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Review Article

Artemisia (Asteraceae) Essential Oils: Compositional Variation and Mechanisms of Its Origin, Biosynthesis of Constituents, Correspondence Between Biological Activities and Ethnomedicinal Usage and Repurposement Prospects

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Many species of the genus *Artemisia*, a taxon in the angiosperm family Asteraceae composed of more than 500 species, are widely used in traditional medicine, on account of the safe multi-curative properties of its secondary metabolites biosynthesized in chloroplasts and cytoplasm of cells, largely in trichomes. The steam distilled *Artemisia* essential oils, into which the volatile organic metabolites get extracted, have been observed to demonstrate enormous intra- and inter-species variation. This review summarises for the *Artemisia* species (artemisias) the nature of compositional variation of the essential oil volatiles, biosynthetic processes of the major classes of the observed volatiles, and mechanisms responsible for the variation in the content of volatiles in essential oils. The inter-relationships between the biosyntheses of volatiles of essential oil and the antimalarial compound artemisinin are delineated. Further, the relationships between ethnomedicinal uses of various artemisias and biological activities detected in their essential oils are discussed with reference to the quality of essential oils. *Artemisia* essential oils offer highly significant repurposement prospects. Future directions of research on artemisias are also outlined.

Keywords: Biosynthetic Pathways; Morpho-Chemi-Genetic Variation; Marker Volatiles; Essential Oil Volatiles; Trichomes; *Artemisia* Species Diversity

Introduction

The genus *Artemisia*, of tribe Anthemideae and family Asteraceae, is known to comprise of more than 500 species (Bremer and Humphries 1993; Bremer 1994; Gregor 1997; Heywood and Humphrey 1997; Mucciarelli and Maffei 2002; Watson *et al*., 2002). The plants in *Artemisia* species are perennial-, biennial- or annual-shrubs or herbs; the large majority are perennial. Following its origin as a herb in the arid-cum-subarid environment of north-central Asia in late Oligocene (24.6 million years ago (mya)), the evolutionary diversification and speciation in *Artemisia* continued in temperate environments of Eurasia and north-west America in late Meiocene (10.8mya) and Pliocene (2.6mya) (Graham 1996; Wang 2004; Sanz *et al*., 2011). Transcontinental dispersal of *Artemisia* species between Asia and North America occurred

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naturally until about 11,000 years ago via the land bridge in Berengia (Riggins and Seigler 2012). The enormous genetic variability present in *Artemisia* species, and seed dispersal by natural processes and by human activities (such as transport of food grains from one area to another) have been responsible for *Artemisia* populations to get distributed in all types of 0-50 cm precipitation ecosystems worldwide, from sea level to sub-alpine mountains (Pellicer *et al*., 2010; Eisenman and Struwe 2011). Several *Artemisia* species are cultivated, as ornaments, for live-stock grazing, for use as condiment-cum-liquor flavouring agents, and/or for isolation of chemical compounds used in cosmeticeutical and pharmaceutical industry. The genetically bred varieties of *Artemisia annua* are being cultivated for the production of several *Artemisia* products (Fig. 1).

The survival of *Artemisia* species (artemisias) in diverse physical environments, in many countries all the continents, in interaction with plant pathogens (viruses, bacteria, fungi, protozoa etc.), parasite pests

Fig. 1: Morphology of *Artemisia annua* (A, B, C, D, E, F, G, H and I) whole plants, flowering stems, leaf and trichomes, and types of inflorescence involucres seen in *Artemisia* species. a and b: Field crops at different stages of development (A, vegetative stage; B, late flowering stage); C and D: Racemose inflorescence bearing stems (C, flowering initiation stage; D, seed formation stage); E: Compound leaf and at its base a pair of compound cochleata stipules; F and G: Diagrammes of the trichomes borne on the epidermis of the shoot organs (F, glandular trichome; G, non-glandular trichome); H: Types of involucres in which Ff is female flower, Hf is hermaphrodite flower, and Hfm is functionally male hermaphrodite flower; and I, seeds. Figures A and B and D have been shared respectively by Sanjay Kumar and Anil Kumar Gupta of the Central Institute of the Medicinal and Aromatic Plants, Lucknow and the figure h has been reproduced with the permission of J. Pellicer

(including nematodes and insects), plant parasites, and vertebrate herbivores, is apparently correlated with their morpho-physiological-cum-secondary metabolite traits. The phytochemicals produced by *Artemisia* species in their various organs include series of terpenes, flavonoids, phenolic acids, coumarins, saponins, glycosides, sterols and phytoacetylenes (Tan *et al*., 1998; Bhakuni *et al*., 2001; Weathers *et al*., 2014; Goel *et al*., 2018b). In the course of their migration, settlement and civilizational development, populations of *Homo sapiens* (humans of modern anatomy), while inventing agriculture by domestication of selected plant species into crops and animals such as cattle, goat and sheep into sources of milk and meat (Diamond 2002; Zeder *et al*., 2006; Hirst 2014; Kumar *et al*., 2016), adapted themselves to *Artemisia* species, by using them as food for farm animals and for themselves and for medicinal purposes. They used *Artemisia* to cure ailments such as fever and chills, cough and influenza, body pain, dysmenorrhoea, jaundice, internal infections of worms and parasites and external sores, boils and other skin disorders (Read 1977; Rastogi and Mehrotra 1995; Moerman 1998; Mueller *et al*., 2000; Wright 2002; Guarrera 2005; Bora and Sharma 2010 and 2011; Abad *et al*., 2012; Turi *et al*., 2013). Since *Artemisia* species are mostly highly aromatic, from the ancient times herbalists used the essential oils extracted from *Artemisia* plants to treat some common disease such as those mentioned above (altmed/treatment/aromatherapy; www.umm.edu/health/medical/essentialoilsacademy. com/history/ ; redwheelweiser.com). On account of their vast spread and ethnopharmacological usage, *Artemisia* species are serving as important biological system to study variation in plant secondary metabolism, especially in the terpenoids of the essential oil and among the artemisinic compounds useful in modern medicine, such as the antimalarial molecule artemisinin (Wen and Yu 2011). Scores of studies have revealed wide, intra- and inter- species and organ-wise intra-plant, compositional hetero-geneity in essential oils distilled from plants of *Artemisia* species growing wild or cultivated in similar and different geographical locations/agro-ecosystems. Many of these oils were also screened for a variety of biological activities. A few model species in the genus *Artemisia*, such as *Artemisia annua*, have been used to understand the terpenoid bio-synthetic process. This review identifies the features *A. annua* that make it a model species suitable to study terpenoid biosynthesis, major components of essential oils of many *Artemisia* species, illustrates the compositional differences in the essential oils of the different organs, and the effects of genotype x environment, interaction and plant developmental stages on the essential oil of the same strain of *Artemisia* species.

The review relates the major volatile organic compounds and biological activities detected in essential oils with the ethnopharmacology of the respective *Artemisia* species. The structures of the sites of essential oil biosynthesis and progress in understanding the genetic control of essential oil biosynthesis are also discussed. The general morphological features of *Artemisia* species, especially in respect of leaves and reproductive system, are also briefly summarized. The inter-relationships between biosynthesis of artemisinin (a terpenoid, non-extractable in hydro-distilled essential oil) and volatile terpenoids in essential oils have also been discussed. The essential oil compositional variability is shown to relate to the reproductive system and other genetic variation generating mechanisms operating in the genus *Artemisia*. Directions for future research are also identified.

Morphological and Reproductive System Variation

Artemisia plant morphology has relationship with variation in *Artemisia* essential oils; and all organs of the plant synthesize and/or store essential oil constituents. *Artemisia* species harbor considerable morphological variation about leaf, inflorescence, flower structure and seed morphologies (Mucciarelli and Maffei 2002; Wright 2002 and 2003) (Fig. 1). The leaves are alternate, simple or compound of varying shapes, sizes, colour and texture; in most species leaves are dissected/compound in different patterns. Stipule pairs at the base of each leaf, when present have the same morphology as the leaves (*cochleata* phenotype). The inflorescence is in the form of capitula arranged in racemose, paniculate or capitate fashion. A capitulum is small spheroidal to ovoid on whose receptacle, protected by bracteate involucre, are inserted a large number of tubular florets. The receptacle is glabrous or hairy. Floret composition-wise, the capitula may be homo- or hetero-gamous (Valles and McArthur 2001; Valles and Garnatze

2005). Pollination mechanism is mostly via wind (pollen release by the wind induced vibrations in stamens), rarely by insects; in only a small number of *Artemisia* species reproduction occurs via self-pollination. Pollen grains possess microechinate ornamentation. Corollas are inconspicuous having white, yellow or purple colour. The ovary of each fertile floret has one basally located ovule. The fruit is a laterally compressed obovoid achene which is pappus-less in most species (Tkach *et al*., 2008; Hayat *et al*., 2009a and b; Bogawski *et al*., 2016). In *Artemisia annua*, an open-pollinated species, selfed seeds have been obtained by covering the flowering stems with perforate plastic bags (Alejos-Gonzalez 2013 and 2015).

The genus *Artemisia* has been divided into six subgenera based on the morphology of capitula, nature of florets and whether or not pappus is present on the seeds: *Absinthium, Artemisia* (or *Abrotanum), Dracunculus, Seriphidium, Tridentatae* and *Pacifica*. *Absinthium* is characterized by capitulla that have hairy receptacle (invoulcre) and bear outer fertile female florets and inner/central fertile hermaphrodite florets and pappus-less seeds. The species of *Artemisia* and *Pacific* subgenera have glabrous receptacle of capitula that bear florets in the fashion of *Absinthium*. Seeds are pappus-less in *Artemisia* but have pappus in *Pacifica*. The capitula of *Dracunculus* have glabrous receptacle, outer female fertile florets and functionally male hermaphrodite inner florets and seeds free of pappus. The species of *Seriphidium* and *Tridentatae* subgenera have capitula bearing glabrous receptacle, and only one kind of florets – fertile hermaphrodite; their seeds are pappus-less. (Torrell *et al*., 2001; Valles and McArthur 2001; Valles and Garnatze 2005; Sanz *et al*., 2011; Hobbs and Baldwin 2013; Koloren *et al*., 2016).

Artemisia species are mostly short day flowering plants; their inflorescence system is of huge size. *Artemisia* individual plants can produce many thousand ($\sim 10^5$) of wind dispersed seeds in a flowering season (Goel *et al*., 2011). The reproductive stage *Artemisia* plants are a richer resource of essential oil than vegetative stage plants because of higher density of glandular trichomes, which produce and store essential oil, on inflorescence and leaves of plants on which flowering has set in (Woerdenbag *et al*., 1994; Ferreira and Janick 1995; Tellez *et al*., 1999; Soetaert *et al*., 2013). Whereas several *Artemisia* species, including *Artemisia annua*, are commercial resource of essential oils, presently *A. annua* is the only commercial *Artemisia* resource of the antimalarial terpenoid drug artemisinin. Because of their long life cycle, artemisias do not fit into the conventional crop rotations practiced in the sub-tropical agroclimates.

Emergence of Artemisia annua as a Model Plant for The Dissection of Biosynthesis and Functional Analysis of Secondary Metabolites

Artemisia species (artemisias) synthesize an array of secondary metabolites-terpenoids, phenolics, alkaloids and sulphur containing compounds-, which provide them properties of wide ecological adaptation, success in survival against pathogens, pests and competitive plant species, and profuse seed production (WHO 2005; Dong *et al*., 2016; Goel *et al*., 2018). The commercially exploited secondary metabolites of artemisias in the main are terpenoids. Especially, artemisias are resource of terpenoid rich essential oils, of differential medicinal, cosmeticeutical and insecticidal properties and the antimalarial terpenoid compound artemisinin (WHO 2005; Bilia *et al*., 2014; Tholl 2015; Vivaldo *et al*., 2017). In recent years, artemisinin and its semi-synthetic derivative drugs such as artesunate, artemether and arteether have saved lines of millions of people worldwide from different forms of drug resistant malaria, by being used in two and three drug combination therapies. Besides, there are experimentally- and clinical-trials- proven possibilities of using artemisinin and its derived compounds to cure several kinds of metabolic disorders, cancers and viral-, bacterial-, fungal- and protozoa-caused infectious diseases, in humans and livestock (Weathers *et al*., 2014; Goel *et al*., 2018).

Artemisinin is known to be biosynthesized in a number of Artemisia species: *A. absinthium, A. afftangutica*, *A. apiacea, A. bushriences, A. campestris, A. cina, A. desertii, A. diffusa, A. dracunculus, A. dubia, A. indica, A. japonica, A. lanceolata, A. marschelliana, A. moorcraftiana, A. parviflora, A. persica, A. roxburghiana, A. scoparia, A. sieberi,* and *A. vulgaris* (Brown 2010; Salehi *et al*., 2018). However, the bulk of artemisinin in medicinal usage is extracted from the foliage of field grown crops of *A. annua* strains selected for high content of artemisinin (Ferreira *et al*., 2005). Since, essential oil can be extracted from the foliage

already extracted for artemisinin (Jain *et al*., 1999) and since artemisinin is in greater demand, essential oil has become a byproduct and artemisinin the main product from cultivated *A. annua*. Among *Artemisia* species, *A. annua* is the most extensively used species and therefore preferred choice to analyze the artemisinome and essential oil volatilome of artemisias.

Artemisias annua, which is granted GRAS (Generally Recognised as Safe) rating, has several hereditary features that make it a model plant suitable for fundamental studies on secondary metabolites: annual habit; diploid genome with x = 9, the least basic chromosome number of the family Asteraceae; abundant seed production potential, possibility of developing selfed lines, ease in raising plants under varying field conditions or controlled environments, enormous genetic variability in wild populations, availability of methodologies to obtain plants from isolated individual cells, tissues and organs, and stem cuttings (Mathur and Kumar 1996; Alejos *et al*., 2013; Pandey *et al*., 2016; Wetzstein *et al*., 2018). It's nuclear and chloroplast genomes have been sequenced (Shen *et al*., 2017 and 2018). A genetic map is available on which several loci that determine artemisinin yield have been placed (Graham *et al*., 2010). Many genes that determine artemisnic and essential oil metabolomes have been identified via forward and reverse genetic approaches and transcriptome analyses and cloned (Misra *et al*., 2012; Ma *et al*., 2015; Czechowski *et al*., 2016; Hao *et al*., 2017; Catania *et al*., 2018). *Artemisia annua* has proved facile for the generation of transgenics using its own and foreign genes in recombinant forms (Tang *et al*., 2014; Kiani *et al*., 2015), to under- or over-express specific gene(s) (Xie *et al*., 2016; Ma *et al*., 2017b). *A. annua* is emerging to be a prominent species among other Asteraceae species, including *Helianthus annus, Carthamus tinctorius, Lactuca sativa, Cynara scolymus* and *Smallanthus sonchifolius,* undergoing detailed investigations on account of their agricultural/horticultural importance. Aspects about essential oils and artemisinin in artemisias are presented in the following sections.

Variability in The Chemical Composition of *Artemisia* Essential Oils

Plants have evolved in them convergent pathways for biosynthesis of volatile organic compounds (VOCs). Species of various plant families are known to synthesize different combinations of the same set of VOCs, via the secondary metabolite pathways encoded by nuclear, plastid and mitochondrium genomes (Maffei 2010; Brown 2010). The inter-species variation in VOC contents has seemingly arisen from allelic polymorphism among the VOC pathway genes and regulatory genes controlling the expression of VOC pathway genes, originally inherited from a common ancestor. The observed variation is thought to be related to interaction of individual species with their biotic and abiotic environment and success in reproduction in the course of species evolution.

The volatiles are synthesized in all of the plant organs (root, stem, leaf, flower components, fruit and seed), constitutively and/or in response to environmental stimulus. The volatile organic compounds belong to several chemical classes, that vary in their diversity: terpenes > phenylpropanoids/ benzenoids> fatty acid derivatives > aminoacid and carbohydrate derivatives. The functions performed by the volatiles include guidance of pollinators, attraction of seed dispersers, protection against oxidative damage, pathogens and herbivores, and suppression of parasites and competing plant species (Dudareva *et al*., 2013; Loreto *et al*., 2014; Tholl 2015, Vivaldo *et al*., 2017). There are wide qualitative and quantitative differences in ability to synthesize volatile organic compounds, between plant families and taxa and species within individual families (Kumari *et al*., 2014). The plants that synthesize volatile organic compounds in large quantities are called aromatic plants. The family Asteraceae is rich in aromatic taxa and one of its genus rich in aromatic species is *Artemisia*.

Essential oils are hydrophobic liquids, that are complex mixtures of volatile organic compounds (lipophilic, high vapour pressure and of low molecular mass d" 300) that get extracted from plant material by use of a variety of extraction processes, including steam- and hydro-distillation, use of solvents, and percolation and carbon dioxide processes (Rassem *et al*., 2016; Vidic *et al*., 2018). Hydro distillation is a convenient and widely used essential oil extraction procedure for the large majority of commercial aromatic plant materials.

Essential oils are analyzed for their chemical

composition using the gas chromatography-mass spectrometry method (Staschenko and Martinez 2014). The essential oils extracted from a plant can vary organ-wise and those extracted from different populations of a species can vary organ-wise, developmental stage-wise and plant growth environment-wise. Inter-population comparisons within and between species are made on essential oils extracted from the identified plant organs at the corresponding stage of development.

The essential oils of *Artemisia* species are used widely in the ethnopharmaceutics and cosmetics (Abad *et al*., 2012), therefore these have been undergoing detailed examination. Wild populations of many species of *Artemisia* growing in geographical areas of widely different agro-environments have been examined for the quality of essential oils of their specific organs and bulk foliage (entire shoot) at different stages of plant development. Such investigations have led to breeding of improved varieties of *Artemisia* species for high yields of high quality essential oils (Wright 2003). In general, the steam- or hydro-distilled *Artemisia* oils have been found to contain varying amounts of several to many scores of volatile organic compounds. The compositional diversity observed in *Artemisia* essential oils is immense, such that a compound that is barely detectable or absent in essential oil of some species occurs at e"80% concentration in oil of a different species. Since the number of volatiles present in the essential oils is large, the oils are often compared in terms of their major constituents. Certain strikingly differential colours of essential oil of some *Artemisia* species make the oil colour a noteworthy character. Some important features of the *Artemisia* essential oil yield and quality are discussed below; to identify the volatiles whose presence in the essential oils may be emphasized in the future breeding programmes of artemisias.

Colour as a Marker of Essential Oil in Artemisia

A large majority of essential oils distilled from *Artemisia* species have yellowish colour, varying from greenish yellow, yellow, pale yellow to yellowish brown, examplified by the oils of the *A. afra, A. annua, A. campestris, A. dracunculus, A. japonica, A. judiaca* and *A. vulgaris* species of *Artemisia* (Dob *et al*. 2005; Dob and Chelghoum 2006; Goel *et al*. 2008; Rashmi 2014; Hussein *et al*., 2016; Amel *et al*., 2017; Bedini *et al*., 2017). However, essential oils of some species have distinctly different colours. For example essential oils of *A. arborescens, A. herba-alba* and *A. lavandulaefolia* are known to be greenish blue to dark blue in colour (Sacco *et al*., 1983; Aloui *et al*., 2016; Zhou *et al*., 2018). The essential oil of *A. absinthium* has purple colour (Msaada *et al*., 2015). The *A. gmelini* oil has orange colour (Shreshthaa *et al*., 2013). The blue/violet/purple colour of the essential oils, such as of *A. arborescens* and *A. absinthium*, is due to the presence of the sesquiterpenoid molecule chamazulene, biosynthesized by carboxylation of the sesquiterpene matricin (Safayhi *et al*., 1994).

All Organs of Artemisia Plants Yield Essential Oil

Artemisia annua, the natural source of the antimalarial compound artemisinin, has emerged as a model plant species in the genus *Artemisia*. Being a highly aromatic species of *Artemisia*, studies have shown that volatile organic compounds are synthesized in the roots, stems, leaves, capitula and seeds, and therefore it has been possible to extract essential oils from all these organs of *A. annua* plants (Goel *et al*., 2007a and b; Habibi *et al*., 2013). The observations summarized in the Table 1 list the major volatiles present in the essential oils of root, stem, leaf and petal organs of *A. annua* cultivar Jwarharti. The essential oils of the four organs differ widely in their constituents, including the major constituents; whereas the root and stem oils are rich in sesquiterpenes, contrastingly the leaf and petal oils are rich in monoterpenes. Large compositional differences have also been reported between the essential oils extracted from the leaves, stems and capitula of a population of *A. herba-alba* (Tilaoui *et al*., 2015). Seed oils of *A. annua, A. campestris* and *A. aucheri* were found to be rich in monoterpenes (Table 1). Altogether these observations suggest that the genetic programs for the expression of pathways for the biosynthesis of volatile organic compounds in different organs are tailored differentially.

Essential Oil Yield is Highest from the Flowering Stage Artemisia Plants

Artemisia plants biosynthesize volatile organic compounds throughout their life span, from seedling stage to senescence stage at seed maturity in annual

Table 1: Organ-wise differential composition of essential oil hydro-distilled from *Artemisia* species

Five major compounds arranged in decreasing order of their % concentration	*Artemisia annua* cv Jwarhart				*Artemisia annua* accession from Iran	*Artemisia aucheri* accession from Iran	*Artemisia campestris* accession from Morocco
	Root	Stem	Leaf	Petal	Seeds		
1	cis-Arteannuic alcohol (25.9%)	Caryophyllene oxide (10.0%)	Camphor (23.2%)	trans-Sabinol (10.25) 4-ol (22.3%)	Trans-3(10)-Caren-	Linalool (27.1%)	β-Pinene (12.0%)
2	(E)-β-Farnesene (6.7%)	9-epi-Caryophylla-1 (12), 8(15)-diene-14-ol (8.7%)	1,8-Cineole (6.4%) diene-3-ol (10.1%)	Para-Mentha-1,4(8)- (18.6%)	Artemisia ketone	Borneol (7.8%)	Spathulenol (10.8%)
3	β-Malliene (6.3%)	β-Caryophyllene (6.1%)	Germacrene D (3.4%)	1,8-Cineole (6.8%)	1,8-Cineole (14.9%)	Decane (5.4%)	α-Pinene (7.5%)
4	β-Caryophyllene (5.5%)	(z)-α-trans Bergamotal acetate (5.9%)	â-Caryophyllene (2.6%)	Myrcene (5.9%)	β-Selinene (13.0%)	Caryophyllene oxide (4.7%)	Limonene (7.0%)
5	Caryophyllene oxide (4.4%)	(E)-β-Farnesene (4.3%)	p-Cymene (2.5%)	(E)-β-Farnesene (5.4%)	α-Pinene (8..2%)	Lavendulol (4.1%)	o-Cymene (5.4%)
Remarks	Highly sesquiterpene rich (72.7%); mono- and di- terpene presence very low (~ 0.5%)	Rich in sesquiterpenes (42.3%) and low in monoterpenes (5.1%)	Highly rich in monoterpenes (47.7%) and low in sesquiterpenes (8.1%)	Highly rich in monoterpenes (52.2%) and low in sesquiterpenes (4.0%), the predominant compound in leaf oil, Camphor was absent from the petal oil	Rich in monoterpenes		
Reference	Goel *et al*. (2007a)	Goel *et al*. (2007b)	Goel *et al*. (2007b)	Goel *et al*. (2007b)	Habibi *et al.* (2013)	Asghari *et al.* (2012)	Jahid *et al.* (2017)

species and until death in perennial species. It has been observed in the shoots of annual species *A. annua* cv Jeevanraksha plants that the essential oil concentration is only 0.2 to 0.25% at pre-flowering stages. The essential oil concentration increases as the plant enters the flowering stage and reaches 1.3% at the full bloom stage. However, certain genotypes of *A. annua* are known to yield ~ 4% of essential oil (Bilia *et al.*, 2014). Since the size of capitula in the inflorescence is small, the bulk of essential oil is present in the leaves at both pre- and post-flowering stage plants. Seed maturity and related senescence of shoot organs lowers the concentration of essential oil in the foliage (or leaves + capitula and other parts of inflorescence) (Mallavarupu *et al.*, 1989; Gupta *et al.*, 2002). These observations imply that the *Artemisia* populations cultivated to yield essential oil should be harvested soon after the onset of flowering to obtain high quality oil in maximum yield.

