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Interaction between mycorrhizal and medicinal plants towards enhancement of secondary metabolites

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Abstract
Arbuscular mycorrhizae fungi (AMF) are symbiotic relations between plants and fungi, it has a long history of more than 400 million years. AMF mycelium colonizes the plant root system forming structures like root hairs which are considered as functional site for absorbing nutrient from soil and transfer them into the plant root. AMF increase nutrients uptake from soil as well as improving disease resistance against many pathogens. Medicinal plants are used across the world as primary form of therapy in the all known traditional medical systems which considered safer, cheaper and effective compared with chemicals ones. These plants metabolites are classified as primary metabolites and secondary metabolites, these secondary metabolites are subdivided in three major classes: alkaloids, terpenoids, and phenolics. They contain numerous phytochemicals with beneficial therapeutic as well as preventive effects. AMF inoculation on medicinal plants decreased the infection of bacterial and fungal pathogens, in addition to that The AMF–medicinal plants interaction causes chemical and biological changes lead to change in the secondary metabolite concentrations. In this review, we have summarized the effect of different arbuscular mycorrhizae fungi on increasing or decreasing the secondary metabolites of some medicinal plants and it was discussed about the secondary metabolites pathways involved in AMF–medicinal plants interaction.

Keywords: Interaction, mycorrhizal, medicinal, towards, enhancement

Introduction

Arbuscular mycorrhizae (AMF) came from the words “arbusculum”, “mycos” and “rhiza” which mean little tree, fungus, and root, respectively. These fungi have a collaborative effect on plant growth performance in comparison to any microbes by increasing the biomass of the root system and enhancing the root surface area for absorption of minerals and water (Leake *et al*. 2004) [44]. The AMF mycelium colonizes the plant root system causing increase in root surface area and passing the reachable and unreachable nutrients from soil to the plant’s roots because this mycelium is thinner than roots, allowing it to penetrate through root’s pores (Smith *et al*., 2000; Allen, 2011) [70, 3], helping in absorbing nutrient from soil and transfer them into the plant root (Balestrini *et al*., 2015) [7]. AMF are associated with improved growth of many plant species due to increased nutrients uptake, production of growth promoting substances, In addition to an enhanced nutritional supply, AMF provide other benefits to plants, such as improving tolerance against drought and salinity and synergistic interaction with other beneficial soil microorganisms such as N-fixers and P-solubilizer (Augé *et al*., 2015) [6], as well as enhancing disease resistance against many pathogens (Pozo and Azcón Aguilar, 2007) [53]. Recently, these fungi caused increasing in secondary metabolite contents of many important compounds in the medicinal plants (Varma *et al*., 2017) [91]. A medicinal plant is a plant that is used with the intention of maintaining health, to be administered for a specific condition, or both, whether in modern medicine or in traditional medicine. The Food and Agriculture Organization estimated in 2002 that over 50,000 medicinal plants are used across the world. Herbal medicine, botanical medicine or phytotherapy, is the primary form of therapy in the all known traditional medical systems, namely, the Chinese, Ayurveda, and Greco-Arab medicine, these medicines are considered safer, cheaper and effective compared with chemicals ones.

For therapeutic application, specific parts of the herb (aerial parts, root, leaves, fruit, flowers, and seeds) are formulated into a suitable preparation, e.g., tablets, teas, extracts, creams, or tinctures. The efficacy of herbal medicines is often described in very general terms, such as anti-inflammatory, anticancer, antiseptic (antimicrobial substances that are applied to living tissue/skin to reduce the possibility of infection), laxative (induces bowel movements or to loosen the stool), demulcent (an agent that forms a soothing film over a mucous membrane, relieving minor pain and inflammation of the membrane), antitussive (cough suppressants), or carminative (prevents formation of gas in the gastrointestinal tract or facilitates the expulsion of said gas). It is difficult to determine the accurate number of medicinal plants on earth, but as of 2010, there is thought to be 300–315 thousand species. About one third of these plants are in use throughout the world (Saad 2014; Saad and Said, 2011; Pan *et al.*, 2014) [94, 95, 96]. AMF inoculation on medicinal plants decreased the infection of bacterial and fungal pathogens by morphological modification like thickening of the cell wall, stronger vascular bundles and physiological modification like improving the levels of phenolics, sulfur-containing amino acids (Boby and Bagyaraj, 2003). These fungi are associated with medicinal plants by symbiotic relationship with *Panax ginseng* (Zhang *et al*., 2011) [96], with *Salvia miltiorrhiza* and *S. offcinalis* (Meng and He, 2011; Nell *et al*., 2009) [46], and with *Ocimum basilicum* (Prasad *et al*., 2011) [91]. The AMF– medicinal plants interaction causes chemical and biological changes lead to change in the secondary metabolite concentrations such as terpenoids, alkaloids, and phenolics (Cai *et al*., 2008) [17]. Some medicinal plants like *Anethum graveolens*, *Trachyspermum ammi*, *Foeniculum vulgare* and *Ocimum basilicum* showed increasing in the essential oil levels (which contains many important secondary metabolites) when AMF and phosphate fertilizer applied together (Kapoor *et al*., 2004) [41], but in *Origanum vulgare* medicinal plant, phosphate fertilizer application alone without AMF did not increase in the concentration of essential oil compared to control (Kapoor *et al*., 2007) [100] AMF is known to enhance contents of secondary metabolites such as terpenoids, alkaloids, and phenolics in many economically and industrially significant crops such as production of flavonoids, cyclohexanone derivatives and apocarotenoids, phytoalexins, phenolic compounds, triterpenoids, and glucosinolates in herbal, and medicinal important plants colonized by AMF has been reported Kapoor *et al*. (2017) [100] found that enhanced phosphorus uptake in the mycorrhizal plants has been largely credited for the increase in terpenoid production which are commercially valued for their medicinal properties in medicinal plants (Adeoyo *et al*. 2019; Gianinazzi *et al*. 2010) [59, 99].

