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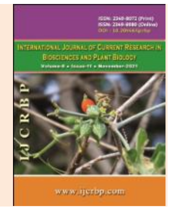

Review Article

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Microbiomes of medicinal plants and their potential avenues as bioresources – A review

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Abstract

Sustainable enhancement in bioactive production of medicinal plants must encompass a balanced use of inorganic, organic, and biofertilizer sources of plant nutrients to augment and maintain soil fertility, productivity and quantity. This necessitates an intricate analysis of the inter-relationships between microbial communities and their impact on host plant productivity. A large variety of fungi and bacteria is recognized in phyllosphere, endosphere and rhizosphere of medicinal plant that showed significant effect in secondary metabolite alteration and uptake of plant nutrients. Significant phytotherapeutic compounds are actually produced by associated microbes through interaction with their host plant which lead to recognition of microbe and plant interaction. In modern medicine and agriculture, medicinal plant are considered rich bioresources yet their ecological role of microbiome is unexplored. Plant-associated microbes form holobiont which is responsible for the beneficial interplay of the host and its microbiome by maintaining host plant fitness, health, nutrition and increased tolerance to abiotic stresses, adaptation to environmental variations promotion of the establishment of mycorrhizal association. Some genera are ubiquitous and can be found distributed over the entire plant, such as the well-known plant-associated genera *Bacillus* and *Pseudomonas*. The objective of this review is to introduce insights into plant-microbe interaction in medicinal plants.

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Introduction

Phytotherapeutic compounds are actually produced by associated microbes or through interaction with their host, medicinal plant research primarily focused on bioactive phytochemicals, however, the focus is currently shifting due to the recognition in modern medicine and agriculture. Medicinal plants provide an enormous bioresources of potential use, yet their microbiome is largely unknown. It has been concluded that the effect of long-term cultivation of medicinal and aromatic plants (MAPs) on microbial diversity, which may affect soil health and productivity. This information will help to identify good agricultural practices that could restore the state shift, minimizing loss in soil health and maintaining ecosystem functionality and environmental sustainability (Misra et al., 2019).

Plants live in association with microbes in both above and below ground parts, as some are beneficial and some are harmful to the plant. Microbes which are found in the phyllosphere, endosphere and rhizosphere, can have beneficial, neutral, or detrimental effects on plant health and development (Köberl et al., 2013). Several works have been done on plant-microbe interactions and microbial diversity of the rhizospheric region of medicinal plants. The biogeochemical reactions and plant metabolism influence by the plant secondary metabolite and root exudates which include various sugars and organic acids. Signalling molecules like strigolactones induce the colonisation of the mycorrhiza fungi with plant roots and stimulate the germination of the parasitic plant. Leguminous roots secreted flavonoids thus increase the growth of symbiotic and non symbiotic nitrogen-fixing bacteria similarly and also attract pathogenic oomycetes as well. Hence, plant growth enhanced by root-associated microflora and endophytes (fungi or bacteria) due to the secretion of phytohormone (auxin/cytokinin) and nutrients like phosphorus, nitrogen, and iron. Microbial association with roots may induce plant resistance against the several biotic and abiotic stresses, such as toxic metals, pathogens, drought, high temperature, saline soils, adverse soil pH, and transplant shock. In the era of next-generation sequencing, studying the plant-microbe interaction opens a new way to understand their association as well as help in improvement of sustainable agriculture by plant growth and improve crop yield. Enhancement of secondary metabolites in medicinal plant by exploration of rhizospheric microbes in the future for might be a new vista opened for sustainable agriculture practices. In this review we will focus our attention to the role of medicinal plant-microbe interaction derived ingredients.

Plant-microbe associated bioactive compounds

The significant numbers of natural products are actually produced by microbes and microbial interactions with the host from where they were isolated, and for several medicinal plants it's presumed that the plant-associated microbiome, especially the complex community of the endomicrobiome, is directly or indirectly involved within the production of bioactive phytochemicals. Presently, however, only a little subset of potential microbial strains might be definitively attributed to phytotherapeutic properties (Strobel et al., 2002; Strobel and Daisy, 2003; Miller et al., 2012a; Miller et al., 2012b) and their relative contribution to the recognized valuable bioactivity of medicinal plants isn't clear as of yet.

