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Chemical composition, traditional uses and biological activities of artemisia species

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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, antinociceptive, 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 are assessed and compiled in this paper. The literature revealed that 1, 8-cineole, beta-pinene, thujone, artemisia ketone, camphor, caryophyllene, camphene and germacrene D are the major components in most of the essential oils of this plant species. Oils from different species of genus *Artemisia* exhibited strong antimicrobial activity against plant pathogens and insecticidal activity against insect pests. However, only few species have been explored for antioxidant activity.

Keywords: Anti-malarial, artemisia, herbal drugs, Mugwort, secondary metabolites, essential oil, chemical composition, antimicrobial, insecticidal, antioxidant

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 (Chan *et al*., 2010) [40]. 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 (Petrovska, 2012) [139]. Although several synthetic drugs are available to treat various diseases and disorders but, they are not free from side-effects (Rana *et al*., 2014) [145]. 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 (Cubukcu *et al*., 1990) [45]. 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 (Kennedy & Wightman., 2011) [79]. 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 (Obistiou *et al*., 2014).

Artemisia is a widespread genus which encompasses more than 400 species (~474) and is revered as 'Worm wood', 'Mug word', 'Sagebrush' or 'Tarragon' (Tajadod *et al*., 2012) [183]. 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 (Abad *et al*., 2012) [1]. Some species are cultivated as crops while others are used in preparation of tea, tonic, alcoholic beverages and medicines. 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, antibacterial (Altunkaya *et al*., 2014) [13]. Anti-fungal, anti-viral (Rajeshkumar & Hosagoudar., 2012) [142], anti-malarial (Mojarrab *et al*., 2016),antiinflammatory (Taherkhani., 2014) [182] anti-cancer (Shafi *et al*., 2012) [158], anti-tumor (Ashok *et al*., 2013) [17] antihelminthic, anti-diabetic(Joshi *et al*., 2016), anti-spasmodic, hepatoprotective (Hailu *et al*., 2013), anti-pyretic (Yildiz *et al*., 2011) [198] anti-parasitic (Bora & Sharma., 2011) [30] anti-oxidant (Godara *et al*., 2014) [59] antifertility, acaricidal (Saxena., 2015) [153], anti-rheumatic (Tigno *et al*., 2000) [189], anti-hypertensive (Sharopov *et al*., 2012) [161], trypanocidal, trichomonacidal (Bizhani., 2015), wormicidal, emmenagogue, diuretic, abortive (Kim *et al*., 2015) [81] anti-arthritis (Zamanai., 2015) [202], immunomodulatory, neuroprotective (Adams *et al*., 2012) [4], menopause, premenstrual syndrome, dysmenorrhea and attention deficit hyperactivity disorder (Jaleel *et al*., 2016) [70]. Antiulcerogenic (Shoaib *et al*., 2016) [166], analgesic (Saxena, 2015) [153], bile stimulant, antinociceptive, (Ramazani *et al*., 2010) [143], anti-plasmodial, anti-venom, anti-coccidal, anti-leishmanial (Jafroodi *et al*., 2015) [69] anti-hyperlipidemic (Khan., 2015), anti-epileptic and anti-convulsant (Sajid *et al*., 2016) [149], anti-cholesterolemic, cholagogue, diuretic, febrifuge and vasodilator (Nikhta *et al*., 2013) deobstruents (Alli & Abbasi., 2014) [10] disinfectant, choleretic, balsamic, depurative, digestive, emmenagogue, and anti-leukaemia and ant-sclerosis (Gohari *et al*., 2013) [60] vermifuges, febrifuge, anti-biotic, urine stimulant, anti-migraine, insecticidal (Barrero *et al*., 2013) [23] anti-feedant (Zadoks., 2013) [201] abortifacient (Gavanji *et al*., 2015) [58] anti-herpes virus (Mckenna & Hughe., 2014) [110] and antidote to insect poison (Brown., 2010) [36].

Artemisinin is the shining example of a phytochemical isolated from *A. annua*, and is widely used in the treatment of malaria. Artemisinin is a natural sesquiterpene lactone with an unusual 1,2,4-trioxane substructure. It is soluble in most aprotic solvents and is poorly soluble in water. It decomposes in protic solvents, probably by the opening of the lactone ring (Ryden & Kaiser., 2007). The artemisinin biosynthesis proceeds via the tertiary allylic hydroperoxide, which is derived from the oxidation of dihydroartemisinic acid (Brown., 2010) [36].

The aim of this study is to discover the chemical composition of essential oils, phytoconstituents identification, traditional uses and pharmacology of Artemisia species.

Methodology

Systematic literature searches was carried out and the available information on various researches on chemical composition and biological activities conducted on Artemisia species was collected via electronic search (using PubMed, ScienceDirect, Reserchgate, intechopen, BioMed Central, Evidence Based Complimentary and Alternative Medicine, Google Scholar, Web of science and Sci finder) and a library search for articles published in reviewed journals and also locally available books

The Genus Artemisia

Geographical Distribution

The Artemisia species are widely distributed in temperate regions of North America (Mexico, USA, Canada), Mediterranean region, Asia, Africa and Australia. Most species are reported from Asia, from china, from EX-USSR, from Japan, from Iran, from India and from Turkey.

Phytochemistry/Chemical composition of essential oils

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 (Martinez-Diaz *et al*., 2015) [109]. 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, e.g. Limonene (Tabanca *et al*., 2011) [181], is a monoterpene and has many medical and pharmaceutical applications (Singh *et al*., 1989) [168] like anti-carcinogenic actions, in liver tumour models (Mills *et al*., 1995) [116] and as topical medication for both dermal and sub-dermal injuries (Allardyce *et al*., 2003) [12]. Another monoterpene p-Cymene (Liu *et al*., 2016) [99] has shown significant anti-oxidant and anti-microbial activities (Chauhan *et al*., 1977) [41] 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 (Lee *et al*., 2002) [94]. 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 (Suresh *et al*., 2011) [179]. 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.

