

Received: 2017-08-06

Accepted: 2017-12-16

DOI: 10.1515/hepo-2017-0025

REVIEW ARTICLE

# Occurrence of pathogenic and endophytic fungi and their influence on quality of medicinal plants applied in management of neurological diseases and mental disorders

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## Summary

Due to increasing demand of medicinal plants (MPs), quality and safety more attention to the plant health should be paid. Among herb pathogens, especially fungi cause serious diseases in these plants decreasing yield and quality of herbal raw material. Some species, i.e. *Fusarium* sp., *Alternaria* sp., *Penicillium* sp. are known as mycotoxin producers. Paradoxically, self-treatment with herbal raw material can expose the patient to mycotoxin activity. In tissues of some MPs species, asymptotically endophytic fungi residue. It is known that they are able to influence a biosynthesis of secondary metabolites in their host plant or produce biologically active compounds. Until recently these microorganisms have been neglected as a component of MPs, the reason why there have unexplored bioactivity and biodiversity. The paper presents an overview of herbal plants that are used in the treatment of nervous system diseases. Pathogenic fungi that infect these plants are described. It focused mainly on species producing harmful mycotoxins. The publication presents a list of these mycotoxins and a brief description of their effects on human health. The second part of this article provides information on the occurrence of endophytic fungi in herbal plants and their effects on human health. Coexistence of fungi and medicinal plants is not fully understood but can be crucial to ensure health and safety of patients with neurological diseases and mental disorders.

**Key words:** *herbal medicines, phytotherapy, medicinal plant diseases, pathogenic fungi of plants, mycotoxins, endophytes, neurological diseases, mental disorders*

## INTRODUCTION

Medicinal and aromatic plants (MPs) are important in the life of people worldwide [1-3]. Due to beneficial effects of medicinal plants on health and wellness they play a significant role in a social, cultural and ecological aspect of local communities providing people with medicines to maintain health and prevent or cure diseases [4]. In general, derived compounds of the secondary plant metabolism are responsible for the efficacy of medicinal plants. MPs utilization is present in the traditional medicine till today, since significant part of world population still relies on MPs in their medications [5, 6]. The popularity of herbal medicines may be partially explained by the tendency of herbs to work slowly with minimal toxic side effects [7]. In some countries, the economic aspect is also important.

In 20<sup>th</sup> century, a remarkable progress in medicine occurred that made most of the somatic diseases curable. However, medicinal options in neurology and psychiatry are still insufficient. Neither cure nor preventive care exists for major mental disorders, such as major depression, or i.e. for neurodevelopmental disorders represented by heterogeneous autistic spectrum disorders [8]. The World Health Organization [9] claimed that over one billion people worldwide suffer from neurological diseases or mental disorders [10]. Neurological diseases include epilepsy, dementias, migraine and multiple sclerosis. Mental disorders, on the other hand, i.e. anxiety, depression, schizophrenia are severe. As a consequence, they generate enormous costs of hospitalization, loss of working hours and early retirement [8]. Mental, neurological, and substance-addiction disorders affect every community and age group in all countries. Unfortunately, most of people affected (75% in low-income countries) do not have access to the treatment they need [10].

Traditional medicine is used worldwide and it is of great economic importance in the 21<sup>st</sup> century [11]. Recently, in Europe and USA some kind of the renaissance of MPs applications can be noted. They are used widely as a source of biologically active compounds with therapeutic properties. Medicinal plants are extensively applied to cure neurological and psychiatric problems. Stress and anxiety are a normal part of life, but anxiety disorders, affecting 40 million adults, are the most common mental disorder in Europe and USA [12, 13]. In view of steadily increasing demand of MPs quality and safety, more attention should be paid to the plant health.