Importance of arbuscular mycorrhizal fungi

AMF are soil microorganisms, natural fertilizers and key link between plants and soil mineral nutrients. They are obligate symbionts fungi, belonging to the phylum Glomeromycota (Schüßler *et al*., 2001) [64], but before they were under the order *Glomales*, phylum *Zygomycota* (Redecker *et al*. 2000) [56]. They supplied the host plant with mineral nutrients and water, in exchange for photosynthetic products (Smith and Read, 2008) [69]. Olive seedlings inoculated with mycorrhizal fungi *G. mosseae* and planting them in soil contaminated with V. dahliae, reduced disease severity and increased the growth of seedlings (Khrieba *et al*. 2019) [34]. The mechanisms responsible for the increased plant tolerance to stress have yet to be completely explained (Bárzana *et al*., 2015; Sánchez-Romera *et al*., 2016) [9, 63]. Metals such as Fe, Cu and Zn play important characters in several subcellular sections, but they are toxic at high concentrations (Tamayo *et al*., 2014) [73]. AM fungi are known to reduce heavy metal toxicity in the host plants and to tolerate high metal concentrations in the soil (Meier *et al*., 2015) [42]. A Zn transporter has been identified in *Glomus intraradices* (González-Guerrero *et al*., 2005) [27] and, more recently, several putative genes coding for Cu, Fe, and Zn transporters have been identified (Tamayo *et al*., 2014) [73]. AM fungi can also have a direct effect on the ecosystem, as they recover the soil structure and aggregation (Leifheit *et al*., 2015; Rillig *et al*., 2015) [37]. The effect of AM symbiosis on greenhouse gas (GHG) releases has recently been studied (Lazcano *et al*., 2014) [36]. Bender *et al*. (2014) [11] have revealed that AM fungi involved in reducing releases of N2O, which is an important greenhouse gas, AMF could adjust N2O releases by enhancing plant N uptake, which gives a reduction of soluble N in the soil, and therefore, in a limitation of denitrification (Bender *et al*., 2014) [11]. In drought conditions, mycorrhizal fungi enhanced the uptake of the highly mobile nutrient $NO3^-$. AMF could have an indirect impact on GHG releases, and also change soil texture as aeration, moisture, and combination, all of which influence the production and transport of GHG in soil. Lazcano *et al*. (2014) [36] have stated that AMF are primary biotic soil components which, when absent can lead to a less effective ecosystem functioning. The process of increasing the natural level of AMF fertility can represent promising alternative friendly fertilization practices. The main approach assumed to reach this goal is the direct re-introduction of AMF inoculum into a target soil. So many experiments showed that AMF absorb N, P, K, Ca, S, Cu and Zn from the soil and transfer them to the associated plants. The most important nutritional effect of AMF is the enhanced uptake of immobile nutrients; specially P, Cu, and Zn. AMF related with improved chlorophyll levels in leaves and enhanced plant tolerance of diseases, parasites, water stress, salinity and heavy metal toxicity. Hyphae may increase the availability of nutrients like N or P from locked sources by decomposing large organic molecules. Extra radical AM hyphae enhance the uptake of nutrients from up to 12cm away from the root surface (Smith and Read, 2008) [69]. By this association Improved P nutrition has been shown in infertile and P fixing soils of the (Mondal *et al*., 2012) [44].

Importance of medicinal plants

India is rich in medicinal plants and traditional medicinal knowledge. The using of plants in order to get a medicinal purpose is called alternative medicine which has been used nearly in all cultures as Asian and Western countries. Unfortunately, nowadays most of people still trust that effective medicine is the one that has a dosage form (as tablets, capsules). Even though there are many capsules are coming originally from plants such as Aspirin, Digoxin. In the past, plants and herbs were used to get taste food, reduce pain, treat headache, and prevent epidemics' diseases. The knowledge of their therapeutic properties has been transferred from generation to another. Effective compounds produced during secondary metabolism are usually involved in the biological activity of plant species used for treatment of diseases. Currently, many plants have antimicrobial properties, but they are under experiments till now, so, huge amounts of studies are required to explain the mode of action of the chemical composition inside these plants to suppress the microbial growth, separately or with another useful microbial help. There are more than one lakh of plants worldwide are either undiscovered, or their medical activities are not studied yet. It is expected that some plants will play an important role in the medical field, especially in the dealing with dangerous disease as cancer, so their medical ability should be confirmed in the present and future studies. Medicinal plants have many characteristics when used as a treatment, as follow: (1) Synergic medicine: Each plant has many compounds that may act together causing complement or damage to each other. (2) Support of official medicine: The plants' compounds can be used along with chemical products to get the wanted result. (3) Preventive medicine: Some plants' compounds had showed to be active in stopping or decreasing the risk of certain disease like flu, and this can help in reduce the charged and save money. China was one of the first countries to have a medical culture. When compared to Western method, Chinese medicine takes a far different approach. In China and India as well as in most countries of the Arab world, herbal products (e.g., whole plants, plant extracts, tinctures, and creams) are usually sold over the counter. In contrast, herbal remedies are classified in many European countries as drugs; in the United States they are sold as dietary supplements. Germany is the leading country in Europe followed by France in the use of botanicals. Around three quarters of German physicians prescribe herbs. The revival of interest in phytomedicine at the global level has been so dramatic that sales of herbal products in the world are staggering at over 100 billion dollars a year. In India almost all the known medicinal plants can be cultured, India has about 2000 species of medicinal plants, it is already a chief exporter of medicinal plants. It is rated about 86 corers Rs price of raw materials from medicinal plants are exported from India, such as Opium poppy, tropane alkaloid bearing plants etc., The ancient India system of medicines revealed most suitable healing against many diseases as Jaundice, bronchial asthma rheumatoid arthritis diabetes etc. (Thakur and Pathak, 2018; Mohammed, 2019; Saad *et al*., 2017) [92].