Intra- and Inter-Species Compositional Variation in Essential Oils of Artemisia Species

The Table 2 presents major (top five) volatile organic compounds detected in the essential oils of foliage of flowering plants of 176 populations of 66 species of *Artemisia*. In this table 28 species are represented by 2

Table 2: The variability observed in the chemical composition of the essential oils, hydrodistilled from the flowering time foliage, of different species/genotypes of the genus *Artemisia*, growing / grown in various parts of the world

S.No.	Species name in the genus *Artemisia*	Geographical location of the population studied	The major chemical compounds, detected in the oil, arranged in the decreasing order of their percent (%) concentration in the essential oil					Reference (s)
1	*A. abrotanum*	Poland	Piperitone (17.5 %)	Davanone (16.8 %)	1,8-Cineole(12.5 %)	Silphiperfol-5-en-(5.9%) 3-ol A	Germacrene D (6.3%)	Kowalski *et al*. (2007)
2	*A. abrotanum*	Iraq	Soloinene (21.5%)	Myrcene (13.6%)	Limonene (14.4%)	Camphene (12.7%)	β-Pinene (4.1%)	Aljubory *et al*. 2017
3	*A. absinthium*	Tajikstan	cis-Chrysanthanyl acetate (19.7 %)	Myrcene (13.5 %)	Linalool (6.0%)	Germacrene D (5.1%)	β-Thujone (3.3%)	Sharpov *et al*. (2012)
4	*A. absinthium*	Estonia, Population 1	Myrcene (25.6%)	Sabinene (21.2%)	Curcuminoid structure (5.5%)	α-Thujone (4.1%)	α-Thujone (1.7%)	Orav *et al*. (2006)
5	*A. absinthium*	Estonia, Population 2	Epoxy-Ocimene (59.7%)	Sabinyl acetate (23.6%)	Sabinene (1.4%)	Linalool (0.7%)	α-Thujone (0.6%)	Orav *et al*. (2006)
6	*A. absinthium*	Estonia, Population 3	α-Thujone (64.6%)	Sabinyl acetate (18.2%)	Sabinene (3.5%)	Linalool (1.2%)	α-Thujone (1.2%)	Orav *et al*. (2006)
7	*A. absinthium*	Estonia, Population 4	Sabinyl acetate(70.5%)	α-Thujone (2.3%)	Sabinene (1.7%)	Linalool (1.3%)	α-Thujone (1.2%)	Orav *et al*. (2006)
8	*A. absinthium*	France	Neryl butanoate (13.9%)	Curcuminoid structure (11.3%)	Neryl-3-methyl-butanoate (7.3%)	Linalool (5.2%)	α-Thujone (5.1%)	Orav *et al*. (2006)
9	*A. absinthium*	Hungary	Sabinene (18.1%)	Myrcene (17.7%)	β-Thujone (4.5%)	Neryl butanoate (3.3%)	Curcuminoid structure (2.6%)	Orav *et al*. (2006)
10	*A. absinthium*	Belgium	Sabinyl acetate(18.6%)	Sabinene (9.3%)	Myrcene (5.4%)	1,8-Cineole (3.9%)	β-Thujone (3.6%)	Orav *et al*. (2006)
11	*A. absinthium*	Greece	β-Thujone (38.7%)	Neryl-3-methyl butanoate (3.7%)	Sabinene (3.0%)	Myrcene (2.9%)	Neryl butanoate (2.5%)	Orav *et al*. (2006)
12	*A. absinthium*	Scotland	Sabinene (30.1%)	Myrcene (18.0%)	β-Thujone (3.5%)	Linalool (2.5%)	α-Thujone (2.5%)	Orav *et al*. (2006)
13	*A. absinthium*	Maldeev in Indian Ocean	Myrcene (38.9%)	Sabinyl acetate (23.6%)	Curcuminoid structure (9.0%)	Sabinene (9.2%)	Sabinyl acetate (5.7%)	Orav *et al*. (2006)
14	*A. absinthium*	Lithunia	Sabinyl acetate (13.7%)	Curcuminoid structure (6.3%)	β-Thujone (4.0%)	1,8-Cineole (3.6%)	Sabinene (2.7%)	Orav *et al*. (2006)
15	*A. absinthium*	Italy	β-Thujone (40.6%)	epoxy-Ocimene(s) (23.1%)	Sabinene (6.3%)	Myrcene (1.4%)	α-Thujone (1.1%)	Orav *et al*. (2006)
16	*A. absinthium*	Spain	1, 8-Cineole (18.0%)	β-Thujone (6.2%)	Neryl butanoate (5.9%)	Linalool (5.5%)	α-Thujone (5.4%)	Orav *et al*. (2006)
17	*A. absinthium*	Turkistan	Sabinene (17.6%)	Myrcene (11.0%)	Chrysanthenyl acetate (11.0%)	trans-Sabinyl acetate (7.7%)	α-Phellandrene (5.4%)	Baykan-Erel *et al*. (2012)

18	*A. absinthium*	Spain	cis-epoxy-Ocimene (40%)	-cis-chrysanthenol (12%)	dihydro-Chamazulene (6.0%)	Chrysanthenyl acetate (5.3%)	Camphor (4.5%)	Martinez-Diaz *et al*. (2015)
19	*A. absinthium*	Iran	α-Phellandrene (16.4%)	Chamazulene (13.9%)	β-Pinene (12.3%)	Sabinene (8.7%)	p-Cymene (7.1%)	Moghaddam *et al*. (2016)
20	*A. absinthium*	Ethopia	Camphor (27.4%)	Davanone (16.4%)	ethyl-(E)-Cinnamate (5.8%)	Nerolidol (4.6%)	Chamazulene (4.0%)	Tariku *et al*. (2011)
21	*A. absinthium*	Tunisia	β-Thujone (16.7%)	trans-Sabinene hydrate (13.0%)	Chamazulene (32.4%)	Sabinene (5.2%)	Lavendulol (3.0%)	Msaada *et al*. (2015)
22	*A. absinthium*	India	Borneol (16.7%)	Methyl henokiate (12.9%)	Isobornyl acetate (4.7%)	Caryophyllene oxide (4.3%)	β-Gurjunene (4.4%)	Joshi (2013)
23	*A. absinthium*	Brazil	Camphor (19.0%)	(E)-Caryophyllene (9.3%)	Eucalyptol (6.8%)	Germacrene-D (6.7%)	α-Cadinol (6.5%)	Vieira *et al*. (2017)
24	*A. abyssinica*	Yemen	Camphor (38.1%)	Davanone (38.7%)	(E)-Nerolidol (4.5%)	cis-Sabinene hydrate (4.1%)	Terpinen-4-ol (3.3%)	Azedine *et al*. (2010)
25	*A. abyssinica*	Ethopia	Yomogi alcohol (32.2%)	Artemisia alcohol (26.7%)	Nonanone (6.4%)	1,8-Cineole (2.1%)	α-Terpinene (1.8%)	Chauhan (2013)
26	*A. afra*	Zimbabwe	Artemisia ketone (32.6%)	Camphor (24.3%)	1,8-Cineole (13.1%)	Santolina alcohol (3.5%)	Camphene (3.4%)	Chagonda *et al*. (1999)
27	*A. afra*	Zimbabwe	1,8-Cineole (25.9%)	Borneol (18.5%)	Camphor (13.0%)	Camphene (4.0%)	α-Terpinol (4.0%)	Chagonda *et al*. (1999)
28	*A. afra*	Turkey	Camphor (45.5%)	1,8-Cineole (30.4%)	Camphene (6.5%)	α-Terpineol (3.2%)	α-Pinene (3.0%)	Guvenalp *et al*. (1998)
29	*A. afra*	Africa	Camphor (26.8%)	Davanone (16.6%)	Bornyl acetate (3.8%)	4-Terpineol (3.6%)	Chamazulene (3.2%)	Burits *et al*. (2001)
30	*A. alba*	Europe, Madonie	α-Bisbolone oxide A (16.4%)	Davanone (10.5%)	Bisbolone oxide (9.0%)	Santolina triene (7.3%)	γ-Gurjunene (6.4%)	Maggio *et al*. (2012)
31	*A. alba*	Europe, Marche	8-Cedren-13-ol (10.3%)	Borneol (9.3%)	α-Sabinene (7.6%)	Artemisia alcohol (6.0%)	Artemisia ketone (4.6%)	Maggio *et al*. (2012)
32	*A. alba*	Europe, Majella	Eudesmol (42.2%)	cis-Pinocamphone (14.9%)	Piperitone (12.6%)	Germacrene D (4.9%)	trans-Verbenol (1.8%)	Maggio *et al*. (2012)
33	*A. alba*	Europe, Mount Vehri	Piperitone (32.8%)	Germacrene D (10.2%)	(E)-Nerolidol (6.4%)	epi-α-Bisabolol (4.7%)	α-Bisabolol (4.5%)	Maggio *et al*. (2012)
34	*A. anethoides*	China	1,8-Cineole (36.5%)	2-Isopropyl-5-methyl-3-cyclohexen-1-one (10.4%)	Terpinen-4-ol (8.6%)	2-Isopropyl toluene (6.2%)	Pinocarveol (5.1%)	Liang *et al*. (2017)
35	*A. annua (cv Jeevanraksha)*	India (Lucknow)	Camphor (42.6%)	1,8-Cineole (17.2%)	Germacrene D (15.6%)	Myrcene (15.4%)	trans-Pinocarveol (3.6%)	Kumar *et al*. (1999)
36	*A. annua (cv Jeevanraksha)*	India (Banglore)	Camphor (42.6%)	1,8-Cineole (9.2%)	Myrcene (8.3%)	β-Sabinene (3.9%)	Camphene (3.4%)	Rao *et al*. (2014)

37	*A. annua (cv Jeevanraksha)*	India (Hyderabad)	Camphor (34.2%)	1,8-Cineole (17.2%)	Myrcene (15.4%)	Camphene (8.0%)	Artemisia alcohol (4.3%)	Rao *et al*. (2014)
38	*A. annua (cv Jeevanraksha)*	India (New Delhi)	Camphor (13.5%)	trans-Sabinal (7.1%)	p-Mentha-(7), 5-dien-2-ol (6.3%)	Myrcene (4.3%)	(E)-β-Farnesene (3.9%)	Goel *et al*. (2008)
39	*A. annua (cv Suraksha)*	India (New Delhi)	Artemisia ketone (47.0%)	Camphor (5.9%)	α-Pinene (5.2%)	Artemisia alcohol (2.6%)	β-Caryophyllene (3.7%)	Goel *et al*. (2008)
40	*A. annua (cv Arogya)*	India (Lucknow)	Camphor (43.5%)	Germacrene D (15.6%)	trans-Pinocarveol (10.9%)	â-Selinane (9.4%)	β-Caryophyllene (8.9%)	Khanuja *et al*. (2005)
41	*A. annua (cv Sanjeevani)*	India (Lucknow)	(E)-Caryophyllene (10.2%)	Camphor (8.3%)	Germacrene D (7.6%)	1,8-Cineole (5.6%)	β-Chamigrene (3.2%)	Goel *et al* (2018a)
42	*A. annua*	India (Lucknow)	Camphor (21.0%)	Camphene (19.5%)	Germacrene D (4.9%)	Artemisia alcohol (4.5%)	1,8-Cineole (1.1%)	Bagchi *et al*. (2003)
43	*A. annua*	India (Lucknow)	Artemisia ketone (52.9%)	1,8-Cineole (8.4%)	Camphor (6.0%)	α-Pinene (5.2%)	Artemisia alcohol (3.5%)	Jain *et al*. (2011)
44	*A. annua*	Italy	Artemisia ketone (22.1%)	1,8-Cineole (18.8%)	Camphor (16.9%)	Artemisia alcohol (5.9%)	α-Pinene (5.7%)	Bedini *et al*. (2017)
45	*A. annua*	India	1,8-Cineole (15.1%)	α-Terpineol (14.0%)	p-Cymene (12.9%)	Carvone (12.0%)	γ-Elemene (6.2%)	Mukhtar *et al*. (2007)
46	*A. annua*	Ukraine	Artemisia ketone (46.2%)	Camphor (16.4%)	1,8-Cineole (6.1%)	α-Pinene (4.3%)	Myrcene (3.6%)	Khodakov and Kotikov (2009)
47	*A. annua*	China	Borneol (15.9%)	(z)- β-Farnesene (12.9%)	Germacrene D (10.9%)	β-Caryophyllene (6.0%)	Sabinene (3.2%)	Ma *et al*. (2007)
48	*A. annua* (CPQBA 2/39 x PL5)	Brazil	Camphor (22.7%)	1,8-Cineole (20.4%)	p-Cymene (12.2%)	Sabinene (5.4%)	Camphene (5.3%)	Perazzo *et al*. (2003)
49	*A. annua*	Italy	Germacrene D (21.2%)	Camphor (17.6%)	β-Farnesene (10.0%)	β-Caryophyllene (9.0%)	Bicyclogermacrene (4.2%)	Bilia *et al*. (2008)
50	*A. annua*	USA	Artemisia ketone (35.7%)	1,8-Cineole (31.5%)	α-Pinene (11.2%)	Artemisia alcohol (5.2%)	Myrcene (4.6%)	Libbey and Sturtz 1989
51	*A. annua*	Hungary	Artemisia ketone (65.4%)	Artemisia alcohol (22.6%)	Yomogi alcohol (3.8%)	β-Cubebene (2.2%)	â-Pinene (1.9%)	Hethelyi *et al*. (1995)
52	*A. annua*	Bosinia	Artemisia ketone (30.2%)	Camphor (24.0%)	1,8-Cineole (5.3%)	β-Farnesene (4.2%)	β-Myrcene (3.7%)	Vidic *et al.* (2018)
53	*A. annua* var Linneo	Germany	Artemisia ketone (75.3%)	Yomogi alcohol (14.5%)	Camphor (2.9%)	Sabinene (1.7%)	Camphene (0.9%)	Reale *et al.* (2011)[a]
54	*A. annua* (cv Anamed A3)	Germany	Germacrene-D (69.1%)	Isocaryophyllene (8.5%)	γ–Gurjunene (7.4%)	β-Caryophyllene (5.3%)	α-Copaene (2.4%)	Reale *et al*. (2011)[a]
55	*A. annua*	Iran	Camphor (43.5%)	1,8-Cineole (13.9%)	Spathulenol (3.7%)	Artemisia ketone (3.4%)	Terpinol (2.7%)	Mohammadreja (2008)

56	*A. annua*	Vietnam	Camphor (16.9%)	Germacrene D (8.8%)	Myrcene (8.5%)	trans-β-Farnesene (5.3%)	β-Caryophyllene (4.4%)	Woerdenbag *et al*. (1993)
57	*A. annua*	Netherlands	Artemisia ketone (63.9%)	Artemisia alcohol (7.5%)	Myrcene (5.1%)	α-Guaiene (4.7%)	Camphor (3.3%)	Woerdenbag *et al*. (1993)
58	*A. annua*	Bulgaria	β-Caryophyllene (24.7%)	α-Cuvebene (13.5%)	Artemisia ketone (8.5%)	α-Sabinene (8.2%)	α-Copaene (7.4%)	Tzenkova *et al*. (2010)
59	*A. annua*	USA	Artemisia ketone (41.4 %)	Camphor (15.5%)	β-Caryophyllene (4.5%)	allo-Aromadendrene (4.3%)	Sabinene (2.8%)	Charles *et al*. (1991)
60	*A. annua*	USA	α-Pinene (26.7%)	Pinocarvone (15.8%)	Artemisia ketone (11.0%)	1,8-Cineole (8.4%)	Germacrene D (6.1%)	Tellez *et al*. (1999)
61	*A. annua*	Romania	Camphor (17.7%)	α-Pinene (9.7%)	Germacrene D (7.6%)	1,8-Cineole (7.2%)	β-Caryophyllene (7.0%)	Marinas *et al*. (2015)
62	*A. annua*	Romania	Camphor (44%)	Germacrene D (16%)	trans-Pinocarveol (11.0%)	b-Sabinene (9.0%)	b-Caryophyllene (9.0%)	Juteau *et al*. (2002)
63	*A. annua*	Italy	Artemisia ketone (22.1%)	1,8-Cineole (18.8%)	Camphor (16.9%)	Artemisia alcohol (5.9%)	α-Pinene (5.7%)	Bedini *et al*. (2017)
64	*A. annua*	Brazil	1,8-Cineole (21.1%)	Camphor (14.9%)	β-Myrcene (12.4%)	Germacrene D (5.3%)	Sabinene (4.6%)	De Megalhaes *et al*. (2004)
65	*A. annua*	India	Camphor (52.1%)	β-Caryophyllene (11.0%)	1,8-Cineole (5.6%)	Caryophyllene oxide (4.2%)	β-Farnesene (3.8%)	Islamuddin *et al*. (2014)
66	*A. annua*	Italy	Artemisia ketone (22.0%)	1,8-Cineole (19.0%)	Camphor (17.0%)	Artemisia alcohol (5.9%)	β-Pinene (5.7%)	Santomauro *et al*. (2016)
67	*A. arborescens*	Algeria	Chamazulene (30.2%)	β-Thujone (27.8%)	β-Eudesmol (8.1%)	Catalponol (5.5%)	Camphor (3.0%)	Azedine *et al*. (2013)
68	*A. arborescens*	Algeria	Artemisia ketone (51.5%)	Camphor (14.1%)	α-Bisabolol (12.6%)	α-Terpinene (8.7%)	Palmitic acid (2.4%)	Chhetri *et al*. (2015)
69	*A. arborescens*	Turkistan	Camphor (33.4%)	Chamazulene (21.1%)	Eudesmol (7.7%)	Terpin-1-ol (4.8%)	Caryophyllene oxide (4.4%)	Baykan-Erel *et al*. (2012)
70	*A. argyi*	Russia	Selin-11-en-4α-ol (18.0%)	1,8-Cineole (14.2%)	Artemisia alcohol (12.9%)	Borneol (9.7%)	Terpinen-4-ol (4.1%)	Ozek *et al*. (2014)
71	*A. argyi*	China	1,8-Cineole (23.7%)	β-Caryophyllene (10.2%)	Borneol (6.6%)	β-Pinene (5.6%)	α-Cymene (5.0%)	Huang *et al*. (2012)
72	*A. armenica*	Iran	α-Pinene (10.7%)	Nonadecane (10.0%)	6,10,14-Trimethyl-z-pentadecanone	Spathulene (7.5%) (9.4%)	(z)-Verbenol (5.8%)	Mojarrab *et al*. (2013)
73	*A. asiatica*	China	1,8-Cineole (23.4%)	Piperitone (21.2%)	p-Cymene (14.5%)	(Z)-Davanone (9.7%)	Germacrene D (5.2%)	Huang *et al*. (2018)
74	*A. aucheri*	Iran	Verbenone (21.5%)	Camphor (21.0%)	1,8-Cineole (8.3%)	trans-Verbenol (8.1%)	p-Cymene (3.5%)	Sefidkon *et al*. (2002)

75	*A. austriaca*	Iran	Camphor (15.9%)	1,8-Cineole (10.8%)	Borneol (9.2%)	α-Farnesyl alcohol (6.9%)	Camphene (3.6%)	Razavi *et al*. (2014)
76	*A. campestris*	Tunisia, Bengardane	β-Pinene (24.2 %)	p-Cymene (17.4%)	Camphor (10.3%)	Spathulenol (10.0%)	α-Cubebene (6.6%)	Akrout *et al*. (2001)
77	*A. campestris*	Tunisia, Benikhdache	β-Pinene (27.9 %)	p-Cymene (22.3%)	γ-Muurolene (9.6%)	α-Eudesmol (6.0%)	α-Terpinene (5.0%)	Akrout *et al*. (2001)
78	*A. campestris*	Tunisia, Jerba	β-Pinene (25.2 %)	p-Cymene (20.7%)	α-Pinene (11.0%)	Spathulenol (7.1%)	(ar)-Curcumene(6.9%)	Akrout *et al*. (2001)
79	*A. campestris*	India	Caryophyllene oxide (18.2 %)	α-Pinene (15.3 %)	β-Pinene (9.8 %)	Spathulenol (9.3%)	1, 8-Cineole (5.2%)	Guven (1963)
80	*A. campestris*	Turkistan	1,2-dihydro Acenaphthylene (20.7%)	Tremetone (15.8%)	Capillin (10.4%)	Spathulenol (6.5%)	β-Pinene (6.3%)	Baykan-Erel *et al*. (2012)
81	*A. campestris*	Morocco	Spathulenol (10.2%)	Eudesmol (4.1%)	p-Cymene (3.8%)	δ-Cadinene (3.7%)	β-Pinene (2.8%)	Dib *et al*. (2017)
82	*A. campestris*	Serbia	Spathulenol (9.2%)	β-Pinene (9.1%)	α-Pinene (3.4%)	Germacrene D (3.3%)	β-Caryophyllene (3.0%)	Chalchat *et al*. (2003)
83	*A. campestris*	Tunisia	â-Pinene (33.0%)	Limonene (15.1%)	α-Pinene (12.3%)	δ-Terpinene (7.6%)	β-Myrcene (5.5%)	Aloui *et al*. (2016)
84	*A. capillaris*	China	Capillin (24.2%)	β-Pinene (12.1%)	β-Caryophyllene (5.2%)	Limonene (4.5%)	α-Pinene (4.3%)	Yang *et al*. (2015)
85	*A. capillaris*	India	Capillin (42.1%)	β-Caryophyllene (12.5%)	Myrcene (9.2%)	β-Pinene (8.6%)	p-Cymene (6.8%)	Semwal *et al*. (2015)
86	*A. capillaris*	Brazil	â-Citronellol (16.3%)	1,8-Cineole (13.1%)	Camphor (12.6%)	Linalool (11.3%)	α-Pinene (7.2%)	Gao *et al*. (2016)
87	*A. chamaemelifolia*	Iran (Shahkoh)	Artemisia ketone (21.1%)	Borneol (10.8%)	1,8-Cineole (13.8%)	Unknown alcohol-2 (6.4%)	α-Bisabolol (4.5%)	Pirabalouti *et al*. (2013)
88	*A. ciniformis*	Iran	Camphor (30.2%)	1,8-Cineole (23.7%)	trans-Pinocarveol (12.3%)	Pinocarvone (4.9%)	Terpinen-4-ol (3.4%)	Taherkhani (2016)
89	*A. desertii*	Iran	Camphor (45.5 %)	1,8-Cineole (16.7 %)	Piperitone (8.6%)	β-Pinene (5.7 %)	Isoborneol (3.2%)	Rustaiyan *et al*. (2000)
90	*A. dracunculus*	Italy	trans-Anethole (53.4 %)	cis-allo-Ocimene (15.3 %)	cis-Ocimene (10.6 %)	trans-Ocimene (9.0%)	Limonene (7.3%)	Curini *et al*. (2006)
91	*A. dracunculus*	Iran	(z)-Anethole (51.7 %)	(z)- β-Ocimene (8.3%)	methyl Eugenol (8.1%)	Limonene (4.9%)	Linalool (4.4%)	Ayoughi *et al*. (2011)
92	*A. dracunculus*	Turkey	(z)-Anethole (81.0 %)	(z)- β-Ocimene (6.5%)	(E)-β-Ocimene (3.1%)	Limonene (3.1%)	methyl Eugenol (1.8%)	Kordali *et al*. (2005b)
93	*A. dracunculus*	Albania	Terpinolene (25.4 %)	(z)- β-Ocimene (22.2%)	5-Phenyl-1,3-pentadyne (11.7%)	Capillin (4.8%)	methyl Eugenol (3.0%)	Meepagala *et al*. (2002)
94	*A. dracunculus*	Poland	Elemicin (48.8 %)	Sabinene (18.9 %)	(E)-Asarone (13.3%)	Methyl eugenol (7.6%)	Capillin (5.1%)	Kowalski *et al*. (2007)
95	*A. dracunculus*	Italy	methyl Chevicol (73.3%)	Limonene (5.4%)	(E)-β-Ocimene	β-Pinene (3.4%) (5.3%)	1,8-Cineole (3.0%)	Bedini *et al*. (2017)
96	*A. dracunculus*	Europe	Estragole (73.3%)	Limonene (5.4%) (5.3%)	(E)-β-Ocimene	β-Pinene (3.4%)	(z)-β-Ocimene (3.0%)	Fraternale *et al*. (2015)