Plant essential oils are volatile in nature and consist of a complex mixture of monoterpenes and sesquiterpenes, which give strong odor to the essential oils. These essential oils are extracted from plants by various methods such as steam or hydro-distillation methods and are frequently being used in the natural product laboratory (Pandey *et al*., 2014) [135]. Essential oils are composed of more than 60 different components in different concentrations; among them few have higher amounts of composition. From time to time, the chemical composition of essential oils of the genus *Artemisia* has been studied by researchers from the different regions of the world. The essential oil composition of genus *Artemisia* investigated during 2012–2017 as reported 1, 8-Cineole, beta-pinene, thujone, artemisia ketone, camphor, caryophyllene, camphene and germacrene D were the major components reported in the essential oils of *Artemisia* species. This also shows that the composition of essential oil of the same species varied in different investigations depending upon a change of geographical origin. Variation in the volatile components of these plants may occur during plant ontogeny or growth at different altitudes. However, few chemical constituents were restricted to limited species. For instance, methyl chavicol was only reported in higher amounts in *A. dracunculus*, piperitone in *A. judaica*, capillene in *A. stricta* and chamazulene in *A. arborescens* L, artedouglasia oxide in *A. stelleriana*. Most of the investigations into the chemical composition of essential oils were from Iran, followed by India and China.

Pharmacology

Antimicrobial activity of Artemisia species

Since past decades, a lot of studies have been performed to reveal the anticancer, antiinflammatory and antimicrobial properties of different constituents of plants (Jebril 2008) [71]. The exploration of novel antimicrobial compounds with high effectiveness for deadly diseases is today's continuous and dire need (Rojas *et al*., 2003) [147]. Researchers are trying to develop effective drugs against microbial diseases by dragging their attention towards traditional medicine (Benkeblia., 2004) [25]. There are a lot of scientific revelations on the antimicrobial activity of plants (Cowan, 1999) [43] and numerous antimicrobial components have been identified from plant origin which are aromatic or might be some saturated carbon-based compounds. These aromatic compounds are attained by means of ethanolic or methanolic extraction (Nostro *et al*., 2000) [131]. Saponins and sterols are important compounds which can be extracted easily when methanol and ethanol are used as extracting solvents (Hui *et al*., 2007) [65]. Other compounds like polyphenols, alkaloids and terpenoids (Taylor *et al*., 1996) [186] can also be extracted using methanol and ethanol as extracting solvent. On the other hand, dichloromethane is also used for terpenoids extraction (Cowan., 1999) [43]. Fore mostly, the crude alcohol extraction method is employed in initial plant screening for antimicrobial activities and secondly, several other organic extraction methods are implemented. Numerous investigations validate the methanolic and ethanolic extracts of Artemisia species as better antimicrobial candidates (Shoko *et al*., 1999) [167]. In a study antimicrobial efficacy of methanolic extracts of upper section of Artemisia diffusa, Artemisia oliveriana, Artemisia scoparia and Artemisia turanica against S. aureus, B. subtilis, E. coli, C. albicans and P. aeruginosa has been documented. Important compounds like flavones could be obtained from Artemisia giraldii that have extraordinary antibiotic action contrary to several microorganisms including P. aeruginosa, S. aureus, S. lutea, E. coli, Proteus sp, T. viride and A. flavus (Zheng *et al*., 1996) [206]. Essential oils of *Artemisia aucheri* contain compounds such as decane, p-cymene borneol, 1,8-cineole, linalool, lavandulol, triene, bornyl acetate, p-mentha-8-ol, chrysanthenyl acetate and caryophyllene oxide. These all essential compounds are recovered from the upper portions of *Artemisia aucheri* and the oils from seeds of this plant have better antimicrobial activity against E.Coli, S. aureus and Listeria monocytogenes (Ashgari *et al*., 2012). Similarly, in the essential oil of Artemisia spicigera compounds like, camphor-a-theojone, Btheojone, 1,8-cineole and p-cymene are active against various types of bacteria, i.e., Bacillus cereus, Serratia marcescens, E. Coli, Enterobacter aerogenes, Citrobacter amalanoficus, Bacillus megaterium, St. saprophyticus and Bacillus megatarium. Oils obtained from the aerial portion of *Artemisia incana* L. also contain a lot of compounds where camphor and borneol are abundant, showing inhibitory efficacy against twentysix bacteria, fifteen fungi and three yeast species (Cetin *et al*., 2009) [39] Oils from Artemisia feddei also contain important compounds, which are highly active against obligate anaerobic bacteria. Artemisia chamaemelifolia, Artemisia turcomanica and Artemisia sipicigera also possess antibacterial activity. Invitro assessment of essential oil of *Artemisia aucheri* Boiss for antimicrobial effect authenticates better results against B. cereus, P. vulgaris, P. aeruginosa, S. cereviciae, C. utilis, P. digitatum and A. niger.

