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The Artemisia Genus: A Review on Traditional Uses, Phytochemical Constituents, Pharmacological Properties and Germplasm Conservation

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Abstract

Artemisia, being the largest and widely distributed genus of the plant family Asteraceae encompasses more than 400 species. Some popular species are reported to possess several medicinal properties owing to the rich phytochemical diversity. Altogether, eight thirty-nine chemical constituents including volatile and non-volatile compounds in these species are listed together with their references. These have been categorized into phenylpropanoids, flavonoids, terpenes, sterols, lignans, phenolics, fatty acids, fatty esters hydrocarbons and miscellaneous compounds, many of which are responsible for various biological activities such as analgesic, anti-parasitic, anti-inflammatory, hypolipidemic, anti-nociceptive, anti-microbial, anti-oxidant, hepato-protective, antiulcerogenic, anti-malarial, anti-leishmanial, anti-cancer, anti-tumor, anti-diabetic, anticonvulsant, anti-promastigote, anti-convulsant, anxiolytic and anti-depressant. The traditional uses and recent advances in the field of phytochemistry of selected Artemisia species and their respective medicinal, insecticidal and nutritional properties, for the period up to 2017, are assessed and compiled in this paper. Meticulous phytochemical and pharmacological studies on Artemisia species and their sustainable conservation will yield reliable molecules of pharmacological importance, for better healthcare.

Keywords: Anti-malarial; Artemisinin; Herbal drugs; Mugwort; Secondary metabolites

Abbreviation

2,4-D: 2, 4-Dichlorophenoxyacetic acid, AA: ascorbic acid, AIDS: acquired immune deficiency syndrome, BAP: 6-benzyl amino purine, BC: before the Christ's birth, cm: centimetre, DPPH: 1,1-Diphenyl-2 picrylhydrazyl radical-scavenging activity, g: gram, FRAP: ferric reducing antioxidant power, HCl: hydrochloric acid, HPLC: high performance liquid chromatography, HPTLC: high performance thin layer chromatography, IAA: indole 3-acetic acid, KN: kinetin, µM: micromolar, mg: milligrams, ml: millilitre, MS: Murashige and Skoog, MTCC: Microbial Type Culture Collection and Gene Bank, NAA: α-naphthalene acetic acid, TCM: Traditional Chinese medicine.

Introduction

The dependence of human being on plant kingdom for food, fodder, fuel and medicinal purposes is as old as the existence of human on this planet. Plant kingdom is a reservoir of valuable medicinal flora and the use of these plants to cure various diseases can be dated back to 1500 BC. The use of herbs for various purposes is also mentioned in the ancient Hindu texts: Charaka Samhita (1000–800 BC), Rigveda (4500–1600 BC), Sushruta Samhita (800–700 BC) and others (Pal and Jain, 1998) Different medicinal systems such as Siddha, Buddha, Ayurveda, traditional Chinese 51 medicine (TCM) etc. shall remain the unending treasures of knowledge on medicinal herbs [1-3]. In the ancient time, the knowledge of plants for their medicinal value was confined to tribal communities, villagers and priests, but in the modern era, the popularity and faith in the power of herbal drugs have become widespread. Indeed, the knowledge of herbal medicines were identified by a community, practised, and heirloomed to the successive generation [4]. Although several synthetic drugs are available to treat various diseases and disorders but, they are not free from side-effects [5]. On the other hand, there is an increasing demand of the herbal medicines as they are safe, effective, economical, eco-friendly and free from deleterious effects. It has been observed that more than sixty percent of the commercially important drugs are obtained from plant sources and a large portion of the world population is dependent on them for their primary healthcare [6]. Moreover, herbal remedies also provide a cure for certain age-related diseases such as memory loss, immunity related diseases, osteoporosis etc. These days, there are several clinical reports available where natural drugs have shown their promising potential to cure fatal diseases like AIDS, cancer, cardiovascular diseases, and renal disorders. Herbs are a tremendous source of secondary metabolites which protect them against microbes, birds and animals, and attract the plant pollinators too [7]. Several secondary metabolites have proved to be very useful for the production of pharmaceutical drugs for human healthcare. Extensive analysis of the phytochemistry of the genus Artemisia has led to the identification of various biochemically active secondary metabolites including essential oils, flavonoids, terpenes, esters, and fatty acids. Efficacy trials of these bioactive compounds shall lead to the development of novel herbal drugs for betterment of human health [8].