For centuries, several phytotherapeutics have also been known for their anti-inflammatory features, yet despite the progress within medical research, chronic inflammatory diseases such as asthma, arthritis, and rheumatism remain one of the world's leading health problems (Newman and Cragg, 2012). Hence, nature must still harbor plenty of currently unknown active agents that may serve as leads and scaffolds for the development of efficacious drugs needed for a multitude of diseases (Earanna, 2001). Today, globalization has also had an impact on the use of medicinal plants and has proven beneficial in allowing greater access to these medicines for people all across the globe. For example, TCM plants are very popular in Europe, whereas In India has the unique characteristic of having different well-acknowledged traditional systems of medicine, such as Ayurveda, Siddha, Unani, Yoga, naturopathy, and homeopathy. Growth, quality, and health of the medicinal plants are highly influenced and controlled by their microbiota through microbial metabolisms and host interactions.

Plant growth promotion and biological control plant pathogens

Many researchers reported application of PGPR enhanced yield of essential oil and secondary metabolites in many medicinal plants, i.e. *Phyllanthus amarus*, *Withania somnifera*, *Mentha piperita*, *Solanum viarum* and *Ocimum basilicum* (Glass et al., 2002; Kaymak et al., 2008; Selvaraj et al., 2008; Hemashenpagam and Selvaraj, 2011; Ordookhani et al., 2011; Abdullah et al., 2012). Therefore, the use of microbial associations for medicinal plants provides a sustainable approach to improving crop quality and yield. The importance of PGPR on maintaining soil fertility is well studied by many scientists (Das and Singh, 2014; Parewa et al., 2014a; Mantelin and Touraine, 2004). Hemashenpagam and Selvaraj (2011) had reported in a study inoculation of seeds with PGPR significantly increased the values of available P, microbial population, acid phosphatase, alkaline phosphatase, dehydrogenase activity in soil and yields over uninoculated seeds. PGPR communities affect directly or indirectly the plant physiology, nutritional and physicochemical properties of rhizospheric soils through their metabolic activities. They are important components of integrated farming, which help to nourish the crops through required nutrients. Thus, PGPR helps to improve the soil health and increase crop production by fixing atmospheric nitrogen, solubilize and mobilize phosphorus, translocate minor elements like Mo, Zn, Cu, etc. to the plants, produce plant growth-promoting hormones like IAA and GA and improve soil structure by production of polysaccharides, Uptake of nutrient elements like Ca, K, Fe, Cu, Mn and Zn through proton pump ATPase has been increased by PGPR (Bandopadhyay, 2015).

Fungal diseases are the major constraints in the profitable cultivation of medicinal plants. Phytopathogenic problem of medicinal plants not only reduces the yield, but it is also responsible for the deterioration of biochemical and secondary metabolites which are of immense therapeutic value. Imprudent use of insecticides, fungicides, agrochemicals, and fertilizers poses serious threat to the environment. In the present scenario, rhizospheric microbes (biocontrol agents) have gained popularity due to their effectiveness, safety, and eco-friendliness, and hence their demand has gradually increased. The mechanisms of plant disease management such as mycoparasitism, antibiosis, induced systemic resistance, plant growth promotion, root colonization, siderophore production, phosphate solubilization, etc., have been studied well in reference to medicinal plants. Still due to the distinct features of medicinal plants, future research could be a major breakthrough in the significant increase in the production of medicinal plants. Usage of fungicides is not recommended as it is neither economical nor environmentally friendly. Moreover, its long-term use can cause the development of resistant strains of a pathogen (Ashraf and Zuhaib, 2014a; Ashraf and Zuhaib, 2014b) However, research on biological control gained momentum in the last quarter of the tenth century, and several books (Cook and Baker, 1983; Mukerji, 2000) and review articles have come up stressing the potential of microorganisms in disease management. Numerous microorganisms have been reported to cause antagonism against plant pathogenic fungi in laboratory and *in vivo* conditions. A perfect biocontrol agent/rhizosphere microbe must have the subsequent qualities.