Secondary metabolism

Definition

Bennett and Bentley (1989) [12] defined general metabolites as products, created by living organism, necessary to growth and life, and biosynthesized by a limited number of biochemical pathways. But secondary metabolites are products; belong to different taxonomic groups, not necessary to growth and life of the producing organism, and biosynthesized by wide numbers of biochemical pathways (Thompson, 1992) [40]. Years ago, secondary metabolites have been known as unused products, with no importance for the plant. But recently, it is mentioned that secondary metabolites are playing a role in the interaction between the organism and its environment for the survival in its ecosystem (Von Dorhen, 1997) [82]. Secondary metabolites numbers can be collected from the Dictionary of Natural Products as mentioned in Table 1. The largest groups are the terpenoids (33,000) and the alkaloids (16,000) in 1988. Plant metabolites are classified as primary metabolites and secondary metabolites. Basic metabolism comprises all primary metabolites necessary for the cell/tissue survival and is involved in the primary biosynthesis processes of growth, regeneration, reproduction, and maintaining plant tissues. These include carbohydrates, lipids, proteins, nucleic acids, and chlorophyll which are common to all plants. On the other hand, secondary metabolites are those that occur usually only in special, differentiated cells/tissues and are not necessary for the cells/tissues themselves but play an important role for the plant as a whole. It is a well-known fact that the climatic conditions, different places, as well as environmental factors may affect the chemical composition and concentration of herbal secondary metabolites. These secondary metabolites are subdivided in three major classes: alkaloids, terpenoids, and phenolics. They contain numerous phytochemicals with beneficial therapeutic as well as preventive effects. Flavonoids can protect against free radicals generated during photosynthesis. Terpenoids may attract pollinators or seed dispersers, or inhibit competing plants. Alkaloids usually ward off herbivore animals or insect attacks (phytoalexins) The synthesis of secondary metabolites can occur in all plant organs, including the flowers, fruit, seeds, roots, shoots, and leaves (Saad *et al*. 2017; Kabera *et al*., 2014; Riaz *et al*., 2016) [92, 97, 98].

Table 1: Number of secondary metabolites as present in the Dictionary of Natural Products (Wink, 2008) [18]

Secondary metabolites	Number
Aliphatics	5200
Polyketides	2442
Carbohydrates	3210
Oxygen Heterocycles	1348
Simple Aromatics	4527
Benzofuranoids	387
Benzopyranoids	2694
Tlavonoids	8128
Tannins	750
Lignans	1565
Polycyclic Aromatics	2448
Terpenoids	27,463
Amino Acids, Peptides	3921
Alkaloids	15,765

Economic importance

Secondary metabolites are used as specialty chemicals, such as flavours, fragrances, insecticides, dyes and drugs which like morphine, codeine, paclitaxel, vinblastine, vincristine, scopolamine, atropine, pilocarpine, physostigmine and digoxin (Kinghorn and Balandrin, 1993) [35]. Cragg *et al.* (2003) [20] showed that discovered drugs among 1983-1994, are about 6% natural products, 24% natural products derivatives and 9% based on natural product leads. But for anticancer drugs, natural products and natural products derivatives are 48% and 13% respectively. Medicinal plants' market for medicines productions about 250 billion US $ per year. And 80% of the world population depends on traditional medicinal plants for their primary health care (Balick *et al*., 1996; Plotkin, 1991) [8, 51]. The other major group of economically important natural products is that of flavours and fragrances. For example taste and colour of our food and colour of flowers is determined by secondary metabolites. But some of them are harmful for our health as The *Solanum* glyco-alkaloids toxic compound in potatoes (Beier and Nigg, 1992) [10]. Recently, most important targets of secondary metabolites are agricultural pests as phytoalexins and antifeedants which open the way for genetic engineering to use them against diseases and insects (Dawson *et al*., 1989; Dixon and Paiva, 1995) [21, 22].

Classifications of secondary metabolites

Secondary metabolites can be identified in different ways depend on many principles mentioned in Table 2. The largest group in fact is that of the terpenoids. These compounds have in common that they are all derived from the isoprenoid biosynthetic pathway which uses a C5 building block to build up C_{10} (monoterpenes), C_{15} (sesquiterpenes), C_{20} (diterpenes), C_{30} (steroids and triterpenes) and C_{40} (carotenoids) compounds. Secondary metabolites can be classified in another way as mentioned in Table 3.

Table 2: Different ways to classify the secondary metabolites (Wink, 1997; Torsell, 1997) [18, 77]

depends on	classification	examples
chemical characteristics	Alkaloids	Codeine, Scopolamine, And Nicotine
	Basic Nitrogen Function	Solanine
	Phenolics	Coumarines, Gallic, Caffeic, Ferulic Acid
	Basic Skeleton Function	Anthracene, Coumarine,Quinone And Indole
plant origin	Opium Alkaloids	Heroin, Morphine And Codeine
	Strychnos Alkaloids	Strychnine, Brucine And Loganine
	Digitalis Cardenolides	Digoxin And Digitoxin
biosynthetic origin	Terpenoids	Taxol And Vinblastine
	Phenylpropanoids	Flavonoids, Lignin And Coumarins
	Polyketides	Tetracycline And Erythromycin

Table 3: Classifications of secondary metabolites and examples of their compounds, sources and effects. (Agosta, 1996; Bidlack, 2000; Karban and Ian, 1997; Rosenthal *et al*., 1991) [2, 14, 33, 60].