Artemisia is a widespread genus which encompasses more than 400 species (~474) and is revered as 'Worm wood', 'Mug word', 'Sagebrush' or 'Tarragon' [8,9].This genus belongs to the family Asteraceae, sometimes recognized as 'compositae family', 'sunflower family', 'thistle family' or 'daisy family'. The word 'Artemisia' comes from the ancient Greek word: 'Artemis'=The Goddess (the Greek Queen Artemisia) and 'absinthium'=Unenjoyable or without sweetness. The word 'Wormwood' is influenced by the traditional use as a cure for intestinal worms. Most of the Artemisia species are perennial, biannual, annual herbaceous ornamental, medicinal and aromatic plant or shrubs. They are silver green, dark green or blue-green in colour, possess pungent smell and bitter taste due to presence of terpenoids and sesquiterpene lactones [10]. Some species are cultivated as crops while others are

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used in preparation of tea,tonic, alcoholic beverages and medicines. In this review, we have discussed the geographical distribution, botanical description, phytochemistry, traditional uses, biological activities, and conservation of Artemisia species. Apart from non-volatile bioactive compounds, Artemisia species are an excellent source of essential oils like thujone, thujyl alcohol, cadinene, phellandrene, pinene etc. which are reported to possess various biological activities including, anti-bacterial [11]. Anti-fungal [8] anti-viral [12] anti-malarial [13] anti-inflammatory [14] anti-cancer [15] anti-tumor [16] anti98 helminthic [12] anti-diabetic[17-19] anti-spasmodic[14], hepatoprotective [20] anti-pyretic [21] anti-parasitic 5 [22] anti-oxidant [15,20,23,24] anti-fertility [17] acaricidal [25] anti-rheumatic [26] anti-hypertensive [27,28] trypanocidal, trichomonacidal [29] wormicidal [30] emmenagogue, diuretic, abortive [31] anti-arthritis [32] immunomodulatory [33] neuroprotective [34] menopause, premenstrual syndrome, dysmenorrhea and attention deficit hyperactivity disorder [35]. Anti-ulcerogenic [36] analgesic (Saxena, 2015), bile stimulant [26] anti-nociceptive [37] anti-plasmodial [38] anti-venom [39] anti-coccidal [40] anti-leishmanial [41,42] anti-hyperlipidemic [43,44] anti-epileptic and anti-convulsant [45] anti-cholesterolemic, cholagogue, diuretic, febrifuge and vasodilator [46] deobstruents [47] disinfectant, choleretic, balsamic, depurative, digestive, emmenagogue, and anti-leukaemia and ant-sclerosis [48] vermifuges, febrifuge, anti-biotic, urine stimulant [26] anti-migraine [49] insecticidal [50] anti-feedant [51] abortifacient [52] anti-herpes virus [53] and antidote to insect poison [54]. The lack of a comprehensive review on the chemistry of Artemisia genus prompted us to compile a review on the secondary metabolites characterized in its different species. Besides this, emphasis has also been given on the biological activities associated with these compounds.

Geographic Distribution

The Artemisia species are widely distributed in temperate regions of North America (Mexico, USA, Canada), Mediterranean region, Asia, Africa and Australia as shown in (Table 1, included as Supplementary data) and 6 Figure 1. Most species are reported from Asia, 126 140-160 from china, 160-170 from EX-USSR, 127 45-55 from Japan, 30-40 from Iran, 30-45 from India and 15-20 from Turkey (Figure 1).

