The microbiome of medicinal plants: diversity and importance for plant growth, quality, and health

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THE PLANT-ASSOCIATED MICROBIOME: INTRODUCTION INTO STRUCTURE AND FUNCTION

All plant-associated microenvironments are colonized in high abundances by microorganisms, especially the nutrient-rich rhizosphere, the soil area influenced by plant roots, hosts a plethora of microbes that are of central importance for plant nutrition, health, and quality (Hiltner, 1904 in Hartmann et al., 2008, Berg, 2009, Mendes et al., 2011, 2013). The rhizosphere can host up to 10^13 microbial cells per gram root with more than 30,000 different prokaryotic species (Berendsen et al., 2012). These rhizospheric microorganisms from a highly diverse reservoir of soil microbes are attracted by the rhizosphere’s plant root secretions and other rhizodeposits (Compant et al., 2010), and driven via the compositional variability of these exudates (Bais et al., 2006; Doornbos et al., 2012). Each plant species harbors a specific rhizosphere microbiome dependent of the present soil community (Smalla et al., 2013). Besides plant species, the composition and diversity of microbial rhizosphere communities is shaped by soil type and pedoclimate, plant health and developmental stage, climate and season, pesticide treatments, grazers and animals, and several other biotic and abiotic factors (Singh and Mukerji, 2006; Berg and Smalla, 2009; Barnard et al., 2013). Some genera are ubiquitous and can be found distributed over the entire plant, such as the well-known plant-associated genera Bacillus and Pseudomonas (Berg et al., 2011). However, a high degree of specificity for each microenvironment was also observed via comparison of microbial colonization patterns of different microhabitats (Berg et al., 2005b; Fürnkranz et al., 2012; Köberl et al., 2013). Certain plant-associated microorganisms including beneficials and pathogens are also passed down from previous generations via the seed (Hardoim et al., 2012; Hirsch and Mauchline, 2012), and likewise a transmission between plants through pollen grains was recently observed (Fürnkranz et al., 2012). Interestingly, the phylogenetically oldest land plants, mosses, transfer a highly diverse core microbiome of primarily potential beneficial bacteria from the sporophyte to the gametophyte and vice versa (Biagino et al., 2012).

Medicinal plants harbor a distinctive microbiome due to their unique and structurally divergent bioactive secondary metabolites that are most likely responsible for the high specificity of the associated microorganisms (Qi et al., 2012). The analyses of several Chinese medicinal plant microbiomes showed interesting results (Ainsliaea henryi Diels, Dioscorea opposita, Schumach. and Thonn.) cultivated on organically managed Egyptian desert farm and to develop biological control strategies. The soil microbiome of the desert ecosystem was comprised of a high abundance of Gram-positive bacteria of prime importance for pathogen suppression under arid soil conditions. For all three plants, we observed a clearly plant-specific selection of species as important drivers in structural and functional diversity. Lastly, native Bacillus spec. div. strains were able to promote plant growth and elevate the plants’ flavonoid production. These results underline the numerous links between the plant-associated microbiome and the plant metabolism.

Keywords: biocontrol, desert farming, medicinal plants, microbial communities, organic agriculture, soil-borne pathogens

Past medicinal plant research primarily focused on bioactive phytochemicals, however, the focus is currently shifting due to the recognition that a significant number of phytotherapeutic compounds are actually produced by associated microbes or through interaction with their host. Medicinal plants provide an enormous bioresource of potential use in modern medicine and agriculture, yet their microbiome is largely unknown. The objective of this review is (i) to introduce novel insights into the plant microbiome with a focus on medicinal plants, (ii) to provide details about plant- and microbe-derived ingredients of medicinal plants, and (iii) to discuss possibilities for plant growth promotion and plant protection for commercial cultivation of medicinal plants. In addition, we also present a case study performed both to analyse the microbiome of three medicinal plants (Matricaria chamomilla L., Calendula officinalis L., and Solanum dultschum Schumach. and Thonn.) cultivated on organically managed Egyptian desert farm and to develop biological control strategies.
MEDICINAL PLANTS: PLANT- AND MICROBE-DERIVED INGREDIENTS

