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REVIEW ARTICLE

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The Potential of Fungi in the Development of Future Anti-Seizure Medications

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Abstract

***Background*:** While a significant number of epilepsy patients respond well to anti-seizure medications (ASMs), some individuals experience persistent seizures despite undergoing ASM polytherapy, a condition known as drug-resistant epilepsy (DRE). There is a pressing need for the discovery and development of new ASMs to serve as alternative and adjunct therapies for patients with DRE. Fungi are organisms that possess a wealth of anti-inflammatory and antioxidant properties, with some demonstrating neuroprotective effects. Further research and development may position mushrooms as a promising future treatment for seizure management.

***Topics*:** The pathophysiology of epilepsy is closely linked to neuroinflammation and oxidative stress. Mushrooms exhibit potent anti-inflammatory and antioxidant properties, and several species have been investigated for their potential in epilepsy treatment. Notable mushrooms include *Armillaria mellea, Amauroderma rugosum, Auricularia polytricha, Cordyceps militaris, Ganoderma lucidum, Ganoderma neo-japonicum, Hericium erinaceus, Amanita muscaria*, and *Pleurotus ostreatus*. Additional mechanisms through which these fungi may benefit epilepsy patients include enhancing the integrity of the blood-brain barrier, reducing neuronal excitation while promoting inhibition, protecting mitochondrial function, and increasing the expression of vascular endothelial growth factor.

***Conclusion*:** Mushrooms hold significant potential as both alternative and adjunct therapies for epilepsy. Their rich anti-inflammatory and antioxidant content is crucial in reducing seizure frequency, mitigating the progression of epilepsy, and improving patients' overall quality of life.(**International Journal of Biomedicine. 2025;15(1):45-50.**)

Keywords: fungus • seizures • epilepsy • anti-seizure medication

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Introduction

Seizures are among the most common neurological emergencies.[1] They can be triggered by multiple factors. When seizures repeatedly occur without any identifiable provocation, and there are more than 24 hours between episodes, the condition is diagnosed as epilepsy.[2] Typically, epilepsy can be managed with anti-seizure medications (ASM) tailored to the specific type of epilepsy, the patient's age, and any existing comorbidities. However, some individuals continue to experience seizures despite receiving the appropriate combination of ASMs. This situation is known as drug-resistant epilepsy (DRE).[3,4]

Polytherapy in epilepsy patients presents a 'double-edged sword'. Clinicians hope to manage the patient's seizures effectively, yet patients may experience various side effects from the medications. Thus, there is a pressing need to discover new antiepileptic medicines (ASMs) and alternative adjuvant therapies. The identification of such adjunct therapies not only provides potential alternatives to ASMs but also enhances the clinical outcomes for epilepsy patients. Ideally, adjunctive therapies should be cost-effective and less toxic than standard antiepileptic drugs (AEDs).[3,5] Previous research has highlighted the benefits of certain medications, such as brivaracetam and verapamil, as adjunct therapies for epilepsy.[4,6] Additionally, other studies have explored the potential of various drugs as adjuvant therapies, focusing on aspects such as genetic mutations, neuroinflammatory processes, and blood-brain barrier (BBB) dysfunction seen in epilepsy patients.[7]

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Fungi are organisms renowned for their rich content of anti-inflammatory and antioxidant compounds, with some varieties also exhibiting neuroprotective properties. Consequently, therapies utilizing mushrooms are commonly referred to as mycotherapy. The benefits of mushrooms lie in their natural abundance, global availability, and ease of cultivation. With ongoing research and development, mushrooms are anticipated to play a significant role in future seizure management strategies.[8] This literature review aims to elucidate the various types of fungi that may serve as effective adjuvant therapies for epilepsy.