Against certain type of microorganisms, the methanolic extracts of *Artemisia campestris* L. are considered to be vigorous. This might be due to the presence of bioactive metabolites of countless chemical types, like phenolic compounds. Shoko *et al*. confirmed that phenolic compounds are very dynamic substances against microorganisms particularly bacteria. These compounds are quite active in contradiction of few Gram-positive species while the same extracts are weak against some Gram-negative species. Artemisia campestris is not merely an antimicrobial plant but also contains effective phenolic antioxidants. The antimicrobial compounds modes of action in bacteria comprises membrane damage, membrane potential, changes in pH inside the cell, and the synthesis of ATP (Lambert *et al*., 2009) [93]. Another study revealed the effective anti-viral properties of Artemisia Parviflora. The antibacterial effect of crucial oil and crude extracts of Artemisia herba-alba Asoo.

against Listeria monocytogenes have properties, that can hinder the progression of psychrophils resistant organisms. One more study showed that the aqueous and solvent extracts of Artemisia indica were highly active against Gram-positive organism where S. aureus, was maximally inhibited (Sukanya *et al*., 2009) [178]. These inhibitions might be due to the presence of essential compounds like phenols, steroids, triterpenoids, valavinoids, carotenoids, tetratriterpenoids azadirachtin and ketones (Kraus., 1995) [89]. Even though, extracts of few Artemisia species like Artemisia aspera and Artemisia parviflora, were not effective or having negligible inhibition on human and phytopathogenic bacteria (Sukanya *et al*., 2009) [178]. Ethanolic extracts of other species of genus Artemisia like Artemisia abrotanum and Artemisia pallens are active against Pseudomonas cepacia and Bacillus stearothermophilus. These plants extracts not only possess antibacterial activity but also have maximum antifungal activity against Trichosporon beigelii and Saccharomyces cerevisiae. This suggests that the ethanolic extracts of these two novel plants have both antibacterial and antifungal potential. Artemisia nilagirica is another important plant containing numerous compounds including saponins, tannins, steroids, flavonoids, terpenoids, proteins and essential oil with better antibacterial action (Zeng *et al*., 2015) [203]. Studies of Erel *et al*. substantiated that the methanolic extracts and essential oils of Artemisia santonicum and Artemisia scoparia holds fine antimicrobial activity where Staphylococcus aureus was the supreme sensitive bacteria to oils. Also these two plants are active against Candida albicans respectively. Some bacterial species, *viz*., Salmonella enteritidis, Escherichia coli O157, Salmonella typhi, Listeria monocytogenes and Yersinia enterocolitica were tested against the essential oil and compounds of Artemisia annua showing their high sensitivity (Donato *et al*., 2015) [51]. In another study, Javid *et al*. showed the chloroform, butanol and ethyl acetate extracts of Artemisia indica with better inhibitory activities towards Salmonella typhi. On the other hand, chloroform and n-Hexane extracts of this plant fully hinder the progression of fungal species like Aspergillus flavus and Fusariun solani. Another study indicated that the methanolic extracts of Artemisia ludoviciana are more active against Vibrio cholera because these extracts encompasses compounds which are able to disturb the cell membranes of Vibrio cholerae cells with pH reduction, cell membrane hyperpolarization, and cellular ATP reduction. Besides the antibacterial and antifungal activities, compounds from the extracts of Artemisia annua have antialgal activity against Microcystis aeruginosa. This might be due to the presence of artemisinin which escalates the level of reactive oxygen species (ROS) in algae cells.

Anticancerous Activity of Artemisia species

Medicinal plants possess a lot of natural products with better properties for cancer treatment (Shinwari., 2010) [165]. Plants have numerous essential products like lignin and flavonoids of polyphenols. These products are evaluated *in vitro* and *in vivo* to find potential biological activities like antitumor activity (Koyama *et al*., 2006) [88]. Beforehand, a lot of studies have Pharmacological Promises of Genus Artemisia 275 been conducted to unfold the *in vitro* cytotoxic action of various plant extracts for their anticancer action on different types of human cancer cell lines (Shamim *et al*., 2009) [159]. Like previously reported in other plants, several studies confirmed Artemisia species as better cytotoxic and anti-cancerous candidates (Najaran *et al*., 2013) [124]. The poisonousness of Artemisia species on cancer cells has also shown *in vitro* (Willoughby *et al*., 2009) [196] and *in vivo* (Lai & Singh., 2006) [92] respectively. These activities might be due to the presence of one or more essential compounds present in the plant. Among those compounds, Artemisinin, is very active ingredient of many Artemisia species mainly Artemisia annua, having better cellular toxicity against human lymphoid leukaemia cells (Singh & Lai., 2007) [171]. Also the artemisinin and its allied compounds have the capacity to thwart cellular growth of human colorectal and breast cancer (Efferth *et al*., 2001) [52]. Other compounds like terpenoids, cesquiterpen lactones and flavonoids are correspondingly important antitumor constituents acquired from Artemisia species (Wang *et al*., 2001) [194]. Another offshoot of artemisinin, called Artesunate, possess both *in vitro* and *in vivo* anticancer properties (Li *et al*., 2008). A lot of beneficial compounds have also been well-known in Artemisia absinthium and Artemisia vulgaris, which have low molecular weight. These compounds are flavonoids, sesquiterpene, lactones, lignans and monoterpenes (Aberham *et al*., 2010) [3]. These are considered to be the main vigorous anticancerous compounds of these plants (Khan & Gilani., 2009) [80]. Another study corroborate the infusions from aerial parts of Artemisia vulgaris and Artemisia absinthium contain polysaccharides which are used in traditional plant made medicine. Studies showed that the crucial consequence of the vigorous constituents of Artemisia species is apoptosis; it is a programed cell death which is initiated via the cell cycle arrest. Instigation of caspases, mitochondrial membrane depolarization potential or the down governing expression of Bcl-2 gene might also induce apoptosis of cells (Sarath *et al*., 2007) [151]. Kim *et al*. validates the utilization of Artemisia fukudo as a defensive measure against cancer. The most active compound artemisinin induces apoptosis and it does not induce necrosis against human lymphoid leukaemia (Molt-4) cells. Hitosugi *et al*. reported, in the myelogenous leukaemia cell line of human (HL60), Artemisia capillaries smoke and aqueous extracts are responsible for cellular decease, but these extracts are not effective in breast cancer (MCF-7) and other sort of tumour cells. On the other hand, macro molecular constituents of Artemisia capillaris are liable to encourage apoptosis in hepatoma cell lines in human. The water soluble extracts of Artemisia argyi are not very much active against human tumour cell lines and also in breast cancer cell lines, but profoundly active in murine tumour cells. In a study, the induction of apoptosis caused by the smoke and water extracts of Artemisia princeps in human breast cancer MCF-7 cells diminishes cells through the mitochondrial alleyway that seems to be a milestone for breast cancer treatment (Sarath *et al*., 2007) [151]. Artemisia argyi and Artemisia Asiatic also contain essential compound called flavones, which have the potency to impede certain types of cancer by promoting apoptosis including human lung cancer, prostate cancer, myeloid leukaemia, gastric cancer and melanoma (Kim *et al*., 2005) [82]. Nevertheless, other researchers found flavones to be unproductive in contradiction of human breast cancer cells (Adams *et al*., 2006) [5]. Similarly, n-hexane extracts of Artemisia turanica Krash. possess better cytotoxic, antiproliferative and anticancer effects against two leukemic cancer cell lines predominantly HL-60 and K562 (Najaran *et al*., 2013) [124]. In another study dichloromethane, methanol, ethyl acetate, and nhexane extracts from upper parts of different Artemisia species (Artemisia ciniformis, Artemisia diffusa Karasch, and Artemisia vulgaris) have potent antiproliferative properties