Plants contain numerous different biologically active compounds, and plant-derived medicines have been part of traditional health care in most parts of the world for thousands of years. Traditional Chinese medicine (TCM), phytotherapeutic knowledge from the Mayans, the aboriginal medicine of Australia, and several other cultures comprise a huge spectrum of natural remedies that can be exploited as sources for new and effective therapeutic agents. Still widely practiced in the modern era, TCM supplies ethnopharmacological knowledge on over 5,000 plant species used for the treatment of numerous diseases and has already provided the basis for the discovery of many modern drugs, such as anticancer agents (Miller et al., 2012a,b). In general, natural products play a highly considerable role in the drug discovery and development process, as about 26% of the new chemical entities introduced into the market worldwide from 1981 to 2010 were either natural products or those derived directly therefrom, reaching a high of 50% in 2010 (Newman and Cragg, 2012). In the past, medicinal plant research focused primarily on their ingredients, however, recently the focus has shifted to include the structure and function of several medicinal plant microorganisms. Surprisingly, not only were the plants themselves able to produce substances with phytotherapeutic properties, but their associated microbes, in particular endophytes, could as well (Table 1). Currently, research continues to show that a significant number of natural products are actually produced by microbes and/or microbial interactions with the host from whence they were isolated (Gunatilaka, 2006), and for several medicinal plants it is presumed that the plant-associated microbiome, especially the complex community of the endomicrobiome, is directly or indirectly involved in the production of bioactive phytochemicals. Presently, however, only a small subset of potential microbial strains could be definitively attributed to phytotherapeutic properties (Strobel and Daisy, 2003; Strobel et al., 2004; Chandra, 2012). These Gram-positive and often spore-forming bacteria are promising biological control agents (BCAs), such as the genus Streptomycetes that is a known and unique source of novel antibiotics (Goodfellow and Boots, 2010; Nairzula et al., 2010; Nachtingall et al., 2011; Rasmussen and Maizola, 2012).

PLANT GROWTH PROMOTION AND BIOLOGICAL CONTROL FOR MEDICINAL PLANTS

Several rhizospheric microbes interact beneficially via different mechanisms with their host plant. They can have a direct plant growth promoting effect based on improved nutrient acquisition or hormonal stimulation, or indirectly affect the plant health by suppression of phytopathogens (Berg, 2009; Lugtenberg and Kamilova, 2009). Biofertilizers are microbes that supply the plant with nutrients, for example symbiotic root-nodulating rhizobia are the most prominent among the nitrogen-fixing microorganisms. Other microbial biofertilizers, such as mycorrhizal fungi and several rhizobacteria, are able to solubilize plant-available phosphate from either organic or inorganic bound phosphate (Lugtenberg et al., 2002). Microbes that hormonally promote plant growth are termed phytostimulators, and the phytohormone auxin, for instance, produced by fluorescent pseudomonads is one of the best understood examples (Kamilova et al., 2006; Khare and Arora, 2010). Various rhizobacteria, including for example Burkholderia cepacia, Staphylococcus epidermidis, and strains of the Bacillus subtilis group, stimulate plant growth by the emission of volatile organic compounds (VOCs, Ryu et al., 2003; Kai et al., 2007; Effmert et al., 2012; Ritase et al., 2013). VOCs are low molecular weight molecules (<300 Da) that have high vapor pressures and are therefore able to diffuse over long distances through the porous structure of the soil and through water-filled pores (Kai et al., 2007; Insam and Seewald, 2010). Indirectly, the plant growth can be promoted via biological control of phytopathogens. Pathogen growth can be inhibited by antibiotics or VOCs, toxins, biosurfactants, or extracellular cell wall-degrading enzymes, but microbial antagonism can also occur via degradation of pathogenicity factors like toxins, or simply by the competition for nutrients, minerals, or colonization sites (Berg, 2009). Another possible way to reduce the activity of pathogenic microorganisms is the activation of the plant defense mechanisms, or the so called induced
Table 1: Examples for bioactive phytometabolites where microorganisms are involved in their production.