97	*A. echegarayi*	Argentina	β-Thujone (49.3%)	α-Thujone (10.7%)	Borneol (5.3%)	Camphor (5.1%)	Bornyl acetate (4.0%)	Lacier *et al*. (2009)
98	*A. feddei*	Russia	Camphor (31.2%)	1, 8-Cineole (14.2%)	Artemisia alcohol (12.9%)	Borneol (9.7%)	Terpinen-4-ol (4.1%)	Ozek *et al*. (2014)
99	*A. feddei*	Korea	1, 8-Cineole (16.9 %)	Chamazulene (9.0 %)	α-Terpineol (8.2 %)	α-Phellandrene (5.8%)	α-Thujone (5.5%)	Cha *et al*. (2007)
100	*A. fragrans*	Iran	Camphor (31.8%)	1,8-Cineole (29.0%)	cis-p-Mentha-2-en-1-ol (6.2%)	Camphene (4.9%)	trans-p-Mentha-2-en-1-ol (4.0%)	Farghadan *et al*. (2016)
101	*A. fragrans*	Iran	Chrysanthenone (41.1%)	1, 8-Cineole (11.1 %)	n-Pentane (9.1%)	5,5-dimethyl-1-ethyl-1-ethyl-3-cyclopenta-diene (5.8%)	Cis-Jasmone (3.7%)	Amiri *and* Goodraji (2017)
102	*A. frigida*	Mongolia	cis-p-Menth-2-en-1-ol (20.8 %)	1,8-Cineole (12 %)	Borneol (10.2 %)	Lavandulol (9.3%)	Camphor (6.9%)	Liu *et al*. (2014)
103	*A. frigida*	Canada	1,8-Cineole (25.1 %)	Camphor (20.6 %)	Chrysenthenone (7.4%)	Camphene (4.1%)	Borneol (3.8%)	Lopez-Lutz *et al*. (2008)
104	*A. frigida*	Khazakhstan	1,8-Cineole (24.7 %)	Camphor (22.6 %)	Borneol (8.9%)	β-Thujone (5.2%)	Camphene (4.2%)	Atazhanova *et al*. (1999)
105	*A. gilvescens*	China	Camphor (13.5%)	1,8-Cineole (12.1%)	Terpinen-4-ol (9.7%)	Germacrene D (8.6%)	Caryophyllene oxide (4.7%)	Zhu *et al*. (2013)
106	*A. giraldii*	China	β-Pinene (13.2%)	Iso-Elemicin (10.1%)	Germacrene D (5.7%)	4-Terpineol (5.4%)	(z)-β-Ocimene (5.1%)	Chu *et al*. (2012)
107	*A. gmelini*	Russia	Longiverbenone (12.0%)	Isopinocamphene (8.9%)	1,8-Cineole (6.7%)	Camphor (5.8%)	trans-p-Menth-2-en-1-ol (5.3%)	Ozek *et al*. (2014)
108	*A. gmelini*	India	Artemisia ketone (40.7%)	cis-Chrysanthenyl acetate (21.3%)	1,8-Cineole (11.0%)	Pinocarvone (8.9%)		Pandey *et al*. (2015)
109	*A. gmelini*	India	Artemisia ketone (53.3%)	α-Thujone (9.9%)	1,8-Cineole (6.6%)	Artemisia triene (3.9%)	trans-Geraniol (3.1%)	Haider *et al*. (2012)
110	*A. gorgonum*	France	Camphor (28.7%)	Chrysanthenone (10.8%)	Lavandulyl 2-methyl butanoate (9.5%)	α-Phellandrene (5.5%)	Camphene (4.0%)	Ortet *et al*. (2010)
111	*A. haussknechtii*	Iran	Camphor (42.5%)	1,8-Cineole (20.9%)	Isoborneol (7.3%)	Camphene (5.4%)	2,5-Octa-diene (3.5%)	Amiri and Goodrazi (2017)
112	*A. herba-alba*	Algeria	Camphor (39.5%)	Chrysanthenone (10.4%)	1,8-Cineole (8.6%)	α-Thujone (7.0%)	Borneol (3.4%)	Lakehal *et al*. (2016)
113	*A. herba-alba*	Algeria	Camphor (34.3%)	Eucalyptol (13.5%)	α-Thujone (8.4%)	Camphene (8.3%)	Chrysanthenone (6.4%)	Amel *et al*. (2017)
114	*A. herba-alba*	Tunisia	Camphor (36.0%)	1,8-Cineole (13.9%)	Chrysanthenone (8.8%)	α-Thujone (7.7%)	β-Thujone (7.2%)	Aloui *et al*. (2016)
115	*A. incana*	Iran	Camphor (20.4%)	1,8-Cineole (10.3%)	(z)-Verbenol (8.7%)	α-Thujone (8.3%)	α-Thujone (5.6%)	Mojarrab *et al*. (2013)

116	*A. indica*	India	Davanone (30.8%)	β-Pinene (15.3%)	Germacrene D (5.6%)	β-Elemene (4.9%)	p-Cymene (4.3%)	Haider *et al*. (2014)
117	*A. japonica*	India	Linalool (27.5%)	Germacrene D (11.2%)	(E)-β-Ocimene (6.5%)	1,8-Cineole (5.5%)	(z)-β-Ocimene (5.5%)	Joshi (2014)
118	*A. judaica*	Algeria	Piperitone (66.2%)	ethyl Cinnamate isomer (6.1%)	Spathulenol (2.0%)	ethyl Cinnamate (1.7%)	α-Eudesmol (1.5%)	Farah *et al*. (2017)
119	*A. judiaca*	Egypt	Piperitone (32.4%)	Camphor (20.6%)	(E)-ethyl-Cinnamate (8.2%)	Terpinene-4-ol (4.6%)	Chrysanthenone (3.9%)	Abd-Elhady (2012)
120	*A. kotuchovii*	Kazhakistan	Estragole (75.1%)	(E)-β-Ocimene (9.2%)	(z)-β-Ocimene (8.2%)	methyl Eugenol (4.3%)	Limonene (1.0%)	Schepetkin *et al*. (2015)
121	*A. lavandulaefolia*	China	β-Caryophyllene (15.5%)	β-Thujone (13.6%)	1,8-Cineole (13.1%)	β-Farnesene (12.3%)	Germacrene D (9.1%)	Liu *et al*. (2010b)
122	*A. avandulaefolia*	China	β-Caryophyllene (16.1%)	cis-Chrysanthenol (7.0%)	1,8-Cineole (5.6%)	Borneol (5.3%)	trans-β-Farnesene (5.1%)	Cha *et al*. (2005a)
123	*A. longifolia*	Turkey	1,8-Cineole (27.6%)	Camphor (18.5%)	Borneol (5.5%)	Terpinen-4-ol(3.9%)	Camphene (3.3%)	Lopez-Lutz *et al*. (2008)
124	*A. ludoviciana* var. *latiloba*	USA, Population 1	1,8-Cineole (26.2%)	Camphor (20.1%)	Borneol (16.0%)	Linalool (4.1%)	Terpin-1-en-4-ol (2.3%)	Collin *et al*. (2017)
125	*A. ludoviciana* var. *latiloba*	USA, Population 2	Camphor (20.8%)	Borneol (13.9%)	1,8-Cineole (10.8%)	Artemysyl acetate (1.6%)	Yamogi alcohol (1.4%)	Collin *et al*. (2017)
126	*A. maderas-patana*	India	α-Humelene (46.3%)	β-Caryophyllene (9.3%)	α-Copaene (8.2%)	β-Myrcene (4.3%)	(Z,E)-α-Farnesene (3.7%)	Jyotshna *et al*. (2017)
127	*A. manshuria*	Russia	Germacrene D (11.2%)	Rosifoliol (10.1%)	Caryophyllene oxide (6.8%)	Eudesma-4(15)-7-dien-1b-ol (5.6%)		Ozek *et al*. (2014)
128	*A. maritima*	India	1,8-Cineole (23.2%)	Camphor (20.7%)	Borneol (13.9%)	Bornyl acetate (13.2%)	Cis-3-Hexenyl isobutyrate (2.8%)	Sharma *et al*. (2014)
129	*A. minor*	Cold desert, India	1,8-Cineole (22.3 %)	Camphor (12.6%)	Davanone (12.3 %)	Ascaridole (11.1%)	α-Phellandrene (5.2%)	Sharma *et al*. (2011)
130	*A. monosperma*	Libya	β-Pinene (16.9%)	Bornyl acetate (14.1%)	Sabinene (13.2%)	β-Eudesmol (8.0%)	β-trans-Ocimene (5.5%)	El Zalabani *et al*. (2017)
131	*A. montana*	Japan	Borneol (16.3%)	1,8-Cineole (15.4%)	Camphor (13.7%)	Piperitone (5.5%)	β-Caryophyllene oxide (3.9%)	Kunihiro *et al*. (2017)
132	*A. moorcroftiana*	Central Europe	α-Thujone (12.8%)	Artemisia ketone (10.2%)	β-Pinene (7.7%)	1, 8-Cineole (5.8%)	Camphor (5.6%)	Weyerstahl *et al*. (1992)
133	*A. nilagirica*	India	Linalool (32.5%)	iso-Pulegyl acetate (20.7%)	Sabinene (6.6%)	β-Caryophyllene (6.3%)	α-Thujone (3.7%)	Badoni *et al*. (2009 and 2010)
134	*A. nilagirica*	India	α-Thujone (36.4%)	β-Thujone (9.4)	Germacrene D (6.3%)	Terpinen-4-ol (6.3%)	β-Caryophyllene (5.4%)	Sati *et al*. (2013)
135	*A. nilagirica*	India	Artemisia ketone (45.0%)	Chrysanthenone (7.7%)	Germacrene D (6.8%)	β-Caryophyllene (4.3%)	1,8-Cineole (3.0%)	Padalia *et al*. (2014)

136	*A. olgensis*	Russia	Eudesma-4(15), 7-dien-1b-ol (6.9%)	Caryophyllene oxide (5.6%)	Guaia-6,10(14)-dien-4b-ol (5.1%)	Hexadecanoic acid (5.0%)	Germacrene D (4.2%)	Ozek *et al*. (2014)
137	*A. oliveriana*	Russia	α-Thujone (65.4 %)	Camphor (11.5%)	1,8-Cineole (9.2 %)	Pinocarvone (8.8%)	Camphene (0.7%)	As above
138	*A. parviflora,* population 1	India	β-Caryophyllene (15.3%)	Germacrene D (14.8%)	Camphor (11.4%)	Artemisia ketone (7.8%)	1,8-Cineole (5.8%)	Rana *et al*. (2003)
139	*A. parviflora,* population 2	India	Germacrene D (41.0%)	β-Caryophyllene (10.6%)	α-Humulene (7.9%)	Capaene (2.6%)	Artemisia alcohol (2.6%)	Tewari *et al*. (2015)
140	*A. persica*	Iran	β-Thujone (75.2%)	α-Thujone (2.8%)	1,8-Cineole (2.4%)	Terpinen-4-ol (2.2%)	Cuminic aldehyde (1.0%)	Nikbakht *et al*. (2014)
141	*A. phaeolepis*	Mediterranean	1,8-Cineole (11.5%)	Camphor (8.2%)	Terpinen-4-ol (6.4%)	Caryophyllene oxide (6.3%)	β-Caryophyllene (5.4%)	Hsouna *et al*. (2013)
142	*A. roxburghiana*	India	Borneol (18.5%)	α-Thujone (13.1%)	Artemisia alcohol (11.6%)	β-Eudesmol (11.6%)	Eucarvone (2.0%)	Pandey *et al*. (2015)
143	*A. rupestris*	China	α-Terpinyl acetate (37.2%)	Spathulenol (10.7%)	α-Terpineol (10.1%)	Linalool (7.6%)	4-Terpineol (3.9%)	Liu *et al*. (2013b)
144	*A. saharae*	Tunisia, Population 1	α-Thujone (13.0%)	Camphor (10.7%)	Chrysanthenyl acetate (10.2%)	β-Thujone (9.2%)	Sabinyl acetate (7.7%)	Zouari *et al*. (2014)
145	*A. saharae*	Tunisia, Population 2	α-Thujone (11.4%)	Sabinyl acetate (10.8%)	Chrysanthenyl acetate (7.9%)	Chrysanthenone (7.7%)	Sabinyl acetate (7.7%)	Zouari *et al*. (2014)
146	*A. saharae*	Tunisia, Population 3	Chrysanthenyl acetate (21.1%)	Chrysanthenone (14.0%)	Pinocarveol (5.8%)	Spathulenol (3.4%)	Sabinyl acetate (2.8%)	Zouari *et al*. (2014)
147	*A. saharae*	Tunisia, Population 4	Chrysanthenone (14.0%)	Chrysanthenyl acetate (11.5%)	Sabinyl acetate (4.0%)	Davana ether (3.4%)	cis-Jasmone (3.3%)	Zouari *et al*. (2014)
148	*A. saharae*	Tunisia, Population 5	Chrysanthenyl acetate (18.7%)	Chrysanthenone (9.9%)	Sabinyl acetate (6.2%)	Pinocarveol (4.3%)	γ-vinyl-γ-Valero-lactone (3.5%)	Zouari *et al*. (2014)
149	*A. saharae*	Tunisia, Population 6	α-Thujone (20.2%)	Sabinyl acetate (10.3%)	β-Thujone (9.9%)	Chrysanthenone (8.3%)	Chrysanthenyl acetate (9.1%)	Zouari *et al*. (2014)
150	*A. saharae*	Tunisia, Population 7	Chrysanthenone (10.8%)	Sabinyl acetate (10.6%)	α-Thujone (8.2%)	Chrysanthenyl acetate (8.2%)	Camphor (3.4%)	Chhetri *et al*. (2015)
151	*A. santolina*	Iran	Neryl acetate (13.4%)	Bornyl acetate (10.9%)	trans-Verbenol (9.9%)	Lavandulol (8.8%)	Linalool (6.9%)	Sefidkon *et al*. (2002)
152	*A. santolina*	Iran	1,8-Cineole (21.1%)	Camphor (13.1%)	Chrysanthenone (7.0%)	trans-methyl Cinnamate (5.6%)	Lyralyl alcohol (5.2%)	Sardashti *et al*. (2015)
153	*A. santonicum*	Turkistan	Spathulenol (15.6%)	1,2-dihydro Acenapthylene (11.8%)	Caryophyllene oxide (11.4%)	Capillin (5.6%)	p-Cymene (4.0%)	Baykan-Erel *et al*. (2012)
154	*A. scoparia*	Crimea (Ukrane/ Russia)	Capillene (89.4%)	Eugenol (2.6%)	Scoparene (2.5%)	Eugenol acetate (1.0%)	â-Pinene (0.9%)	Khodakov and Kotikov (2009)

155	*A. scoparia*	Turkistan	α-Thujone (39.5%)	β-Thujone (25.1%)	1,8-Cineole (6.7%)	(z)-Jasmone (2.2%)	Camphor (2.0%)	Baykan-Erel *et al*. (2012)
156	*A. scoparia*	Tibbet, China	2-ethenyl-Naptha-lene (45.1%)	β-Pinene (11.2%)	3-Carene (8.7%)	3,7-dimethyl-1,3,6, Octatriene (7.9%)	Limonene (5.4%)	Yao and Bo (2016)
157	*A. sieberi*	Iran	Camphor (44%)	1,8-Cineole (19 %)	Camphene (5%)	Terpinen-4-ol (2.5%)	α-Terpineol (2 %)	Weyerstahl *et al*. (1993)
158	*A. sieberi*	Iran	Camphor (49.3%)	1,8-Cineole (11.1%)	Bornyl acetate (5.8%)	Neryl acetate (4.3%)	trans-Verbenol (3.1%)	Sefidkon *et al*. (2002)
159	*A. sieberi*	Iran	1,8-Cineole (45.9%)	Terpinen-4-ol (3.9%)	α-Terpineol (3.8%)	Camphor (3.4%)		Sardashti *et al*. (2015)
160	*A. sieberi*	Iran	α-Thujone (31.5%)	Camphor (12.3%)	β-Thujone (11.9%)	1,8-Cineole (10.1%)	Camphene (8.9%)	Youssefi *et al*. (2017)
161	*A. sieberi*	Middle East	Camphor (54.7%)	Camphene (11.7%)	1,8-Cineole (9.9%)	β-Thujone (5.6%)	α-Pinene (2.5%)	Negahban *et al*. (2007)
162	*A. sieberi*	Pakistan	β-Thujone (19.8%)	α-Thujone (19.6%)	Camphor (19.6%)	Verbenol (9.7%)	1,8-Cineole (3.5%)	Farzaneh *et al*. (2006)
163	*A. sieberi*	Iran	α-Thujone (31.5%)	Camphor (12.3%)	β-Thujone (11.9%)	1,8-Cineole (10.1%)		Tabari *et al*. (2017)
164	*A. subdigitata* Chu *et al*. (2012)	China	1,8-Cineole (12.3%)	á-Curcumene (10.8%)		â-Pinene (7.4%)	Borneol (6.2%)	Eugenol (5.9%)
165	*A. sieversiana* Liu *et al*. (2010b)	China	1,8-Cineole (9.2%)	Geranyl butyrate (9.1%)		Camphor (7.9%)	Borneol (7.9%)	Germacrene D (5.5%)
166	*A. spicigera*	Turkey	1,8-Cineole (57.8%)	Camphor (20.2%)	Camphene (4.9%)	Thymol (2.0%)	β-Myrcene (1.5%)	Guvenalp *et al*. (1998)
167	*A. spicigera*	Iran	Camphor (30.7%)	1,8-Cineole (27.2%)	Camphene (18.7%)	α-Thujone (14.6%)	β-Thujone (5.0%)	Chehregani *et al* (2013)
168	*A. spicigera*	Iran	1,8-Cineole (47.2%)	Camphor (28.8%)	Spathulenol (8.3%)	α-Thujone (6.1%)	Chrysanthenyl acetate (5.7%)	Chehregani *et al* (2013)
169	*A. spicigera*	Iran	Camphor (15.3%)	1,8-Cineole (9.1%)	α-Thujone (8.4%)	Chrysanthenone (6.6%)	Camphene (3.5%)	Chehregani *et al* (2013)
170	*A. stelleriana*	India	1,8-Cineole (29.6%)	Artedouglasia oxide (22.5%)	Germacrene D (5.6%)	Vulgarone (3.1%)	Davanone B (3.0%)	Padalia *et al*. (2016)
171	*A. stolonifera*	China	1,8-Cineole (32.9%)	β-Pinene (8.2%)	Camphor (6.1%)	Terpinen-4-ol (6.1%)	α-Terpinene (5.9%)	Zhang *et al*. (2015)
172	*A. tourne-fortiana*	Iran	(z)-Nerolidol (22.4%)	β-Caryophyllene (15.6%)	Santolina triene (10.1%)	ä-Cadinene (4.8%)	α-Pinene (4.8%)	Kazemi *et al*. (2013 b)
173	*A. tschernie-viana*	Iran	p-Cymene (21.3%)	β-Pinene (17.8%)	α-Pinene (9.4%)	α-Terpinene (9.1%)	cis-Ocimene (8.8%)	Kazemi *et al*. (2009)
174	*A. turcomanica*	Iran	1,8-Cineole (19.2%)	Camphor (15.5%)	cis-Jasmone (4.3%)	Brevifolin (6.2%)	α-Thujone (2.3%)	Nikbakht *et al*. (2014)
175	*A. vulgaris*	Egypt	Camphor (11.4%)	3,5-Dimethyl cyclohexene (11.4%)	α-Cubebene (8.6%)	Germacrene D (8.6%)	1,8-Cineole (7.5%)	Hussein *et al*. (2016)
176	*A. vulgaris*	Turkistan	α-Thujone (56.1%)	β-Thujone (12.0%)	Caryophyllene oxide (10.2%)	1, 8-Cineole (8.5%)		Baykan-Erel *et al*. (2012)

a = Essential oil obtained via headspace and solid-phase microextraction; Vidic *et al.* (2018) observed high degree of correspondence in the major components of essential oils extracted by headspace and hydro-distillation methods.

to 32 populations and the remainder by only one population. The table includes observations on the essential oils extracted from wild and/or cultivated populations of individual species growing in similar and different agro-environments. Despite that only five constituents have been taken into consideration, it is observed that the essential oils of all of 176 populations are compositionally different. It is further observed from the table 2 that there are in all 160 different volatile compounds (monoterpenes > sesquiterpenes > other classes) that comprise the major constituents of the essential oils of 176 populations. This small number indicates that *Artemisia* species share much of the genetic apparatus coding for the biosynthetic pathways of volatile organic compounds (VOCs) common in them. However, the inter-species differences and intra-species differences can be ascribed to evolutionary mechanisms that selected altered alleles of the same VOC structural and regulatory genes. *Artemisia* species are largely open pollinated which favours origin of varied combinations of the available allelic polymorphism.

Volatile Organic Compounds Preponderant in the Essential Oils of Multiple Artemisia Species

The organic volatile compound that occurs in an essential oil at $\geq$ 20% concentration is treated here as a preponderant component (Table 3). There are in all 35 volatiles that are preponderant among the 160 major ones in the essential oils of 176 populations of 66 *Artemisia* species listed in Table 2. Of these VOCs 12 occur in essential oils of two or more species. Since these cover 39 of the 66 species included in the Table 2, the 12 VOCs identified below can be considered, individually and in permuted combinations, as markers of *Artemisia* essential oils or *Artemisia* taxa itself. The preponderant volatiles present in the essential oils of multiple *Artemisia* species and the concerned species are identified here. The most prevalent such volatiles are camphor and 1,8-cineole, both monoterpenes. Camphor is present in the essential oil of the following 32 *Artemisia* species listed in the table 3: *A. abyssinica, A. absinthium, A. afra, A. annua, A. arborescens, A. aucheri, A. austriaca, A. campestris, A. capillaris, A. ciniformis, A. desertii, A. feddei, A. fragrans, A. frigida, A. gilvescens, A. gorgonum, A. hausknechtii, A. herba-alba, A. incana, A. judiaca, A. longifolia, A. ludoviciana, A. maritima, A. minor, A. montana, A. oliveriana, A. parviflora, A. saharae, A. santolina, A. sieberi, A. spicigera* and *A. turcomanica*. The essential oils of the following 33 species contain the volatile 1,8-cineole: *A. abrotanum, A. absinthium, A. afra, A. annua, A. anethoides, A. argyi, A. asiatica, A. austriaca, A. capillaris, A. chamaemelifolia, A. ciniformis, A. desertii, A. feddei, A. fragrans, A. frigida, A. gilvescens, A. gmelinii, A. haussknechtii, A. herba-alba, A. incana, A. lavandulaefolia, A. longifolia, A. ludoviciana, A. maritima, A. minor, A. montana, A. phaeolepis, A. santolina, A. sieberi, A. spicigera, A. stelleriana, A. stolonifera and A. turcomanica.* The essential oils of the following species have the monoterpene a-thujone in $\geq$20% concentration: *A. echegarayi, A. gmelinii, A. moorcraftiana, A. nilagirica, A. oliveriana, A. saharae, A. scoparia, A. sieberi, A. spicigera* and *A. vulgaris*. The monoterpene b-thujone is preponderant in the essential oils of 9 *Artemisia* species: *A. absinthium, A. arborescens, A. echegarayi, A. lavandulaefolia, A. persica, A. saharae, A. scoparia, A. sieberi,* and *A. vulgaris*. The monoterpene artemisia ketone is preponderant in the essential oils of 7 *Artemisia* species: *A. afra, A. annua, A. arborescens, A. chamaemelifolia, A. gmelinii, A. moorcraftiana* and *A. nilagirica*.

The monoterpene piperitone and sesquiterpene germacrene D are preponderantly present in the essential oils of 5 *Artemisia* species each; piperitone in *A. abrotanum, A. alba, A. annua, A. asiatica* and *A. judiaca* and germacrene D in *A. alba, A. annua, A. japonica, A. maritima* and *A. parviflora*. The monoterpenes p-cymene and linalool are preponderant in the essential oils of 4 species each: p-cymene in *A. annua, A. asiatica, A. campestris* and *A. tschernievana*; and linalool in *A. abrotanum, A. capillaris, A. japonica* and *A. nilagirica*. The benzenoid capillin is preponderant in the essential oils of 3 *Artemisia* species: *A. capillaris, A. campestris* and *A. scoparia*. The phenylpropanoid estragole (methyl chavicol) is preponderant in the essential oils of 2 species: *A. dracunculus* and *A. kotuchovii*. The monoterpenoid cis-chrysanthenyl acetate is present in ^{3}20% concentration in the essential oils of 2 Artemisia species: *A. absinthium* and *A. gmelinii*.

Table 3: The constituents richly (≥20% concentration) present in the foliage essential oils of different populations *Artemisia* species (the information contained in this table has been derived from the Table 2)

S.No.	Essential oil constituent	*Artemisia* species in whose foliage essential oil(s), the specific constituent has been found to occur at the concentration of			
		20-30%	31-40%	41-50%	≥50%
1	Camphor	*absinthium, afra, annua, aucheri, ciniformis, incana, judiaca, maritima, spicigera*	*abyssinica, annua, arborescens, ciniformis, feddei, fragrans, herba-alba, spicigera*	*afra, annua, desertii, herba-alba, seiberi*	*annua, sieberi*
2	1,8-Cineole (Eucalyptol)	*afra, annua, argyi, longifolia, maritima, minor, santolina, spicigera, stellariana*	*afra, anethoides, stolonifera, stellariana*	*sieberi, spicigera*	*spicigera*
3	Artemisia ketone	*annua, chamaemelifolia*	*afra, annua*	*annua, gmelini, nilgirica*	*annua, arborescens, gmelini*
4	β-Thujone	*saharae, sieberi*	*absinthium*	*absinthium, echegarayi*	*absinthium, persica*
5	α-Thujone	*sieberi*	*nilgirica, scoparia, sieberi*		*oliveriana*
6	cis-Chrysanthanyl acetate	*absinthium, gmelini, saharae*			
7	Estragole				*dracunculus, kotuchovii*
8	Piperitone		*alba, judiaca*		*judiaca*
9	Capillin	*capillaris*		*capillaris*	*scoparia*
10	p-Cymene	*campestris, tschernieviana*			
11	Germacrene D	*annua*	*parviflora*		*A. annua*
12	Linalool	*japonica*	*nilgirica*		
Subtotal of species		22	20	11	12
Grand total of species whose essential oils contain one or more of constituents in ≥20% concentration			39		

The Volatiles Abundantly Present in Essential Oils are Markers of Distinct *Artemisia* Populations

Some of the essential oils listed in the table 2 contain certain volatile organic compounds in ≥50% concentration (Fig. 3). It is suggested that such abundantly present volatiles, 12 in all, are perhaps markers of the concerned *Artemisia* populations. The phenylpropanoid volatile trans-anethole marks the populations of *A. dracunculus* originating in Italy, Iran and Turkey. The monoterpene artemisia ketone is the marker for five populations of *A. annua*, namely from India, Hungary, Germany, Bosnia and Netherlands, an Algerian-population of *A. arborescens* and two populations of *A. gmelinii* from India. A population of *A. annua* from India and *A. sieberi* from Middle East are marked by the monoterpene camphor. Germacrene D, a sesquiterpene, is the marker for the *A. annua* cultivar Anamed A3. The benzenoid capillin marks the population of *A. scoparia* from Russia. The monoterpene, 1, 8-cineole is the marker for a Turkish population of *A. spicigera*. Estragole (methyl chavicol), a phenylpropanoid, is the marker for two European populations of *A. dracunculus* and *A. kotuchovii* population from Kazhakistan. The monoterpene cis-epoxy-ocimene is the marker for *A. absinthium* population from Estonia. Piperitone (monoterpene) marks the *A. judiaca* population from Algeria, *A. absinthium* population from Estonia is marked by the monoterpene sabinyl acetate. a-thujone and b-thujone (monoterpenes) are respectively, the markers for *A. vulgaris* (Turkey) and *A. oliveriana* (Russia), and *A. absinthium* (Estonia) and *A. persica* (Iran) populations.