Class	Example Compounds	Example Sources	Some Effects and Uses
Nitrogen-Containing			
Alkaloids	nicotine cocaine theobromine	tobacco coca plant chocolate (cocao)	interfere with neurotransmission, block enzyme action
Nitrogen-And Sulfur-Containing			
Glucosinolates	sinigrin	cabbage, relatives	
Terpenoids			
Monoterpenes	menthol linalool	mint and relatives, many plants	interfere with neurotransmission, block ion transport, anesthetic
Sesquiterpenes	parthenolid	Parthenium and relatives (Asteraceae)	contact dermatitis
Diterpenes	gossypol	cotton	block phosphorylation; toxic
Triterpenes, cardiac glycosides	digitogenin	Digitalis	stimulate heart muscle, alter ion transport
Tetraterpenoids	carotene	many plants	antioxidant; orange coloring
Sterols	spinasterol	spinach	interfere with animal hormone action
Phenolics			
Phenolic acids	caffeic, chlorogenic	all plants	cause oxidative damage, browning in fruits and wine
Coumarins	umbelliferone	carrots, parsnip	cross-link DNA, block cell division
Lignans	podophyllin urushiol	mayapple poison ivy	cathartic, vomiting, allergic dermatitis
Flavonoids	anthocyanin, catechin	almost all plants	flower, leaf color; inhibit enzymes, anti- and pro-oxidants, estrogenic
Tannins	gallotannin, condensed tannin	oak, hemlock trees, birdsfoot trefoil, legumes	bind to proteins, enzymes, block digestion, antioxidants
Lignin	lignin	all land plants	structure, toughness, fiber

Major secondary metabolite pathways

Secondary metabolites in plants follow three pathways: the shikimate pathway, the isoprenoid pathway and the polyketide pathway.

1-The shikimate pathway

It is a seven-step metabolic pathway Fig.1 used by bacteria, fungi, algae and plants for the biosynthesis of folates and aromatic amino acids (phenylalanine, tyrosine, and tryptophan). This pathway is not found in animals (including humans), The seven enzymes involved in this pathway are DAHP synthase, 3-dehydroquinate synthase, 3-dehydroquinate dehydratase, shikimate dehydrogenase, shikimate kinase, EPSP synthase, and chorismate synthase. The pathway starts with two substrates, phosphoenol pyruvate and erythrose-4-phosphate, and ends with chorismate. The fifth enzyme involved is the shikimate kinase, an enzyme that catalyzes the ATP-dependent phosphorylation of shikimate to form shikimate 3-phosphate (Hermann, 1995).

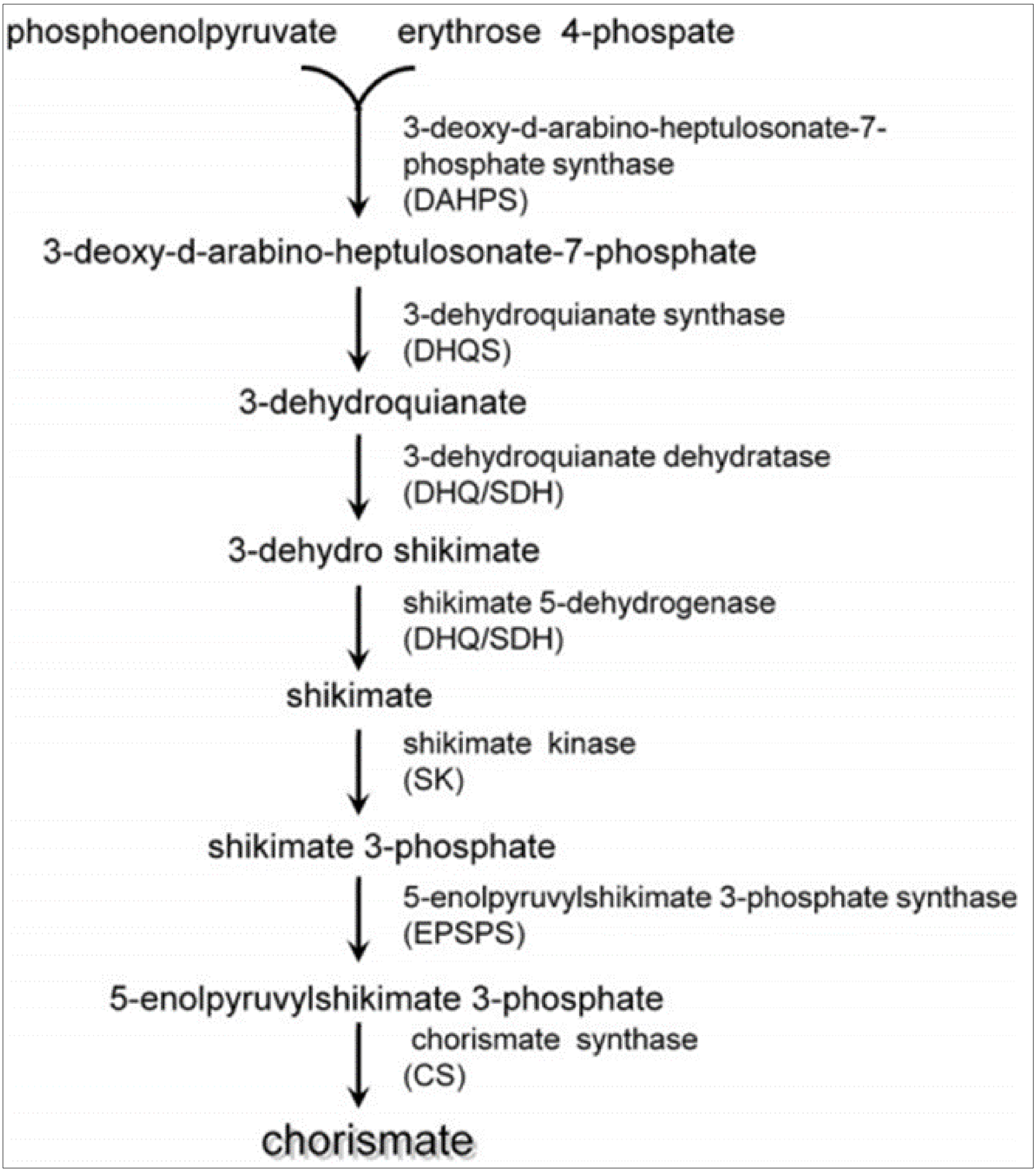

Fig 1: The Shikimate Pathway of secondary metabolites (Tzin and Galili, 2010)