## AIM

The aim of this review was to discuss complexed relationships between microscopic fungi and medicinal plants applied in neurological diseases and mental disorders. On the one hand, microscopic fungi can strongly decrease the quality of MPs raw material. Many species of pathogenic fungi infect such plants: herbs, shrubs or trees. Among pathogens, especially fungi producing mycotoxins (i.e. *Fusarium* spp., *Alternaria* spp., *Penicillium* spp.) cause serious diseases of these plants, decreasing yield and quality of herbal raw material [14, 15]. Paradoxically, people trying to use them in the treatment can be exposed to fatal mycotoxin activity. On the other hand, some microscopic fungi and their metabolites can be a kind of added value. Tissues of some MPs residue (asymptomatic) in endophytic fungi. What is interesting, that they are able to influence a biosynthesis of secondary metabolites in their host plant or produce biologically active compounds, i.e. be useful in the treatment of neurological diseases and mental disorders. Until recent times, these microorganisms were considered to be a 'component' of medicinal plants. That is a reason why there still are a trove of unexplored bioactivity and biodiversity. Currently, the endophytic fungi are expected to be a potential source of natural bioactive compounds with a huge medicinal potential [16, 17]. This fungal-plant interaction is even more complicated considering that in tissue of MPs can exist fungal species able to biosynthesize mycotoxins as well as valuable biologically active compounds.

To summarize, in this review we try to show the influence of pathogenic and endophytic fungi on quality and usefulness of medicinal plants applied to cure neurological and mental disorders.

### **Medicinal plants applied in management of neurological diseases and mental disorders**

Many species of medicinal plants are recommended for neurological diseases and mental disorders (tab. 1). Herbs popular in Europe such as *Melissa officinalis* L., *Valeriana officinalis* L., *Hypericum perforatum* L., *Matricaria chamomilla* L. and *Ocimum basilicum* L. are used in anxiety, insomnia, anxiety and depression.

Lemon balm (*Melissa officinalis* L.) is used for Alzheimer's disease (aromatherapy), attention deficit-hyperactivity disorder (ADHD), accelerated heart-beat and high blood pressure due to nervousness [18].

**Table 1.**  
Medicinal plants applied to cure neurological diseases and mental disorders

Medicinal plant species	Family of medicinal plant species	Common name	Popular use	References
<i>Ocimum basilicum</i> L.	<i>Lamiaceae</i>	sweet basil	headaches	43
<i>Melissa officinalis</i> L.	<i>Lamiaceae</i>	lemon balm	Alzheimer's disease attention deficit-hyperactivity disorder (ADHD) nervousness	18
<i>Hypericum perforatum</i> L.	<i>Hypericaceae</i>	St. John's wort	depression	19
<i>Valeriana officinalis</i> L.	<i>Valerianaceae</i>	valerian	nervous excitability pain migraine anxiety	21, 44, 45
<i>Cannabis sativa</i> L.	<i>Cannabaceae</i>	hemp	depression anxiety pain alleviation	22, 23
<i>Angelica archangelica</i> L.	<i>Apiaceae</i>	garden angelica	disorders of nervous system	24
<i>Galanthus nivalis</i> L.	<i>Amaryllidaceae</i>	snowdrop	Alzheimer's disease	25
<i>Lavandula angustifolia</i> L.	<i>Lamiaceae</i>	lavender	strengthening of the nervous system	20, 26, 27
<i>Matricaria chamomilla</i> L.	<i>Asteraceae</i>	wild chamomile	stress depression insomnia anxiety	1, 28, 29, 42
<i>Mentha piperita</i> L.	<i>Lamiaceae</i>	peppermint	insomnia depression	33, 34
<i>Platycodon grandiflorus</i> (Jacq.) A.DC.	<i>Campanulaceae</i>	ballon flower	neuroprotective nervous excitability	35, 36
<i>Salvia officinalis</i> L.	<i>Lamiaceae</i>	sage	Alzheimer's disease	37
<i>Viburnum tinus</i> L.	<i>Adoxaceae</i>	laurustinus	depression	38
<i>Piper nigrum</i> L.	<i>Piperaceae</i>	black pepper	nervous excitability anxiety	39
<i>Ginkgo biloba</i> L.	<i>Ginkgoaceae</i>	ginkgo	Alzheimer's disease depression	40, 41

St. John's Wort (*Hypericum perforatum* L.) is a herb which thanks to its active compound, hypericin, works as a dopamine-related antidepressant commonly used for its neurological effects [19, 20].

*Valeriana officinalis* L. is well known for its sedative and anticonvulsant qualities and its ability to relax the central nervous system and the smooth muscle groups (pain reliever) used as a sedative, in migraine treatment, and as a pain reliever [21].