which could be a promising chemotherapeutic agent in cancer treatment. Studies confirmed that the ethanolic extracts of Artemisia montana and Artemisia absinthium are rich in essential compounds like, flavonoids and phenolic acids. These compounds have better antioxidant activity and also have cytoprotective influence towards oxidative damage in fibroblast 276 Adil Hussain *et al* like cells. This validates Artemisia montana and Artemisia absinthium both as better nominees for the treatment of skin disorders. Extracts of Artemisia scoparia in human muscle cancer cells have devastating effect against 88-93% cancer cells that endorse anticancer activity of this plant extract. Moreover, the apex parts of two novel species of Artemisia i.e., Artemisia vulgaris and Artemisia absinthium have anthelmintic, antipyretic, cytostatic, stomachic, antibacterial, and antitumor actions (Lorenzi & Matos., 2008) [106] while the *In vitro* assessment of methanol extracts of other species like Artemisia Japonica, Artemisia stolonifera, Artemisia montana, Artemisia selengensis, Artemisia capillaris, Artemisia sylvatica, Artemisia scoparia and Artemisia keiskeana possess better antiinflammatory, anticancer, and antiobesity activity. Studies of Emami *et al*. corroborated Artemisia sieberi, Artemisia kulbadica, Artemisia santolina, Artemisia turanica, and Artemisia diffusa with cytotoxic activity in contradiction of human Caucasian hepatocyte and larynx carcinoma (HepG-2 and Hep-2) cell lines.

Antihelminthic activity of Artemisia species

Helminthic problems are exceedingly widespread, predominantly in the3rd world countries (Dhar., 1982) [87] and documented as the cause of much chronic ailments. Numerous studies have found Artemisia species with potent anthelmintic activity (Cala *et al*., 2014) [38]. Artemisia cina is one of the best candidates with anthelmintic activity which contains santonin, a sesquiterpenic lactone that might be the reason of this activity (Akhtar *et al*., 1982) [7]. Other species like Artemisia santonica L, Artemisia maritima, Artemisia herba-alba, Artemisia absinthium, Artemisia vulgaris, Artemisia afra and Artemisia ludoviciana are also most prominent species with the same activity (Proksch., 2002) [140]. In one study, Extracts from Artemisia vestita and Artemisia maritima are found active against Haemonchus contortus in infected sheep's and indicated significant activity against larvae and adult worms (Irum *et al*., 2015) [68]. Moreover, in ruminants, the water, aqueous, sodium bicarbonate, dichloromethane, and ethanol extracts obtained from leaves of Artemisia annua have better anthelmintic action (Cala *et al*., 2014) [38]. Perennial plant Artemisia indicia also possess this activity. In a study chloroform, methanol and aqueous extracts of this plant confirmed anthelminthic property against adult earthworm Pheretima posthuma. Artemisia absinthium extracts are also a promising way to treat GI nematodes of sheep (Tariq *et al*., 2009) [185]. An important member of Artemisia is Artemisia herba alba, that can be employed for controlling heterakid infection because it induces anthelminthic consequence by dropping worm burden and egg shedding in the diseased birds (Seddiek *et al*., 2011) [155, 156] and also the methanolic extracts from leaves of Artemisia herba-alba possess nematicidal activity. The anthelmintic effects on Haemonchus contortus from methanol and crude aqueous and of Artemisia brevifolia have been proved and it is confirmed that the whole plant holds strong anthelmintic activity against nematodes (Iqbal *et al*., 2004) [66]. On the other hand, the essential oil of Artemisia pallens have tendency of strong anthelmintic action against Taenia solium, Pheritima posthuma and Ascaris lumbricoides. Chloroform extracts of stem and root of Artrmisia siversiana, also hold potency to eradicate H. nana from infected mice. The anthelmintic activity of extracts from Artemisia parvflora and Artemisia sieversiana was evaluated *in vitro* and *in vivo* on Haemonchus contortus, which is a parasitic nematode of small ruminants. Methanolic extract of these plants tested against three different developmental stages using different assays were found to be better anthelmintic candidates (Irum *et al*., 2017) [67]. An *in vitro* study was conducted to find an alternative to anthelmintic praziquantel by checking the activity of the crude aqueous extract of Artemisia absinthium against H. nana. The extract from Artemisia absinthium was found to increase ultrastructural alterations, worm paralysis and ultimately death in a dose-dependent manner. Also a significant decrease in the EPG and worm burden has been noticed in mice treated with A. Pharmacological Promises of Genus Artemisia 277 absinthium (Beshay., 2017) [26]. Such studies clearly indicate Artemisia species with their ability to control helminthic disease to a broad spectrum.