2- The isoprenoid pathway: The other important pathway in plants Fig 2 is that of the terpenoids also known as mevalonate pathway or HMG-CoA reductase pathway is an essential metabolic pathway present in plants, and some bacteria. The pathway produces two five-carbon building blocks called isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP), which are used to make isoprenoids, a diverse class of over 30,000 biomolecules such as cholesterol, vitamin K, coenzyme Q10, and all steroid hormones. The mevalonate pathway begins with acetyl-CoA and ends with the production of IPP and DMAPP. It is best known as the target of statins, a class of cholesterol lowering drugs. Statins inhibit HMG-CoA reductase within the mevalonate pathway (Gershenzon and Croteau, 1993) [26].

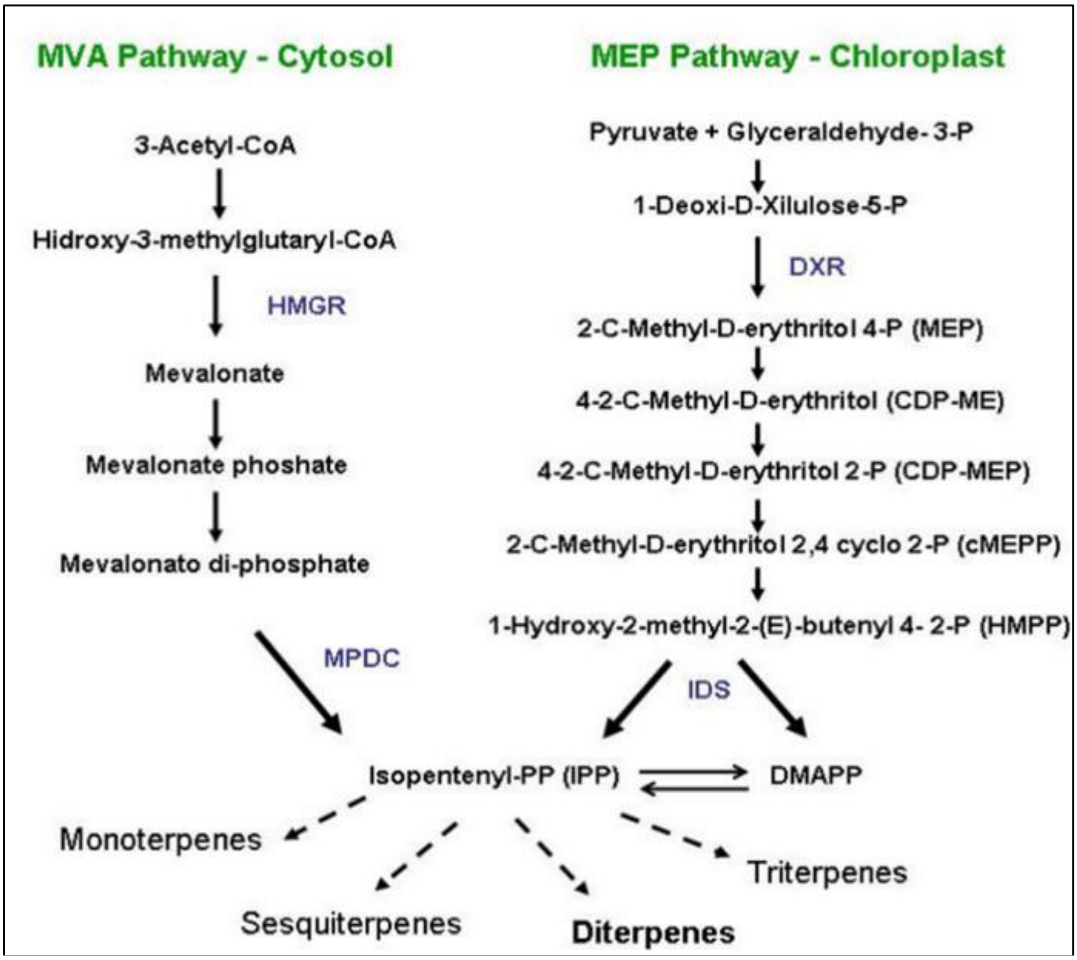

Fig 2: The Isoprenoid Pathway of secondary metabolites (Tiski *et al*., 2007) [75]

3- Polyketide synthases (PKSs) are a family of multi-domain enzymes or enzyme complexes that produce polyketides, a large class of secondary metabolites, in bacteria, fungi, plants, and a few animal lineages. The biosyntheses of polyketides share striking similarities with fatty acid biosynthesis. The PKS genes for a certain polyketide are usually organized in one operon or in gene clusters. In 1953 Birch hypothesized the polyketide pathway Fig. 3 and in 1955 he confirmed the first polyketide from label acetic acid as the building block for 6-methyl salicylic acid isolated from a fungal metabolite (Borejsza and Hrazdina, 1996) [16].