- Prolonged survival, either in active or passive form.
- Greater probability of contact with the pathogen.
- Functional under variable environments.
- Mass multiplication should be easy, feasible, and economical.
- Proficient and cheap.
- Eco-friendly.

A number of rhizospheric microbes such as *Trichoderma*, *Bacillus*, and *Pseudomonas* have been found successful against a number of important fungal diseases of medicinal plants (Benítez et al., 2004; Strashnov et al., 1985; Kaur et al., 2006; Dubey et al., 2007; Abo-Elyousr et al., 2014). The most common species of *Trichoderma* which have been successfully exploited in biological control of pathogenic fungi are *T. virens, T. viride,* and *T. harzianum* (Kumar et al., 2011) *T. harzianum* and *T. viride* are being used as commercial products for the control of plant diseases. Moreover, *Trichoderma* can even stimulate plant growth; reports of which have been found in the case of *T. virens* (Chet et al., 1997) and the stimulation of plant defense mechanisms (Sharma and Gothalwal, 2010). Latha et al., (2009) isolated a strain of *T. viride* with high antagonistic potential against *R. solani* and *S. rolfsii* from soil. It was formulated in talcum powder as a biofungicid. *T. viride* has been found to significantly reduce mycelial growth, a formation of spores, and germ tube formation of *A. solani* and *A. alternate* (Sharma and Trivedi, 2010) *T. harzianum* has been found active against *F. oxysporum* inciting wilt in Ashwagandha (Harman, 2006).

Mechanism of disease suppression by rhizospheric microbes *Trichoderma* spp. is reported to suppress plant pathogenic fungi through a combination of different mechanisms such as mycoparasitism, synthesis of antibiotics (Harman et al., 2004) (Jayalakshmi et al., 2009) enzymes degrading cell wall (Zimand et al., 1996) contesting for the availability of important nutrients and increase in plant health (Komatsu, 1968), parasitism of host fungus (Gao et al., 2001; Sriram et al., 2009), inducing plant defense (Zimand et al., 1996), and/or induced systemic resistance (Jayalakshmi et al., 2009) (Handelsman and Stabb, 1996). Most of the biocontrol agents including *Trichoderma*, *Pseudomonas* spp., and *Bacillus* species produce several types of antibiotics (Chet et al., 1997; Vinale et al., 2014). The antibiotics produced by *Trichoderma* species include gliotoxin (Vinale et al., 2014), harzianic acid (McAlees and Taylor, 1995), trichoviridin (Zafari et al., 2008), viridian (Phuwapraisirisan et al., 2006), viridiol (Aidemark et al., 2010), alamethicin (Goulard et al., 1995), and others (Howell et al., 1983). Gliovirin an antibiotic isolated from *Trichoderma* (*Gliocladium) virens* shows a strong inhibitory effect against *Pythium ultimum* and *Phytophthora species* (Sharma and Gothalwal, 2020). *Thielaviopsis basicola*, *Phymatotrichum omnivorum*, *Rhizopus arrhizus, or*

Verticillium dahliae. B. thuringiensis was not inhibited by gliovirin. Secretion of *T. harzianum* strain against *Gaeumannomyces graminis* exhibited inhibitory effects supporting the fact that bioagent synthesizes antibiotics plays a vital role in the inhibition of the pathogen. Research on the mechanisms responsible for the biocontrol exerted by *Trichoderma* on phytopathogenic fungi has led to a better understanding of mechanisms, as well as to the isolation of several genes encoding either enzymes and structural or regulatory proteins or components of signaling pathways that are involved in processes such as the specific recognition of hosts by *Trichoderma* strains (Weller, 1988).

Bacillus and *Pseudomonas* species are also effective microbes in managing plant diseases by the production of antibiotics (Chet et al., 1997; Whistler et al., 2000). Plant disease suppression due to *P. fluorescens* may be due to synthesis of pyoluteorin, phenazine, oomycin A, IAA, siderophores, phenazine, siderophore (Schoonbeek et al., 2002; Suzuki et al., 2003; Johri et al., 2003; Rachid and Ahmed, 2005; Siddiqui, 2006) extracellular hydrolytic enzymes (Bagnasco et al., 1998), alginate, HCN (Bagnasco et al., 1998) and pseudomonic acid.