Insecticidal Activity of Artemisia species

Research has been conducted to see the effect of *Artemisia* oils against insect pests of agricultural crops, especially pests of stored products, in order to search out their efficacy as a repellent, insecticidal agent or antifeedant. From several national and international research institutions, investigators evaluated the essential oils from different species of genus *Artemisia* against storage and field insect pests. *A. arborescens* essential oil exhibited insecticidal effects against stored grain pest *Rhyzopertha dominica* at the dose of 50 µL in Petri dish (Bouzenna & Krichen., 2013) [35]. A 37 µL/L and 24 h of exposure time of *A. sieberi* oil was sufficient to cause 100% mortality of *Callosobruchus maculatus*, Sitophilus oryzae and *Tribolium castaneum.* LC_{50} (lethal concentration) values estimated for oil were 1.45 µL/L against *C. maculatus*, 3.86 µL/L against *S. oryzae* and 16.76 µL/L against *T. castaneum* (Neghaban *et al*., 2007). In a filter-paper arena test, *A. vulgaris* oil had a very strong repellent activity against *T. castaneum* adults at a 0.6 µL/mL (*v*/*v*). In fumigation tests, 8.0 µL/mL dose of *A. vulgaris* oil exhibited 100% mortality of *T. castaneum* adults; mortality of larvae achieved was only 53%. A 20 µL/L air and a 96h exposure of the oil showed 100% ovicidal activity; however, at a higher dose (60 µL/L) of this oil no larvae, pupae and adults were observed (Wang *et al*., 2006) [193]. In fumigant toxicity test, 11.2 and 15.0 mg/L air LC_{50} values were reported against *Sitophilus zeamais* adults, while in a contact toxicity test LD_{50} (lethal dose) were 55.2 and 112.7 mg/adult for *A. lavandulaefolia* and *A. sieversiana* oils, respectively (Liu *et al*., 2010) [42]. In another study (Liu *et al*., 2010) [42], they found LC_{50} 5.31 and 7.35 mg/L, respectively for *A. capillaris* and *A. mongolica* essential oils against *S. zeamais* adults in fumigant bioassay, while in contact bioassay LD_{50} values were 105.95 and 87.92 µg/adult, respectively. Again, *A. scoparia* essential oil achieved 100% mortality of *C. maculatus* at 37 µL/L air (24 h) in fumigant bioassay with LC_{50} for the oil was 1.46 µL/L against *C. maculatus* and 2.05 µL/L air against *S. oryzae* and *T. castaneum* (Negahban *et al*., 2006) [128]. Similarly, 80–90% mortality of granary weevil, *S. granarius* (L.) was reported due to *A. absinthium*, *A. santonicum* and *A. spicigera* oils at a dose of 9 µL/L air after 48 h of exposure (Kordali *et al*., 2006) [83]. Against *S. oryzae*, *A. princeps* oil when mixed with *Cinnamomum camphora*, it showed strong repellent effect in 1:1 ratio and 1000 µg/mL of dose exhibited

insecticidal action (Liu *et al*., 2006) [99]. LC_{50} value for *A. vestita* oil against *S. zeamais* in fumigant bioassay was 13.42 mg/L air, while LD_{50} reported was 50.62 mg/adult in contact bioassay (Chu *et al*., 2010) [101, 102, 103]. Later on, using same insect, they determined 6.29 and 17.01 mg/L air LC_{50} of *A. giraldii* and *A. subdigitata* oils in fumigant test and that of corresponding LD_{50} 40.51 and 76.34 µg/adult, in a contact test. EC_{50} for *A. annua* oil was estimated to be 2.6 and 4.1 µL/mL against *C. maculatus* and *T. castaneum*, respectively (Tripathi *et al*., 2000) [190], and LD_{50} value of *A. rupestris* oil was 414.48 µg/cm^2 against *Liposcelis bostrychophila* and *L. bostrychophila* and 6.67 mg/L air LC_{50} against *L. bostrychophila* (Liu *et al*., 2013) [100]. This oil has also been proved as an effective insecticide against larval, pupal and adult stages of *Helicoverpa armigera* (Anshul *et al*., 2014) [9]. *Plodia interpuntella*, a polyphagous insect pest of different stored products worldwide, is found to be controlled by *A. khorassanica* essential oil (LC_{50}: 9.6 µL/L air) with lethal time reported at 2.07 h (Borzoui *et al*., 2016) [33]. Sharifian *et al*. found that *C. maculatus* was more susceptible (LC_{50} 52.47 µL/L air) and *T. castaneum* was more tolerant (LC_{50} 279.86 µL/L air) towards *A. vulgaris* essential oil after 24 h of exposure. Respective LD_{50} and LC_{50} values of *A. argyi* essential oil determined by Zhang *et al*. were 6.42 µg/adult and 8.04 mg/L air against *Lasioderma serricorne* adults. Their other report on *A. stolonifera* oil (Zhang *et al*., 2015) [199] showed LD_{50} 8.60 µg/adult against *T. castaneum* and 12.68 µg/adult against *L. serricorne*. The oil showed 1.86 mg/L air LC_{50} value in fumigant test against *T. castaneum*. Liu *et al*. reported that *A. frigida* essential oil exhibited 17.97 µg/adult and 254.38 µg/cm^2 LD_{50} in contact toxicity test and 69.46 and 1.25 mg/L air LC_{50} in fumigant test against adults of *S. zeamais* and *L. bostrychophila*, respectively. In contact toxicity, the corresponding LD_{50} values of *A. absinthium* and *A. herba-alba* oils against *T. castaneum*, red flour beetle reported were 0.209 and 7.432 µL/L air. In their further study with *Oryzaephilus surinamensis* LC_{50} and LD_{50} values of *A. herba-alba* and *A. absinthium* reported in fumigant and contact toxicity bioassay were 30.22 and 0.209 µL/L, respectively (Bachrouch *et al*., 2015) [19]. Recently, Liang *et al*. reported insecticidal activity of *A. anethoides* oil by contact and fumigant tests against *T. castaneum* (LD_{50} 28.80 µg/adult and LC_{50} 13.05 mg/L air, resp.) and *L. serricorne* (LD_{50} 24.03 µg/adult and LC_{50} 8.04 mg/L air, resp.) adults.