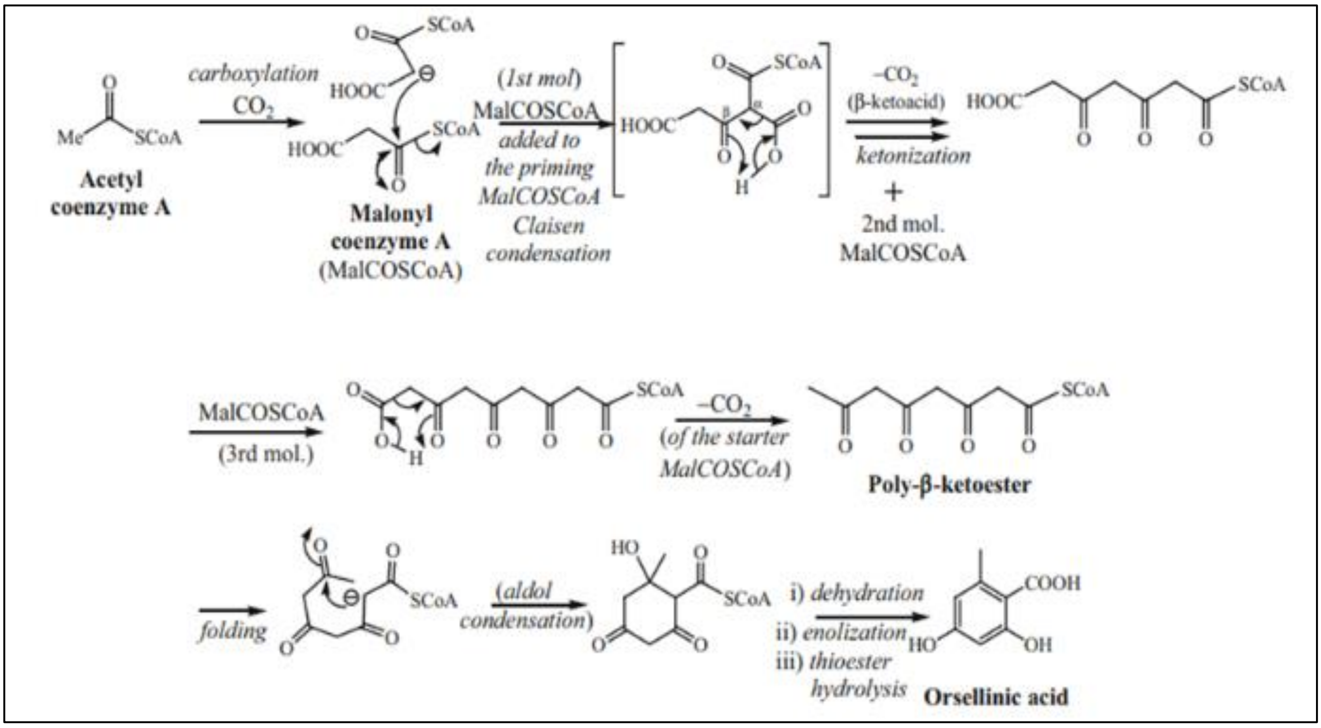

Fig 3: The Polyketide Pathway of secondary metabolites (Talapatra and Talapatra, 2015) [72]

Regulation

So many plants produce secondary metabolites which serve specific function as antimicrobial, antioxidant or/and anesthetic. These different functions result from different pathways, for example, the pathway of secondary metabolite which responsible in color and volatile producing in flower tissues to attract pollinators, is different from the pathway of secondary metabolite which responsible in toxin producing in leaves tissues to repulse insects. One anther hand, some pathways are stimulated by gene/s which promotes specific enzymes to convert specific compounds into biologically active compounds after wounding, such as HCN from cyanogenic glycosides. Other pathways are capable to be formed on gene level by outdoor signals, such as elicitors signal molecules such as salicylic acid or jasmonate which play important roles in plant defense systems (Ibrahim and Jaafar, 2011).

Importance of AMF in medicinal plants and its applications

Using AMF in medicinal plants cultures improve plant growth (Table 4, 5, 6 and 7), nutrition, and secondary metabolite contents of many important compounds (Rajan *et al*., 2000). They also improve mineral nutrition as N, P, Fe, Cu, Zn, and B which helps in the synthesis of chlorophyll leading to improving photosynthetic rate (Toussaint, 2007). For example, in *Mentha arvensis* plant colonized by *Glomus clarum*, *Glomus etunicatum*, *Gigaspora margarita* and *Acaulospora scrobiculata* showed increasing in the essential oil levels in the absence of phosphate (Freitas *et al*. 2004) [58]. But in another side, AMF form a symbiotic association with medicinal plants. The host plant provided the fungus with soluble carbon sources and the fungus provides the host plant with an increased capacity to absorb water and nutrients from the soil to become more resistant to stresses as drought, salt, heavy metals or attack by pathogens. Inoculation of AMF in medicinal plant soil should undergo to some factors as cultivation conditions, sterilizing methods, soil pH, different host plants and different AMF (Yang *et al*., 2008) [85]. Radhika and Rodrigues (2010) mentioned that around forty two AMF belong to *Glomus, Acaulospora*, *Scutelllospora*, *Gigaspora,* and *Ambispora* were isolated from thirty medicinal plants rhizospheric soils, and *Glomus fasciculatum* was the most dominant genera among the AMF colony. Mondal *et al*. (2012) [44] observed that maximum colonization and establishment of mycorrhizae occurred in summer season due to high temperature and light intensity. It was observed that there is inverse proportionality between soil phosphorus content and the colonized root by AMF (Chatterjee *et al.*, 2009).

