Artemisia, which is an important genus with many species having medicinal properties, is used widely in traditional as well as in modern medicine. Since it is widely demanded, the majority of the natural populations of the species either have been eradicated or are exposed to detrimental harvesting, hence availability of these plant species is progressively declining in the wild (45). The target plant species is endemic to a limited area of the Himalayas. In addition to the limited distribution, the harvesting of whole plant is one of the causes for being threatened. This critically endangered species is enlisted in Appendix I of Conservation on International Trade in

Endangered Species of Wild Fauna and Flora (CITES). The species is one of the 37 Himalayan endangered medicinal herbs that have been designated as being very important for *in situ* and *ex situ* conservation (46). Being a narrow endemic species to the Himalaya and the operative threats in the region make it more vulnerable to extinction (46, 47).

7. The Way Forward

A multi-dimensional approach to retain the resource base that involves *in situ* and *ex situ* conservation and selection of better-quality genotyped followed by their multiplication (by both biotechnological and conventional approaches) might lead to a remedy for the problem.

7.1. Biotechnological Interventions

Facilitating the germplasm conservation of *Artemisia amygdalina*, an *in vitro* propagation protocol of this herb has been developed (48). The authors reported that plant growth regulators in various concentrations and combinations give best results particularly when 10 µM NAA and 10 µM BAP were supplemented to full strength MS medium on nodal explants. Regenerated node explants gave the best results when MS medium was supplemented with

Table 1: Ethno-Medicinal Uses and the Method of Application of *A. amygdalina*.

Ailment	Methods of Applications	Reference
Gastrointestinal ailments	Powder of above ground parts is roasted in mustard oil and the paste is applied on stomach.	43
Cough and cold	Powder is taken with warm water	6
Throat infection		
Fever	Powder heated with oil is massaged to the affected area	
Rheumatism and painful joints	Leaves and branches are grinded, mixed with salt applied to the affected area and bandaged to keep it warm.	
Luster and growth of hair	Hair is washed with decoction. Mustard oil is heated with powder and the oil used as topical application on hair	
Amenorrhea and dysmenorrhoea		43, 44
Epilepsy		6
Headache	Paste of the upper parts is applied	
Exhaustion	Above ground parts are burnt in 'hookah' and the smoke inhaled	6, 43
Anti-inflammatory	Leaves are grinded, mixed with salt and turmeric, applied to the affected area with gauze.	41, 43
Preservative	Intact dried leaves are added to spices as preservatives against insects and odour loss.	6
Insecticides	Dried leaves are kept in woolen clothes to protect them from insects.	6, 41

various concentrations of BAP and Kinetin for further shoot proliferation after separation and was sub-cultured on half strength MS medium and produced higher shoots. The highest rooting was reported by the authors on half strength MS medium supplemented with 2, 4-D, and such plants survive upon hardening and developed into mature plants (7).

Conclusion

Artemisia species are used to treat of various diseases in allopathic and herbal systems of medicine. It has been indicated that he genus *Artemisia* has a vast range of biological activities, including anti-hepatotoxic, antibacterial, antifungal anti-malarial, cytotoxic, anti-inflammatory, and antioxidant activities. It has already been reported that different active compounds isolated from *Artemisia amygdalina* have medicinal properties. Phytochemical screening revealed the existence of terpenes, alkaloids, phenolics, tannins (polyphenolics), cardiac glycosides, steroids, phenolics tannins, cardiac glycosides, flavonoids, saponins resins, etc. Several biological activities such as anti-inflammatory, hepatoprotective, anti-ulcer, antidiarrheal, antiparasitic, and antimicrobial activities have been reported from the secondary metabolites of the plant species. It is also considered as plant species with regard to veterinary medicine and is used in the treatment of the heart diseases of cattle. The oil obtained from *A. amygdalina* is very valuable and is used in perfumery. The root is regarded as an efficient insect repellent. The results of various studies have empirically confirmed that *Artemisia amygdalina* is an effective anti-inflammatory agent.

The plant species are used in traditional medicine, with a narrow geographical range and are potential candidates in the pharmacology and discovery of new leads. Therefore, it is also important to devise mechanisms for the sustainable development of this plant species.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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