| Bioactive compound | Therapeutic properties | Host plant | Producing microorganism | Reference |
|--------------------|------------------------|------------|--------------------------|-----------|
| Munumbicins        | Antibacterial, antifungal, antiflammatory | Kennedia nigricans | Streptomyces sp. | Castillo et al. (2002) |
| Kakadumycins       | Antibacterial, antiflammatory | Grevillea pteridifolia | Streptomyces sp. | Castillo et al. (2003) |
| Coronamycins       | Antifungal, antiflammatory | Monstera sp. | Streptomyces sp. | Enna et al. (2004) |
| Ocydin A           | Antimicrobial (Oomycota) | Pfaffia paniculata | Seratia marcescens | Strobel et al. (1995a) |
| Cryptocandin       | Antimicrobial | Tripterigium vulrifoli | Cryptosporiopsis quercina | Strobel et al. (1995b) |
| Collatonic acid    | Antimicrobial | Arctemia mongolica | Colleotrichum gloeosporioides | Zou et al. (2000) |
| Artemisinarin      | Antiflammatory | Artemisia annua | Colletotrichum sp. | Wang et al. (2001) |
| Cestalidin         | Antimicrobial, antiflammatory | Salvia officinalis | Chaetomium sp. | Debatab et al. (2009) |
| Botryohydronides   | Antimicrobial, antiflammatory | Bidens plosa | Botryosphaeria rhodina | Abdou et al. (2010) |
| Pestacin and isoperstacin | Antimicrobial, antiflammatory | Terminalia montebansia | Pestalotiopsis microspora | Strobel et al. (2002), Harper et al. (2003) |
| Phomol             | Antiflammatory, antifungal | Erythrina cristagalli | Phomopsis sp. | Weber et al. (2004) |
| Podophylotoxin     | Antimicrobial | Podophyllum hexandrum | Alternaria sp. | Yang et al. (2003), Kusari et al. (2009a) |
| Paclitaxel (Taxol) | Antimicrobial, antiflammatory | Taxus brevifolia | Aspergillus fumigatus | Wani et al. (1971), Stierle et al. (1985), Kim et al. (1999), Immaculate et al. (2011) |
| Phomol             | Antiflammatory, antifungal | Aloe vera | Phoma sp. | Phoma sp. | Webster et al. (2011) |
| Campstemacin       | Antimicrobial, anti-HIV | Norkkwydathie haabda | Entrophospora infrequens | Puri et al. (2005), Amma et al. (2006), Kusari et al. (2009b) |
| Maytansine         | Antimicrobial | Pueraria thunbergii | Fusarium solani | Wang et al. (2013) |
| Rohitukine         | Antiflammatory, immunomodulatory | Dymyxolium binectarifere | Fusarium subglutinans | Mohana Kumara et al. (2012) |
| Subglutinols       | Immunomodulatory | Tripterigium vulrifoli | Fusarium subglutinans | Lee et al. (1995) |

systemic resistance (ISR) triggered by certain non-pathogenic rhizobacteria. Flagella, lipopolysaccharides, siderophores, VOCs, and several other bacterial components are thought to be involved in activating the non-pathogenic rhizobacteria-mediated ISR signaling pathway (van Loon et al., 1998; Lugtenberg and Kamilova, 2009).

Biological control of plant pathogens as well as plant growth promotion with microorganisms has been intensively studied over the past decades and is becoming a realistic alternative to chemical pesticides and fertilizers in sustainable agriculture (Wellner 2007). Several microbial inoculants have already been successfully commercialized (Borg 2009, 2013), 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.