The antimicrobial compounds discussed above are responsible to cause fungistasis, inhibition of spore germination, and degradation of a mycelial wall and also induce other fungicidal effects (Berg and Smalla, 2009) Several microbial inoculants have already been successfully commercialized (Berg et al., 2011; Yang et al., 2018) but a specific biological control strategy for medicinal plants, which are increasingly affected by different soil-borne phytopathogens, has not been available until now. While specific biocontrol agents for medicinal plants are needed, their associated microbiomes with outstanding metabolic activities also provide a promising source for novel BCAs

Impact of environmental factors on phytochemical generation

Medicinal plants are sessile organisms, they have evolved numerous mechanisms for accommodating changes arising in their fluctuating growth conditions to enable functional flexibility under the influence of environmental factors without affecting cellular and developmental physiological processes (Arnold et al., 2019; Berini et al., 2018) by producing repertoire of secondary metabolites (SMs) that play variety of roles in response to changing environment, growth and development(Kroymann, 2011; Chetri et al., 2013). The changes may be induced by environmental components that include local geo-climatic and seasonal changes, external conditions of temperature, light, humidity and developmental processes, among others, and impact biomass production and biosynthesis of plant secondary metabolites (PSMs) (Ramakrishna and Ravishankar, 2011; Zykin et al., 2018; Ncube and van Staden, 2015). The secondary molecules are produced occasionally in living plant cells and do not play much of significant role in the primary life of plants that produce them, with the production been at low concentration commensurate with growth physiology of a plant species (Edreva et al., 2008). Production of the metabolites by the plants is regarded an adaptive capacity in coping with stressful constraints during challenging and changing environment of growth that may involve production of complex chemical types and interactions in the structural and functional stabilization through signaling processes and pathways (Vashisth et al., 2018). In many recent studies, it had been shown that SM system in plants is a response to the stress and defensive situations that leads to an enhanced biosynthesis of the metabolites in an integrated defense mechanism through dynamic ways (Table 3). However understanding the signaling processes involved and their interconnection with the primary metabolism is yet unclear, and very few had been investigated in some taxonomic groups, based on plant tissues or organs evaluated with rare reports on whole plant system evaluation or cellular levels.

Approach to natural product discovery

Innovative drug discovery from natural products requires a multidisciplinary approach utilising available and innovative technologies to package such natural product compounds for medical practice and drug development (Fig.1). The successful use of such an approach will allow the development of next-generation drugs to combat the ever-increasing health challenges of today and the future

A systems biology approach coupled with application of available technologies such as genomics, transcriptomics, proteomics, metabolomics/ metabonomics, automation and computational strategies will potentially pave the way for innovative drug design leading to better drug candidates.

Table 1. Plant-microbe interaction derived bioactive compound from below and above ground regions.