Table 4: Traditional uses, especially medicinal uses, of the plants of various *Artemisia* species of the family Asteraceae, from the wild populations growing in various parts of the world

S.No.	Name of *Artemisia* species	Geographical area(s) of traditional use	Documented traditional uses	Reference(s)
1	*A. abrotanum*	Europe	Used as: stomachic, nervine and hair tonic, anthelmintic, cholagogue, emmenagogue, insect repellant and as poultice to heal wounds and cure skin diseases	Wright (2003); www.pfaf.org/USER/Plant.aspx?Latinname= Artemisia + abrotanum
2	*A. absinthium*	North America, Europe, Southeast Asia, South Asia, Africa	Used in: brewing of wormwood wine and making of other alcoholic apertifs and tonic water, improving of memory (as Alzheimer's treatment), appetite and liver function, and relieving ailments such as atherosclerosis and related hypertension, gallstones, diabetes; used as: antipyretic, diuretic, antispasmodic, anti-inflammatory, antimalarial, antiseptic, anthelmintic, acaricidal, cholagogue, emmenagogue, abortifacient, insect-repellant, insecticidal and as poultice to heal abcesses, wounds, sores, bites and other skin diseases	Jansen (1981); Wake *et al*. (2000); Van Wyk and Wink (2004); Guarrera (2005); Bora and Sharma (2010); Lachanmeier (2010); Sharpov *et al*. (2012); Goud *et al*. (2015); Msaada *et al*. (2015)
3	*A. abyssinica*	Eurasia, Africa	Used for relief from ailments such as cough, bronchitis, tonsilitis, dyspepsia, diabetes, syphilis, gonorrhoea, leprosy, malaria; used as: antispasmodic, antirheumatic, anthelmintic and treatment of sores	Mossa (1985); Abebe and Ayehu (1993); Tadesse (2004); Geyid *et al*. (2005)
4	*A. afra*	South Africa, South Asia	Used for relief from respiratory and bronchial system ailments such a cold, cough, bronchitis, influenza, pneumonia and asthma etc., dyspepsia, hemorrhoids, arthritis, rheumatism; used as: diuretic, stomachic, anti-inflammatory, growth promoter in children and topical application to cure sores and skin diseases	Van Wyk and Wink (2004); Thring and Weitz (2006); Liu *et al*. (2009); Patil *et al.* (2011)
5	*A. annua*	Southeast- and South-Asia, North America	Used for flavoring of alcoholic drinks; used as: febrifuge (and antimalarial), narcotic, stomachic, anti-inflammatory, cholagogue, emmenagogue, vermifuge; treatment of hemorrhoids, wounds, abcesses and other skin diseases (by application of poultice)	Klayman (1985 and 1993); Mueller *et al*. (2000); Kindersley (2001); Harris (2003); Van der Kooy and Sullivan (2013); Yarnell (2014); Kumar *et al*. (2015)
6	*A. arborescens*	Middle East	Used to make tea along with mint and as anti-inflammatory	Ballero *et al*. (2001)
7	*A. argyi*	Southeast Asia, North America	Used to relieve ailments of liver, spleen and kidney	Otsuka (1992)
8	*A. biennis*	North America	Powdered leaves are used to cure infections and applied topically to treat sores and wounds	Kershaw (2000)
9	*A. bervifolia*	Eurasia	Used to cure earache and as purgative, anthelmintic and respiratory stimulant	Hamayun (2007)
10	*A. campestris*	Temperate areas of northern hemisphere	Used as: febrifuge, stomachic, antiseptic, cholagogue, emmenagogue, abortifacient, nervine and hair tonic, anti-inflammatory, diuretic; used to cure: hepatitis, hypertension, jaundice, gallstone, diabetes, soreness in eyes, eczema, applied topically to treat sores and abcesses and other skin diseases; roots are used as an item of perfumery	Grieve (1931), Hammiche and Maiza (2006), Leporatti and Ghedira (2009), Dib *et al.* (2017)
11	*A. capillaris*	China	Used as: nervine tonic, treatment of dysmenorrhea and applied topically for skin diseases	www.chinese_herbs.org/artemisia/
12	*A. carvifolia*	Southeast- and South-Asia	Used as tonic, stomachic and depurative, vermifuge, antimalarial, insect repellant and to cure respiratory	Yeung (1985); Chopra *et al*. (1988); Brown (1995);

			problems such as cold and cough, and applied as poultice to cure sores, abcesses, boils and other skin diseases	Chevallier (1996)
13	*A. cina*	China and Central Asia	As a potent anthelmintic	Grieve (1931), Hammond *et al*. (1997)
14	*A. douglasiana*	North and South America	Used to treat dyspepsia, dysmenorrhea, arthritis and as abortifacient	Hunn (1990); Chevallier (1996)
15	*A. dracunculus*	North america, Eurasia, Southeast Asia and South Asia	Used as: a condiment, narcotic, febrifuge, diuretic, stomachic, vermifuge, emmenagogue, anti-inflammatory and insect repellant, relief from insomnia, dyspepsia and tooth ache; poultice for gout, rheumatism, cuts, wounds and ulcers	Swanson-Flatt *et al*. (1991); Kindersley (2001); Harris (2003); Singh and Chauhan (2005); Aglarova *et al*. (2008); Obolskiy *et al*. (2011); Joshi *et al*. (2016)
16	*A. echegarayi*	South America	Used as condiment	Obolskiy *et al*. (2011)
17	*A. filifolia*	Southwest America	Used as stomachic, cholagogue and emmenagogue, and as treatment of dyspepsia, snake bites, boils, wounds etc.	Johnson (1999)
18	*A. frigida*	Asia and North America	Used: as condiment, disinfectant, insect repellant, vermifuge, stomachic, emmenagogue; to cure toothache, respiratory tract infections	Usher (1974); Hodgson (1998); Moerman (1998)
19	*A. fukudo*	Southeast Asia	Used as condiment and for its anti-inflammatory, anti-infective and anti-tumor effects	Lee (1979)
20	*A. glacialis*	Europe	Used as condiment, sedative, stomachic and applied as poultice to heal wounds	Chiej (1984)
21	*A. gmelini*	Southeast Asia, Europe	Used to treat cholecystosis, hepatitis and hyperlipidemia	Chancellor (2005)
22	*A. herba-alba*	Eurasia	Used in relieving ailments such as depression, insomnia, Alzheimer's, hypertension, epilepsy, dyspepsia, diabetes, cough, tooth aches, malaria; used as febrifuge, emmenagogue, antispasmodic, vermifuge, immunomodulator	Lee (1979); Al-Waili (1986); Friedman *et al*. (1986); Ziyyat *et al*. (1997); Wright (2002); Laid *et al*. (2008); Alzweiri *et al*. (2011); Moufid and Eddouks (2012)
23	*A. indica*	Southeast- and South-Asia	Leaves are used; as condiment, stomachic, antispasmodic, febrifuge, anthelmintic, antiseptic, emmenagogue, insecticidal, insect repellant; to treat conjuctivitis and wounds	Kunkel (1984); Chopra *et al*. (1988); Facciola (1990); Manandhar (2002); Kala (2005); Haider *et al*. (2014)
24	*A. japonica*	Southeast Asia	Used to cure dyspepsia, vaginitis, skin diseases, and as febrifuge and insect repellant; young leaves are used as vegetables	Duke and Ayensu (1985); Foster and Duke (1990)
25	*A. judaica*	Eurasia, North America	Used: as anthelmintic, stomachic, diaphoretic, analgesic and insect repellant	Liu *et al*. (2004); Van Wyk and Wink (2004); Mahmoud and Gairola (2013); El-Sayed *et al.* (2013)
26	*A. lactiflora*	Southeast Asia	Used as tonic and emmenagogue	Brown (1995)
27	*A. lancia*	Southeast Asia, South Asia	Used: as vegetable, condiment, febrifuge; to cure dyspepsia, cough and cold, and boils and wounds	Read (1977); Kunkel (1984); Manandhar (2002)
28	*A. ludoviciana*	North and South America	Used: as stomachic, anti-inflammatory, febrifuge, emmenagogue, insect repellant; to treat dyspepsia, cough, eye infections; topically to cure itching, rashes, eczema, spider bites, sores and abcesses	Monroy-Oritz and Castillo-Espava (2007)
29	*A. maritima*	Eurasia, Southeast- and South-Asia	Used as tonic (the species is a source of santonin), febrifuge, stomachic, antispetic, anthelmintic, cholagogue,	Grieve (1984); Duke and Ayensu (1985); Baquar

			emmenagogue; and to treat jaundice, hypochondriasis and hepatitis	(1989); Kumar *et al*. (2011)
30	*A. mexicana*	North and South America	Used as anthelmintic and emmenagogue and its poultice is applied to cure sores, abcesses, bites etc.	Mabey (1974), Weiner (1980), Foster and Duke (2000); Moerman (1998)
31	*A. nilagirica*	South Asia	Used: as tonic, carminative, antiseptic; stomachic, cholagogue and insecticide; to treat insomina, diabetes, epilepsy, depression and skin diseases	Bhattacharjee (2000); Kapoor (2000); Ganesan and Paulsamy (2011)
32	*A. princeps*	Southeast Asia	Used to get relief from dyspepsia, inflammation and hypertension	Park (1999)
33	*A. scoparia*	Eurasia	Used: as febrifuge, stomachic, diuretic, anthelmintic, anti-inflammatory, vasodilator, cholagogue, emmenagogue, insecticidal; to treat diseases such as Alzheimer's, hepatitis, jaundice, gall bladder inflammation and hypertension	Yeung (1985); Gruenwald (2000); Singh *et al*. (2009); Rana *et al*. (2010)
34	*A. sieversiana*	Southeast- and South-Asia	Used: as tonic, aperiant, anthelmintic, febrifuge, antiseptic, anti-rheumatic, emmenagogue and to treat: diabetes, jaundice, boils	Kunkel (1984); Chopra *et al*. (1988); Manandhar (2002); Uniyal *et al*. (2006); Joshi *et al*. (2016)
35	*A. spicigera*	Eurasia	Used: as stomachic, antiseptic, insecticidal; is applied topically to treat vaginitis, ulcerative sores	Baytop (1984); Guvenalp *et al*. (1998); Kordali *et al*. (2005a); Afshaw *et al*. (2011)
36	*A. tridentata*	North America	Used: as a food resource for farm animals and among human populations as vegetables, nervine and hair tonic, stomachic, emmenagogue, febrifuge and anti-inflammatory; to treat cold, cough, influenza, asthma; and for wound healings	Kelley *et al*. (1992); Kay (1996); Moerman (1998); Adams and Garcia (2009); pharmacytoothache informatics-2014-csab.blogspace
37	*A. vestita*	Eurasia, Southeast- and South-Asia	Used: as febrifuge, anthelmintic, antiphlogistic, and anti-inflammatory; and to treat fungal infections such as tinia, and oral and vaginal thrashes	Foster and Duke (2000); Tan *et al*. (1998); Yin *et al*. (2008); Sun *et al*. (2006); Sikdar and Dutta (2008)
38	*A. vulgaris*	North America, Europe, Asia, Africa	Used: as nervine tonic, febrifuge, stomachic, cholagogue, anthelmintic, antilithic, anti-inflammatory; to treat: hypertension, rheumatism, asthma, epilepsy, dysmenorrhoea; to induce labour and cause miscarriage; to cure ulcerative sores, oral and vaginal thrushes, and sundry skin diseases	Triska (1975); Stuart (1977); Chiej (1984); Grieve (1984), Yeung (1985); Lust (1985); Allardice (1993); Duke and Ayensu (1985); Foster and Duke (2000); Brown (1995); Hamayun (2007); Joshi *et al*. (2016)

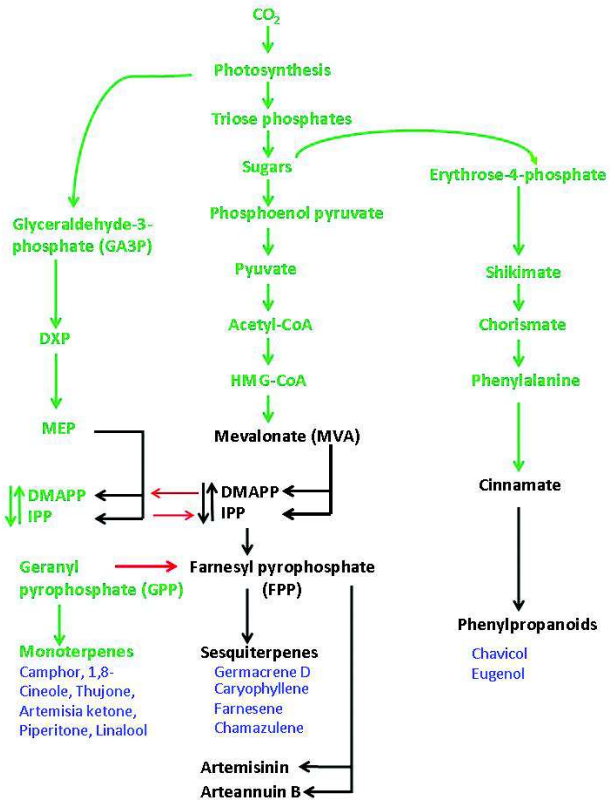

Fig. 2A: Volatilome of the terpenoids and phenylpropanoid extracted in hydro-distilled essential oils and artemisinome of *Artemisia annua*. The steps of MEP, MVA and phenylpropanoid pathways accomplished in chloroplast (plastids) are shown broadly in green colour and those performed in cytoplasm (cytosol) are shown in black color. The cross-talk between MEP and MVA pathways is shown in red colour. The abbreviation used are: DXP, 1-deoxy-D-xylulose-5-phosphate; MEP, 2-C-methyl-D-erythritol-4-phosphate; DMAPP, dimethyallyl pyrophosphate; IPP, isopentenyl pyrophosphate; HMG-CoA, 3-hydroxy-3methyl-glutaryl coenzyme A. The steps of the MEP, MVA and Cinnamate pathways are detailed in the figures 2c, 2b and 2e respectively. The biosynthetic steps for artemisinin are shown in the figure 2d

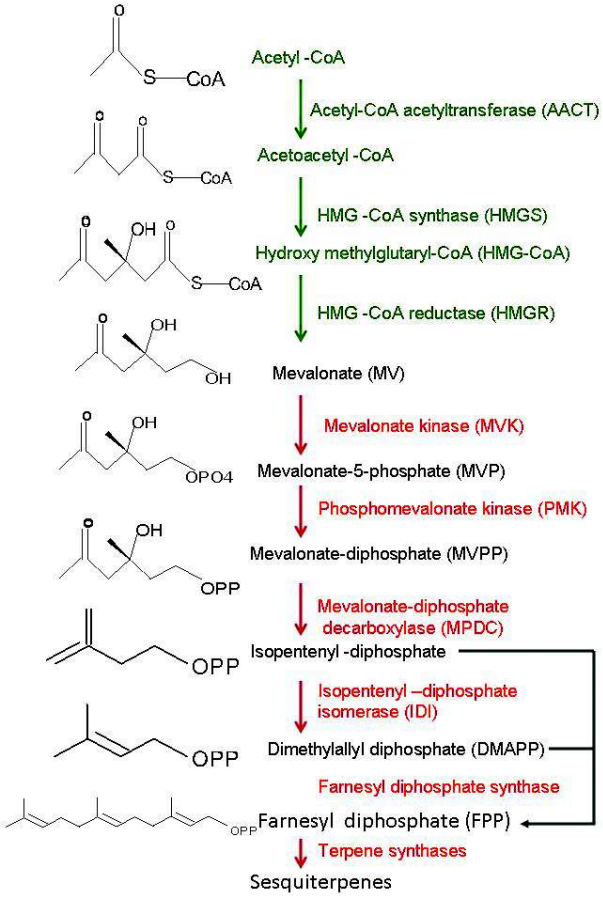

Fig. 2b: Mevalonic acid (MVA) pathway that produces building blocks for the terpene biosynthesis including sesquiterpenes and artemisinin in cytoplasm of the glandular trichome cells in *Artemisia annua*

Conclusion

The discussion in this section suggests that the future selection programme of breeding for essential oil quality, in *A. annua* and in artemisias in general, should emphasize on the following three kinds, for various applications. (i) Essential oils that are rich in combination with monoterpenes such as camphor, 1, 8-cineole, artemisia ketone and thujones. (ii) Sesquiterpene rich oils especially for germacrene D, farnesene, caryophyllene and chamazulene. (iii) Oils that have moderate concentrations of terpenes listed in (i) and (ii) above. All three kinds may have presence of phenylpropanoids such as chavicol and eugenol, and benzenoids such as capillin.

Sites of Synthesis of Essential Oils

In *Artemisia* species, essential oils are synthesized in secretory cells in trichomes borne as appandages on epidermis, and in cortical parenchymatous cells surrounding the resin ducts. All species of *Artemisia* whose essential oils have been characterized are known to bear grandular trichomes. (Duke and Paul 1993; Ferreira and Janik 1995; Kjaer *et al.*, 2014; Salehi *et al.*, 2018). Among the two types of trichomes, glandular and non-glandular (filamentous), the former are the pre-dominant producers of essential oils. The glandular trichomes are formed on leaves,

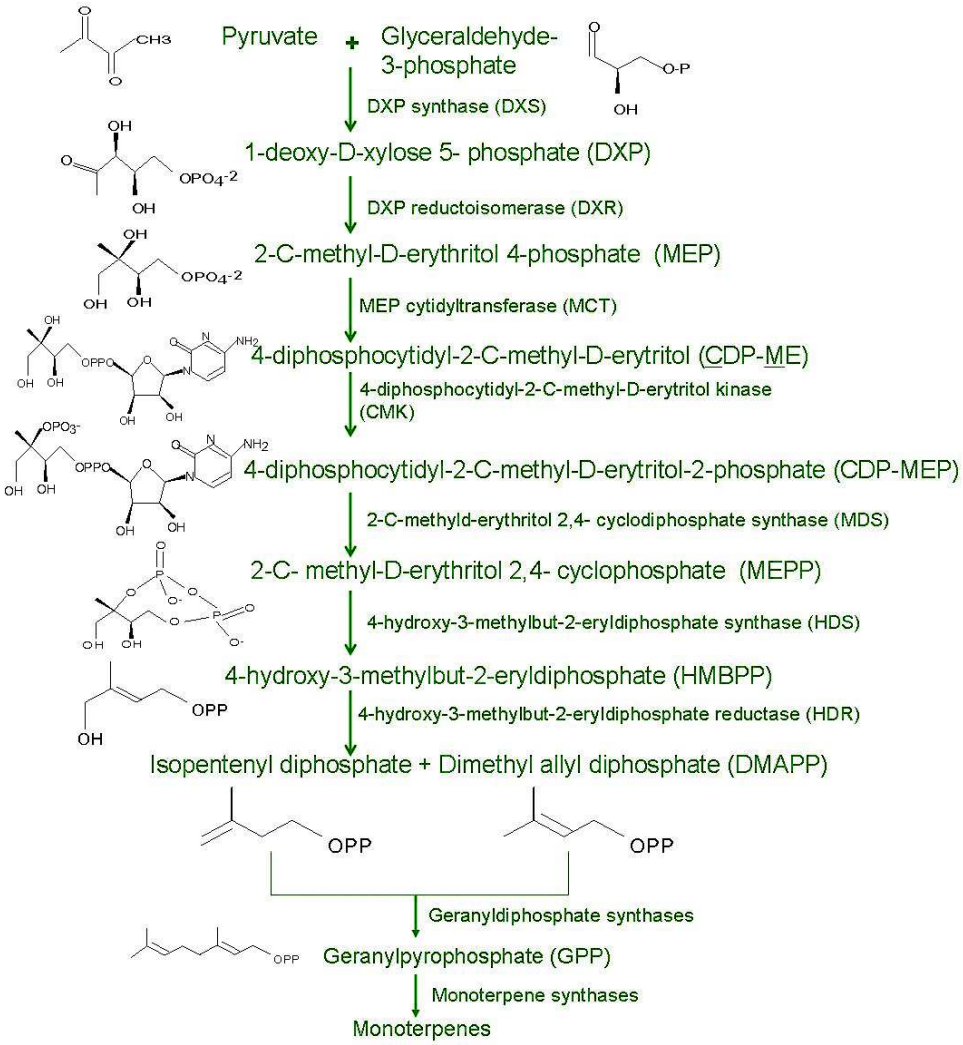

Fig. 2c: Methyl erythritol phosphate (MEP) pathway that produces building blocks for the terpene (monoterpenes) biosynthesis in chloroplasts of the glandular trichome cells in *Artemisia annua*

stem and inflorescence (integuments, flowers and seeds). The resin ducts run parallel to the vascular tissue, ramify root, stem, leaves and inflorescence and thus allow the essential oils secreted from the cortical parenchymatous cells, that are unlignified and leucoplastic, to be shared between organs (Lange 2015). *Artemisia* species have been observed to harbor considerable variation in their essential oil productivity and in trichome morphology and distribution (Hayat *et al*., 2009). Since the glandular trichomes of *Artemisia annua* produce artemisinin, the peroxide bridge containing terpenoid sesquiterpene lactone whose derivatives are ingredients of the prevalent and successful antimalarial combination therapy, in plants exclusively, therefore these have been studied in greater detail (Duke *et al*., 1994; Tellez *et al*., 1999; Olsson *et al*., 2009). In addition to artemisinin, the glandular trichomes of *Artemisia annua* biosynthesize and store more than 600 secondary metabolites of which few hundred are volatile organic compounds that constitute the essential oil (Brown 2010). Production of the phytotoxic compounds, such as artemisinin and many other secondary metabolites, in trichomes is a biological mechanism of self-protection against phytotoxins produced by *Artemisia annua*, and other species.

Both the glandular and non-glandular trichomes of *Artemisia annua* (Fig. 1) are multicellular protuberances of differentiated cells growing out of a fraction of epidermal layer cells of various shoot organs. They begin to form with the emergence of

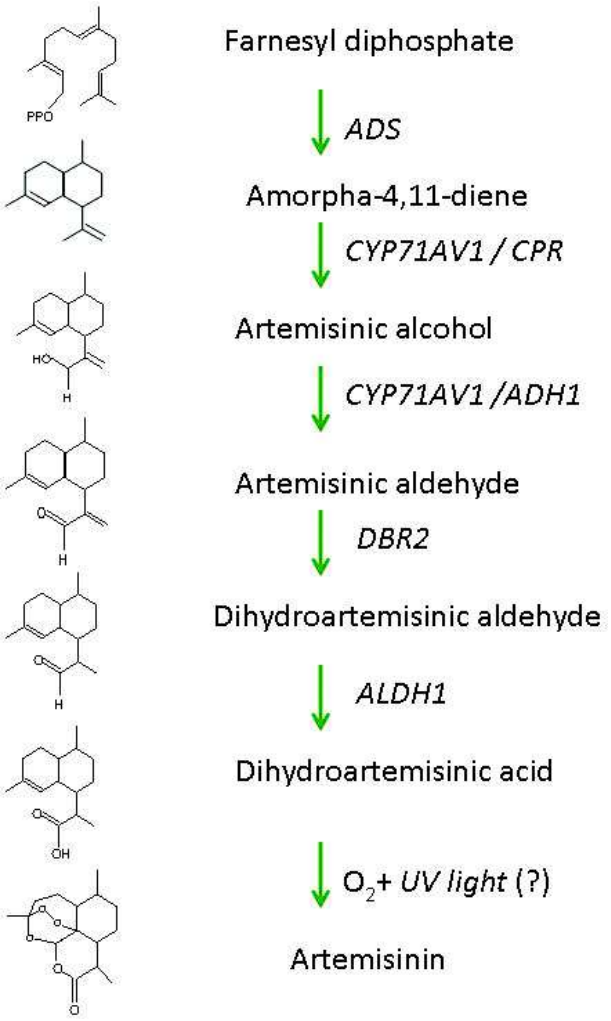

Fig. 2d: Biosynthetic pathway that produces artemisinin and arteannuin B in the cytoplasm of glandular trichomes of *Artemisia annua*. Abbreviations: *ADH* gene for Amorph-4, 11-diene synthase; *CYP71AV1* gene for cytochrome P450 mono-oxygenase 71AV1; *CPR* gene for Cytochrome P450 oxido-reductase; *ADH* gene for Alcohol dehydrogenase 1; *DBR2* gene for Artemisinic aldehyde β-11 (13) reductase; *ALDH1* gene for Aldehyde dehydrogenase 1

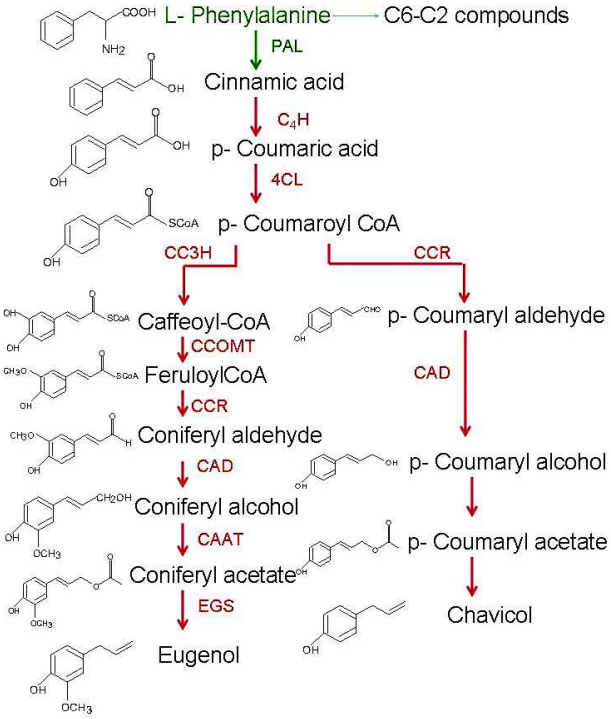

Fig. 2e: Pathway of phenylpropene (C6-C3) biosynthesis that produces phenylpropanoid volatiles in the cytoplasm of glandular trichome cells of *Artemisia annua*. Abbreviations: PAL, Phenylalanine ammonia-lyase; C4H, Cinnamate 4-hydroxylase; 4CL, 4-Coumarate-CoA ligase; CC3H, p-Coumaroyl-CoA-3-hydroxylase; CCOMT, Caffeoyl-Co-A-O-methyl transferase; CCR, Cinnamoyl CoA-reductase; CAD, Cinnamyl alcohol dehydrogenase; CAAT, Coniferyl alcohol acetyl transferase; EGS, Eugenol (and chavicol) synthase. Whereas phenylalanine is biosynthesized via shikimate and aromatic amino acid pathway in chloroplasts, the phenylpropenes are synthesized in cytoplasm of the glandular trichomes, in *Artemisia annua*

first leaves on seedlings and continue to form on various organs until the plant growth ceases. The non-glandular trichome consists of 5 cells stacked ladder-like; the oblong upper most cell imparts to the hairy trichome the shape of a T (Ferreira and Janik, 1995; Kjaer *et al*., 2014). The function of non-glandular trichomes appears to be a kind of structural insulation against environmental factors (heat, cold, moisture etc.), deterrence against herbivores and facility for seed dispersal.