Phytochemistry

Biochemical investigations have revealed a total of 839 compounds from the different plant parts (leaves, stem, roots) of fourteen *Artemisia* species viz. *A. abrotanum L., A. absinthium L., A. afra, A. annua L., A. arborescens, A. capillaris Thunb., A. caruifolia, A. chamaemelifolia, A. cina, A. dracunculus L., A. herba-alba, A. indica Willd., A. japonica Thunb., A. vulgaris* [55,56] as shown in Table 1, included as Supplementary data. These species mainly comprise of terpenoids, flavonoids, coumarins, caffeoylquinic acids, sterols and acetylenes. The hydrocarbon and oxygenated terpenes are the most abundant compounds found in the genus *Artemisia*. These are mostly acyclic monoterpenes (citronellol, myrcenol, linalool, artemisia ketone, Artemisia alcohol etc.), monocyclic monoterpenes viz. p-menthanes (menthol α-terpinene, p-cymene, terpinen-4-ol, 1,8-Cineole piperitone etc.), bicyclic monoterpenes viz camphanes (borneol, camphor etc.) pinanes (α-pinene, myrtenol, myrtenal, 3-pinanol etc.), thujanes (α-thujene, sabinene, sabina ketone etc.), acyclic sesquiterpenes viz. farnesanes (farnesal, farnesol etc.), monocyclic sesquiterpenes viz. bisabolanes (α-bisabolol, cis-lanceol etc.), germacranes (germacrene A, germacrene B, germacrene C, germacrene D etc.), elemanes (α-elemene, β- elemene, γ-elemene, δ-elemene etc.) humulanes (α-Humulene, Humulene epoxide I etc.), caryophyllanes (β-caryophyllene, γ-caryophyllene etc.), bicyclic sesquiterpenes viz. eudesmanes (α-selinene, β-eudesmol , kongol , artemisin etc.), cadinane (artemisinol, δ-Cadinene , γ-Cadinene etc.), muurolanes (γ-muurolene, δ-Muurolene etc.), amorphanes (4,7(11)-Amorphadien-12-al, 4-Amorphen,3,11-diol, Arteannuin A, Arteannuin B, Arteannuin C, Arteannuin D etc.), guaianes (α-guaiene, β-guaiene, γ-gurjunene etc.), aromadendranes (α-Aromadendrene, globulol etc.), tricyclic 151 sesquiterpenes viz. cedranes (cedrol, cedryl acetate etc.). These species also contain higher terpenoids viz. diterpenes (phytol, isophytol etc) and triterpenes (β-amyrin, α-amyrin, friedelin etc.). The various class of compound reported here possess several pharmacological properties (Figure 1), e.g. Limonene (64), is a monoterpene and has many medical and pharmaceutical applications (Singh et al., 1989) like anti-carcinogenic actions, in liver tumour models [57,58] and as topical medication for both dermal and sub-dermal injuries [59]. Another monoterpene *p*-Cymene (81) has shown significant anti-oxidant and anti-microbial activities [60] The next major class of compounds are flavonoids (apigenin, luteolin, chrysoeriol, cirsiliol, kaempferol, rhamnocitrin, quercetin, tamarixetin, mikanin, casticin, cirsilineol, eupatin, mearnsetin, chrysosplenol E etc.) and flavonoid glycosides (kaempferol-3-O-glucoside, isorhamnetin 3-glucoside etc.) which belongs to a large group of phenolic secondary metabolites of plants [61]. The later compounds are extensively studied components, which have been evidenced to have antioxidative activity. Moreover, partial structure-activity relationship has been studied, demonstrating that the ability of anti-oxidative activity is relevant to the structure of sugar moiety [62]. The phenylpropanoids (anethole, eugenol, methyl eugenol) are produced by the shikimate pathway, which is unique to plant. Many other compounds like cyclic and acyclic hydrocarbons, alkynes, lignans, cyaromatic acids, saturated and unsaturated fatty acid, alcohol, ketones, esters were isolated from *Artemisia*, several pure compounds evidenced to perform biological action. The isolated have been identified using various techniques like GC-MS, HPLC-MS, HPLC, 1D and 2D NMR, X-ray crystallography etc. (Figure 2).