One of interesting natural sources of compounds used to relieve different types of pain and for protection of nervous system is extract from *Cannabis sativa* L. without psychotropic cannabinoids. Medicinal properties of *C. sativa* have been explored for centuries. It is well established that active compounds of this herb act through two cannabinoid receptors (CB1,

CB2) [22]. Health benefits are well documented, from depression and anxiety relief to reduced blood pressure, pain alleviation and glaucoma treatment. It is not addictive, does not kill brain cells [22, 23].

The roots of garden angelica (*Angelica archangelica* L.) are used in the traditional Austrian medicine internally as tea or tincture for treatment of disorders of nervous system and also for the gastrointestinal and respiratory tracts. This herb works calmingly [24].

Snowdrop (*Galanthus nivalis* L.) is a well-known medicinal plant. It contains an active substance called galantamine, which is an acetylcholinesterase inhibitor. Galantamine (or galanthamine) can be helpful in the treatment of Alzheimer's disease, however, it is not a cure [25].

Lavender (*Lavandula angustifolia* L.) has healing properties. It has been traditionally used as an antiseptic and for mental health purposes. There are some scientific evidence that lavender is effective for most mental health uses [20, 26, 27].

Chamomilla (*Matricaria chamomilla* L.) has been used over thousands of years for a variety of conditions, including insomnia, anxiety, and gastrointestinal conditions such as upset stomach, gas, and diarrhea [1, 28]. Inhalation of the vaporized essential oils derived from chamomile flowers is recommended to relieve anxiety and general depression [7].

*Mentha piperita* L. has a history of medicinal use for a variety of conditions, including not only nausea, indigestion but insomnia and depression [29-34]. The extracts and purified platycoside compounds (saponins) from the roots of *Platycodon grandiflorus* may exhibit neuroprotective, antimicrobial, anti-inflammatory, anti-cancer, anti-allergy, improved insulin resistance, and cholesterol-lowering properties [35, 36].

*Salvia officinalis* L. has influence to improve cognitive function in patients with mild to moderate Alzheimer's disease [37].

*Viburnum tinus* L. has also medicinal properties. The active ingredients are viburnin (a substance or more probably a mixture of compounds) and tannins. Tannins can cause dyspepsia. Infused leaves have antipyretic properties. The fruits have been used as purgatives against constipation. Lately, the tincture has been used in herbal medicine as a remedy for depression. The plant also contains iridoid glucosides [38].

A constituent of pepper (*Piper nigrum* L.) – piperine, protects against oxidative damage by inhibiting free radicals and reactive oxygen species. Piperine has also sedative properties [39].

Ginkgo (*Ginkgo biloba* L.) is one of the oldest living tree species. It is also one of the best-selling herbal supplements in the United States and Europe. *G. biloba* leaf is often administered orally for memory disorders including Alzheimer's disease. It is also used for conditions that seem to be due to reduced blood flow in the brain, especially in elderly. Ginkgo leaf is also used for thinking disorders related to Lyme disease, chemotherapy, and depression [40, 41].

### Pathogenic and toxigenic fungi infecting medicinal plants

Fungi are the primary cause of medicinal plant diseases. Considering MPs properties for treatment or

prevention of human diseases the most important are fungal species which biosynthesizes toxic substances (tab. 2). Mycotoxins are highly toxic secondary metabolic products of fungi, mainly those belonging to genera *Fusarium*, *Aspergillus*, *Penicillium* and *Alternaria*. It has been estimated that about 300 of these fungal metabolites are toxic to animals and humans [46].

*Alternaria* are a well-known and commonly occurring plant pathogens. This fungus infects species of herbal plants very often. It occurs on raw herbal material, despite the lack of evidence of infestation [47]. Species of *Alternaria* can produce toxins associated with animal and human disorders. Most of the toxins produced by *Alternaria* are dangerous to human health. The most studied is tenuazonic acid. The principal mode of action is the inhibition of protein synthesis. Alternariol and alternative monomethyl ether exhibit phytotoxic, teratogenic and mutagenic effects [48, 49].