Topics

Armillaria mellea

A. mellea, commonly known as honey fungus, is a widespread species globally, particularly in Asia. This fungus exists in three forms: it can develop saprophytically on stumps, parasitically infect the roots of deciduous and coniferous trees, or live symbiotically with Gastrodia elata. Despite its facultative parasitic nature, *A. mellea* is widely consumed and recognized for its traditional medicinal applications.[9,10] The composition of A. mellea includes carbohydrates, sterols, sphingolipids, fatty acids, sesquiterpenoids, indole compounds, peptides, enzymes, and minerals. These components exhibit potential properties such as antibacterial, anticancer, immunostimulant, and protective effects for brain and bone marrow cells.[10] In vitro and in vivo studies indicate that *A. mellea* has potential as a treatment for epilepsy.[10] This mushroom can be categorized into three parts: mycelium, rhizomorph, and sporophore. Most research primarily focuses on the mycelium and rhizomorph components.[11] However, sporophores of *A. mellea* have been employed in traditional Chinese medicine to address various ailments, including epilepsy.[12]

Fermentation of *A. mellea* extract has been shown to elevate seizure thresholds in mice.[13] The bioactive compounds present in *A. mellea* may decrease excitatory neurotransmission while enhancing inhibitory processes. This action can diminish hyperarousal in neurons, ultimately reducing neuronal excitability and alleviating seizures. Additionally, this mushroom has the ability to lower levels of IL-1β, TNF-α, the expression of ionized calcium-binding protein molecule adapter 1, and the formation and accumulation of intracellular reactive oxygen species (ROS), while also restoring mitochondrial membrane potential.[8] Studies have explored the effects of *A. mellea* on cognition, depression, and Alzheimer's disease,[14-16] but research specifically targeting epilepsy remains limited.

Amauroderma rugosum

A. rugosum, commonly called the "epileptic child mushroom," is found in tropical and subtropical regions, including China, the South Pacific, Indonesia, Taiwan, and Australia.[17] This fungus typically grows in rotten conifer wood, dry dipterocarp forests, and upper mixed deciduous forests, emerging from the soil.[18] *A. rugosum* has been employed in various traditional medicinal practices in China and Malaysia. Indigenous tribes in Malaysia, for instance, use this mushroom in necklaces to help prevent seizures in infants.[17,19] Both the mycelium and sporophores of *A. rugosum* have been the subject of extensive research,[17] with one study focusing on its potential benefits for managing epilepsy.

Mitochondria serve as the primary source of reactive oxygen species (ROS) and are particularly vulnerable to oxidative stress. The development of seizures and epilepsy is closely linked to oxidative damage in mitochondria, which ultimately disrupts mitochondrial function and initiates cell death signals. Consequently, the use of antioxidants represents a vital neuroprotective strategy in managing epilepsy.[20] *A. rugosum* demonstrates the ability to scavenge ROS, reduce oxidative stress, prevent mitochondrial dysfunction, inhibit apoptosis, and protect hippocampal neurons from excitatory neurotoxins, including glutamate-induced neurotoxicity.[8] Research involving rats with epileptic seizures indicated a reduction in symptoms induced by kainic acid following the administration of this fungus.[17]

A. rugosum exhibits anti-inflammatory properties by reducing the expression of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and enhancing the expression of anti-inflammatory cytokines like interleukin-10 (IL-10).[17] Seizures and epilepsy are closely linked to inflammatory processes, making *A. rugosum* a valuable treatment for various inflammatory conditions, including epilepsy.[18,19] Additionally, *A. rugosum* offers other benefits, including anticancer, antimicrobial, and neuroprotective effects.[8]

Auricularia polytricha

A. polytricha is commonly known as the "black ear fungus" in Indonesia. This fungus thrives on decayed wood or tree trunks in several Asian countries. Besides being a staple in everyday cuisine, A. polytricha is utilized in various traditional medicine practices due to its antimicrobial, antitumor, cytotoxic, immunomodulatory, and hepatoprotective properties.[21]

One of the pathophysiological mechanisms underlying epilepsy is the impairment of astrocyte function, which leads to glutamate excitotoxicity.[22] Glutamate, an excitatory neurotransmitter, can become toxic at elevated concentrations, resulting in neuronal death, synaptic disruption, and neurodegeneration.[23] Current anti-seizure medications primarily focus on suppressing seizures; however, no effective disease-modifying drug has been identified that can prevent the progression of epilepsy.[22] *A. polytricha* can be utilized in various extract forms, including hexane (APH), ethanol (APE), and water (APW) extracts. Research indicates that both APE and APH can potentially reduce glutamate toxicity in HT-22 cells. *A. polytricha* exhibits neuroprotective effects through multiple mechanisms, particularly through the suppression of intracellular reactive oxygen species (ROS) accumulation and neuronal death, with APE being particularly effective. By decreasing intracellular ROS buildup, the cellular damage caused by glutamate is also mitigated.[23] In a study conducted on mice, seizures were induced using maximal electroshock (MES) and isoniazid, and it was found that the administration of aqueous extract of *A. polytricha* at doses of 400 and 600 mg/kg body weight significantly reduced the duration of seizures and delayed their onset.[24]