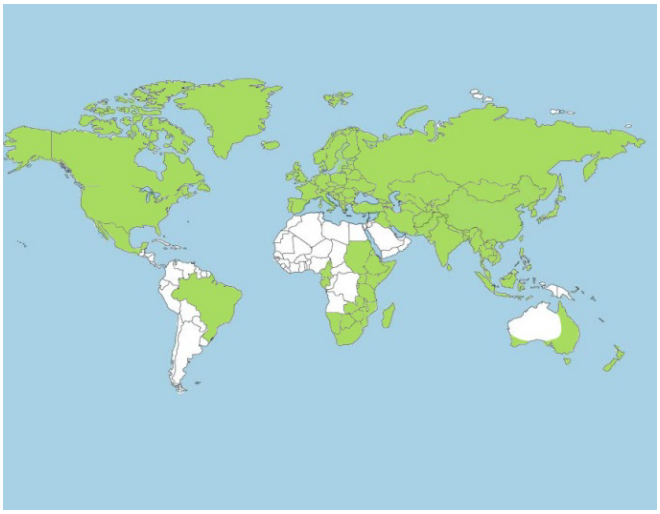

Figure 1: The Artemisia species are widely distributed in temperate regions of North America (Mexico, USA, Canada), Mediterranean region, Asia, Africa and Australia.

Traditional Uses and Biological Activities

Artemisia genus harbours important medicinal plant species which have been used since ancient times for pharmacological and certain culinary purpose (Table 2, included as Supplementary data). Therefore,

Figure 2: Artemesia Health Benefits.

several biopharmaceutical products containing *Artemisia* extracts are available nowadays in the market to treat specific ailments (Table 3, included as Supplementary data).

Artemisia abrotanum L. (southernwood)

Formulations obtained from this species act as an astringent, stimulant, spasmolytic, anti-septic, and febrifuge [10,63]. The ethanolic extracts of powdered aerial parts has shown anti-fungal and anti-bacterial activities against various fungal and bacterial strains [64] The active compounds like cineole, borneol, *p*-cymene etc. derived from this species also exhibit insect-repellent activity against *Aedes aegypti* [65] Essential oil-extracts prepared from the fresh plant material are used as nasal sprays for the treatment of respiratory disorders and allergic rhinitis.

Artemisia herba-alba Asso (white wormwood)

This plant is also known as desert wormwood and in Arabic culture it is known as 'shih' [66] Since ancient times this plant has been used by the natives of many cultures for the preprations of traditional medicines to treat diabetes and hypertension [67]. Aqueous extracts obtained from aerial parts of the plant possess anti-oxidant and anti-microbial properties [68] Herbal tea prepared from this species exhibits anti-bacterial, analgesic and anti-spasmodic properties. This plant is also utilized as a fodder plant for the livestock in plateau regions of Algeria 197 [69].

Artemisia absinthium L. (wormwood)

In Turkish traditional medicines *A. absinthium* is used for treating sepsis, fevers, worms, stomach-ache and act as a diuretic. In Chinese folk medicines, it is used to cure chill and fever, cancer, dysentery and neurodegenerative 201 diseases [70]. It is also used in herbal medicines to cure many ailments such as gastric pain, cardiac stimulation and to increase the cognitive activities in the cortical membranes of human cerebrum [71]. The aromatic compounds of this plant have been utilized for the preprations of many alcoholic drinks, foods, soft drinks etc. and also as 206 flavouring agents [11]. Essential oils obtained from aerial parts of the plant exhibited anti-microbial potential when tested with *Saccharomyces cerevisiae* and *Candida albicans* [72]. The methanol extracts of the powdered plant material showed considerable anti-oxidant activity [66]. Crude aqueous and ethanol extract of aerial parts of the plant possess a significant anti-helmintic property as compared to the drug 'albendazole' (anti-helmintic), against the nematodes found in sheep intestine [73]. Several other biological activities such as anti-parasitic [22]. Anti-microbial [74] anti-oxidant [11] and hepatoprotective [66] are also reported. Caffeic acid, myricetin, ferulic acid and gallic acid are the major phenolic compounds isolated from leaves of *A. absinthium* exhibiting strong anti-oxidant potential [75]. β-myrcene from *A. absinthium* and camphor from *A. austriaca* have shown notable anti-microbial activity [11].