Table 4: AMF influence in Alkolide secondary metabolites of medicinal plant

Medicinal plants Species	Families	plant organ	Secondary metabolites	Medicinal value	AMF	Change in secondary metabolite	References
Allium sativum	Liliaceae	leaves, flowers, and cloves	Alliin	to treat fevers, diabetes, rheumatism, intestinal worms	*G. fasciculatum*	Significant increase	Borde *et al.*, 2009 [15]
Castanospermum austral	Fabaceae	Seed	Castanospermine	HIV inhibitors, treatment of AIDS, anti-cancer, anti-inflammatory, properties	*G. intraradices*, *G. margarita*	Signifcant increasing with *G. intraradices*	Abu-Zeyad *et al*., 1999 [1]
Catharanthus roseus	Apocynaceae	Aerial part	Vinblastine and vincristine	diabetes, malaria, Hodgkin's lymphoma, and leukemia	*Glomus species*	Signifcant increase	Andrade *et al*., 2013 [4]
Coleus forskohlii	Lamiaceae	Root	Forskolin	for Angina, Anti-inflammatory activity, Antihypertensive and cures placebo	*A. laevis*, *G. monosporum*, *S. calospora*	Significant increase	Singh *et al.*, 2013 [68]
Datura stramonium	Solanaceae	Seed and fruit	Hyoscine, hyoscyamine	stomach and intestinal pain toothache, and fever from inflammation	*G. mosseae*, *G. epigaeum*	Significant increase	Wei and Wang, 1989 [38]
Eclipta prostrata	Asteraceae	Leave	scopolamine	diabetes type II, dizziness, haemoptysis, and liver diseases	*Rhizophagus irregularis, Funneliformis mosseae, Claroideoglomus etunicatum, Claroideoglomus claroideum, Rhizoglomus microaggregatum,* and *Funneliformis geosporum*	0.34% increasing	Vo *et al.*, 2019
Gloriosa superba	Colchicaceae	tuber	colchicine	snake bites, scorpion stings, parasitic skin diseases, urological pains, colic, chronic ulcers, piles	*Glomus mossae, Glomus fasciculatum, Gigaspora margarita and Gigaspora gilmorei*	1.9% increasing	Pandey *et al.*, 2014 [49]
Phellodendron amurense	Rutaceae	Bark	Berberine, jatrorrhizine, palmatine	antibacterial, antirheumatic, aphrodisiac, diuretic, expectorant	*G. mosseae*, *G. etunicatum*,*G. versiforme*, *G. diaphanum*	Significant increase	Cai *et al.*, 2008 [17]
Pinellia ternata	Araceae	Tuber	L-ephedrine, guanosine	nausea, morning sickness, cough and inflammation	*G. intraradices*, *G. mosseae*	Significant increase	Chen *et al.*, 2009 [19]
Prosopis laevigata	Fabaceae	Root and leaves	trigonelline	antiseptic, antidysenteric, antidiarrheic, and emollient	*Gigaspora rosea*	1.8-fold increase in roots	Rojas-Andrade *et al.*, 2003 [59]

Table 5: AMF influence in Flavonoids secondary metabolites of medicinal plant

Medicinal plants Species	Families	plant organ	Secondary metabolites	Medicinal value	AMF	Change in secondary metabolite	References
Anadenanthera colubrina	Fabaceae	Bark and Leaves	catechin	respiratory problems and inflammations	*Acaulospora longula and Gigaspora albida*	Signifcant increase	Pedone-Bonfim *et al.*, 2013 [50]
Angelica dahurica	Apiaceae	root, seed, and fruit	Imperatorin, total coumarins	heartburn, intestinal gas, loss of appetite and trouble sleeping	*Glomus* spp.	significant increase	Zhao and He, 2011 [87]
Curcuma longa	Zingiberaceae	rhizomes	curcumin	as joint pain and skin inflammation	*Glomus, Gigaspora* and *Acaulospora sp*	26.32% increasing	Dutta and Neog, 2016 [24]
Eclipta prostrata	Asteraceae	whole plant	Quercetin	diabetes type II, dizziness, haemoptysis, liver diseases	Mixture of *G. intraradices, G. mosseae, G. etunicatum, G. claroideum, G. microaggregatum and G. geosporum*	0.87% increasind	Vo *et al.*, 2019
Glycine max	Fabaceae	*Root, seed. leaved and flower*	*Isoflavonoids*	weakly diaphoretic and stomachic, treatment of colds, fevers and headaches, insomnia, irritability	*F. mosseae*	Significant increase	Morandi and Bailey, 1984 [45]
Hypericum perforatum	Hypericaceae	aerial parts	Hesperetin	neuralgia, anxiety, depression, nerve tonic and wound healing	*Glomus intraradices, G. mosseae, G. constrictum and G. geosporum*	significant increase	Zubek *et al.*, 2012 [88]
Libidibia ferrea	Fabaceae	Stem's Bark and Leaves	anthocyanin	diabetes, anti-inflammatory Anticancer, pain relief, and anti-inflammatory drugs	*Claroideoglomus etunicatum, Gigaspora albida and Acaulospora longula*	186% increasing	Dos Santos *et al.*, 2017 [23]
Lolium multiflorum	Poaceae	*Shoots and root*	kaempferol and myricetin	diarrhoea, haemorrhages and malaria, antioxidant	*R. intraradices*	insignificant increase	Ponce *et al.*, 2009 [52]
Medicago sativa	Fabaceae	root	Formononetin	for kidney, bladder and prostate conditions, to increase urine flow, used for high cholesterol and asthma	*Glomus intraradix*	significant increase	Volpin *et al.*, 1994 [81]
Passiflora alata	Passifloraceae	Root	*C*-glycosides of apigenin	alcoholism, anxiety, migraine, nervousness, insomnia, asthma, bronchitis	*Glomus clarum and Glomus spurcum*	Significant increase	Riter *et al.*, 2014 [58]