Researchers also tested chemical constituents extracted from different species of *Artemisia* in order to make the botanical insecticides with a single and effective constituent. *Trans*-ethyl cinnamate (LD_{50} 0.37 µg/larva) isolated from *A. judaica* oil was more potent than piperitone (LD_{50} 0.68 µg/larva) against *Spodoptera littoralis* and also both these compounds caused complete inhibition of feeding activity at 1000 µg/mL (Abdelgaleil *et al*., 2008) [2]. 1,8-cineole and terpinen-4-ol (extracted from *A. absinthium*, *A. santonicum* and *A. spicigera* oils) were more effective against *S. granaries* with 100% mortality at 0.5, 0.75 and 1.0 µL/L air doses after 12 h of exposure (Kordali *et al*., 2007). Similarly, among chemical constituents of *A. mongolica* essential oil, 4-terpineol exhibited strongest contact toxicity (LD_{50} 8.62 µg/adult) against *L. serricorne* adults and camphor and alpha-terpineol in fumigant toxicity (LC_{50} 2.91 and 3.27 mg/L air, resp.) (You *et al*., 2015). α-Terpinyl acetate (LD_{50} 92.59 µg/cm^2) of *A. rupestris* oil showed more contact toxicity than α-terpineol (140.30 µg/cm^2), 4-terpineol (211.35 µg/cm^2), and linalool (393.16 µg/cm^2) against book lice *L. bostrychophila* infesting stored cereals (Liu *et al*., 2013) [100]. Some chemical constituents of *A. argyi* oil such as camphor (11.30 µg/adult), eucalyptol (15.58 µg/adult), β-caryophyllene (35.52 µg/adult) and β-pinene (65.55 µg/adult) exhibited more toxicity against *L. serricorne* adults having lower LD_{50} values than that of α-terpinyl acetate, 4-terpineol, and linalool isolated from *A. rupestris* oil. In their fumigant toxicity test eucalyptol (LC_{50} 5.18 mg/L air) and camphor (LC_{50} 2.91 mg/L air) had more toxicity than β-pinene (LC_{50} 29.03 mg/L air). Essential oil of *A. ordosica* possessed less toxicity (LC_{50} 18.65 mg/L air) against *T. castaneum* adults than its chemical constituents capillene, capillin, capillinol, *cis*-dehydromatricaria ester (LC_{50} 4.06 to 6.16 mg/L air) tested individually, however, among the essential oil and compounds tested, capillin showed strong repellency (100%) at 62.91, 12.58 and 2.52 µL/cm^2 after 2 h of exposure (Zhang *et al*., 2017). This revealed that the toxic properties of the oil could be attributed to the synergistic effects of its diverse major and minor components. All these results evidence that essential oils from these species of *Artemisia* oils and their constituents can be used in the formulation of botanical insecticides against the said insects for the long-term preservation of food commodities infested by these insects. The mechanism behind the insect mortality in the contact toxicity test is that the volatiles penetrate in the insect body via the respiratory system and result in abnormal breathing, which leads to asphyxiation and finally the death of insects. During fumigant application, main target sites of essential oils and their constituents in insects is the octopaminergic system. When insects are exposed to the essential oils, a breakdown of the nervous system of insects occurs (Kostyukovsky *et al*., 2007) [86] which lead to the blockage of the nerve impulse, later paralysis and then death of the insects occurs.

Antioxidant Activity of Artemisia species

Essential oils and chemical constituents of several *Artemisia* species have been investigated in the laboratory to protect against oxidative damage by inhibiting or quenching free radicals and reactive oxygen species. They have been proved as alternative antioxidants of synthetics. The antioxidant properties of the oils were assessed by several methods such as β-carotene bleaching (BCB) test, the 2,20-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging method, thiobarbituric acid reactive species (TBARS), Trolox equivalent antioxidant capacity assay (TEAC I-III assay), Total radical-trapping antioxidant parameter assay (TRAP assay), N,N-dimethyl-p-phenylendiamine assay (DMPD assay), 2,2′-Azinobis 3-Ethyl-benzothiazoline-6-Sulphonate (ABTS), 2,2-diphenyl-l-picrylhydrazyl assay (DPPH assay), Photochemiluminescence assay (PCL assay) and Ferric reducing ability of plasma assay (FRAP assay) (Singh *et al*., 2015). We assessed the antioxidant activity of *A. nilagirica* essential oil in our laboratory and found that the oil significantly inhibited radical cation formation, with 15.729 µL IC_{50} (Inhibitory concentration) and 13.539 µL IC_{50} preventing the bleaching of β-carotene. While this oil exhibited higher antioxidant activity in the experiment of Sandip *et al*. in the DPPH (IC_{50} 6.72 µg/mL) test, they reported the *A. chamaemelifolia* essential oil as weak antioxidant. Oil of *A. scoparia* induced secondary metabolites production in root cells *viz*., scavenging enzymes—superoxide dismutase, catalase, ascorbate and guaiacol peroxide and was phytotoxic to root growth causing its inhibition (Kaur *et al*., 2012) [77]. The *A. annua* essential oil (IC_{50} 27.07 mg/mL) was able to reduce the stable violet DPPH radical to the yellow DPPH-H, reaching 50% of