Bioactive compound	Therapeutic properties	Host plant	Producing microorganism	Reference
Munumbicins	Antibacterial, antimycotic, antiplasmodial	*Kennedia nigriscans*	*Streptomyces* sp.	Castillo et al., (2002)
Kakadumycins	Antibacterial, antiplasmodial	*Grevillea pteridifolia*	*Streptomyces* sp.	Castillo et al.,(2003)
Coronamycins	Antimycotic, antiplasmodial	*Monstera* sp.	*Streptomyces* sp.	Ezra et al.,(2004)
Oocydin A	Antimycotic (Oomycota)	*Rhyncholacis penicillata*	*Serratia marcescens*	Strobel *et.al.* (1999a)
Cryptocandin	Antimycotic	*Tripterigeum wilfordii*	*Cryptosporiopsis quercina*	Strobel et al.,(1999b)
Colletotric acid	Antibacterial, antimycotic	*Artemisia mongolica*	*Colletotrichum gloeosporioides*	Zou et al.,(2000)
Artemisinin	Antiplasmodial	*Artemisia annua*	*Colletotrichum* sp.	Wang et al., (2001)
Cochliodinol	Antibacterial, antimycotic, anticancer	*Salvia officinalis*	*Chaetomium* sp.	Debbab et al., *(*2009)
Botryorhodines	Antimycotic, anticancer	*Bidens pilosa*	*Botryosphaeria rhodina*	Abdou et al., (2010)
Pestacin and Isopestacin	Antimycotic, antioxidant	*Terminalia morobensis*	*Pestalotiopsis microspora*	Strobel et al., (2002), Harper et al.,(2003)
Subglutinols	Immunomodulatory	*Tripterigeum wilfordii*	*Fusarium subglutinans*	Lee et al., (1995)
Podophyllotoxin	Anticancer, antiphlogistic	*Podophyllum hexandrum; Juniperus communis*	*Alternaria* sp.; *Aspergillus fumigatus*	Yang et al., (2003), Kusari et al.,(2009a)
Paclitaxel (Taxol)	Anticancer	*Taxus brevifolia; Ginkgo biloba; Aloe vera*	*Taxomyces andreanae; Alternaria* sp.; *Phoma* sp.	Wani et al.,(1971), Stierle et al.,(1993), Kim et al.,(1999),Immaculate et al.,(2011)
Camptothecin	Anticancer, antiviral (HIV)	*Nothapodytes foetida; Camptotheca acuminate*	*Entrophospora infrequens; Fusarium solani*	Puri et al., (2005), Amna et al., (2006), Kusari et al., (2009b)
Maytansine	Anticancer	*Putterlickia verrucosa*	*Actinosynnema pretiosum*	Wings et al.,(2013)
Rohitukine	Antiphlogistic, anticancer, immunomodulatory	*Dysoxylum binectariferum*	*Fusarium proliferatum*	Mohana Kumara et al.,(2012)

Table 2. Plant growth promoting microorganisms of medicinal plant and their mode of action.

Medicinal plant	Microorganisms	Response	References
Ocimum tenuiflorum	*B. thuringiensis* A5-BRSC, *B. megaterium* ATCC 9885	Accelerate the growth rate of plants	Bandopadhyay(2015)
Coleus forskohlii	*Pantoea* sp. (Cf 7), *Pseudomonas* sp. (Te 1, Av30)	Enhanced plant growth and total biomass	Damam et al.,(2014)
Ocimum basilicum	*Pseudomonas + Azotobacter + Azospirillum*	Increased root fresh weight, N content and essential oil yield	Ordookhani et al., (2011)
Withania somnifera	*Azospirillum, Azotobacter, Pseudomonas, Bacillus*	Increased plant height, root length and alkaloid content	Rajasekar and Elango (2011)
Solanum viarum	*G. aggregatum + B. coagulans + T. harzianum*	Increased plant height, root lngth and alkaloid content	Hemashenpagam and Selvaraj (2011)

Table 3. Production of some plant secondary metabolites under various in *vivo* growth conditions of plants.

Secondary metabolite	Plant source	Tissue analyzed	Growth condition	References
Artemisinin	*Artemesia annua*	Whole seedling (treated and control)	Salt, drought and water logging	Vashisth et al. (2018)
Camptothecin	*Camptotheca acuminata*	Seedlings	Nitrogen, drought and anti-transpiration agents	Feng et al.(2002); Sun et al. (2008)
Codeine	*Papaver somniferum*	Plantlets	Drought stress	Szabo et al.(2003)
Rohitukine	*Dysoxylum binectariferum*	Seedling (roots, collar region of stem and young leaves)	Normal	Kumara et al. (2016)
Stevioside	*Stevia rebaudiana*	Leaves (dried)	Hydroponic culture, salt stress	Zeng et al. (2013); Srivastava et al. (2014); Shahverdi et al. (2015)
Allicin	*Allium sativum*	Whole plant	Pot experiment on light effect	Jeong et al. (2013)
Andrographolide	*Andrographis paniculata*	Leaves and stem	Open field experiment with plant populations	Saravanan et al. (2009)
Betalain pigments	Caryophyllales members	Different plant parts	Different growth condition	Polturak et al. (2018)
Saikosaponins	*Bupleurum chinense*	1-year-old plants, plants	Drought, watering and re-watering, fertilization	Zhu et al. (2009)
Sennosides	*Cassia augustifolia*	Pre-, post and flowering plants	Pot culture experiment	Arshi et al. (2006)
Indole alkaloids	*Catharanthus roseous*	Leaves	Greenhouse under binary stress-induced condition	Zhu et al. (2015)
Asiaticoside and madecassoside	*Centella asiatica*	Leaves (post-harvest)	Low temperature and water dehydration	Plengmuankhae et al. (2015)
Valepotriates	*Valeria* species	All organs	Normal growth condition (Iran)	Hassan et al. (2008)
Rutin	*Dimorphandra mollis*	All plant parts at different growth stages	Normal, drought, flooding and salinity	Lucci et al. (2009)