The growth of a glandular trichome in *Artemisia annua* initiates with an anticlinal division in a parental epidermal cell (Duke and Paul 1993; Ferreira and Janik, 1995; Olsson *et al*., 2009; Kjaer *et al*., 2014). The daughter cells then undergo periclinal divisions until 5 pairs of cells are formed. In the resulting 10 cell biseriate trichome, the lower most cell pair serve as stalk, the cell pair above the stalk makes the base, and the apex formed by the apical cell pair and two subapical cell pairs is supported by the base. The apex gets covered by an extracellular cellulosic cuticular cavity. The subcuticular sac so formed serves as the site for the storage of secondary metabolites excreted into it from the trichome cells. Upon rupturing, the

Table 5: The significant biological activities detected in the essential oils hydro-distilled from the flowering time plant foliage of various populations of different species of the genus *Artemisia* of the family Asteraceae

S.No.	Species name in the genus *Artemisia*	Geographical location of the population studied	Percent content of the major compounds present in the essential oil	Biological activity(ies) concluded to be present in the essential oil on the basis of relevant experimental observations	Reference(s)
1	*A. abrotanum*	Europe	1,8-Cineole (32.6%), Borneol (13.5%), Presilphiperfolan-9α-ol (10.2%)	Repels *Aedes aegypti* (Mosquito)	Tabanca *et al*. (2011)
2	*A. asiatica*	China	1,8-Cineole (23.4%), Piperitone (21.2%), p-Cymene (14.5%)	*Hemophilus influenzae* killed via damage to cell wall	Huang *et al*. (2018)
3	*A. absinthium*	Europe	β-Thujone (26.0%), (z)-6,7-Epoxyocimene (24.1%), Sabinene (5.5%)	Fungicidal towards *Candida albicans* and *Saccharomyces cerevisiae*	Juteau *et al*. (2003)
4		Turkey	Chamazulene (17.8%), Nuciferol butanoate (8.2%), Nuciferol propionate (5.1%)	Has antioxidant and free radical scavenging a ctivities and kills *Fusarium oxysporum*, *Penicillium jensenii*, *Rhizoctonia solani*, *Sclerotium minor* and *Verticillium albo-atrum* (Fungii)	Kordali *et al*. (2005a)
5		India	(E)-β-Farnesene (31.6%), (z)-en-yn-Dicycloether (11.1%), (z)-β-Ocimene (27.8%)	Insecticidal against *Anopheles stephensi*, *Anopheles subpictus*, *Aedes aegypti*, *Aedes albopictus*, *Culex quinquefasciatus* and *Culex tritaeniorhynchus*	Govindrajan and Benelli (2016)
6		Canada	Sabinyl acetate (26.4%), Myrcene (10.8%), trans-Thujone (10.1%)	Bacteriocidal against several *Staphylococcus* strains	Lopez-Lutz *et al*. (2008)
7		Turkey	Sabinene (17.6%), Myrcene (11.0%), Chrysanthenyl acetate (11.0%)	Has antioxidant-, free radical scavenging- and antimicrobial-activities; kills *Candida albicans*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Enterobacter cloaceae*, *Escherichia coli*, *Salmonella* sp.	Baykan-Erel *et al*. (2012)
8		India	Borneol (18.7%), methyl Henokiate (11.9%), Isoborneol acetate (4.0%)	Bacteriocidal against *Micrococcus luteus*, *M. flavus* and *Bacillus subtilis*; fungicidal to *Penicillium chrysogenum* and *Aspergillus fumigatus*	Joshi (2013)
9		Iran	1,8-Cineole (36.5%), Borneol (26.0%), Camphor (10.2%)	Has antioxidant and free radical scavenging activity, kills *Candida albicans* and *Leishmania donovani* and is toxic to HeLa cells and lymphocytes	Taherkhani *et al*. (2013) and Taherkhani (2014)
10		Spain	cis-Epoxyocimene (40%), cis-Chrysanthenol (12%), anhydro-Chamazulene (6%)	Lethal to *Trypanosoma cruzi* and *Trichomonas vaginalis* (parasites); toxic to the cancer cell lines A549, H292, HCT116, MCF-7 and SK-MEL-5	Martinez-Diaz *et al*. (2015)
11		Tunisia	Chamazulene (32.6%), β-Thujone (16.7%), trans-Sabinene hydrate (13.0%)	Is bacteriocidal to *Staphylococcus aureus* and fungicidal to *Fusarium graminearum*, *F. culmorum*, *F. oxysporum* and *Rhizoctonia solani*	Msaada *et al*. (2015)
12		Brazil	Camphor (19.0%), E-Caryophyllene (9.3%), Eucalyptol (6.8%)	Has bacteriocidal activity against *Streptococcus mitis*	Vieira *et al*. (2017)

13		India	Chrysanthenyl acetate (49.2%), β-Pinene (39.6%), Sabinyl acetate (3.4%)	Has antioxidant-cum-free radical scavenging activities	Wani *et al*. (2014)
14		Ethiopia	Camphor (27.4%), Davanone (16.4%), ethyl-E-Cinnamate (5.8%)	Inhibits pro- and a- mastigotes of *Leishmania donovani*	Tariku *et al*. (2011)
15		Iran	α-Phellandrene (16.4%), Chamazulene (13.9%), β-Pinene (12.3%)	Lethal to *Escherichia coli* and *Staphylococcus aureus*	Moghaddam *et al*. (2016)
16		Brazil	Camphor (19.0%), E-Caryophyllene (9.3%), 1,8-Cineole (6.8%)	Bacteriocidal to *Streptococcus mitis*	Vieira *et al*. (2017)
17	*A. abyssinica*	Yemen	Camphor (38.1%), Davanone (38.7%), (E)-Nerolidol (4.5%)	Parasiticidal to *Leishmania donovani* and *Trypanosoma cruzi*	Chhetri *et al*. (2015)
18		Ethiopia	Yomogi alcohol (38.5%), Artemisyl acetate (24.9%), Artemisyl alcohol (6.7%)	Lethal towards *Leishmania donovani*	Tariku *et al*. (2010)
19	*A. adamsii*	Mongolia	α-Thujone (64.4%), β-Thujone (7.1%), 1,8-Cineole (15.2%)	Bacteriocidal towards *Staphylococcus aureus* and *S. epidermidis*	Horvath *et al*. (2013)
20	*A. afra*	South Africa	α-Thujone (78.7%), β-Thujone (13.1%), 1,8-Cineole (8.2%)	Bacteriocidal towards *Streptococcus pyogens*, *Listeria monocytogens*, *Acinetobacter johnsonii* and fungicidal against *Hanseniaspora virae* and yeast	Mangena and Muyima (1999)
21		South Africa	Camphor (26.8%), Davanone (16.6%), Bornyl acetate (3.8%)	Has antioxidant activity	Burits *et al*. (2001)
22	*A. anethoides*	China	1,8-Cineole (36.5%), 2-Isopropyl-5-methyl-3-cyclohexen-1-one (10.4%), Terpinen-4-ol (8.0%)	Fumigant- and contact-toxicity and repellant activities towards *Tribolium castaneum* and *Lasioderma serricorne*	Liang *et al*. (2017)
23	*A. annua*	India	Camphor (42.6%), 1,8-Cineole (17.2%), Germacrene D (15.6%)	Repellant to *Tribolium castaneum* and *Callosobruchus maculatus*	Tripathi *et al*. (2000)
24		Brazil	1,8-Cineole (21.1%), Camphor (14.9%), β-Myrcene (12.4%)	Bacteriocidal against *Bacillus subtilis*, *faecium*, *Streptococcus faecium* and *Enterococcus Staphylococcus aureus*	De Megalhaes *et al*. (2004)
25		Turkey	Camphor (31.7%), Artemisia ketone (22.3%), 1,8-Cineole (10.1%)	Fungicidal to *Botrytis cinerea*, *Phytopthera infestans*, *Sclerotima sclerotiorum*	Soylu *et al*. (2005)
26		Europe	Camphor (44%), Germacrene D (16%), trans-Pinocarveol (11%)	Bacteriocidal to *Enterococcus hirae* and fungicidal to *Candida albicans* and *Saccharomyces cerevisiae*	Juteau *et al*. (2002)
27		Europe	Artemisia ketone (30.7%), Camphor (15.8%), Artemisia alcohol (6.5%)	Bacteriocidal to *Enterococcus faecalis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Micrococcus luteus* and fungicidal to *Candida krusei*	Cavar *et al*. (2012)

28		Iran	1,8-Cineole (11.4%), Linalool (8.1%), Spathulenol (5.0%)	Bacteriocidal to *Escherichia coli*, fungicidal to *Candida albicans* and *Saccharomyces cerevisiae*	Massiha *et al*. (2013)
29		Italy	Germacrene D (21.2%), Camphor (17.6%), β-Farnesene (10.2%)	Kills *Aspergillus fumigatus*	Bilia *et al*. (2008)
30		Iran	Camphor (48.0%), Artemisia ketone (13.9%), 1,8-Cineole (9.4%)	Bacteriocidal to *Staphylococcus aureus*, *Enterococcus faecalis*, *Bacillus cereus*, *Escherichia coli* and *Pseudomonas aeruginosa*	Verdian-Rizi *et al*. (2008)
31		Italy	Artemisia ketone (22.1%), 1,8-Cineole (18.8%), Camphor (16.9%)	Oviposition of *Calliphora vomitoria* completely inhibited as well as adulticidal to insect via fumigation and direct contact	Bedini *et al*. (2017)
32		Europe	Artemisia ketone (35.7%), α-Pinene (16.5%), 1,8-Cineole (5.5%)	Bacteriocidal to *Staphylococcus aureus* and *Sarcina lutea* and fungicidal to *Aspergillus fumigatus*	Radulovic *et al*. (2013)
33		India	β-Caryophyllene (11.0%), 1, 8-Cineole (5.6%), β-Caryophyllene oxide (4.2%)	Kills *Leishmania donovani* parasite	Islamuddin *et al*. (2014)
34		Iran	Artemisia ketone (24.2%), α-Pinene (12.1%), 1,8-Cineole (9.8%)	Bacteriocidal towards *Klebsiella pneumoniae* and fungicidal towards *Candida albicans* and *Saccharomyces cerevisiae*	Rasooli *et al*. (2003)
35		Spain	Artemisia ketone (22%), 1,8-Cineole (19%), Camphor (17%)	Fungicidal effect on *Candida* spp.	Santamauro *et al*. (2016)
36		Italy	Artemisia ketone (22.1%), 1,8-Cineole (18.8%), Camphor (16.9%)	Fumigant and contact toxicity and repellant activities towards *Calliphora vomitoria* insect	Bedini *et al*. (2017)
37		Romania	Camphor (17.7%), α-Pinene (9.7%), Germacrene D (7.6%)	Bacteriocidal towards *Streptococcus aureus*, and *Bacillus subtilis*, and fungicidal towards *Candida albicans*	Marinas *et al*. (2015)
38	*A. arborescens*	Italy	β-Thujone (45.0%), Chamazulene (22.7%)	Bacteriocidal to *Listeria monocytogens*	Militello *et al*. (2011)
39		Turkey	Camphor (33.4%), Chamazulene (21.1%), β-Eudesmol (7.7%)	Has antioxidant activity, is bacteriocidal for *Staphylococcus aureus*, *S. epidermidis*, *Pseudomonas aeruginosa*, *Enterobacter cloaceae*, *Escherichia coli* and is fungicidal to *Candida albicans*	Baykan-Erel *et al*. (2012)
40		Tunisia	Chamazulene (31.9%), Camphor (25.8%)	Kills the fungus *Rhizoctonia solani* and has contact toxicity towards *Rhysopertha dominica* (insect)	Bouzenna and Krichen (2013)
41	*A. argyi*	China	1,8-Cineole (27.5%), Bornyl formate (19.9%), Iso-Caryophyllene oxide (13.7%)	Causes loss of infectivity in Tobacco mosaic virus (TMV)	Lu *et al*. (2013)
42		China	1,8-Cineole (23.7%), Caryophyllene (10.2%), Borneol (6.6%)	Inhibits melanin synthesis, and has metal-ion chelation activity	Has fumigant and Huang *et al*. (2012)

43		China	1,8-Cineole (22.0%), β-Pinene (14.5%), β-Caryophyllene (9.2%)	Ccontact toxicity and repellant activity towards *Liposcelis bostrychophila* (insect)	Liu *et al*. (2013a)
44		Russia	Selin-11-en-4a-ol (18.0%), 1,8-Cineole (14.2%), Artemisia alcohol (12.9%)	Fungicidal towards *Colletotrichum aculatum*, *C. fragariae* and *C. gloeosporoides*	Ozek *et al*. (2014)
45		China	1,8-Cineole (25.4%), Borneol (5.9%), Camphor (5.2%)	Has anti-inflammatory activity	Ge *et al*. (2016)
46		Middle East	Linalool (27.1%), Borneol (7.8%), Caryophyllene oxide (4.7%)	Bacteriocidal to *Staphylococcus aureus*, *Listeria monocytogens* and *Escherichia coli*	Asghari *et al*. (2012)
47		Canada	(z)-β-Ocimene (34.7%), (E)-β-Farnesene (40.0%), (z)- and (E)-en-yn-dicycloether (11.0%)	Has antioxidant activity; kills the fungi *Cryptococcus neoformis*, *Fonsecaea pedrosi* and *Aspergillus niger*	Lopez-Lutz *et al*. (2008)
48		Italy	Terpinen-4-ol (22.0%), p-Cymene (7.6%), α-Terpineol (3.0%)	Fungicidal to *Rhodotorula* spp, *Alternaria* spp and *Fusarium* spp	Petretto *et al*. (2013)
49		Italy	Davanone (17.5%), cis-Sabinene hydrate (5.2%), Terpinen-4-ol (4.7%)	Has antioxidant activity and is toxic to the tumor cell lines A375, MDA-MB231 and HCT 116	Ornano *et al*. (2016)
50	*A. campestris*	Turkey	1,2 dehydro acenaphthylene (20.7%), Trematone (15.8%), Capillin (10.4%)	Bacteriocidal to *Staphylococcus aureus*, *S. epidermidis*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Escherichia coli* and fungicidal to *Candida albicans*	Baykan-Erel *et al*. (2012)
51		Algeria	α-Pinene (18.7%), β-Pinene (16.8%), β-Myrcene (17.3%)	Kills the fungus *Fusarium graminearum*	Houicher *et al*. (2016)
52		Tunisia	β-Pinene (33.4%), Limonene (13.9%), β-Pinene (12.3%)	Kills pro- and a-mastigotes of *Leishmania infantum*	Aloui *et al*. (2016)
53		Middle East	Germacrene D (16.4%), β-Pinene (16.3%), Limonene (9.2%)	Has antioxidant and anti-acetyl cholinesterase activities	Younsi *et al*. (2017)
54		Morocco	Spathulenol (10.2%), β-Eudesmol (4.1%), p-Cymene (3.8%)	Has antioxidant, antiplatelet and vasorelaxant activities	Dib *et al*. (2017)
55	*A. capillaris*	Mongolia	1,8-Cineole (13.8%), Germacrene D (10.4%), Camphor (8.6%)	Has fumigant and contact toxicity for the *Sitophilus zeamais* insect	Liu *et al*. (2010a)
56		India	1,8-Cineole (23.2%), Camphor (20.7%), Borneol (13.7%)	Bacteriocidal to *Staphylococcus aureus* and *Bacillus subtilis*	Semwal *et al*. (2015)
57		China	Capillin (24.2%), β-Pinene (12.1%), β-Caryophyllene (5.2%)	Bacteriocidal to *Streptococcus pyogenes*, *S. pneumoniae*, *Klebsiella pneumoniae*, *Haemophilus influenzae* and *Escherichia coli*	Yang *et al*. (2015)
58		Brazil	β-Citronellol (16.3%), 1,8-Cineole (13.1%), Camphor (12.6%)	Protective against chloroform induced liver injury	Gao *et al*. (2016)

59	*A. chamoeme-lifolia*	Iran	Unknown alcohol (21.1%), Borneol (10.8%), 1,8-Cineole (13.8%)	Bacteriocidal to *Bacillus subtilis*, *Listeria monocytogens*, *Pseudomonas aeruginosa* and *Salmonella typhimurium*	Pirabalouti *et al*. (2013)
60	*A. ciniformis*	Iran	Camphor (30.2%), 1,8-Cineole (23.7%), trans-Pinocarveol (12.3%)	Is bacteriocidal to *Acinetobacter baumannii*, *Escherichia coli* and *Staphylococcus aureus* and fungicidal to *Candida albicans*; has antimutagenic activity and toxicity towards HeLa cell line	Taherkhani (2016)
61	*A. dracun-culus*	Italy	trans-Anethole (53.4%), cis-allo-Ocimene (15.3%), cis-Ocimene (10.6%)	Bacteriocidal to *Xanthomonas maltophilia* and *Proteus mirabilis* and fungicidal to *Candida albicans*, *C. lusitaniae*, *C. glabrata* and *C. tropicalis*	Curini *et al*. (2006)
62		Iran	(z)-Anethole (51.7%), (z)-Ocimene (8.3%), methyl Eugenol (8.1%)	Has antioxidant and free radical scavenging activity	Ayoughi *et al*. (2011)
63		Italy	Methyl chevicol(73.3%), E-β-Ocimene (5.3%), Limonene (5.4%)	Is completely inhibitory to oviposition of blow fly *Calliphora vomitoria* and kills *Streptococcus aureus* and *Candida albicans*	Bedini *et al.* (2017)
64		Iran	methyl Chevicol(84.8%), trans-Ocimene (3.9%), (z)-β-Ocimene (3.4%)	Has antioxidant activity and is bacteriocidal against *Serratia marcesens*, *Shigella dysentriae*, *Listeria monocytogens* and *Alcaligens faecalis*	Chaleshtori *et al*. (2013)
65		Italy	methyl Chevicol(73.3%), Limonene (5.4%), (E)-β-Ocimene (5.3%)	Repels and has fumigant and contact toxicity towards *Calliphora vomitoria* (insect)	Bedini *et al*. (2017)
66	*A. dubia*	China	Terpinolene (19.0%), Limonene (17.4%), 2,5-etheno[4.2.2] propella-3,7,9-triene (11.3%)	Has fumigant toxicity against the stored product insect pest *Liposcalis bostrychophila*	Liang *et al.* (2018)
67	*A. echegarayi*	Argentina	β-Thujone (49.3%), α-Thujone (10.7%), Borneol (5.3%)	Bacteriocidal to *Escherichia coli*, *Listeria monocytogenes*, *Bacillus cereus*, *Staphylococcus aureus*	Laciar *et al*. (2009)
68	*A. eriopoda*	China	Germacrene D (21.6%), 1,8-Cineole (14.2%)	Fumigant and contact toxicity towards *Sitophilus zeamais* (insect)	Jiang *et al*. (2012)
69	*A. feddei*	Korea	1,8-Cineole (16.9%), Chamazulene (9.0%), α-Terpineol (8.2%)	Bacteriocidal to *Streptococcus* spp, *Fusobacterium nuleatum*, *Prevollela intermedia* and *Prophylomonas gingivitis*	Cha *et al*. (2007)
70		Russia	Camphor (31.2%), 1,8-cineole (17.6%), α-Thujone (5.7%)	Fungicidal to *Colletotrichum aculeatum*, *C. fragariae* and *C. gloeosporoides*	Ozek *et al*. (2014)
71	*A. fragrans*	Mediterranean	Camphor (31.8%), 1,8-cineole (21.9%), cis-p-Menth-2-en-1-ol (6.2%)	Has anti-inflammatory activity	Farghadan *et al*. (2016)
72		Iran	Chrysanthenone(41.1%), 1,8-Cineole (11.1%), n-Pentane (9.1%)	Possesses antioxidant activity	Amiri and Goodarzi (2017)
73	*A. frigida*	Mangolia	cis-p-Menth-2-en-1-ol (20.8%), 1,8-cineole (12.0%),Borneol (10.2%)	Fumigant and contact toxicity towards *Liposcelis bostrychophila* (insect)	Liu *et al*. (2014)
74	*A. fukudo*	Korea	α-Thujone (48.3%), β-Thujone (12.7%), Camphor (7.0%)	Inhibitor of pro-inflammatory cytokines	Yoon *et al*. (2010)

75	*A. gilvescens*	China	Camphor (13.5%), 1,8-cineole (12.1%), Terpinen-4-ol (9.7%)	Has larvicidal activity towards *Anopheles anthrophagus* (mosquito)	Zhu and Tian (2013)
76	*A. giraldii*	China	β-Pinene (13.2%), iso-Elemicin (10.1%), Germacrene D (5.7%)	Has fumigant and contact toxicity towards *Sitophilis oryzae* (insect)	Chu *et al*. (2012)
77	*A. gmelini*	Russia	Longiverbenone (12.0%), Isopinocamphene (8.9%), 1,8-Cineole (6.7%)	Has larvicidal activity for the mosquito *Aedes aegypti*	Ozek *et al*. (2014)
78	*A. gorgonum*	France	Camphor (28.7%), Chrysanthenone (10.8%), Lavandulyl 2-methyl butanoate (9.5%)	Has antioxidant and antiplasmodial (antimalarial) activity	Ortet *et la*. (2010)
79	*A. hausske-nechtii*	Iran	Camphor (42.5%), 1,8-Cineole (20.9%), Isoborneol (7.3%)	Has high levels of antioxidant activity	Amiri and Goodarzi (2017)
80	*A. herba-alba*	Tunisia	Germacrene D (14.5%), Camphor (10.8%), 1,8-Cineole (8.9%)	Has antioxidant activity	Kadri *et al*. (2011)
81		Mediterranean	Verbenol (21.8%), Farnesene epoxide (17.1%), Bisabolol oxide (17.6%)	Has toxicity towards cancer cell lines P815 and BSR (kidney carcinoma)	Tilaoui *et al*. (2015)
82		Algeria	Camphor (34.3%), 1,8-Cineole (13.5%), α-Thujone (8.4%)	Has repellant activity and fumigant and contact toxicity to adults and larvicidal against *Ephestia kuehniella* (moth)	Amel *et al*. (2017)
83		Algeria	Camphor (18.7%), β-Pinene (16.8%), β-Myrcene (17.3%)	Bacteriocidal activity against *Staphylococccus aureus*, *Bacillus cereus* and *Escherichia coli*	Lakehal *et al*. (2016)
84		Tunisia	Camphor (36.0%), 1,8-Cineole (13.9%), Chrysanthenone (8.8%)	Kills pro- and a-mastigotes of *Leishmania infantum*	Aloui *et al*. (2016)
85		Middle East	Camphor (19.6%), α-Thujone (19.4%), β-Thujone (9.4%)	Has antioxidant activity and antiacety-lcholinesterase activity	Younsi *et al*. (2017)
86		Jordan	β-Thujone (25.1%), α-Thujone (22.7%), 1,8-Cineole (20.1%)	Has anti-inflammatory activity and is fungicidal to *Trichophyton rubrum*, *Epidermophyton floccosum*, *Cryptococcus neoformans* and *Candida albicans*	Abu-Darwish *et al*. (2016)
87		Tunisia	β-Thujone (12.5%), α-Thujone (8.8%), Sabinyl acetate (8.6%)	Has highly potent repellent activity against *Tribolium castaneum*, the stored food insect	Chaieb *et al.* (2018)
88		Labenan	α-Pinene (45.9%), Borneol (11.3%), 1,8-Cineole (10.5%)	Highly active against *Candida albicans* and *Streptococcus aureus*	Hatem *et al.* (2018)
89	*A. indica*	India	Artemisia ketone (42.1%), Germacrene D (8.6%), Borneol (6.1%)	Has toxicity towards human cancer cell lines: THP1 (leukemia), A-549 (lung), HEP2 (liver) and CaCo-2 (colon)	Rashid *et al*. (2013)
90		Italy	Camphor (13.0%), Caryophyllene oxide (10.9%)	Has antiplasmodial activity	Tasdemir *et al*. (2015)