reduction. However, IC_{50} reported in ABTS method was 5.97 mg/mL lower than that of DPPH method. This oil was also 50% able to reduce the ferric ions to ferrous ions (Fe^{2+}) at 127.17 mg/mL. This oil showed 18% antioxidant activity of the reference compound (tocopherol) (Juteau *et al*., 2002) [75]. Phenolic compounds present in the *A. campestris* essential oil contributed its major antioxidant activity, where 47.66 µg/mL EC_{50} was reported in radical scavenging activity, 5.36 µg/mL in FRAP, 0.175 µg/mL in superoxide scavenging activity and 0.034 µg/mL in OH scavenging activity (Saoudi *et al*., 2017) [150]. Thus, this oil can be used as an antioxidant in the pharmaceutical industry.

The pronounced antioxidant activity may be due to the phenolic constituents. *A. campestris* oil showed maximal DPPH activity at dose of 2 mg/mL (Dib *et al*., 2017) [50], however, *A. herba-alba* oil showed strong DPPH activity (IC_{50} 6 µg/mL) than ABTS assay (IC_{50} 40 µg/mL). In another study, IC_{50} values of *A. turanica* oil reported were 7.00 mg/mL, 9.69 µg and 14.63 µg, in DPPH, nitric oxide and superoxide anion radicals, respectively. The oil showed ferrous-ion chelating activity at 16.97 µg of IC_{50}. Ali *et al*. reported that 0.005 mg/mL of ethyl acetate fraction of *A. macrocephala* oil showed 121.5% radicle scavenging activity. However, essential oil of *A. deserti* exhibited more antioxidant activity by DPPH free radical scavenging method (57.2%) than that of β-carotene bleaching test (50%). In the β-carotene method, *A. dracunculus* oil also showed 50% scavenging activity. On the contrary, essential oils from *A. absinthium*, *A. biennis*, *A. cana*, *A. dracunculus*, *A. frigida*, *A. longifolia* and *A. ludoviciana* from Western Canada showed poor antioxidant activity in both the β-carotene/linoleate model and DPPH radical scavenging tests (Lopez-Lutz *et al*., 2008). In addition, the antioxidant and DPPH radical scavenging activities of camphor and 1, 8-cineole isolated from *Artemisia* species were determined *in vitro* (Kordali *et al*., 2005) [84, 85]. Singh *et al*. reported more IC_{50} (146.3 µg/mL) of *A. scoparia* than that of the antioxidant BHT (140.9 µg/mL) in DPPH bioassay. The residue essential oil also scavenged OH with an IC_{50} of 145.2 µg/mL in the Fenton reaction using a deoxyribose assay. However, unlike scavenging of OH, residue essential oil exhibited a decreased scavenging activity towards H_2O_2 (IC_{50} 270.1 µg/mL). They also reported that OH scavenging activities of citronellal and citronellol (25–200 µg/mL) were 8–34 and 11–55%, respectively. For the *A. afra* oil, 50% DPPH radicle scavenging inhibition was reported at 1.1 µL/mL, while it increased for *A. abyssinica* (28.9 µL/mL) oil. In lipid peroxidation bioassay only 0.09 µL/mL of oil is required for 50% inhibition (Burits *et al*., 2001) [37]. From Tunisia, Riahi *et al*. reported the variable IC_{50} values (28.2 and 46.5 g/mL of leaf and flower oils, resp.) in *A. absinthium* oil. Additionally, essential oils from leaves (595.26 mol Fe^{2+}/L) and flowers (286.42 mol Fe^{2+}/L) also exhibited significant ferric-reducing antioxidant activity. From Serbia, *A. annua* oil showed 50% scavenging of radicle cations at 2.90 µg/mL in DPPH bioassay, and 50% antioxidant activity at 0.640 µg/mL in ABTS assay. However, oil did not show superoxide-scavenging activity. IC_{50} values for the chemical constituents in DPPH and ABTS methods reported were 4.00 and 1.79 µg/mL for Artemisia ketone, 87.0 and 30.1 µg/mL for α-pinene, 47.9 and 6.46 µg/mL for 1,8-Cineole, and 34.4 and 23.6 µg/mL for camphor, respectively. Mohammadi *et al*. showed that *A. absinthium* essential oils extracted before flowering stage exhibited strong DPPH activity (EC_{50} 3.307 mg/mL) than that of the oils extracted at flowering (EC_{50} 4.11 mg/mL), and after flowering stage (EC_{50} 4.26 mg/mL). This may be due to presence of effective compounds such as sabinene, beta-pinene, alpha-phellandrene, p-cymene, and chamazulene which were more (58.36%) before flowering stage than that of at flowering (48.98%) and after flowering (53.99%). This may be also due to synergistic effect of the compounds (Rafiq *et al*., 2016) [141].

Traditional uses and biological activities of individual Artemisia Species

Artemisia genus harbours important medicinal plant species which have been used since ancient times for pharmacological and certain culinary purpose. Therefore, several biopharmaceutical products containing Artemisia extracts are available nowadays in the market to treat specific ailments.