Cordyceps militaris

C. militaris thrives in forests, particularly in various Asian nations such as Japan, Korea, Nepal, India, and China.

This fungus acts as a parasite to the pupae of Lepidopterans, as well as to the larvae of both Lepidopterans and Coleopterans. Besides its parasitic nature, *C. militaris* has been widely used in traditional medicine.[25] The fungus exhibits multiple beneficial effects, including anti-tumor properties by inducing apoptotic homeostasis, as well as anti-inflammatory and antioxidant effects, along with neurotropic benefits.[26]

Patients experiencing seizures often show elevated levels of pro-inflammatory cytokines, including cyclooxygenase-2 (COX-2)/prostaglandin E2, interleukin-1β (IL-1β), and TNF-α, particularly in the epileptogenic foci. This neuroinflammatory response can lead to the activation of microglia, damage to endothelial cells in the blood-brain barrier (BBB), and the infiltration of plasma proteins, granulocytes, and neutrophils into the intracranial space. Thus, it can be concluded that there is a relationship between seizures and the neuroinflammatory process. Consequently, the administration of anti-inflammatory drugs derived from *C. militaris* may prove beneficial for patients with seizures. This particular mushroom also exhibits properties that mitigate the hyperactivation of Rho-associated kinase-2 protein in epilepsy patients and promote the downregulation of p-Akt/Akt signaling.[8] While *C. militaris* has been studied in various contexts, including ischemia-induced neuronal death, cognitive impairment, depression, asthma, and allergic responses,[27-30] research specifically focused on seizure cases remains limited.

Ganoderma lucidum

G. lucidum can be found across Europe, Asia, and North America.[31] This mushroom thrives in deciduous forests, particularly on dead or dying trees, including species such as oak, maple, and elm. In coniferous forests, it can also be located on trees like pine, spruce, and fir. *G. lucidum* is noted for its various health benefits, including anti-inflammatory, antioxidant, antimicrobial, anticancer, cardioprotective, and neuroprotective effects. Its antioxidant properties are highlighted by its capacity to eliminate reactive oxygen species (ROS), neutralize free radicals, and reduce oxidative stress. Additionally, as a neuroprotector, *G. lucidum* promotes neurogenesis via the signaling pathways of mitogen-activated protein kinase kinase/extracellular signal-regulated kinase (MEK/ERK1/2) and phosphoinositide-3-kinase/protein kinase B (PI3K/Akt).[32] This profile presents promising avenues for further research, particularly concerning epilepsy cases. This mushroom has a long history of use in traditional medicine in China, Japan, and Korea.[31]

G. lucidum exhibits antiepileptic effects by reducing calcium ion (Ca2+) accumulation in hippocampal neurons, enhancing the expression of CaMK 11α, and inhibiting both NF-κB and n-cadherin expression in these neurons.[-] Additionally, this mushroom diminishes astrocytic activity and lowers the expression of IL-1β and TNF-α.[8] Research involving mice indicates that administering 100 to 400 mg/kg of *G. lucidum* extract can elevate the threshold for psychomotor seizures as measured in the 6-Hz seizure test. At higher doses, specifically 400 to 600 mg/kg, no sedative or anxiolytic-like effects were observed.[-] Furthermore, a study with 18 epilepsy patients demonstrated that taking 1000 mg of *G. lucidum* spore powder three times daily for eight weeks could significantly reduce the frequency of seizures on a weekly basis and enhance the overall quality of life.[-]

Ganoderma neo-japonicum

G. neo-japonicum is predominantly found in Asia, particularly in Malaysia. This fungus thrives on decayed bamboo or dead coniferous trees. Inland tribes in Malaysia have utilized *G. neo-japonicum* as a remedy for various ailments.[-,-] Among these rural communities, the mushroom stems are cut into bead-like pieces, strung together, and worn as necklaces by individuals with epilepsy.[-]