Artemisia afra Jacq ex Wild

A. afra Jacq ex Wild is one of the oldest medicinally important plant of Southern Africa [76]. This plant has long been used to cure several diseases such as cold, dyspepsia, headaches, coughs, malaria, diabetes and disorders of kidney and bladder [76] Nower days, it is used to cure various ailments including cough, colds, diabetes, heartburn [77] bronchial and stomach related disorders [69] The aqueous leaf-extracts holds anti-microbial potential against several bacterial strains [78].

Artemisia annua L. (sweet wormwood, sweet Annie, annual wormwood, qinghao, huang hua hao)

Artemisia annua L. is a native of China and is revered in the Chinese folk medicines for the treatment of fevers (including malaria) and chills [10]. It has been naturalized in the United States, Europe and South America. This plant is widely-cultivated in Africa with a long tradition of use in the treatment of malarial fever and has now become a popular medicinal plant in recent times, because of the active principle 'artemisinin' which is the backbone of the global malaria eradication campaign. The Chinese scientist Youyou Tu was awarded in 2015 with the Nobel Prize in Medicine for the discovery of artemisinin and its application as an anti-malarial drug [79]. Artemisinin compound is a sesquiterpene lactone (seven stereogenic centres) and is effective against multidrug-resistant malaria, with no significant side-effects. Dihydroartemisinic acid (DHAA) is the precursor to artemisinin [80]. Recently, the molecular mechanism for enhanced production of artemisinin during cold stress has been elucidated. Jasmonic acid (JA) biosynthetic genes, LOX1, LOX2, allene oxide cyclase (AOC) and jasmonate resistant 1 (JAR1) are induced during cold stress, leading to an increase in endogenous JA content, which subsequently increases the artemisinin content [81]. In the 1970's when the malarial parasite had acquired resistance to the discovery of artemisinin (structuraly unrelated to quinine) brought great relief. Apart from activities such as anti-oxidant, anti-microbial, anti-inflammatory, anti-coccidial and anti-parasitic, *A. annua* possess potent anti-cancer and anti-leishmaniasis activity [82-84]. In order to prevent resistance in parasites artemisinin may be used in combination with other anti-malarial drugs (AMD'S). But, because of unanticipated cases of hepatotoxicity, combinations 250 of artemisinin-type drugs with other medicines are not recommended without cofirmed clinical trials [85,86]. The glandular trichomes of the leaves sequester artemisinin but, due to the low and variable quantity the demand of the pharmaceutical industries cannot be met from the current plant yields [87]. In order to meet the growing demands of artemisinin complementary strategies have been undertaken which include crop-improvement and microbially-based semi-synthesis. The recent approaches include breeding of *A. annua* plants and molecular approaches to develop its genetic map (Graham et al., 2010). Techniques for production of large quantity seeds with high