91	*A. judiaca*	Egypt	Piperitone (32.4%), Camphor (20.6%), (E)-ethyl-Cinnamate (8.2%)	Has fumigant toxicity for *Callosobruchus maculatus* (insect)	Abd-Elhady (2012)
92		Algeria	Piperitone (66.2%), ethyl Cinnamate ester (6.1%), (*E*)-Longipinane (2.6%)	Has potent radical scavenging-, strong anti-*Listeria monocytogenes*-, and anti-*Leishmania major* and *Leishmania infantum*-activity	Farah *et al*. (2017)
93		Algeria	Piperitone (66.2%), ethyl Cinnamate (7.8%), Spathulenol (2.0%)	Kills *Leishmania major* and *L. infantum* parasite forms	Farah *et al*. (2017)
94		Jordan	Piperitone (30.4%), Camphor (16.1%), ethyl Cinnamate(11.0%)	Has anti-inflammatory activity and is fungicidal to *Cryptococcus neoformans* and *Candida albicans*	Abu-Darwish *et al*. (2016)
95	*A. kotuchovii*	Europe	Estragole (75.1%), (E)-β-Ocimene (9.2%), (Z)-β-Ocimene (8.2%)	Modifies the immune response	Schepetkin *et al*. (2015)
96	*A. lancea*	China	1,8-Cineole (34.6%), Camphor (16.7%)	Ovicidal for the nematode *Haemonchus contortus*	Zhu *et al*. (2013a)
97	*A. lavandu-laefolia*	China	Caryophyllene (15.5%), β-Thujone (13.6%), 1,8-Cineole (13.1%)	Has fumigant and contact toxicity for *Sitophilus zeamais* (insect)	Liu *et al*. (2010b)
98		China	Chamazulene (40.4%), 1, 8-Cineole (16.0%), β-Caryophyllene (11.5%)	Has fumigant toxicity that controls the cigarette beetle *Lasioderma serricorne*	Zhou *et al.* (2018)
99	*A. maderas-patana*	India	α-Humulene (46.3%), β-Caryophyllene (9.3%), α-Copaene (8.2%)	Inhibits acetylcholinesterase	Jyotshana *et al*. (2017)
100	*A. manshuria*	Russia	Germacrene D (11.2%), Rosifoliol (10.1%), Caryophyllene oxide (6.8%)	Fungicidal towards *Colletotrichum aculatum*, *C. fragariae* and *C. gloeosporoides*	Ozek *et al*. (2014)
101	*A. maritima*	India	1,8-Cineole (23.2%), Camphor (20.7%), Borneol (13.7%)	Bacteriocidal towards *Staphylococcus aureus* and *Bacillus subtilis*	Sharma *et al*. (2014)
102	*A. mesat-lantica*	Mediterranean	β-Thujone (33.7%), Camphor (7.5%), 1,8-Cineole (6.9%)	Inhibits corrosion of mild steel under acidic conditions	Boumhara *et al*. (2014)
103	*A. minor*	India	1,8-Cineole (22.3%), Camphor (12.6%), Davanone (12.3%)	Bacteriocidal to *Bacillus subtilis*, *Staphyl-ococcusepidermidis*, *Pseudomonas fluorescens*, *Salmonella typhimurium* and *Acinetobacter* sp.	Sharma *et al*. (2011)
104	*A. mongolica*	Mongolia	α-Pinene (12.7%), Germacrene D (8.4%), γ-Terpinene (8.2%)	Has fumigant and contact toxicity for *Sitophilus zeamais* (insect)	Liu *et al*. (2010a)
105	*A. monos-perma*	Libya	β-Pinene (16.9%), Bornyl acetate (14.1%), Sabinene (13.2%)	Is lethal towards *Escherichia coli*, *Staphy-lococcus epidermidis* and *Aspergillus fumigatus*	El Zalabani *et al*. (2017)
106	*A. montana*	Japan	Borneol (16.3%), 1,8-Cineole (15.4%), Camphor (13.7%)	Has sedative activity	Kunihiro *et al*. (2017)
107	*A. nilagirica*	India	α-Thujone (41.9%), Borneol (10.8%), β-Thujone (9.1%)	Fungicidal to *Phytopthera capsici*	Shafi *et al*. (2004)

108		India	α-Thujone (36.4%), β-Thujone (9.4%), Germacrene D (6.3%)	Fungicidal towards *Rhizoctonia solani* and *Sclerotium rolfsii*	Sati *et al*. (2013)
109	*A. olgensis*	Russia	Eudesma-4 (15), 7-dien-1b-ol (6.9%), Caryophyllene oxide (5.6%), Guaia-6, 10 (14)-dien-4b-ol (5.1%)	Larvicidal towards *Aedes aegypti* mosquito	Ozek *et al*. (2014)
110	*A. persica*	Iran	β-Thujone (75.2%), α-Thujone (2.8%), 1,8-Cineole (2.4%)	Toxic to the cancer cell line MCF-7	Nikbakht *et al*. (2014)
111	*A. phaeolepis*	Mediterranean	1,8-Cineole (11.3%), Camphor (8.2%), Terpinen-4-ol (7.3%)	Bacteriocidal to *Listeria monocytogens*, *Bacillus subtilis*, *Staphylococcus aureus*, *Salmonella enterica*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* and fungicidal to *Aspergillus niger*, *Fusarium graminearum*, *F. oxysporum* and *F. culmorum*	Hsouna *et al*. (2013)
112	*A. princeps*	China	Bornane (12.2%), Chamazulene (11.8%), Cyclohexanediol (10.1%)	Repellant to and contact toxicity for *Sitophilus oryzae* and *Bruchus rufimanus* (insects)	Liu *et al*. (2006)
113	*A. rupestris*	China	α-Terpinyl acetate (37.2%), Spathulenol (10.7%), α-Terpineol (10.1%)	Repellant- and fumigant- and contact toxic activity for *Liposcelis bostrychophila*	Liu *et al*. (2013b)
114	*A. santonicum*	Turkey	Camphor (18.2%), 1,8-Cineole (7.5%), β-Eudesmol (7.2%)	Has contact toxicity towards the insect *Sitophilus granarius*, is bacteriocidal to *Xanthomonas* sp., *Bacillus subtilis*, *Enterobacter cloaceae*, *Escherichia coli* and *Klebsiella planticola* and fungicidal to *Alternaria alternata*, *Fusarium oxysporum*, *F. sambucinum*, *Penicillium jensenii*, *Rhizoctonia solani*, *Sclerotium minor*, *Verticillium alboatrum* and *V. tenerum*	Kordali *et al*. (2005a and b)
115		Turkey	Spathulenol (15.6%), Caryophyllene oxide (11.4%), 1,2-dehydro acenapthylene (11.8%)	Bacteriocidal to *Enterobacter cloaceae*, *Escherichia coli* and *Salmonella typhimurium*	Baykan-Erel *et al*. (2012)
116	*A. scoparia*	Iran	β-Pinene (19.0%), Capillin (17.5%), Limonene (15.1%)	Has contact toxicity for *Callosobruchus maculatus*, *Sitophilus oryzae*, and *Tribolium castaneum* insects	Negahban *et al*. (2006)
117		Turkey	α-Thujone (39.5%), β-Thujone (25.1%), 1,8-Cineole (6.7%)	Bacteriocidal to *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Enterobacter cloaceae*, *Escherichia coli* and *Salmonella typhimurium*	Baykan-Erel *et al*. (2012)
118	*A. sieberi*	Pakistan	β-Thujone (19.8%), α-Thujone (19.6%), Camphor (19.6%)	Kills the fungus *Rhizoctonia solani*	Farzaneh *et al*. (2006)
119		Iran	α-Thujone (31.5%), Camphene (12.3%), β-Thujone (11.9%)	Has repellence and fumigant and contact toxicity for *Dermanyssus gallinae* (insect)	Tabari *et al*. (2017)
120		Iran	cis-Verbenol (16.1%), Myristicin (13.8%), (E)-epoxy-Ocimene (9.8%)	Has antioxidant property	Aghajani *et al*. (2014)

121		Middle East	Camphor (54.7%), Camphene (11.7%), 1,8-Cineole (9.9%)	Has contact insecticidal toxicity towards *Callobruchus maculatus*, *Sitophilus oryzae* and *Tribolium castaneum*	Negahban *et al*. (2007)
122	*A. sieversiana*	China	1,8-Cineole (9.2%), Geranyl butyrate (9.1%), Camphor (7.9%)	Has fumigant and contact insecticidal activity for *Sitophilus zeamais*	Liu *et al*. (2010b)
123	*A. spicigera*	Turkey	Camphor (34.9%), 1,8-Cineole (9.5%), Borneol (5.1%)	Has insecticidal effect on *Sitophilus granarius*, is bacteriocidal to *Bacillus subtilis*, *Enterobacter cloaceae*, *Escherichia coli* and *Klebsiella pneumoniae*, and is fungicidal to *Fusarium sambucinum*, *Penicillium jensenii*, *Rhizoctonia solani*, *Sclerotium minor* and V*erticillium albo-atrum*	Kordali *et al*. (2005a and b)
124		Iran	1,8-Cineole (47.2%), Camphor (28.8%), Spathulenol (8.3%)	Bacteriocidal to *Citrobacter amalonaficus*	Chehregani *et al*. (2013)
125		Iran	Camphor (15.3%), 1,8-Cineole (9.1%), α-Thujone (8.4%)	Bacteriocidal to *Streptococcus saprophyticus*, *Bacillus megaterium* and *Bacillus cereus*	Chehregani *et al*. (2013)
126		Iran	Camphor (30.7%), 1,8-Cineole (27.2%), Camphene (18.7%)	Bacteriocidal to *Escherichia coli*, *Enterobacter aerogenes*, *Serratia marsescens* and *Staphylococcus aureus*	Chehregani *et al*. (2013)
127	*A. stolonifera*	China	1,8-Cineole (32.9%), α-Pinene (8.2%), Camphor (6.1%)	Fumigant and contact insecticidal activity on *Tribolium castaneum*	Zhang *et al*. (2015)
128	*A. subdigitata*	China	1,8-Cineole (12.3%), α-Curcumene (10.8%), β-Pinene (7.4%)	Fumigant and contact insecticidal activity on *Sitophilus oryzae*	Chu *et al*. (2012)
129	*A. tourne-fortiana*	Iran	(Z)-Nerolidol (22.4%), β-Caryophyllene (15.6%), Santolina triene (10.1%)	Bacteriocidal to *Bacillus subtilis*, *B. cereus*, *Citrobacter* sp., *Enterobacter* sp., *Escherichia coli, Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and fungicidal to *Aspergillus niger* and *Candida albicans*	Kazemi and Akhavani (2013)
130	*A. tschernie-viana*	Iran	p-Cymene (21.3%), β-Pinene (17.8%), α-Pinene (9.4%)	Bacteriocidal to *Bacillus subtilis*, *B. cereus*, *Escherichia coli* and *Klebsiella pneumoniae* and fungicidal to *Candida albicans*	Kazemi *et al*. (2013a)
131	*A. turco-manica*	Iran	Camphor (19.2%), Filifolone (15.5%), Brevifolin (6.2%)	Has toxicity towards the cancer cell line MCF-7	Nikbakht *et al*. (2014)
132	*A. vestita*	China	Grandisol (40.3%), 1,8-Cineole (14.9%), Camphor (11.4%)	Has fumigant and contact insecticidal activity on *Sitophilus zeamais*	Chu *et al*. (2010)
133	*A. vulgaris*	Turkey	α-Thujone (56.1%), β-Thujone (12.0%), 1,8-Cineole (8.5%)	Bacteriocidal to *Enterobacter cloaceae*, *Escherichia coli* and *Salmonella typhimurium* and fungicidal to *Candida albicans*	Baykan-Erel *et al*. (2012)

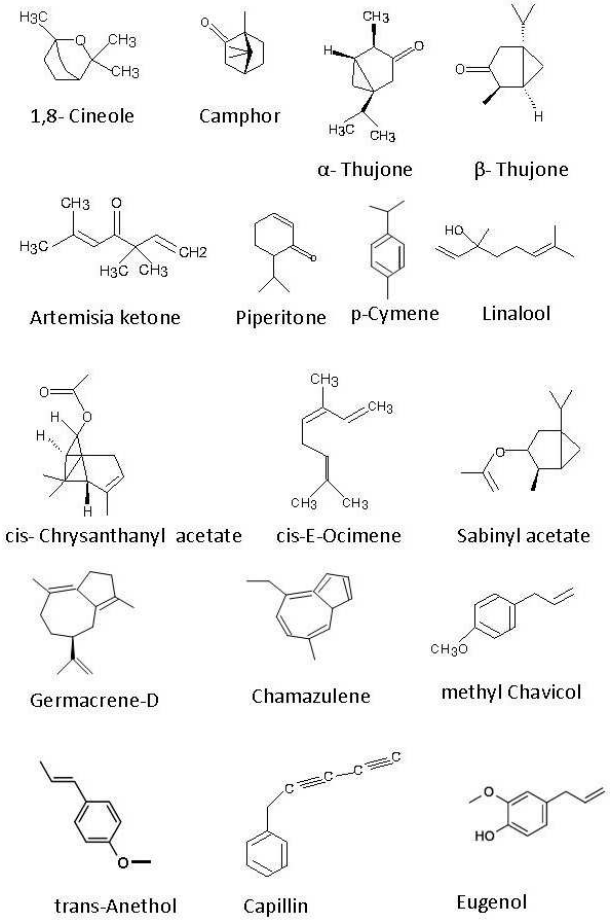

Fig. 3: Molecular structures of some of the volatile organic compounds that are markers of *Artemisia* species/ populations

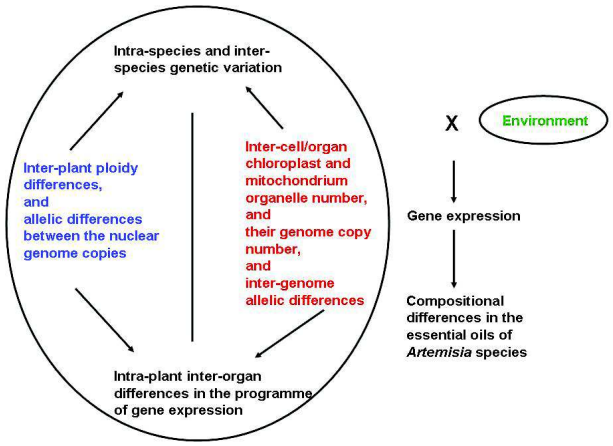

Fig. 4: The kinds of genetic factors that affect, in interaction with environment, the quality of *Artemisia* essential oils

sac releases the stored material into the environment. The glandular trichomes measure 40-65 mm in height and 25-30 mm in width and occur with a frequency of 10-30/mm^2 on both adaxial and abaxial surfaces of bifacial organs such that there are more trichomes adaxially than abaxially. The glandular trichomes release their contents into the atmosphere spontaneously, from leaves and other organs undergoing senescence, or in response to injury.

Several genes have been identified in *Artemisia annua* that are involved in the initiation of glandular trichome formations and/or determination of trichome structure. These include: *Aa TTG1* (*Transpatent Testa Glabra 1*), *AaGL3* (*Enhancer Glabra 3*), *AaTFARI* (*Trichome specific Fatty Acyl-Coenzyme A Reductase 1*), *AaMYB1* and *AaMIXTA* (R_2R_3-*Myoblastosis genes*), *AaHD1* (*Homeodomain Protein 1*), and *AaTAR1* (*Trichome and Artemisinin Regulator 1*) (Liu *et al*., 2009; Maes *et al*., 2011; Tan *et al*., 2015; Covello and Nieuwerburg 2016; Yan *et al*., 2016; Matias-Hernandez *et al*., 2017; Shi *et al*., 2017). Overexpression of *AaMIXTA* and *AaMYB* in *Artemisia annua* led to significant increase in the number of glandular trichomes and in the biosynthesis of sesquiterpenes (Matias-Hernandez *et al*., 2017; Shi *et al*., 2017). Elicitors such as methyl jasmonate have been found to increase the density and size of trichomes and expression of secondary metabolite pathways in trichomes (Lies *et al*., 2011; Dangesh *et al*., 2014). Transcriptome analysis has indicated that some of the genes of terpenoid biosynthesis expressed in glandular trichomes are also expressed in non-glandular trichomes (Soetaert *et al*., 2013). *Artemisia annua* transgenics for the b-glucosidase (*BGLI*) gene of *Trichoderma reesei* tagged with vacuole targeting sequence have been found to produce 20% and 60% more glandular trichomes on leaves and flowers respectively (Singh *et al*., 2016). The glandular trichome deficient genotype(s) of *Artemisia annua* have been observed to synthesize smaller number of volatile organic compounds, mainly sesquiterpenes as compared to trichome plus genotype (Duke *et al*., 1994; Tellez *et al*., 1999). Studies of the transcriptome of the non-glandular trichomes have revealed that some sesquiterpene compounds, not including artemisinin, are synthesized in them (Soetaert *et al*., 2013).

There is evidence that roots of *A.annua* contain essential oil but little artemisinin (Goel *et al*., 2007a). It is also known that hairy roots of *Artemisia annua*,

Table 6: Significant allelopathic/herbicidal activities detected in the essential oils hydro-distilled from the foliage of various species of the genus *Artemisia*

S.No.	*Artemisia* species; source; and organs whose essential oil was tested	Percentage-wise order of main components of the essential oil	Plants against which allelopathic effect observed	Reference (s)
1	*A. dracunculus*; Italy; flowering wigs	Estragole (73.3%); Limonene (5.4%), (E)-β-Ocimene (5.3%)	*Raphanus sativas, Lepidium sativum, Papaver rhoeas, Avena sativa*	Fraternale *et al*. (2015)
2	*A. dubia*; Nepal	Chrysanthenone (29.0%), Coumarin (18.3%), Camphor (16.4%)	Seed germination and seedling growth arrested in: *Lolium perennae* and *Lactuca sativa*	Satypal *et al*. (2012)
3	*A. herba-alba*; Iran: flowering twigs	cis-Pinocarveol (17.5%), Artemisia ketone (13.0%), trans-Sabinene hydrate (8.5%)	Seed germination in *Agropyron desertorum* and *A. cristatum*	Tilaki *et al*. (2013)
4	*A. herba-alba*; Tunisia	Camphor (39.1%), Chrysanthenone (15.0%), cis-Thujone (7.8%)	Radical growth arrested in *Raphanus sativus*, *Lepidium sativum*, *Sinapis arvensis*, *Triticum durum* and *Phalaris canariensis*	Amri *et al*. (2013)
5	*A. indica*; Nepal	Ascaridole (9.9%), trans-p-Menth-2,8-dien-1-ol (9.7%), trans-Verbenol (8.4%)	Seed germination and seedling growth arrested in: *Lolium perennae* and *Lactuca sativa*	Satyapal *et al*. (2012)
6	*A. princeps*; China; flowering twigs	Bornane (12.2%); Chamazulene (11.8%); Cyclohexanediol (10.1%)	*Triticum aestivum* germination	Liu *et al*. (2006)
7	*A. scoparia*; India; flowering twigs	β-Myrcene (30.2%), p-Cymene (12.8%), dl-Limonene (12.4%)	*Avena fatua*, *Cyperus rotundus*, *Phalaris minor*	Singh *et al*. (2009)
8	*A. scoparia*; India; leaves	β-Myrcene (29.3%), Limonene (13.3%), (z)-β-Ocimene (13.4%)	*Triticum aestivum* and *Amaranthus viridis*, *Bidens pilosa*, and some other weeds at all stages of growth and reproduction	Singh *et al*. (2008) ; Kaur *et al*. (2010 and 2017)
9	*A.campestris*; Tunisia; foliage	β-Pinene (35.0%); 1, 8-Cineole (14.4%)	*Daucus carota*	Dhifi *et al.* (2018)

which are green in colour, produce artemisinin (Liu *et al*., 1997; Giri *et al*., 2001; Patra *et al*., 2013). Whether or not hairy roots possess trichome-like structures on their surface and produce essential oil therefrom remains unknown. The sites of synthesis of essential oil in normal roots and of artemisinin in hairy roots of *Artemisia annua* also remain to the found out. One of the possibilities is that the synthesis of volatile organic compounds in roots occurs in the resin ducts of the vascular system.

The route to increase the essential oil yield is to increase the density and size of glandular trichomes on all shoot organs of artemisias. To design new approaches to increase essential oil content of *Artemisia* plant, it is important to understand the mechanism which represses the expression of volatiles in the ground tissues of shoot organ for manipulating them genetically.

Biosynthesis of Terpenoid and Phenylpropanoid Volatiles Extracted as Major Components in *Artemisia* Essential Oils

Many *Artemisia* species are intensely aromatic on account of their genetic property of synthesizing a variety of volatile organic compounds, of high vapour pressure, constitutively, in trichomes present on shoot organs and resin ducts present in all plant organs. The volatile organic compounds that get extracted into essential oil upon hydrodistillation of aromatic plant organs in general include terpenes, benzenoids/phenyl-

Table 7: Somatic chromosome numbers (2n) in some of the *Artemisia* species listed in the Table 1

S.No.	Name of Artemisia species	Chromosome number(s) per cell observed in same or different populations of the species, with reference to the basic chromosome number (x)		No. of B chromosomes observed	Reference(s) and those cited in the Table
		x=9	x=8[b]		
1	*A abrotanum*	18,36,54		0-4	Kreitschitz and Valles 2003; Zhen *et al*. 2010; Tabur *et al*. 2012; Korobkov *et al*. 2014
2	*A absinthium*	18,36			Murin 1997; Kreitschitz and Valles 2003; Konowalik *et al*. 2010, Tabur *et al*. 2012
3	*A afra*	18			Valles and Mc Arthur 2001
4	*A. alba*	36			Xirau and Siljak-Yakovlev 1997
5	*A annua*	18			Zhen *et al*. 2010; Kreitschitz and Valles 2003
6	*A arborescens*	18			Tabur *et al*. 2012
7	*A austriaca*	36,54	16[c],32,48		Pellicer *et al*. 2011; Tabur *et al*. 2012
8	*A argyi*	34[a],36,50[a]			Park *et al*. 2009
9	*A. barrelieri*	36			Xirau and Siljak-Yakovlev 1997
10	*A campestris*	36	31[a,c],48		Kreitschitz and Valles 2003; Torrell *et al*. 2001
11	*A capillaris*	18,27,36			Gupta *et al*. 2014
12	*A chamaemelifolia*	18,36		0-5	Tabur *et al*. 2012
13	*A dracunculus*	18,36,54,72,87[a],88[a],89[a],90			Murin 1997; Kreitschitz and Valles 2003; Pellicer *et al*. 2011
14	*A fragrans*	18,36			Atri *et al*. 2009; Abdolkarim *et al*. 2010; Chehregani and Mehanfar 2008 ; Siddique and Jeelani 2016
15	*A frigida*	18,36,54		0-3	Stahevitch and Wojtas 1988; Korobkov *et al*. 2014
16	*A gmeleni*	18,36,54		0-1	Gupta *et al*. 2014; Gurmet *et al.* 2018
17	*A herba-alba*	18,36			Bougoutaia *et al*. 2016
18	*A incana*	18,36	16[c],24,32	0-2	Atri *et al*. 2009; Chehregani and Mehanfar 2008; Tabur *et al*. 2012
19	*A indica*	34[a],36			Park *et al*. 2009
20	*A japonica*	18,36			Hoshi *et al*. 2003; Abdolkarim *et al*. 2010; Zhen *et al*. 2010
21	*A judaica*		16	0-1	Badr *et al*. 2012
22	*A. khorassanica*	18, 36		0-1	Salehi *et al.* 2018
23	*A lavendulaefolia*	54	16[c]		Xiong *et al*. 1995; Hoshi *et al*. 2003
24	*A manshuria*	36			Hoshi *et al*. 2003; Pellicer *et al*. 2007
25	*A maritima*	18,36,54		0-2	Siddique and Jeelani 2016; Gupta *et al*. 2014
26	*A montana*	52[a]			Park *et al*. 2009
27	*A nilgirica*	18,54		0-4	Gupta *et al*. 2014
28	*A parviflora*	18,36			Gupta *et al*. 2014
29	*A roxburghiana*	18		0-2	Gupta *et al*. 2014
30	*A. santonicum*	52[a]			Tabur *et al.* 2014

31	*A scoparia*	18,36,54	16[c]		Abdolkarim *et al*. 2010; Chehregani and Mehanfar 2008; Gupta *et al*. 2014; Korobkov *et al*. 2014
32	*A sieberi*	18,36			Jalili *et al*. 2012
33	*A subdigitata*	36			Pellicer *et al*. 2011
34	*A sieversiana*	18			Zhen *et al*. 2010; Korobkov *et al*. 2014
35	*A spicigera*	18,27,36,45,54,72			Atri *et al*. 2009; Abdolkarim *et al*. 2010; Chehregani and Mehanfar 2008
36	*A stolonifera*	36			Hoshi *et al*. 2003; Park *et al*. 2009
37	*A tournefortiana*	18			Tabur *et al*. 2012
38	*A. taurica*	36, 40[a], 54[a]		0-4	Tabur *et al*. 2014
39	*A vulgaris*	18,36,45,54,90	16[c],24,40		Tabur *et al*. 2012; Gupta *et al*. 2014; Barney and Di-Tommaso 2003

a = Aneuploids; b = The basic chromosome x=8 is thought to be a product of dysploidy or Robertsonian fusion of two chromosomes event in a x=9 species; c = Such events appear to have occurred several times in the evolution of biodiversity in the genus *Artemisia*.

propanoids and fatty acid – and amino acid – derivatives. In the essential oils whose major components are listed in the tables 1, 2 and 5, the principal volatiles are terpenes and phenylpropanoids. The progress in understanding of their biosynthetic pathways of these types of compounds is discussed below:

Synthesis of Phenylpropanoid Volatiles

It will be seen from Table 2 that certain phenylpropene volatile molecules, such as eugenol, methyl eugenol, chavicol and methyl chavicol are present in essential oils of several *Artemisia* species in high concentrations. Phenyl propenes (C6-C3) consist of a benzene ring (C6) having a propyl side chain. The benzene ring is modified; in eugenol and chavicol a para-hydroxyl group modifies the benzene ring. The amino acid L-phenylalanine (Phe) is the precursor of phenylpropenes. Whereas Phe is synthesized in plastids, the phenlpropanoids from it are synthesized in cytosol, in glandular trichomes. Many studies on a variety of plant species have contributed to the present understanding of the phenylpropene biosynthetic pathway summarized in Figs. 2a and 2e (Gang *et al*., 2002; Koeduka *et al*., 2006; Vassao *et al*., 2006; Vogt 2010; Maeda and Dudareva 2012; Dudareva *et al*., 2013; Rastogi *et al*., 2013; Koeduka 2014; Peled-Zehavi *et al*., 2015).