MEDICINAL PLANTS AND (POTENTIAL) HUMAN PATHOGENS: OCCURRENCE AND POSSIBLE BIOCONTROL

Traditional medicinal plants are often consumed raw, such as berries or other edible fruits, or in dried form as herbal brews or teas. Therefore, it is of crucial importance that any potentially harmful effect of associated microorganisms or of an applied biocontrol agent on human health be avoided completely. Recently, for instance, bacterial strains closely related to Stenotrophomonas maltophilia and Rhodococcus sp. were isolated from the roots of oregano (Origanum vulgare L.) cultivated in a sub-Himalayan region (Bafana, 2013). Similarly, Ochrobactrum and Rhodococcus were also detected on the studied medicinal plants in Egypt (Matricaria chamomilla L., Calendula officinalis L., and Solanum ditterichii Schumach. and Thonn.; Köberl et al., 2011). Among several others, these bacterial genera are known for their ambiguous interactions with eukaryotic hosts whereby the mechanisms responsible for plant growth promotion are similar to those also responsible for opportunistic infections in humans.
and animals (Berg et al., 2005a). In addition to the suppression of phytopathogens, antagonistic activity against potentially harmful human pathogens should also be considered in the biocontrol strategy.

Conversely, ethanolic extracts from the Chinese medicinal plants Mallotus yunnanensis Pax et. Hoffm., Schima superba (Hemsl. et. Wils) Airy-Shaw., Garcinia morella Desf., Evodia daweili (Benn) Hemsl., Meliosma squamulata Hance., Skimmia arborescens Anders., and Brandisia hanci Hook. f. were determined as highly active against the clinical pathogens Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, and Candida albicans which corresponds to their traditional applications in skin and other infections (Zuo et al., 2012). Promising antimicrobial activities against human multi-drug resistant pathogens have been observed for Mexican medicinal plants as well (Jacobo-Salcedo Mdel et al., 2011). As previously discussed for phytotherapeutic properties, the suppression of human pathogens can also be frequently attributed to medicinal plant-associated microbes and their secondary metabolites (Miller et al., 2012b; Mousa and Rainzada, 2013).

In conclusion, 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 source for bioactive compounds and microorganisms of potential use in modern medicine, agriculture, and pharmaceutical industry. As such, more research is necessary to exploit this immense reservoir for mankind.

**A CASE STUDY: THE MICROBIOME OF MEDICINAL PLANTS GROWN ON A DESERT FARM UNDER ORGANIC MANAGEMENT**

In comparison to soils of humid areas, the soil microbiome of the Egyptian desert farm Sekem was comprised of a high abundance of Gram-positive, spore-forming bacteria primarily of the Firmicutes branch with 37% of the total bacterial soil community as nearly all isolated antagonists with activity against potential pathogens should also be considered in the biocontrol strategy.

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FIGURE 1 | Community shift in the soil microbiome after long-term agricultural use of the desert under organic management.

FIGURE 2 | In situ visualization of the bacterial root colonization of Matricaria chamomilla. Volume rendering (A) and three-dimensional reconstruction model (B) of confocal laser scanning microscopy stacks: (A) yellow = Alphaproteobacteria, pink = Betaproteobacteria, red = other subbacteria, cyan = root tissue, scale bar = 30 μm. (B) green = Alphaproteobacteria, blue = Betaproteobacteria, red = other subbacteria, beige = root tissue, scale bar = 15 μm.
compared to Solanum ditticum (Köberl et al., 2013). This effect may have been intensified as a result of the close relationship between Matricaria chamomilla and Calendula officinalis which both belong to the Asteraceae family and therefore produce more similar bioactive metabolites. Furthermore, both Matricaria chamomilla and Calendula officinalis are annual herbal medicinal plants, while Solanum ditticum is a perennial plant thus providing a longer timeframe to specifically select a stable associated microbiome.