viability and vigor is crucial for sustainable production of *A. annua* and atemisinin as well. In order to opt for successful hybridization in *A. annua*, its reproductive biology must be well studied and the onset of flowering among the parental must be synchronized for pollen release and stigma receptivity. Therefore, an understanding of floral biology, pollination biology and seed development is necessary for successful breeding in *A. annua* [88,89]. Recently reported that dried leaves of *A. annua* (DLA) are effective against *Plasmodium* sp., in rodent malaria. The efficacy of DLA was also observed on malaria patients who did not respond neither to artemisinin combination therapy (ACT) nor intravenous artesunate (As). The encapsulation or mixing of DLA with peanut based products did not affect the bioavailability of artemisinin, which was confirmed by simulated digestion [90]. It was also observed that DLA and *A. annua* essential oil enhances the artemisinin soubility and availability. Thus, these techniques are less expensive and more effective compared to traditional medication for malaria. A novel and short chemoenzymatic process of dihydroartemisinic aldehyde synthesis (key intermediate in the biosynthesis of artemisinin) has been proposed in order to cut down the cost of the artemisinin 275 treatment, poor bioavailability, poor water solubility and short-half life, several drug delivery systems containing artemisinin and its derivatives have been designed along with genetic engineering approaches to increase the artemisinin production (Pulice et al., 2016; Aderibigbe, 2017).

Artemisia arborescens (Vaill.) L.

It is a woody, aromatic, evergreen shrub, which is used in preparation of folk medicines, flavouring dishes (because of its good aroma) and liquers [91]. It has also been used as an anti-inflammatory agent in traditional medicines. Several other biological activities such as phyto-toxicity [92]. Anti-bacterial and anti-viral properties [93,94] have also been reported in the plant extracts. Aqueous extract of aerial parts inhibits the growth of *Listeria monocytogenes* and thus exhibits its anti-bacterial potential [91]. The plant essential oils also possess anti-viral activity against Herpes simplex virus [53].

Artemisia vulgaris Linn. (mugwort)

It is an important aromatic medicinal species with pungent smell and sharp taste [95]. It has been used to cure epilepsy, depression, irratibility, stress and insomnia in folk remedies. In Philippines, this herb is known as 'herbaka' and is used against hypertensive diseases [10]. In Asia, this plant is widely used for flavouring rice dishes and tea and in western culture it is an important culinary herb. The plant extracts also possess analgesic, allelopathic, anti-oxidant, larvicidal [96] cyto-toxic [97] anti-malarial [98] and anti296 hyperlipidemic activity [32].

Artemisia capillaris-thunb

A. capillaris has been used as food additives and as a folk medicine in Korea to cure inflammation, microbial infections, malaria and hepatitis [71]. In traditional oriental remedies, this plant has been used to cure dampness, 300 fever and jaundice. It is a famous traditional Chinese medicinal herb and is used for the treatment of epidemic hepatitis. This herb contains active ingredients such as capillarisin, apigenin, hesperidin and coumaric acid which are vital for their allelopathic, anti-cancer and anti-microbial properties [71]. Tablets prepared from *A. capillaris* have the potential to inhibit the replication of hepatitis B virus and thus, act as a potent remedy for hepatitis B disease. Many compounds which act as anti-feedants have also been identified from the developing buds of *A. capillaris* [99]. Coumarin and flavonoids extracted from buds of the plant exhibit significant antihepatotoxic property confirmed by carbon tetrachloride-induced liver lesions in cultured rat hepatocytes. It has been reported that β-caryophyllene, β-pinene and capillene obtained from *A. capillaris* represented anti-microbial activity when tested against fifteen different strains of oral bacteria. An aqueous extract of dried plant material exhibits protective effects against oxidative stress induced by 2, 2′-azobis (2-amidinopropane) dihydrochloride in Sprague-Dawley male rats. Methanol extract of plant material exhibits an anti-carcinogenic property by suppressing the activation of NF-kappaB (protein complex which controls DNA transcription). Catechins extracted from *A. capillaris* possess a strong anti-oxidant potential [100]. GC-MS and TLC techniques on *A. capillaris* have identified four compounds namely 1-borneol, camphor, achillin and coumarin with potential anti318 carcinogenic property and five other compounds namely α-pinene, β-pinene, β- caryophyllene, capillin and piperitone which hold a strong anti-bacterial potential [101]. Another compound germacrene D isolated from the essential oil of *A. capillaris* possesses significant fumigant property (Zoubiri and Baaliouamer, 2014).