Phenylalamine is deaminated to trans-cinnamic acid by the action of L-phenylalanine ammonia lyase (PAL). The enzyme cinnamate 4-hydroxylase acts on cinnamic acid to form p-coumaric acid. A class II 4CL (4-coumarate CoA ligase) specific to phenylpropanoid metabolism then converts p-coumaric acid to p-coumaroyl-CoA. From here onwards the pathway branches to produce coniferyl alcohol on the one hand and coumaryl alcohol on the other hand. At this stage an acetyl transferase acetylates coniferyl alcohol to coniferyl acetate and coumaryl alcohol to coumaryl acetate. Subsequently, the eugenol/chavicol synthase (EGS), the NADPH-dependent reductase, derives eugenol from coniferyl acetate and chavicol from p-coumaryl acetate. Methyl eugenol and methyl chavicol are formed by the action of eugenol-o-methyl transferase (EOMT) and chavicol-o-methyl transferase (EOMT) on eugenol and chavicol, respectively.

Synthesis of Terpenes

In the essential oils of *Artemisia* species, the principal volatile organic compounds are terpenes. Monoterpenes, sesquiterpenes and diterpenes and their modified forms comprise the bulk of *Artemisia* essential oils (Table 2). Here, the current understanding about the biosynthesis of terpenes is briefly discussed. The pathway used in glandular trichomes of plants to produce volatile terpenes is accomplished in three phases: first, production of C5 building blocks; second, condensation of C5 units to produce C10, C15, C20, C25 prenyl diphosphates; and third, use of prenyl diphosphates to produce terpenes (Sun *et al*., 2006; Lange and Ahkami 2013; Dudareva *et al*., 2013; Tholl 2015).

Phase 1: The C5 isomeric molecules isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) are produced in the cytoplasm (cytosol, endoplasmic reticulum and peroxisomes) by the mevalonic acid (MVA) pathway and in plastids by the methylerythritol phosphate (MEP) pathway (Figs. 2a, 2b and 2c) (Simkin *et al*., 2011; Pulido *et al*., 2012; Vranova *et al*., 2013).

The MVA pathway consists of six enzymatic reactions (Figs. 2a and 2b) (Cordier *et al*., 1999; Lange *et al*., 2000; Rodriguez-Concepcion *et al*., 2001). Three molecules of acetyl-CoA undergo stepwise condensation to form 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA). Mevalonate is formed by the NADPH – reduction of HMG-CoA in two steps. Mevalonate is converted into IPP in three steps, two phosphorylation steps and a decarboxylation/elimination step, all three ATP-dependent. The MEP pathway (Fig. 2a and 2c) consists of seven enzymatic steps. In the first step, 1-deoxy-D-xylulose 5-phosphate (DXP) is formed by condensation of D-glyceraldehyde 3-phosphate (CoAP) resourced from glycolysis and pentose phosphate pathway and plastidic pyruvate (PYR). MEP is formed from DxP by its isomerization and NADPH dependent reduction. In five more steps MEP is converted into IPP and DMAPP, with a ratio of 5 to 6:1 (Rohmer 2003; Hseih *et al*., 2008; Tritsch *et al*., 2010; Rohdich *et al*., 2002). In both MVA and MEP pathways, IPP is converted into DMAPP upon isomerization by isopentenyl diphosphate isomerase (IDI) (Phillips *et al*., 2008; Berthelot *et al*., 2012). The MEP and MVA pathways are interconnected such that MEP pathways supplies IPP and DMAPP to the cytoplasm (Hemmerlin *et al*., 2012).

Phase 2: In cytoplasm and plastids, the C5 building blocks of terpenes, IPP and DMAPP are condensed to produce a series of prenyl disphosphates, including the following: GPP (C10, geranyl diphosphate), NPP (C10, neryl diphosphate), FPP (C15, farnesyl diphosphate), GGPP (C20, geranyl geranyl diphosphate), and GFPP (C25, geranyl farnesyl diphosphate. The higher order prenyl phosphates, such as C30 and C40, are formed by condensation of lower order (FPP and GGPP) prenyl phosphates. A range of short-chain prenyl transferases catalyse the condensation reactions. Various prenyl diphosphates serve as the precursors of different classes of terpenes (Kharel and Koyama 2003; Schilmiller *et al*., 2009; Vandermoten *et al*., 2009; Surmacz and Swiezewska 2011; Coman *et al*., 2014). Besides, chloroplasts/plastids and cytoplasm, volatiles are also synthesized in mitochondria, all in the same cells of trichomes (Koranke *et al*., 2017).

Phase 3: This phase comprises of enzymatic reactions that synthesize terpenes and further modify them. In both plastids and cytoplasm, prenyl diphosphates are converted into terpenes by the action of terpene synthases (TPSs). Monoterpenes, sesquiterpenes and diterpenes are synthesized from GPP and NPP, FPP and GFPP and GGPP respectively. Some terpene synthases produce multiple terpene kinds from the same prenyl diphosphate (Croteau *et al*., 2000; Dudareva *et al*., 2005; Degenhardt *et al*., 2009; Chen *et al*., 2011; Falara *et al*., 2011; Gao *et al*., 2012; Liu *et al*., 2016. The enzymatic reactions mediated structural modifications such as cyclization, hydroxylation, dehydroxylation, oxidation, reduction or glycosylation on specific terpenes produce their variants (Whittington *et al*., 2002; Dudareva *et al*., 2005; Christianson 2006; Tholl *et al*., 2011; Zhou *et al*., 2012).

All the genes involved in the phase 1 and phase 2 pathways upto the synthesis of GPP and FPP and many terpene synthase genes have been cloned and sequenced and their expression profiled organ-wise at different stages of *A. annua* plant growth and development. The observed expression levels of the above mentioned genes in *A. annua* plant organs can be, in general, arranged in the following order: lower leaves < higher leaves < flower buds < mature flowers (Ma *et al*., 2015).

Genetical Determination of The Content and Composition of *Artemisia* Essential Oils

As seen above, there exists much natural intra- and inter-species variation in the content and composition of volatile organic compounds present in essential oils extracted from the herbage of artemisias. The differences in essential oil content/yield among various *Artemisia* genotypes are dependent in the main on the total plant growth, distribution, density and size of glandular trichomes over the shoot organs, biosynthesis levels of volatile compounds in the glandular trichomes and genotype x environment interactions. *Artemisia* species are annual, biennial or perennial herbs and

shrubs. Generally, the shoot organs can be arranged in the following order in terms of the density of glandular trichomes: inflorescence > leaves > stem (Hayat *et al*., 2009; Bilia *et al*., 2014; Shi *et al*., 2017; Salehi *et al*., 2018). Progressively formed leaves in the developing plants have denser presence of trichomes (Lommen *et al*., 2006). Compositional differences have been noted in the essential oils extracted from plants of same genotype harvested at different stages of development: early vegetative, late vegetative, early flowering, and late flowering (Mallavarupu *et al*., 1999; Masotti *et al*., 2003; Mohammadreja 2008; Maes *et al*., 2011; Padalia *et al*., 2011; Pirabalouti *et al*., 2013; Rana *et al*., 2013). The yield and quality of essential oil are therefore dependent on the development stage at which wild or cultivated annual/biennial or perennial artemisias are harvested (Mallavarupu *et al*., 1999; Gupta *et al*., 2002).

Biosynthesis of the volatile organic compounds, that comprise essential oil, has been studied in artemisias (Lu *et al*., 2002; Kessler *et al*., 2006; Wu *et al*., 2012; Bilia *et al*., 2014; Pratt *et al*., 2014; Ma *et al*., 2015 and 2017a and b; Salmon *et al*., 2015; Shi *et al*., 2017) and more extensively in a variety of heterologous plant systems, including the model plant species such as *Arabidopsis thaliana* (Christianson 2001; Rodriguez-Concepcion 2001; Keszei *et al*., 2008; Degenhardt *et al*., 2009; Baldwin 2010; Ramak *et al*., 2014; Lange 2015; Nieuwenhuizen *et al*., 2015; Tholl 2015; Rehman 2016; Fujita *et al*., 2017). The information elicited from various aromatic plants collectively suggests that the quantitative variation in the productivity of volatile organic compounds in the site of their synthesis, such as glandular trichomes, depends on the availability of the starting substrates produced by primary metabolism, expression levels of MVA and MEP pathway and downstream genes and catalytic efficiency of the gene products (Estevez *et al*., 2001; Munoz-Bertomen *et al*., 2006; Cordoba *et al*., 2009; Ramak *et al*., 2014). Perhaps at the flowering stage in plants there is greater input of photosynthesis products into secondary metabolism, at sites of their synthesis in flowers than in leaves.

The MVA and MEP pathways are regulated at multiple levels of their expression via gene copy number, transcription of genes, post translational controls, feedback repression and inverse signaling between nuclear encoded cytoplasmic products and chloroplast products (Chappell *et al*., 1995; Cordoba *et al*., 2009; Banerjee *et al*., 2013; Nieuwenhuizen *et al*., 2015; Tholl 2015). It is known that the overexpression of *DXS*, *DXR*, *MDS*/or *HDR* genes in the MEP pathway and pre-mevalonate genes in the MVA pathway can increase the levels of terpenes variously, up to 100 folds (Neuwenhuizen *et al*., 2015 and references therein). In *Artemisia annua*, overexpression of *HDR* has been found to increase the sesquiterpene levels at the expense of monoterpenes and reverse was observed upon the suppression of *HDR* gene (Ma *et al*., 2017b). The *TPS* genes occur in two families, each of considerable size, the *TPS-a* family for sesquiterpenes and *TPS-b* for monoterpenes. Contrasting profiles of terpenes result from variation in the copy numbers of various *TPS-a* and *b* family genes and polymorphism among the gene copies and by means of terpene modifying enzymes. (Christianson 2006; Chen *et al*., 2011; Lange 2015; Nieuwenhuizen *et al*., 2015; Tholl 2015, Booth *et al*., 2017). It is realized now that terpenoid-cum-phenylpropanoid profile of essential oil is a phenotypic marker of the species/genotype of the concerned *Artemisia* (Niederbacher *et al*., 2015; sections De and Df).

Formation of glandular trichomes in artemisias appears to be a developmentally regulated process. Accordingly, the synthesis of volatile organic compounds in glandular trichomes is a constitutively expressed property of artemisias. To what extent, in artemisias, the formation of glandular trichomes and synthesis of volatiles in them is induced by biotic and abiotic factors is largely unknown. Whereas treatment of plants with methyl jasmonate has been found to increase the density of glandular trichomes in *Artemisia annua*, that with salt has been reported to decrease as well as increase the frequency of glandular trichomes (Maes *et al*., 2011; Kjaer *et al*., 2014; Dangesh *et al*., 2014; Yadav *et al*., 2014). The observed induced variation indicates possibilities of developing genotypes of *Artemisia annua* and perhaps of other *Artemisia* species that hyper produce glandular trichomes.

Studies on volatile organic compounds of a variety of aromatic plants, of the kind synthesized in glandular trichomes of *Artemisia annua*, have been shown individually and in mixtures, to be

multifunctional: to provide protection against abiotic stresses such as drought and heat, and attack from herbivores and pathogens; to attract pollinators, seed dispersers and beneficial organisms (such as mycorrhizae); and to combat sympatric heterologous competing plant species. (Runyon *et al*. 2006; Gershenzon and Dudareva 2007; Rodriguez *et al*., 2014; Loreto *et al*., 2014; Gols 2014; Pierik *et al*., 2014; Copulovici and Ninemets 2016; Dong *et al*., 2016; Pichersky and Raguso 2016; Korankye *et al*., 2017). The natural roles of volatiles present in the essential oils of *Artemisia* species remain to be studied comprehensively. Since individual terpenes and essential oils of their presence, extracted from *Artemisia* species, are known to possess species specific antimicrobial, anti-insect and anti-seed germination properties, the character of synthesis of volatile organic compounds in glandular trichomes has been perhaps acquired and selected in artemisias for warding off herbivory, pathogens and parasites and to succeed in competition with other plant species.

The shoot organs and/or roots of locally growing *Artemisia* species have been used variously by the native populations in all the continents for hundreds of years, especially as components of traditional medicinal treatments for a variety of conditions. In recent years *Artemisia* species have been receiving considerable attention for the analysis of their secondary metabolites, especially the volatile organic compounds that constitute the essential oil extractable from them. These studies have identified many biological activities in the individual and mixtures of volatile compounds. Therefore, the essential oils of *Artemisia* species and their components are being examined for use in modern medicine (Paduch *et al*., 2007; Zwenger and Basu 2008; Jansen and Shenvi 2014; Pichersky and Ruguso 2016; Dhifi *et al*., 2016). These aspects are discussed in a section below:

Effect of Inter-Relationship Between Artemisinic - And Monoterpenoid-Cum-Nonartemisinic Sesquiterpenoid- Pathways on the *Artemisia Annua* Essential Yield and Quality

Artemisinin is a product of the artemisinic (ART) biosynthetic pathway that uses farnesyl diphosphate (FPP) as the precursor to convert it into amorph-4, 11-diene by the action of the enzyme amorph-4, 11-diene synthase (ADS) (Bouwmeester *et al*., 2009). The ART pathway is complex as it is known to produce artannuin B, artemisitene and arteannuin X in addition to artemisinin; the pathway is not fully elucidated (Liu *et al*., 2009; Brown 2010; Czeckowski *et al*., 2016; Xie *et al*., 2016). The steps of ART pathway by which artemisinin is synthesized are diagrammed in Figures 2a and 2d. Amorph-4, 11-diene is hydroxylated into artemisinic alcohol by the action of amorphadiene monooxygenase (CYP71AV1), a cytochrome P450 enzyme in cooperation with cytochrome P450 oxidoreductase (CPR) (Ro *et al*., 2006; Paddon *et al*., 2013). Next, artemisinic alcohol is oxidized to artemisinic aldehyde by CYP71AV1 in cooperation with alcohol dehydrogenase 1 (ADH1) (Paddon *et al*., 2013). Artemisinic aldehyde is reduced to dihydroartemisinic aldehyde by artemisinic aldehyde delta 11 (13) reductase (or double bond reductase 2, DBR2) (Zhang *et al*., 2008). Dihydroartemisinic aldehyde is oxidized to dihydroartemisinic acid by aldehyde dehydrogenase 1 (ALDH1) (Teoh *et al*., 2009; Zhang *et al*., 2011). In the final step a non-enzymatic light mediated photo-oxidation process converts dihydroartemisinic acid into artemisinin (Brown and Sy 2004; Brown 2010; Czechowski *et al*., 2016). All the above mentioned genes of ART pathway have been cloned and sequenced and recombinationaly reconstructed for overexpression using viral promoter in *A. annua* plants (Tang *et al*., 2014; Ma *et al*., 2015). The content of artemisinin was lower in *A. annua* control plants than in corresponding transgenic plants that overexpressed the genes listed singly or jointly as follows: *AaERF1, AaERF2, AaWRKY1, ADS, CYP71AV1, DBR2, ALDH1* singly and *ADS-CYP71AV1-CPR-ALDH1* jointly (Tang *et al*., 2014 and references therein). These observations suggested that the content of precursor for each of the step of artemisinin pathway (Fig. 2d) was present in *A. annua* control plants abundantly, but was used only partly. Suppression of the expression of the following non-artemisinic sesquiterpene synthase genes, that share farnesyl diphosphate with ART-pathway, increased the content of artemisinin but decreased the content of the concerned non-artemisinic sesquiterpenoids: β-caryophyllene synthase and squalene synthase (Zhang *et al*., 2009; Chen *et al*., 2011). These observations show that contents of artemisinic- and non-artemisinic-sequiterpenoids are negatively correlated. Increase in the content of volatile monoterpenes and

sesquiterpenes over control was observed in *A. annua* transgenic plants that overexpressed the following genes of MVA and MEP pathways: IDI and HMGR (Fig 2b); DXR and HDR (Fig. 2c) (Xiang *et al.* 2012; Ma *et al*., 2017a and b). These observations indicate possibilities of raising the yield of essential oil by means of genetic changes at the loci governing the MEP and MVA pathways. There is evidence both MEP and MVA pathways contribute to the contents of artemisinic and non-artemisinic compounds in *A. annua* plants. In this regard, it is known that IPP is transferred from plastids to cytosol (Towler and Weather 2007) and DMAPP from cytosol to plastids, the latter is converted into GPP (Figs. 2a and 2c) and transported to cytosol for conversion into FPP (Figs. 2a and 2b) (Sehramek *et al*., 2010). This indicates that selection for high artemisinin content may reduce the content of monoterpenes in the essential of *A. annua*.

The accessions from the wild and cultivars developed as hybrids between accessions and selections from accessions of *A. annua* fall into two groups with distinctive artemisinic phenotypes (Sy and Brown 2002; Ferreira *et al*., 2018). A class consists of *A. annua* genotypes whose plants are richer in artemisinic acid and arteannuin B contents, as compared to dihydroartemisinic acid and artemisinin, which has been called as LAP (Low Artemisinin Plant) type. The class called HAP (High Artemisinin Plant) type consists of genotypes of *A. annua* that are richer in dihydroartemisinic acid and artemisinin and low in artemisinic acid and arteannuin contents. The essential oils of HAP varieties are richer in sesquiterpenes and that of LAP varieties contain mainly monoterpenes. For example the essential oils of the HAP varieties Anamed A3 (artemisinin content 1.2%) and Sanjeevani (artemisinin content 1.0%) were respectively found to contain sesquiterpenes in 97.3 and 57.8% and monoterpenes in 4.9 and 31.0% concentrations (Reale *et al*., 2011; Gupta *et al*., 2016; Goel *et al*., 2018a). contrastingly, the essential oils of LAP varieties Linneo (artemisinin < 0.1 %) and Asha (artemisinin < 0.1%), respectively contained monoterpenes in 92 and 86% concentrations and sesquiterpenes in minor amounts (Jain *et al*., 2002; Reale *et al*., 2011). These observations imply that the selection for high artemisinin content is diverting the C5 building blocks of MEP and MVA pathways for the synthesis of farnesyl dipfosphate the precursor for both artemisinic- and non-artemisinic sesquiterpenes. These results further suggest that it is possible to construct strains of *A. annua* whose oils will have differential quality suitable for various kinds of uses/repurposement.

The experiments to reveal the effects of over-expression of volatile pathway genes and on glandular trichome genetic determinants in relation to the yield and quality of the essential oils and yield of artemisinin have been largly carried out on LAP genotypes of *A. annua.* To take advantage of the results of such experiments in future planning of genetic alteration in *A. annua*, the entire set of an experimentation needs to be repeated on HAP genotypes

Indigenous Medicinal Uses of *Artemisia* Species and Biological Activities Discovered in the Essential Oils of *Artemisia* Species of Traditional Medicine

Artemisia *Species in Traditional Medicine*

Plants have undergone natural selection to synthesize, store and use more than 100,000 secondary metabolites, of many distinct classes (Wink 2015; Tokimatsu *et al*., 2017). These compounds have the ability to interact with nucleic acids, proteins and/or biomembranes in cells (Wink 2015) of the plant producing them as well as those of heterologous organisms which happen to absorb them. Secondary metabolites have multiple functions (Korankye *et al*., 2017; Niederbacker *et al*., 2015; Loreto *et al*., 2014): they (a) adapt plant growth, development and reproduction to the variation via abiotic environmental factors; (b) attract pollinators, seed dispersers and symbiotic microorganisms (that fix atmospheric nitrogen etc.); and (c) ensure survival against parasites, pests and pathogens. Volatile organic compounds comprise a large group (>40,000) of secondary metabolites that have low molecular weight and low boiling point (Sun *et al*., 2016; Tholl 2015). Many of these volatiles are emitted by plants into their environment. Species of plants that emit the volatile metabolites in voluminous amounts have been called as aromatic plants. The essential oils extracted from the aromatic plants contain hundreds of volatile secondary metabolites, many of them in very high concentrations. Aromatic plants and their essential oils have medicinal uses.

Humans (*Homo sapiens*), in the course of their migration, settlement and development of ethnologically cultured societies, learnt by experience the use of locally available specific plants to cure a variety of infectious and chronic ailments. Many of the plant species used in the indigenous systems of medicine, evolved and practised in different parts of the world, are aromatic and include many species of the genus *Artemisia*. The selection of *Artemisia*, by early human societies in Africa, central-, east-, southeast- and south-Asia, Europe, Americas and Australia, as medicines for a wide range of disease conditions appears to be rational in retrospection. The *Artemisia* species synthesize and store their secondary metabolites in glandular trichomes that are structurally fragile. Therefore, suspension of fresh or dry foliage from artemisias rapidly releases the metabolites carried in trichomes into cold or hot/boiling water or alcohol and upon direct application on body parts as poultice. On account of their efficacy, several of the traditional treatments using raw herb, infusion, tea, tincture or essential oil of artemisias developed over thousands of years have become now evidence based and continue to be used in the present time. Actually, certain modern medicines, such as santonin and artemisinin and their derivatives, have been developed based on the curability of decoctions of *Artemisia* species herbage containing the specific natural substance(s) (Willcox 2009; Chinthakindi *et al*., 2017).

Table 4 summarises the traditional medicinal uses of 38 *Artemisia* species; the major volatile components of the essential oils of 29 of the species are identified in the Tables 1, 2 and 5. It is noted from the table 4 that human populations settled in widely different geographical areas of the world found medicinal use of *Artemisia* species to treat a large variety of infectious diseases, known to be caused by viruses, bacteria, fungi, protozoa and worms, and diseases of the human body's immune-, respiratory-, digestive-, cardiovascular-, nervous- and reproductive-system, among others. Clearly, few if any other plant taxa have saved human lives from debilitating and lethal disease conditions more than *Artemisia*. It is noteworthy that indigenous systems of medicine, that evolved in Eurasia, America and Africa use the individual *Artemisia* species for the same set of illnesses. For example, in southeast, south and central Asia, Africa, Europe and North America, *Artemisia absinthium* came to be used as tonic, febrifuge, stomachic, anthelmintic, abortifacient and wound healer. Another noteworthy feature about medicinal uses of artemisias is that for certain ailments, within the same geographical area, more than one *Artemisia* species became the medicines of choice. For example, a number of *Artemisia* species, including *A. absinthium, A. annua, A. caroifolia, A. dracunculus, A. indica, A. maritima, A. sieversiana* and *A. vestila* have been in use as febrifuge in South Asia. Being genetically inter-related, it is expected that different combinations of *Artemisia* species will share qualitatively and quantitatively the secondary metabolite spectrum and therefore the medicinal properties. In the table 4 there are few dozen examples of multiple *Artemisia* species as medicine for a disease condition. It is also noteworthy that the evolving early human societies in various parts of the world identified *Artemisia* species which could serve as feed as well as veterinary medicines (Beigh and Garai 2017; Da Silva *et al*., 2017; Popvic *et al*., 2017).

Biological Activities Detected in Artemisia Essential Oils

Modern medicine for a disease comprises of one or more natural or synthetic chemical compound(s), tested rigorously for efficacy and safety first on model animals, and subsequently on humans. The modern medicines, comprising of phytochemical(s), currently in use were largely indicated by traditional systems of medicine. The first step in the process of modern drug development from a phytochemical is the obtainment of evidence of biological activity(ies) in it against the cause of disease, corresponding with its usage to control a disease condition in traditional medicines. *Artemisia* essential oils, rich in a variety of volatile compounds, need to be explored for new drug development. In order to convert the disease curability effects of essential oils of *Artemisia* species known in traditional medicine into modern medicine, the biological activities of essential oils and their major constituents, singly and in combinations, have been tested in many studies. However, it is noted that these studies have not been comprehensive in that the selected oils have been checked against targets selectively. The observed activities in respect of human body functions, infectious organisms and insects; and on allelochemical effects against plants are listed respectively in the table 5 and Table 6. It is noted that *Artemisia* essential oils possess a wide

spectrum of activities against bacteria, fungi, protozoa and insects that are known to cause diseases in man, farm animals and crop plants. Many *Artemisia* essential oils possess antioxidant and radical scavenging activities. Some *Artemisia* essential oils possess vasorelaxant/sedative activity. Altogether they comprise a big resource of useful compounds, which need to be investigated for repurposement singly and in combinations to give new antibiotics and or pesticides.