Table 6: AMF influence in Phenolics secondary metabolites of medicinal plant

Medicinal plants Species	Families	plant organ	Secondary metabolites	Medicinal value	AMF	Change in secondary metabolite	References
Catharanthus roseus	Apocynaceae	Aerial part	Rutin, quercetin, and kaempferol	High Blood Pressure, Anticancer ability espically Lung Cancer	*Glomus sp.*	Significant increase	Andrade *et al.*, 2013 [4]
Dioscorea bulbifera	Dioscoreaceae	bulbils	Diobulbinone	of Piles, dysentery, syphilis, ulcers, cough, leprosy, diabetes, asthma, and cancer	*G. clarum, G. etunicatum*	Significant increase	Lu *et al.*, 2015
Echinacea purpurea	Asteraceae	root and aerial parts	Phenolics and Cichoric acid	cold, coughs, bronchitis, upper respiratory infections	*Glomus intraradices*	Significant increase	Araim *et al.*, 2009 [5]
Libidibia ferrea	Fabaceae	Fruit	Gallic acid	Antianemic, antidiabetic and for treatment pulmonary hemolytic disorders, Preventing cancer	*Claroideoglomus etunicatum*	21% increasing	Silva *et al.*, 2014 [66]
Melissa officinalis	Lamiaceae	leaves	Citronellal and neral	For digestive, carminative, antispasmodic, sedative, analgesic, tonic, and diuretic properties	*Claroideoglomus etunicatum, Claroideoglomus claroideum and Rhizophagus intraradices*	11 - 17% increasing	Engel *et al.*, 2016 [25]
Mentha spicata	Lamiaceae or Labiatae	leaves	Caffeic acid, rosmarinic acid, and luteolin	Fevers, headaches, digestive disorders. The herb is antiemetic, antispasmodic and carminative	*G. etunicatum, G. mosseae*	Significant increase	Bharti *et al.*, 2013 [13]
Myracrodruon	Anacardiaceae	stem bark	Coumaric	gingival bleeding and	*Acaulospora* longula	81.03%	Oliveira *et*

urundeuva			and ferulic acids	gynecological disorders and neuro-diseases		increasing	*al.*, 2013 [48]
Salvia miltiorrhiza	Lamiaceae	Root	Salvianolic acid	coronary heart diseases and cerebrovascular diseases	*G. mosseae*, *G. aggregatum*	Significant increase	Yang *et al.*, 2017 [85]
Valeriana jatamansi	Caprifoliaceae	rhizome and root	Gallic acid, chlorogenic acid, catechin, hydroxyl benzoic acid	Insect repelling and antihelmethic properties, antidepressant, antioxidant, and antimicrobial activities	*G. intraradices*	Significant increase	Jugran *et al.*, 2015 [30]
Viola tricolor	Violaceae	Aerial part	Caffeic acid	epilepsy, skin diseases and eczema, and for respiratory problems such as bronchitis, asthma	*Rhizophagus irregularis*	Significant increase	Zubek *et al.*, 2015 [89]

Table 7: AMF influence in Terpene secondary metabolites of medicinal plant

Medicinal plants Species	Families	plant organ	Secondary metabolites	Medicinal value	AMF	Change in secondary metabolite	References
Atractylodes macrocephala	Asteraceae	rhizome	Atractylol	Antitumor, Antiviral, and Anti-Inflammatory efficacy	*Glomus mosseae*	Significant increase	Lu and He, 2005
Anethum graveolens	Apiaceae	Seed	Anethole	carminative, stomachic and diuretic	*G. macrocarpum*, *G. fasciculatum*	90% increasing	Kapoor *et al.*, 2002 [32]
Artemisia annua	Asteraceae	dried aboveground parts	Artemisinin	fever, inflammation, and malaria, cough, stomach and intestinal upset	*G. macrospermum*, *G. fasciculatum*, *G. mosseae*	15.2–32.8% increasing	Huang *et al.*, 2011 [29]
Arnica montana	Asteraceae	Fresh or dried flower	Sesquiterpene lactones	bruises, sprains, muscle aches, wound healing, superficial phlebitis and joint pain	*G. geosporum*, *G. constrictum*	Significant increase	Jurkiewicz *et al.*, 2010 [31]
Coriandrum sativum	Apiaceae	seeds or leaves	β-caryophyllene, p-cymene, geraniol	upset stomach, loss of appetite, hernia, nausea, diarrhea, bowel spasms, and intestinal gas	*Glomus hoi*	Significant improvement	Rydlová *et al.*, 2016 [61]
Ocimum basilicum	Lamiaceae	Seed	Linalool and geraniol	headaches, coughs, diarrhea, constipation, warts, worms, and kidney malfunctions	*Gigaspora margarita*, *Gigaspora rosea*	Significant increase	Rasouli-Sadaghiani *et al.*, 2010 [55]
Pogostemon cablin	Lamiaceae	leaves	Patchoulol	antioxidant and antibacterial *properties*, used to treat colds, headaches, fever	*Acaulospora laevis*, *G. mosseae*, *Scutellospora calaspora*	Significant improvement	Singh *et al.*, 2012 [67]
Stevia rebaudiana	Asteraceae	leaves	Stevioside, rebaudioside-A	diabetes, skin abrasion, dental caries, depression and hypertension	*Rhizophagus fasciculatus*	Significant increase	Mandal *et al.*, 2013 [41]
Trachyspermum ammi	Apiaceae	Fruit	Thymol	carminative properties, remedial atonic dyspepsia, diarrhea, bronchial problems, lack of appetite	*G. fasciculatum*	51.21% increasing	Kapoor *et al.*, 2002 [32]
Valeriana officinalis	Caprifoliaceae	Root	Valerenic acid	insomnia/sleep disorders, attention deficit-hyperactivity disorder, anxiety disorders, depression, epilepsy, chronic fatigue syndrome, and tremors	*G. intraradices*	Relative increasing	Nell *et al.*, 2010 [46]

Conclusion

With the exception of few studies that did not implicate AMF with enhanced secondary metabolite production in medicinal plants, a pleothora of studies revealed that AMF inoculation improved quality characteristics, growth rates and increase in secondary metabolites of certain medicinal plants, that might lead to enhancement in biological properties of the medicinal plants.

Some studies showed that arbuscular mycorrhizae fungi do not affect secondary metabolites production in medicinal plants. But plenty studies revealed that AMF inoculation improved quality characteristics, growth rates and increasing of secondary metabolites of certain medicinal plants, that would lead to provide better biological properties of the medicinal plants, such as antimicrobial property. Thus for future researches should focus on (1) isolation and selection of promising, effective and adapted AMF strains, (2) strategies development of increased production of mycorrhizal medicinal seedlings (3) Focusing on cultivation of medicinal plants which have important biochemical compounds, (4) improving the strategies by which AMF inhance the secondary metabolites production in medicinal plants.

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