Artemisia dracunculus L. (Tarragon)

A. dracunculus is a perennial herb which has long been used in culinary preparations as well as in herbal medicines due to its various health benefits. In Iranian traditional medicines, this herb is famous for its anti-coagulant 325 and anti-hyperlipidimic property. In Arabic cultures, it is used to treat insomnia. In the folk remedies of Azerbaijan, tarragon is used as laxative, anti-epileptic, carminative, and anti-spasmodic agent. In Russia and central Asia, it has been used intensively for the treatment of allergic rashes, skin wounds, irritations and dermatitis. In the Northern districts of Jammu and Kashmir and Ladakh, the whole plant extract has also been used in the traditional medicines for the treatment of various fevers and as a vermifuge. The extract obtained from this plant has the potential to decrease the risk of coronary heart disorders in humans. Additionally, it has also been used as an anesthetic for aching teeth, sores and cuts. Two of its main constituents - estragole and methyleugenol are hyperglycemic activity when ethanol extract of the seeds was tested against the diabetic male Sprague-Dawley rats.

Artemisia japonica Thunb

This plant has been widely used in folk remedies for the treatment of eczema and fever. Tribal people use various parts such as leaves, stems and fruits of the plant because of their wound healing, digestive and depurative properties [102].

Artemisia indica H. Hara

This plant is a perennial herb of the Western Himalayas with local name "Titepati" and is used by the indigenous people to cure the ailments like dyspepsia, chronic fever and other hepatic ailments [103]. In Nepal, the plant juice is used for the treatment of dysentery, abdominal pain and diarrhea. The young leaves of *A. indica* are eaten after cooking with barley and they also provide color and flavour to rice. There are plenty of reports which ensure the food utility of *A. indica*. The tribal people living in Garo (Nokrek Biosphere Reserve of Meghalaya, India) eat the tender shoots as vegetable [104]. The people of Okinawa (isolated island of Japan) also use it as a food plant along with some other plants. Nepalese use the leaf-juice for the treatment of skin-ailments while the dried leaves and flowers are used as an insect repellent. Volatile oils such as β-thujone, herniarin, 1, 8-cineol, estragole, sabinyl acetate, cis chrysanthenyl acetate, davanone oil and terpineol possess anti-fungal property [8]. Chromatographic distillation of *A. judaica* L. led to the isolation of two new compounds - trans-ethyl cinnamate and piperitone.

Both of these compounds hold anti feedent and anti-oxidant properties [105]. An alcoholic extract of *A. asiatica* possesses two compounds, selin-11-en-ol and 1,8- cineole which harbour significant anti-bacterial and anti-fungal properties [70]. An elite compound 'artemisolide', extracted from *A. asiatica* acts as an inhibitor of nuclear factor (NF)-KB which suppresses the production of nitricoxide and prostaglandin in macrophages and thus exhibits essential anti-inflammatory property [106]. Another important compound 'eupatilin' extracted from various *Artemisia* species holds promising anti-cancer as well as anti-oxidant potential [107] β- myrcene, (Z)- β- ocimene, (+)-limonene and γ-terpinene obtained from essential oil of *A. scoparia* exhibit phytotoxic potential and have been used for sustainable weed management [10]. All these compounds have a promising potential to cure various ailments and thus, demand sincere attention and efforts of the scientists for further experimental trials to estimate their side-effects too.