In general, high degree of correspondence is noted between the diseases addressed by *Artemisia* species and biological activities observed in the respective oils. The *Artemisia* essential oils possess various levels of anti-bacterial, -fungal, -protozoa and -insect activities, together with antioxidant, radical scavenging and anticancer activities. *Artemisia* essential oils and their components, such as those listed for 133 essential oils of 60 different *Artemisia* species in the Table 5 offer possibilities of developing effective drugs against bacterial, fungal and protozoal pathogens, insecticides against food grain pests and mosquitoes. The qualities of 9 essential oils of 7 different species of *Artemisia*, listed in the Table 6, suggest possibilities of developing agricultural weedicides, active against both mono- and di-cots, from among the constituents of the allelopathic essential oils. Weedicides developed from allelopathic plant materials like *Artemisia annua* essential oil, are expected to be relatively harmless to farmers and consumers of the produce in comparison to some of the synthetically derived weedicides in current usage. Further intensified work is desired in the following directions. There are distinct possibilities for developing formulations (a) for the protection of different kinds of stored foods, (b) control of infectious diseases in livestock, (c) treatment of microbial infections in humans and (d) to control weeds in major food grain crops.

Recently, a highly cost effective clinical treatment of multi-drug resistant malaria has been developed which uses powdered dry leaves of *Artemisia annua* varieties containing $\geq$1% artemisinin (Daddy *et al*., 2017). This treatment has possibilities of repurposement against a variety of diseases that are cured by artemisinin or extracts of *A. annua* leaves (Goel *et al*., 2018b). The antimalarial cure comprises of two tablets or capsules a day for 5 days, each tablet/capsule prepared from 500 mg of dried leaves of *A. annua*. It is inferred that the diverse classes of chemicals present in the leaves, including artemisinic-, flavonoid-, terpene-, phenolic acid-, and sulphated polysaccharide-compounds, act complimentarily and provide an antimalarial treatment that is safe and resilient against resistance development. Such a treatment is likely to be effective against the infectious diseases–acanthamoebiasis, coccidosis and leishmaniasis and metabolic disorders such as fatty liver and diabetes that are known to be cured by extracts of *A. annua* leaves in model animals (Kim *et al*., 2011; Islamuddin *et al*., 2012 and 2014; Dragan *et al*., 2014; Helal *et al*., 2014, Derda *et al*., 2016). An example of repurposement of powdered *Artemisia annua* leaves is the demonstration that tablets, prepared by combining 500 mg of *Artemisia annua* leaf powder and 100 mg of black paper powder, are effective in protecting grains and other food materials against stored grain insects, such as *Tribolium castaneum* (Goel *et al*., 2018c).

Causes of Variation in the Chemical Composition of Artemisia Essential Oils

There are significant intra-plant, intra-species and inter-species chemical quality differences in the essential oils extracted from plants of *Artemisia* species. As shown in the Fig. 7, the compositional differences in the *Artemisia* essential oils are affected by a variety of genetic factors and the interaction of genotype of *Artemisia* cells synthesizing the essential oil components with the environment.

In *Artemisia* species, the volatile organic compounds that appear in essential oils are synthesized in the secretory cells of trichomes borne on shoot organs and resin ducts of vascular tissue of all organs. The genes that specify pathways for the synthesis of different classes of volatile molecules are present in the nuclear, chloroplast/plastid and mitochondrium genomes. Each mature cell of *Artemisia*, like in cells of angiosperm plants in general, has one nucleus and upto 500 mitochondria and 150 chloroplasts (Cole 2016). The nucleus has two copies of each chromosome in diploid species (2n = 14 in *Artemisia pattersonii;* 2n = 16 in *Artemisia scoparia*; and 2n = 18 in *Artemisia annua*) and upto 16 copies of each chromosome in polyploid species (2n = 144 in *Artemisia medioxima*) (Torrell *et al*., 2001; Valles and McArthur 2001; Sanz *et al*., 2011; Tabur *et al*.,

2011 and 2012; Pellicer *et al*., 2007, 2011 and 2014; Valles *et al*., 2011 and 2013; Gupta *et al*., 2014). The mitochondria and chloroplasts may respectively contain 1 or 2 and 1000 or more copies of their genomes (Cole 2016). The mitochondrial and chloroplastidic populations may not be numerically identical between cells (trichome cells) of different organs. Further, the genomes (DNA molecules) within individual chloroplasts and mitochondria within and between cells may carry allelic differences. There is complimentary exchange of gene products between the cytoplasms of a cell and of mitochondria and chloroplasts present in it such that the interactions between their products determine the gene expression from each kind of genome. Since each organ has its own gene expression programme, therefore there are gene expression differences, from cumulative genomes of cells, between plant organs. The genetic causes enumerated above are thought to be responsible for the kinds of compositional differences observed between essential oils extracted from different organs, of a crop of the cultivar Jwarharti of *Artemisia annua*, as exemplified in the Table 1.

The inter-plant intra-species essential oil chemical quality differences are expected among the progeny plants of a parent plant for the following reasons. Plants of *Artemisia* species are largely cross pollinated and therefore found to carry heterozygosity at many loci in their nuclear genome (Shen *et al*., 2018). *Artemisia* being an angiosperm, male and female gametes are formed as products of meiosis in anthers and ovules, respectively. During gamete formation the homologous chromosomes undergo recombination and independent assortment. Thus, both the male and female gametes irrespective of whether produced on the same or different plants are likely to be of different genotypes, for each progeny seed. Another source of genetic variation among different seeds borne on a plant will be via inheritance of chloroplasts and mitochondria. The random clusters of chloroplasts and mitochondria transmitted from the mother plant to different female gamete will carry different patterns of allelic variation in the genomes of both kinds of organelles. Therefore, the female gametes formed on a plant may inherit genetically different sets of mitochondria and chloroplasts. Thus, the progeny seeds produced on a mother plant are likely to carry allelic variation in their nuclear, mitochondrial and chloroplastidic genomes. Such variation will be the cause of inter-plant differences, among the progeny plants of a mother plant of the *Artemisia* species, in the quality of essential oil extracted from them (different progeny plants of a parent plant). Many examples of the intra-species-population differences and intra-species-varietal differences in the chemical compositions of essential oils yielded by them are seen in the Table 3. For example, large differences in essential oil's major constituents are seen among *Artemisia absinthium* populations growing in different geographical areas of the world (rows 3 to 23 in the Table 2) and among *Artemisia annua* varieties growing in similar Indian agroclimates (rows 35 to 43 in the Table 2).

Intra-species and inter-species ploidy differences among *Artemisia* species are a major source of variation in the chemical quality of *Artemisia* essential oils (Table 7). Larger the genome or chromosome complement, greater is the accumulation of alternate alleles in the genes coding and regulating the pathways of synthesis of volatile organic compounds. *Artemisia* species demonstrate enormous nuclear genome size or karyotype variation. Large majority of *Artemisia* species have polyploid populations. Diploid species too demonstrate considerable genome size variation. The nuclear DNA content in *Artemisia annua* a diploid species is (2C = 3.5 pg) 9 fold lower than the polyploidy species *Artemisia copa* (2C = 31.5 pg) and 4.4 fold less than the diploid species *Artemisia leucodes* (2C = 15.4 pg) (Valles *et al*. 2011 and 2012).

The nuclear and chloroplast genomes of the model plant species for the analysis of artemisias huge volatilome, *Artemisia annua,* have been sequenced. The chloroplast genome consists of 150,995 base pairs and encodes 113 genes (80 protein coding and 33 non-coding). The nuclear genome size is 1.74 gigabase pairs which encodes 63,226 protein coding genes. The numbers of non-coding genes remain to be determined. The nuclear genome is rich in repeat sequences and several to many genes for terpenoid biosynthesis occur in multiple copies. More than 20,000 protein coding genes have been observed to be expressed in trichomes (Shen *et al*., 2017 and 2018).

Artemisia nuclear genomes comprise of four basic chromosome numbers: x =7, 8, 9 and 17. The x = 7 and x = 8 chromosome complements are thought to have arisen from x = 9 complement by Robertsonian fusion(s) between chromosomes (Valles *et al*. 2011

and 2012). The basic chromosome number x = 17 is believed to be a result of fusion of x = 8 and x = 9 chromosome complements via allopolyploidy (Valles *et al*. 2011 and 2012). The *Artemisia* species fall in the following order in terms of the frequency of basic chromosome numbers: x = 9 > x = 8> x = 7 > x = 17. Ploidy levels of 2x, 3x, 4x, 5x, 6x, 8x, 10x, 12x and 16x are known (Valles *et al*. 2011 and 2013). The basic x = 7 (2n = 14) has been reported for *A. pattersonii* and x = 9 (2n = 144) for *A. macrantha* (Weins *et al*. 1996). It will be seen from the table 7 that the species *Artemisia dracunculus* has populations with 2n = 2x, 4x, 6x, 8x and 10x. The polyploidy is largely autopolyploid; allopolyploidy is rare. Polyploidy and dysploidy have been responsible for the evolution of species in the genus *Artemisia*. Aneuploidy and presence of B chromosomes has also been recorded in many *Artemisia* species (Table 7) (Pellicer *et al*., 2007, 2011 and 2014; Valles *et al*., 2011, 2012 and 2013; Tabur *et al*., 2014). Whereas autopolyploidy increases copy number of gene complement of a species and provides opportunity for intra-genic variation to occur simultaneously in a genotype, the allopolyploidy, besides increasing the copy number of genes, brings in already selected intra-genic variation and a new complement of genes, selected in a different species of genus. The interaction in cells between the nuclear ploidy and ploidy of mitochondrial and chloroplast genomes is also expected to affect the yield and profiles of the volatile organic compounds synthesized and therefore the essential oil chemical quality. *Artemisia* species offer opportunities to explore interactions between nuclear genome size, organelle number and genome copy number in organelles and relative expression levels of genes from three kinds of genomes involved in synthesis of volatile organic compounds, in trichomes.

Direction of Future Research to Improve and Establish Consistency in the Yield and Quality of *Artemisia* Essential Oils and Yield of Artemisinin

Three products of artemisias are of international importance: essential oils from several artemisias, including *A. annua*, used in the perfuming of the cosmetics, flavouring of foods and pest control formulations; and artemisinin and tablets/capsules of dry leaves of *A. annua* for the treatment of malarias. The objectives of future applied research of artemisias should be to improve yield and/or quality of the harvests, from the field cultivated crops or crops cultured in environment controlled glass/plastic houses, via suitable genetic changes in the existing accessions/ varieties to evolve new cultivars. In all the genetic improvement experiments involving *A. annua*, the use of high artemisinin yielding cultivars such as Anamed A3, Artemis F3, Jeevanraksha and Sanjeevani may be prefered. Artemisias being largely open-pollinated, it is also desirable that the genotypes of new cultivars are carried forward over generations consistently. Genotypic constancy will be achieved if the planting material of a genotype is produced via vegetative means (micropropagations, cuttings etc.). To achieve genetic consistency self-pollination by covering racemes with perforated plastic bags or seed production in isolation of other genotypes need to be practised. The quality requirements of Artemisia essential oils should conform those mentioned in conclusion of an earlier section. Some of the possible approaches to derive improved cultivars of artemisias are outlined below:

Breeding in Artemisia Species

Obtainment of Relatively Greater Consistency in Yield and Quality of Commercial Essential Oils from Artemisia Species : The commercially used *Artemisia* essential oils are usually being extracted from the wild populations of *A. absinthium*, *A. afra, A. annua, A. argyi, A. campestris, A. cappilaris, A. dracanculus, A. herba-alba, A. maritima, A. pallens* and *A. vulgaris* in one or more countries of Africa, Americas, Asia and Europe. Cultivars for high yields of desirable quality of essential oils could be developed from each of the above species via application of plant breeding procedures. The process should begin by screening of individual progeny plants, raised from seeds of a few wild plants of the conventionally used population of a species, for selection of the most desirable genotypes. The crops of selected genotypes will be raised from micropropagated propagules or from seeds produced in isolation of other genotypes.

Construction of Inter-specific Hybrid Genotypes to Obtain Both Artemisinin and Quality Essential Oils in High Yield

It is desirable to produce inter-specific hybrid genotypes of *A. annua* into *Artemisia* species that

are resource of commercial essential oils but contain artemisinin only in minute amount, examplified by *A. absinthium, A. dracunculus* and *A. vulgaris*. In these three species diploid (2n = 18) as well as tetraploid (2n = 36) plant populations are known to exist naturally (Table 7). Thus to evolve hybrids between *A. annua* and each of these identified species, to complement the genetic apparatii for artemisinin and volatiles, is considered an important objective. The feasible approaches to construct inter-specific hybrids can be: selections from among the products of fusion of protoplast of the heterologous species; and selections from among the allotetraploids produced via *in vitro* cross-fertilization and *in vivo* cross-pollination, followed by chromosome complement doubling.

Tried and tested procedures for fusing the protoplast and raising of plants from fusion products are described (Melchers *et al*., 1978; Sink *et al*., 1992; Assani *et al*., 2005). In the absence of selectable markers, the inter-specific tetraploid hybrid plants produced by fused protoplast will be identified by the presence of hybridity in karyotype and morphology. The protoplast-fusion hybrids in which artemisinin content is e" 1% and the essential oil yield and quality are also desirable will be maintained and multiplied by micro-propagation and used as cultivars. Their seeds will be produced by growing them in isolation and individual progeny plants will be characterized for the selected traits and self-fertility. Seeds from highly self-fertile and otherwise desirable plants will be collected and the individual plants of progeny population will be screened to undergo selection. This process will be followed in several subsequent filial generations to develop fertile cultivars.

The plantlets resulting from the accomplishment of intensively described *in vitro* cross-fertilization procedures (Kranze 2001; Kranze and Scholten 2008; Bhojwani and Dantu 2013) will be treated with colchicine to induce chromosome doubling. The adult *in vitro* produced tetraploid hybrids will be maintained and multiplied vegetatively and characterized for karyotype, morphology, artemisinin content and essential oil yield and composition. Further processing of the hybrid genotypes will be like that for protoplast-fusion-produced inter-specific hybrids. Separately, any seeds formed on the racemes of the heterologous species being crossed by covering them together in crossing bags will be collected. Since, such seeds could of parents or hybrid, the plants raised from them will be screened by karyotying and for morphology. The micro-plantlets produced vegetatively from them will be treated with colchicine to double the chromosome number. From among a population of plants obtained from colchicine treated propagules, allo-tetraploids will be identified and characterized for desirable traits. The selection process will proceed further like in *in vitro* cross-fertilization experiment.

Derivation of Improved Cultivars in A. annua

Induction of Tetraploidy: There is evidence that an induced tetraploid strain of *A. annua* accession from Vietnam accumulated much more artemisinin than in the control plants (Banyai *et al*., 2011). However, the effect of induced tetraploidy on the essential oil yield and quality remains unknown. The procedures to induce tetraploidy described for *Artemisia* and other plant species should be used to develop new tetraploid strains from artemisinin rich cultivars of *A. annua*. From among the produced tetraploids those that are richer in artemisinin from respective controls and give essential oils of good quality in high yield should be developed into cultivars.

Construction of Transgenics Over-Expressing One or More Genes Involved in the Generation of C5 Building Blocks of Terpenoids and Formation of Glandular Trichomes

On the one hand several genes, including AaTTG1, AaGL3, AaTFAR1, AaMYB1, AaMIXTA and AaHD1 regulate glandular trichome formation. On the other hand over-expression of AaHMGR, AaIDI, AaDXR and AaHDR increases the overall syntheses of the inter-convertible C5 compounds IPP and DMAPP that are the building blocks/ precursors for sub-pathways of the terpenoid metabolite biosynthesis. It will be important to construct transgenics from the Jeevanraksha variety, for example, to over-express one or more of the above listed genes. Selections will be for the transgenics in which there is improvement in the biosynthesis of monoterpenes and sesquiterpenes comprising the essential oil and artemisinin. The transgenics possessing the desirable phenotype will be maintained and multiplied vegetatively, as well as selfed to obtain homozygosity for the transgene. The selected transgenics will be

processed further like mutants.

Salinity Resistant Mutants

It is known that the salinity resistant mutants of *Catharanthus roseus* produce and accumulate alkaloids in high concentrations due to hypomethylation (epigenetic change) in their genomic DNA (Kumari *et al*., 2013). A saline resistant somaclone of *A. annua* is known to express ART pathway at high levels and accumulate artemisinin in higher concentration than the control plants (Pandey *et al*., 2016). To develop artemisinin and essential oil rich genotypes that carry pleiotropic changes in characters that determine the expression of terpenoids, via induction of salt tolerant mutations, is a highly promising experimental area to persue. It is expected that in the mutants the pathways that make plants tolerants to biotic and abiotic stresses will get expressed constitutively.

Short Life Cycle Mutants

Crops of presently available improved *A. annua* cultivars take 9-12 month (December/January to October/November/December) from sowing to harvesting in semi-temperate areas such as in India because of the requirement of an extended period of short days for flowering. Therefore, in fields cultivated with *A. annua*, the usual crop rotation systems can not be followed. Also there is problem of properly drying the harvested foliage because of the relatively low temperature from October to December. It is known that drying of the foliage *in planta* mediates conversion of DHAA to artemisinin (Ferreira *et al*., 2018), which will be possible if the *A. annua* crops could be harvested around June end. Therefore, it is desired to shorten the period taken to flowering in *A. annua*. The starting genotype will be the varieties like Jeevanraksha and Sanjeevani that produce artemisinin in high amount and the desired quality of oils in high yields. Selfed seeds will be mutagenized and M1 plants will be selfed to produce M2 generation. The M2 plants that may come to flower in 12-18 weeks will be identified and studied for artemisinin content and essential oil yield and quality. The selected mutant plants will be selfed to raise M3 plants. The following generations up to M6 will be pursued to select the desirable plants from selfed seeds. The breeders seeds of the new varieties will be produced in field conditions in isolation.

Isolation of Mutants with Certain New Features for Further Exploration

It appears important to use random and wherever possible directed mutagenesis procedures to isolate mutants with the following kinds of phenotypes: leaves of larger size, less compounded and full of glandular trichomes; more chloroplasts per cell and more genomic DNA molecules per chloroplast; higher self-fertility; conditional expression of the volatile pathways in varied kinds of cells in shoot organs in addition to trichomes.The mutagenesis should be attempted in a variety such as Jeevanraksha. It will be possible to recombine the useful mutations from Jeevanraksha to other varieties.

Summary

The natural or cultivated populations of one or more of $\geq$500 described species of the genus *Artemisia*, some annual but largely perennial, are found growing in nearly all agro-climates and serving as resource of materials for ethnomedicines, animal food and essential oils and compounds widely used in food, flavouring, cosmeticeutical and pharmaceutical industry. The evolving *Homo sapiens* populations, in the course of their migration from Africa and settlement in various parts of the world, have depended on foliage and/or essential oils of artemisias (*Artemisia* species) for treating fevers and chills, cough and influenza, body pains, dysmenorrhoea, jaundice, internal infections of worms and parasites, external body sores and skin diseases and as tonic as well as aborti-facient. In recent years the compound artemisinin extracted from the foliage of *Artemisia annua* has allowed substantial control of the malarial disease worldwide (several million lives saved).

The artemisias are mostly aromatic plants, such that their inflorescence, leaves, stems, roots and seeds yield essential oils that are rich in volatile organic compounds (VOCs) of the monoterpenes, sesquiterpenes, phenylpropanoids and benzenoids classes. Glandular trichomes consisting of 10 cells and produced densly on inflorescence parts and leaves are the major sites of synthesis of VOCs that get extracted into essential oils. In the stems and roots, VOCs are synthesized in parenchyma cells of resin ducts that run parallel to the vascular system. Whereas phenylpropanoids and benzenoids are synthesized in the cellular cytoplasm, terpenoids are synthesized in

cytoplasm as well as the organelles plastids (chloroplasts) and mitochondria. The C5 building blocks of terpenes, isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP), are synthesized in multiple steps of the methylerithritol phosphate (MEP) pathway in plastids and mevalonic acid (MVA) pathway in cytoplasm. Subsequently IPP and DMAPP are condensed into a series of prenyldiphosphates which then serve as precursors of terpenoids. Terpenes synthesized in cytoplasm, plastids and mitochondria are later variously modified.

The present survey of foliage (leaves + inflorescence) essential oils of 176 populations of 66 species of artemisias, exemplifies the enormous compositional variability demonstrated within and between *Artemisia* species. The major volatiles ($\geq$ 20%) in the essential oils of the species fall in the following order of the frequency of their occurrence: camphor, 1, 8-Cineole > borneol, α- and β-thujone, artemisia ketone, β-pinene (all monoterpenes) > davanone (sesquiterpene) > caryophyllene (sesquiterpene) > artemisia alcohol, piperitone (monoterpenes), germacrene D (sesquiterpene) > chrysanthenone, p-cymene, linalool (monoterpenes) > capillin (benzenoid), myrcene, sabinene, bornyl acetate, camphene (monoterpenes), caryophyllene oxide, spathulenol (sesquiterpene) > estragole (phenylpropanoid), cis-chrysanthenyl acetate, sabinyl acetate, trans-pinocarveol, α-terpineol (monoterpenes), 1, 2-dihydro-acenapthalene (benzenoid), chamazulene, trans- β-farnesene (sesquiterpenes). The following VOCs are present in essential oils of certain *Artemisia* populations in more than 50% concentrations, serving as markers of the concerned artemisias: trans-anethole and estragole (phenylpropanoids), capillin (benzenoid), artemisia ketone, camphor, 1, 8-cineole, cis-epoxy-ocimene, piperitone, sabinyl acetate and α- and β- thujones (all monoterpenes), methyl chavicol and germacrene D (sesquiterpenes). In *A. annua*, the biosynthesis of the anti-malarial sesquiterpene lactone compound artemisinin occurs from a sub-pathway for which the precursor is farnesyl diphosphate (FPP) formed from 2 IPP and 1 DMAPP building blocks. FPP is converted into artemisinin via amorph-4, 11-diene, artemisinic alcohol, artemisinic aldehyde, dihydroartemisinic aldehyde and dihydroartemisinic acid (DHAA). Over-expression of *HMGR* and *IDI* genes of the cytosolic MVA pathway and *DXR* and *HDR* genes of the MEP pathway increases the biosynthesis of essential oil volatiles as well as artemisinin in *A. annua* transgenics. The essential oils of HAP (High Artemisinin Plant type) *A. annua* cultivars such as Anamed A3 and Sanjeevani are sesquiterpene rich because of channelling of C5 building block(s) like IPP from plastids to cytosol for FPP synthesis.

In *Artemisia* species, the genetic information for the synthesis of VOCs is present in their 2n nuclear genome, one thousand or more DNA genomes of each of 150 or more chloroplasts per cell and 1 or 2 DNA genomes of 500 or more mitochondria per cell. The nuclear genome copies, each genome copy of chloroplasts and mitochondria may carry allelic differences in the genes for VOCs. *Artemisia* species being cross pollinated, they are prone to produce genetically heterogenous progenies on account of recombination between- and independent assortment of- homologous chromosomes. Intra-species and inter-species variation in essential oil composition also results from enormous variation in nuclear genome size and presence of B chromosomes. There is auto- and or allo-ploidy of 10X level in certain species. Essential oils of many *Artemisia* species have been investigated for biological activities and a close relationship has been observed between the biological activities of essential oils and ethnomedical use of the species. Survey of 133 essential oils of 60 *Artemisia* species has shown that essential oils possess anti-bacterial, - fungal, - protozoan and – insect and weedicidal activities. The whole essential oils and their specific components possess radical scavenging, vasorelaxant, anti-cancer and a wide variety of other activities. There is need to use these materials in the cure and prevention of infectious diseases and metabolic disorders, in new ways and repurposement in agriculture, food and cosmeticeutical industry.

Future frontiers of research to be pursued include the following lines of investigations. Production of true breeding genotypes of artemisias from which commercially important essential oils are resourced. Inter-specific hybridization between *A. annua* and other artemisias from which commercial essential oils are produced to generate genotypes that would yield both artemisinin and commercial quality essential oils in high amounts. Induction of auto-tertaploidy and construction of transgenics in *A. annua*. The transgenics would over-express MEP and MVA

pathway genes so that the volatiles of essential oil and artemisinin will be hyper-synthesized. Isolation of mutants with a variety of new traits such as: photoperiod insensitive short life cycle plant type that will fit into the crop rotations and dry in the field before harvest to maximize the conversion of DHAA into artemisinin *in planta*; salinity resistant mutants in which the epigenetic changes will allow pleiotropic phenotype for increased yield of essential oil and artemisinin; mutants which produce larger and less compounded leaves with more trichomes; mutants with high self-fertility; and mutants in which the entire terpenoid pathway will be conditionally expressed in epidermal and ground tissues of leaves, stems, involucres and flowers, in addition to expression in trichomes.

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