The presence of a number of species from the *Fusarium* genus has been found on many herbal plants. *Fusarium* species were isolated from different parts of *O. basilicum*, *H. perforatum*, *A. archangelica*, *M. chamomilla*, *G. biloba*, *M. piperita*, *V. officinalis*, and *C. sativa* [50-57].

*Fusarium* species also produce mycotoxins harmful to human health. These are: trichotecenes, zearalenone, fumonisins, moniliformin, aflatoxin [58-60]. Acute mycotoxicosis caused by high doses of micotoxins is rarely observed in humans. However, even low amounts may impair intestinal health, immune function and/or pathogen fitness, resulting in altered host pathogen interactions and thus a different outcome of infection [58, 61, 62]. Accumulation of mycotoxins produced by *Fusarium* fungi can cause, for example, colibacillosis and salmonellosis, as well as inflammation of intestines [63-66].

Species from the *Aspergillus* genus are also found on herbal plants (tab. 1). These fungi grow in the vegetation period of plants as well as on the raw material stored in inappropriate conditions [67]. Pathogenic *Aspergillus* spp. also produces mycotoxins. These toxins are known for their strong and varied biological activities. For example, aflatoxin, the well-known and well-investigated mycotoxin, is known to carry the most potent carcinogenic activity as a natural product. It also carries acute toxicity to various human cells such as hepatocytes, renal cells, lung epithelioid cells, etc., as well as various immunosuppressive

**Table 2.**  
Fungal species that biosynthesize toxic substances documented in medicinal plants

Fungal species	Mycotoxins	Infected medicinal plants	Reference
<i>Alternaria</i>	Alternariol	<i>Salvia officinalis</i> L.	79-81
	Monomethyl ether Alternuene	<i>Hypericum perforatum</i> L.	
	Altetoxins I, II, III	<i>Ginkgo biloba</i> L.	82, 83
	Tenuazonic acid	<i>Mentha piperita</i> L.	47, 84
<i>Aspergillus</i>	Aflatoxin	<i>Matricaria chamomilla</i> L.	57, 58, 67
	Ochratoxin	<i>Mentha piperita</i> L.	
	Gliotoxin	<i>Melissa officinalis</i> L.	
	Fumagilin		
	Helvalic acid		
	Fumitrenorgin A		
	Asp-hemolysin		
<i>Fusarium</i>	Trichotecenes	<i>Ocimum basilicum</i> L.	50-53, 55, 85
	Zearalenone	<i>Hypericum perforatum</i> L.	
	Fumonisin	<i>Melissa officinalis</i> L.	56, 57
	Moniliformin	<i>Angelica archangelica</i> L.	86, 87
	Aflatoxin	<i>Matricaria chamomilla</i> L.	88
		<i>Ginkgo biloba</i> L.	58, 82, 83
		<i>Mentha piperita</i> L.	51
		<i>Valeriana officinalis</i> L.	56, 57
		<i>Cannabis sativa</i> L.	32
<i>Penicillium</i>	Penicilic acid	<i>Hypericum perforatum</i> L.	81
	Citrinin	<i>Salvia officinalis</i> L.	
	Patulin	<i>Valeriana officinalis</i> L.	56, 57, 77
		<i>Matricaria chamomilla</i> L.	67, 91

activities [63, 64, 68]. Species from the genus *Aspergillus* produce mainly: aflatoxin, ochratoxin, gliotoxin, fumagilin, helvalic acid, fumitrenorgin A, asp-hemolysin [69-75].

Species of the *Penicillium* genus are probably best known as dangerous to human health. There are several dozen species of this pathogen. Many of these species live on herbal plants and produce mycotoxins. Mycotoxins produced by *Penicillium* species are: penicilic acid, citrinin and patulin [76-78]. This causes accumulation of produced mycotoxins in herbal raw material. These toxins are of a carcinogenic effect [63].