***Artemisia abrotanum* L. (southernwood)**

Formulations obtained from this species act as an astringent, stimulant, spasmolytic, anti-septic, and febrifuge (Abad *et al*., 2012) [1]. The ethanolic extracts of powdered aerial parts has shown anti-fungal and antibacterial activities against various fungal and bacterial strains. The active compounds like cineole, borneol, p-cymene etc. derived from this species also exhibit insect-repellent activity against Aedes aegypti. 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' 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 (Mighri *et al*., 2010) [113]. Aqueous extracts obtained from aerial parts of the plant possess anti-oxidant and anti-microbial properties. Herbal tea prepared from this species exhibits antibacterial, analgesic and anti-spasmodic properties. This plant is also utilized as a fodder plant for the livestock in plateau regions of Algeria 197 (Bora & Sharma., 2010) [31].

***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 (Joshi., 2013). 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. 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. Essential oils obtained from aerial parts of the plant exhibited anti-microbial potential when tested with Saccharomyces cerevisiae and Candida albicans (Seddiek *et al*., 2011) [155, 156]. The methanol extracts of the powdered plant material showed considerable antioxidant activity. 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 (Hristova *et al*., 2013) [64]. Several other biological activities such as anti-parasitic. Anti-microbial, anti-oxidant and hepatoprotective (Mouffid & Eddouks., 2012) [121] 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 (Bhat., 2014) [28]. β-myrcene from A. absinthium and camphor from A. austriaca have shown notable anti-microbial activity.

***Artemisia afra* Jacq ex Wild**

A. afra Jacq ex Wild is one of the oldest medicinally important plant of Southern Africa. This plant has long been used to cure several diseases such as cold, dyspepsia, headaches, coughs, malaria, diabetes and disorders of kidney and bladder (Patil *et al*., 2011) [138] Nowerdays, it is used to cure various ailments including cough, colds, diabetes, heartburn (Kriel., 2010) [90] bronchial and stomach related disorders. The aqueous leaf-extracts holds anti-microbial potential against several bacterial strains (Muleya *et al*., 2014) [123].

***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 (Abad *et al*., 2012) [1]. 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 (Daugoska., 2015). 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 (Tian *et al*., 2016) [188]. 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 (Liu *et al*., 2016). 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 antileishmaniasis activity (Ortiz & Wei., 2012) [134]. 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 (Efferth., 2017) [53]. 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. 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) [62]. 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 (Graham *et al*., 2010) [62]. 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. 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 (Aderibigbe, 2017) [6].

***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. It has also been used as an anti-inflammatory agent in traditional medicines. Several other biological activities such as phyto-toxicity (Araniti *et al*., 2013) [15]. Anti-bacterial and anti-viral properties (Erel *et al*., 2012) [55] 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 (Millitello *et al*., 2011). The plant essential oils also possess antiviral activity against Herpes simplex virus.

***Artemisia vulgaris* Linn. (mugwort)**

It is an important aromatic medicinal species with pungent smell and sharp taste (Borzabad *et al*., 2010) [32]. 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. 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, cyto-toxic (Erel *et al*., 2011) [56] anti-malarial (Aslam & Chaudary., 2006) and anti296 hyperlipidemic activity.

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. 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 (Tajehmiri *et al*., 2014) [184]. 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 (Liu *et al*., 2010) [100-103]. 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 (Akhtar *et al*., 2015) [8]. 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 (Yang *et al*., 2015) [197]. Another compound germacrene D isolated from the essential oil of A. capillaris possesses significant fumigant property.

***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 (Paramakrishnan *et al*., 2012) [136].

***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 (Rashid *et al*., 2013) [146]. 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 (Singh *et al*., 2012). 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. 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 (Bossou *et al*., 2013) [34]. 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. 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 (Jeong *et al*., 2014) [72]. Another important compound 'eupatilin' extracted from various Artemisia species holds promising anti-cancer as well as anti-oxidant potential (Shawi *et al*., 2011) [162] β- myrcene, (Z)- β- ocimene, (+)-limonene and γterpinene obtained from essential oil of A. scoparia exhibit phytotoxic potential and have been used for sustainable weed management (Abad *et al*., 2012) [1]. 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.

Conclusions

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**.**

This review also covers the chemical composition of essential oils from different geographical regions where a significant difference in the composition of different species of the same genus is observed. Major components consisted of several terpenes, terpenoids and phenolic compounds; and 1, 8-cineole, beta-pinene, thujone, artemisia ketone, camphor, caryophyllene, camphene and germacrene D were dominant in several species. The different *Artemisia* oils and their compounds have been reported as effective antimicrobial, insecticidal and antioxidant agents. Some oils also exhibited poor to moderate potency against pests and pathogens. Antioxidant activity found in oils is basically due to presence of phenolic compounds. The information summarized here is intended to serve as a reference tool to people in the field of plant protection and natural products chemistry. Although the current review focuses on the antimicrobial role of *Artemisia* essential oils against phytopathogens, it has also shown promising results against several human and animal pathogens. Recently this genus has attracted attention of the world when it commanded a Nobel prize regarding its use in traditional medicine for combating malaria. Although preliminary studies have been done on several species

of *Artemisia* regarding its antimicrobial, antioxidant, insecticidal properties, elaborate bioprospection on its probable bioactivites against plant pathogens and pests is needed at field level. Recent times are desperate times where research interest has shifted towards exploration of natural compounds, especially for human welfare. More accurate reporting and data analysis is still needed. Other major issues such as mammalian toxicity, residual toxicity, phytoxicity and legal regulations/obligation and its long-term physiological and ecological effects of the effective oils need to be answered.

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