Artemisia species conservation

As this genus is a reservoir of various bioactive compounds, it is being overexploited due to the increasing demands of pharmaceutical industries and other anthropogenic activities. Therefore, the germplasm of this genus is at risk of extinction and so serious measures should be taken for its conservation. Anthropogenic activities (land cultivation, heavy grazing and collection by people for 375 preparation of traditional medicines) will lead to the loss of biodiversity of this genus. Some early reports also show that conventional methods of propagation of *Artemisia* species are unsuccessful because of the small seed size which need symbiotic association with microflora for the germination. While micro-propagation is a praiseworthy technique for rapid-multiplication, production of disease-free, uniform and genetically stable progenies and for the production of plant secondary metabolites [53,21]. Seasonal variations, environmental pollution, fungal and bacterial infection alter the medicinal properties of *Artemisia*, while *in vitro*-culture maintains the medicinal properties. The gernplasm conservation of critically endangered species like *A. chamaemelifolia* and their sustainable propagation can be achieved through tissue culture techniques only. Several reports on *Artemisia* tissue culture are available (Table 4, included as Supplementary data). Among these, *A absinthium*, *A. vulgaris*, and *A. annua* took much attention of the scientists [108] examined the effect of different ratio and concentrations of growth regulators on micro-propagation of leaf, root and hypocotyl explants of *A. absinthium*. An experiment was conducted to validate the genetic stability of *in vitro* raised *A. absinthium* plants using SSAP (sequence-specific amplification polymorphism) and ISSR (inter-simple sequence repeats) molecular markers [109]. In another recent report, successful *in vitro* propagation of *A. absinthium* was performed using the nodal segments as explants [110]. Effects of various ratio and concentration of phytohormones was also tested for micro-propagation of *A. vulgaris* from shoot tips and it was observed that MS medium supplemented with BAP and KIN gave the best response. Successful *in vitro* plant regeneration was achieved using leaf [95] and encapsulated somatic embryos as explants [111]. Artemisinin, a potent anti-malarial compound (2014), successfully regenerated this important medicinal plant *in vitro* using axillary buds as explants. In another recent report, different concentrations of cytokinins and auxin are applied for successful callus formation from stem and leaf explants [6]. Many other species of this genus such as *A. herba-alba A.racunculus* [112] *A. chamaelifolia* [74] *A. nilagirica* [113] and *A. aucheri* [53] have been reported to regenerate under *in vitro* conditions at optimal concentrations of growth hormones. There is still a tremendous scope for a robust and reproducible protocol of *Artemisia* species micropropation and secondary metabolites production, without yield penalty.

Future Perspectives

In recent years, phytochemical investigation of herbal flora has received much attention of the scientists and pharmaceutical industries so as to know about novel herbal compounds which can be screened for their therapeutic potential to treat several health disorders without any side effects. This genus could be a promising source for the development of novel strategies to cure fatal maladies. Undoubtedly, *Artemisia* genus possesses a wide range of properties, as evidenced from almost all records of herbal medicine. Because of the dramatic growth in popularity, reliance and extensive demands of pharmaceutical industries. To sustain the production and availability of *Artemisia*, we must ensure its mass cultivation through conventional and micropropagation protocols. The artemisin content in *A. annua* is usually low, its bioavailablity is low, high relapse rates have been observed in patients using the infusion, and compatiability with other anti-malarial drugs for a combination therapy still requires optimization and clinical trials.The low content of artemisinin (only 425 synthesized in the glandular trichomes) in *A. annua* has made the drug relatively expensive. However, genetic manipulation of *A. annua* with the *AaMYB1* transcription factor has shown overexpression of artemisininbiosynthesis genes, its content and shall lower the production-cost in future. On the contrary, the active ingredients of the Artemesia species make it a habit-forming drug hence these herbs are not recommended to be taken for long period of time as it can cause nausea, insomnia, vomiting, and vertigo. *Artemisia vulgaris* (mug wort) contains an active compound thujone with medicinal properties but large doses of thujone are toxic and unsafe for human health. Besides this, the safety and toxicity of these compounds should not be neglected. Further consideration, standardization and clinical trials of pharmacological potential of genus *Artemisia* is essential for its recommendation as a medicine at safer level. The information summarized above will serve as a reference tool for the research groups working in the area of developing alternatives of synthetic drugs.

Conflict of Interest

The authors declare no conflicts of interest.

Author contributions

BK conducted the research and IS wrote the paper. PT, AK and TA prepared the tables and the chemical structures.

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