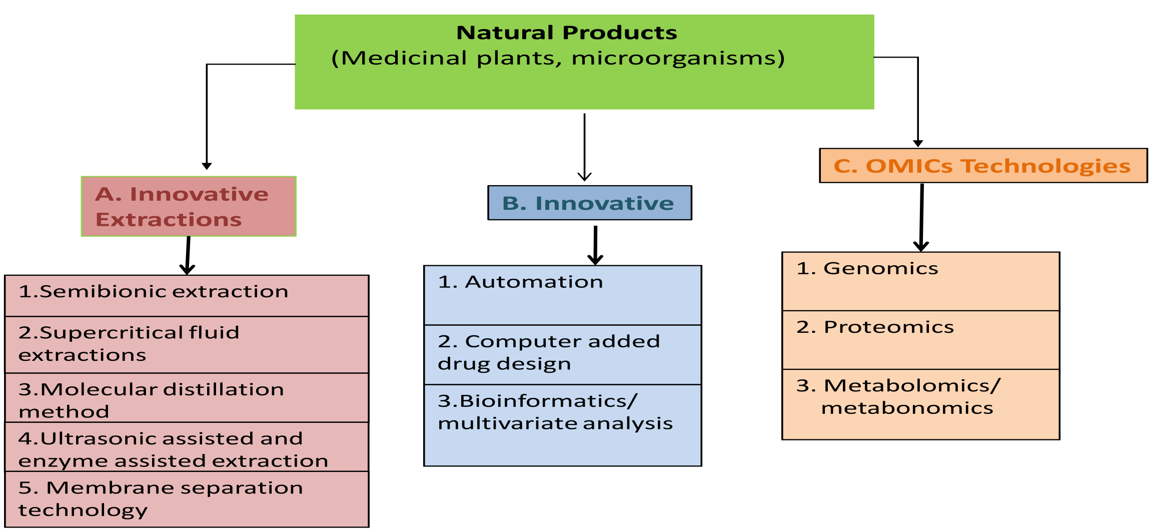

Fig. 1: Innovative technologies for natural product drug discovery (Thomford et al., 2018).

Molecular libraries of lead compounds from natural products R&D will serve as sources of lead compounds/herbal tinctures for innovative drugs. In the application of innovative technologies combined with systems biology, the focus should not be a reductionist approach of trying to source a single active compound but to consider the synergistic effects of compounds. It is important to emphasize that innovative drug discovery from natural products will require a non-reductionist strategy to understand their complex mechanisms of action at the molecular level (Thomford et al., 2018). Thus systems biology guided approach provides a different angle in natural products pharma-sciences. Hamdard Laboratories, Zandu Ayurveda, Patanjali Ayurveda, Himalaya Wellness, Baidyanath are some top herbal pharmaceuticals companies of India.

Future perspective

Medicinal plants should be considered as meta-organisms that comprise both the plant themselves and their microbiome. As meta-organisms, they are a largely untapped and enormous bioresources for bioactive compounds and microorganisms of potential use not only in biocontrol but also used in modern medicine, agriculture, and pharmaceutical industry. As such, more research is necessary to exploit this immense reservoir for mankind.

Fewer studies had been quoted on medicinal plants and microbial interaction drive secondary metabolites. These metabolites have unique characteristics which make them an important candidate for discovery of new drugs and lead molecules. So far the major lacuna in the area of plant metabolite research is the identification and scientific validation of the secondary metabolite and their biosynthetic mechanism with an upsurge in the demand for phytocompounds, the advanced sequencing technologies such as transcriptomic data, metabolomics and proteomics study in combination with computational biology for faster research and better molecular characterization of natural products.

Conflict of interest statement

Authors declare that they have no conflict of interest.

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