In contrast to the highly specific bacterial communities associated with cultivated medicinal plants, fungal communities were less discriminative and characterized primarily by potential pathogens. Phytopathogenic species such as Fusarium, Verticillium, and several others were frequently identified, and, apart from Rhizoctonia, were the main soil-borne pathogens on the investigated desert farm that caused high yield losses on a wide host range of economically important crops, including the medicinal plants. To biologically control these soil-borne diseases, different desert habitats were screened for potential BCAs adapted to the unique and arid conditions of desert farming. Due to this high content of potential plant pathogens in the fungal community, the selection of antagonists was focused on the indigenous bacterial microbiome. An in vitro screening of 1,212 bacterial isolates linked with the comprehensive ecological data resulted in an antagonistic collection of 45 genotypically different antifungal strains. In a hierarchical evaluation including their antifungal properties against Verticillium dahliae, Rhizoctonia solani, and Fusarium culmorum in addition to their antagonistic activity against the soil-borne plant pathogenic bacteria Stenotrophomonas rhizophila and the nematode Meloidogyne incognita, three promising drought- and heat-resistant biocontrol candidates were selected: Streptomyces subtilis Wb2n-11 isolated from desert soil in Sinai, Bacillus subtilis subsp. subtilis Co1-6 obtained from the rhizosphere of Calendula officinalis, and Paenibacillus polymyxa Mc5Re-14 isolated from the endorhiza of Matricaria chamomilla. Each belongs to risk group 1 and poses no risk for humans or the environment. These three potential BCAs have already shown promising activity in vitro plant growth-promoting activities and stress tolerances; Bacillus subtilis Co1-6 exhibited high drought and salt resistance, pesticide and glucanase activity, and the production of siderophores, Paenibacillus polymyxa Mc5Re-14 had a lower tolerance to abiotic stresses in comparison to the Bacillus strain, but also tested positive for siderophores and glucanase activity, and the desert bacterium Streptomyces subtilis Wb2n-11 showed hydrolytic degradation of chitin and glucan. All of them produced antibiotics against the nematode Meloidogyne incognita, however, their antibacterial activities were highly specific. While Bacillus subtilis and Streptomyces subtilis exhibited antagonistic suppression of the plant pathogen Raileotonia solanacorum, only the Paenibacillus isolate was active against the opportunistic human pathogen Escherichia coli (Köberl et al., 2013).

These three autoclonohous Gram-positive strains were selected for ad planta evaluation in the field under desert farming conditions in comparison to three allclonohous Gram-negative strains already known for their beneficial plant-microbe interactions in humid soils. Pseudomonas fluorescens LI3-6-12 isolated from the rhizosphere of potato (Solanum tuberosum), Stenotrophomonas rhizophila P69 from oilseed rape (Brassica napus) rhizosphere, and Serratia plymuthica 3Re18 from the endorhiza of potato (Lottmann and Berg, 2001; Wolf et al., 2002; Kue et al., 2007; Zachow et al., 2010; Alavi et al., 2013). The first results revealed that priming chamomile seedlings with the autochthonous strains not only showed a stabilizing effect on plant performance, but Bacillus subtilis Co1-6 and Paenibacillus polymyxa Mc5Re-14 were also able to further elevate the plants’ flavonoid production. Higher contents of the bioactive compounds apigenin-7-O-glucoside and apigenin, which belong to the major flavonoids of chamomile flowers (Kato et al., 2008; Srivastava and Gupta, 2009), were measured in blossoms of plants treated with the two Bacillales strains compared to blossoms of other treatments and uninoculated control plants (Schmidt et al., 2013). These findings demonstrate that a targeted bacterial treatment could influence the metabolic activity of the plant, and therefore represent one of the many poorly understood links between the structure and metabolic profile of the plant-associated microbiome and the plant metabolome.

AUTHOR CONTRIBUTIONS
Conceived and designed the experiments: Gabriele Berg, Rudolf Bauer, Elshahat M. Ramadan and Martina Köberl. Performed the experiments: Martina Köberl and Ruth Schmidt. Analyzed the data: Martina Köberl, Ruth Schmidt and Gabriele Berg. Contributed reagents/materials/analysis tools: Gabriele Berg. Wrote the paper: Martina Köberl and Gabriele Berg.

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