### Metabolic activity of endophytic fungi infesting medicinal plants

Endophytes are polyphyletic group of diverse, primarily ascomycetous fungi capable of asympto-

matic infestation of apparently healthy plant tissue [92]. Therefore, a fungus can be considered to be endophyte after the demonstration of its hyphae in the living tissue. The term 'endophyte' (Gr. *endon*, within *phyton*, plant) was first used by de Bary in 1866 [93]. The existence of fungi inside the plants tissues without causing any identifiable disease symptoms to the host has been known since the end of the 19<sup>th</sup> century. Endophytes are synergistic to their host plant [94]. Over the long evolution, co-existing endophytes and their host plants have established a unique relationship which can significantly influence the formation of metabolic products in plants [95]. Plants inhabited with specific endophyte became stronger and able to grow faster due to, for example, production of phytohormones [96-99]. The bioactive metabolites belong to diverse chemical groups such as alkaloids, steroids, flavonoids, terpenoids, quinones, lactones etc. [96]. Faeth and Fagan [97] notified that endophytic fungi have played a very important role in affecting the

Table 3.

Host medicinal plants common in Europe and endophytic fungi producing plant-secondary metabolites

Host medicinal plant	Fungal endophyte	Secondary metabolite	Bioactivity	References
<i>Hypericum perforatum</i> L.	<i>Chaetomium globosum</i>	hipericin	anti-depressant	104
	<i>Thielavia subthermophila</i>	hipericin emodin	anti-depressant anti-cancer	105
<i>Piper nigrum</i> L.	<i>Colletotrichum gleosporioides</i>	piperine	anti-depressant	106
<i>Gingko biloba</i> L.	<i>Alternaria</i> sp.	paclitaxel	anti-cancer	83
	<i>Aspergillus nidulans</i>	quercetin	anti-inflammatory	107
	<i>Fusarium oxysporum</i>	ginkgolide	anti-allergic	83
	<i>Pestalotiopsis uvicola</i>	bilobalide	neuroprotective	107

quality and quantity of the crude drugs through a particular fungus-host interaction.

Research on the biosynthetic potential of endophytes was accelerated after discovery of fungal strains capable to synthesize *de novo* various bioactive compounds previously considered as host plant products [100]. For the first time, such possibility was comprehended and published by Stierle *et al.* [101], following the discovery of endophytic *Taxomyces andreanae* that produces anticancer compound called paclitaxel, which was isolated from *Taxus brevifolia*. The success of obtaining fungal taxol has initiated a lot of studies focused on microorganisms able to produce metabolites displaying antitumor bioactivity [100, 101]. More than 100 anticancer compounds have been reported alone from fungal endophytes in 1990–2010 [101]. Unfortunately, the knowledge about endophytes from herbs applied to cure neurological and psychiatric illness remain still limited, especially considering medicinal plants cultivated and common used in Europe (tab. 3).

An example of interesting medicinal plant-endophyte relationship is *Hypericum perforatum* and *Thielavia subthermophila*. *H. perforatum* produces hypericin (2,2'-dimethyl-4,4',5,5',7,7'-hexahydroxymesonaphthodianthrone), a photodynamic, red-coloured anthraquinone-derivative [102] which is synthesized in the specialized glandular structures dispersed over all above-ground parts of the plant [103-105] discovered endophytic fungus that have been evolutionarily co-adapted to protect itself from the photodynamic effects and produce hypericin even in axenic cultures. The *hyp-1* gene, suggested to encode for the Hyp-1 phenolic coupling protein in plant cell cultures, was not found in endophyte genome. Kusari *et al.* [105] proposed that emodin

anthrone is the common precursor of both hypericin and emodin in the fungal endophyte, which is governed by a different molecular mechanism than in the *H. perforatum*. Thus, the metabolic activity of endophyte increases hypericin content in plant crude extract.

*Piper nigrum* is pharmaceutically remarkable because of the presence of the alkaloid: piperine that exhibits broad bioactive properties ranging from antidepressant to anticancer activities. Chithra *et al.* [106] found the isolate belonging to *Colletotrichum gloeosporioides* species complex that was able to biosynthesize piperine. It is worth mentioning that *C. gloeosporioides* is known as a pathogenic fungus causing anthracnose and fruit rot on hundreds of economically important host plants. This highlights the complexity of plant-fungal interaction.

Recently, studies on new biologically-active metabolites from endophytic microorganisms residing in a well-known medicinal plant *Gingko biloba* have shown that some endophytes belonging to *Alternaria* and *Aspergillus* genera produce anticancer and anti-oxidant secondary metabolites but no anti-depressant fungal product was detected [107]. Cui *et al.* [108] explore an endophytic fungus *Fusarium oxysporum*, isolated from *G. biloba*, with the capability to produce biologically active ginkgolide B. Qian *et al.* [83] proved that endophytic fungus *Pestalotiopsis uvicola* isolated from *G. biloba* leaves can produce bilobalide, identical like this produced by host plant.

Undoubtedly, many unknown fungal endophytes capable to produce other associated plant secondary metabolites are of therapeutic influence on human nervous system. They still remain to be discovered and characterized.

## CONCLUSIONS

Coexistence of fungi and medicinal plants is not fully understood but can be crucial to ensure health and safety of neurological and psychiatric patients. On the one hand, pathogenic fungi can cause plant diseases decreasing quantity and quality of yield. Some of them biosynthesise secondary metabolites toxic to plants or affect human health. Paradoxically, within some fungal species (i.e. *F. oxysporum*), isolates producing mycotoxins as well as isolates able to produce valuable bioactive compounds can be found [103].

Endophytic fungi isolated from plant tissues seems to be not fully understood but promising source of bioactive compounds. The production of therapeutic secondary metabolites by endophytic fungi nurtures expectations of use as alternative sources of these valuable compounds. However, commercial production of desirable substances by endophytic fungi seems to remain a distant future. The biotechnological application of endophytes is hampered by suppression of secondary metabolite production on repeated subculturing under axenic monoculture conditions [104]. Moreover, even slight changes in the *in vitro* cultivation conditions can impact the kind and range of secondary metabolites they produce [104]. More understanding of the particular relationships between endophytic fungi and medicinal plants recommended for neurological diseases and mental disorders is required.

*Ethical approval: The conducted research is not related to either human or animal use.*

*Conflict of interest: Authors declare no conflict of interest.*

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## Występowanie patogenicznych i endofitycznych grzybów i ich wpływ na jakość roślin zielarskich stosowanych w leczeniu chorób neurologicznych i psychicznych

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## Streszczenie

Ze względu na stały wzrost zapotrzebowania na jakość i bezpieczeństwo roślin zielarskich, należałoby zwrócić większą uwagę na ich zdrowotność. Wśród patogenów roślin zielarskich, szczególnie grzyby powodują poważne choroby, zmniejszając plon i jakość surowców roślinnych. Niektóre gatunki m.in. *Fusarium* sp., *Alternaria* sp., *Penicillium* sp. znane są jako producenci toksycznych metabolitów. Paradoksalnie ludzie próbujący leczyć się samodzielnie (używając surowców zielarskich), mogą być narażeni na działanie tych mykotoksyn. W tkankach niektórych roślin zielarskich występują (bezobjawowo) pozostałości grzybów endofitycznych. Wiadomo, że mają one zdolność wywierania wpływu na biosyntezę wtórnych metabolitów rośliny żywicielskiej lub wytwarzają związki biologicznie czynne. Do niedawna te mikroorganizmy były przeoczane jako „składnik” roślin zielarskich, co spowodowało, że nadal są polem niezbadanej bioaktywności i bioróżnorodności. W artykule przedstawiono przegląd roślin zielarskich stosowanych w leczeniu chorób układu nerwowego. Opisano grzyby patogeniczne dla tych roślin. Skupiono się głównie na gatunkach biosyntetyzujących szkodliwe mykotoksyny. Publikacja obejmuje listę tych mykotoksyn oraz krótki opis ich wpływu na zdrowie człowieka. Druga część artykułu dostarcza informacji o występowaniu grzybów endofitycznych w roślinach zielarskich i wpływie endofitów na zdrowie człowieka. Współistnienie grzybów i roślin leczniczych nie jest w pełni zrozumiane, a może być bardzo istotne dla zapewnienia zdrowia i bezpieczeństwa pacjentów z zaburzeniami neurologicznymi i psychicznymi.

**Słowa kluczowe:** *leki ziołowe, fitoterapia, choroby roślin zielarskich, grzyby patogeniczne dla roślin, mykotoksyny, endofity, zaburzenia psychiczne, zaburzenia neurologiczne*