Further research indicates that this mushroom possesses various beneficial properties, including antioxidant, anti-inflammatory, anticancer, antiviral, immunomodulatory, neuritogenic, and hepatoprotective effects.[-,-] *G. neo-japonicum* has been shown to mitigate seizures by affecting the MEK/ERK1/2 and PI3K/Akt pathways, similarly to *G. lucidu*m.[8] Additionally, by triggering the downregulation of pro-inflammatory cytokine mRNA levels such as IL-1β, IL-6, and TNF-α, *G. neo-japonicum* can reduce the expression of nitric oxide synthase and COX-2. This fungus also alleviates lipopolysaccharide-induced oxidative stress by inhibiting reactive oxygen species (ROS). Furthermore, *G. neo-japonicum* extract has the potential to stimulate neurogenesis through the MEK/ERK1/2 and PI3K/Akt pathways.[-] Notably, the antioxidant content is higher in wild mushroom basidiocarps compared to cultivated varieties.[-] However, specific research investigating the content and effects of *G. neo-japonicum* on epilepsy remains limited.

Hericium erinaceus

H. erinaceus, commonly known as lion's mane, is a fungus found across Europe, Asia, and North America. This species typically grows on dead wood and the heartwood of living trees, and it can also be cultivated.[-] Lion's mane contains several bioactive compounds, including aromatic compounds, steroids, alkaloids, lactones, terpenoids, cerebrosides, phenols, and sterols. These compounds offer a range of health benefits, including anti-inflammatory, antioxidant, antimicrobial, anticancer, cardioprotective, hepatoprotective, neuroprotective, and nephroprotective properties.[8,-]

Extracts from *H. erinaceus* have demonstrated neuroprotective effects by enhancing the expression of vascular endothelial growth factor (VEGF). VEGF is essential not only for angiogenesis but also for improving neurological recovery following injuries, including epilepsy. Insufficient levels of VEGF can lead to a decrease in neuronal survival. In another study conducted on mice, which were induced into an epileptic state using pilocarpine and subsequently treated with *H. erinaceus* extract, the results revealed that doses of 60 and 120 mg/kg of the extract could effectively prevent neuronal death and lower COX-2 levels in the hippocampus. This subsequently resulted in a reduction of seizures and conferred a neuroprotective effect.[-] Furthermore, this fungus has the capacity to stimulate the synthesis of nerve growth factor, protect against neuronal death due to oxidative stress, and promote neurogenesis in the hippocampus. Ethanolic extracts of *H. erinaceus* have also been shown to reduce levels of pro-inflammatory cytokines in serum, including iNOS, IL-

1β, IL-6, and TNF-α.[-] These findings suggest a promising area for further research, particularly in relation to epilepsy.

Muscimol

Muscimol is an active compound obtained from the fungus *Amanita muscaria*, alongside other notable substances such as muscarine, ibotenic acid, and tropane alkaloids. *A. muscaria* typically grows on various angiosperm trees, including those of the Castanea, Cistus, and Quercus species, as well as coniferous trees such as Pinus. This fungus is predominantly found in the southern hemisphere. When consumed directly, it is toxic and can lead to symptoms including hallucinations, restlessness, ataxia, incoordination, impaired consciousness, and gastrointestinal disturbances.[-] In 50-70 grams of fresh *A. muscaria*, there are approximately 6 mg of muscimol. Muscimol is capable of easily crossing the blood-brain barrier (BBB) through an active transport system. Once it enters the central nervous system, muscimol functions as a gamma-aminobutyric acid (GABA) agonist, specifically targeting $GABA_A$ receptors. In addition to being a strong $GABA_A$ receptor agonist, muscimol acts as a partial agonist at $GABA_C$ receptors; however, it shows no activity toward $GABA_B$ receptors. Given these properties, muscimol holds the potential for development as an anti-seizure medication.[-]

Muscimol has been the subject of considerable research. In 2019, a phase one clinical trial was conducted involving three patients with drug-resistant epilepsy who received intracerebral muscimol infusions directly into the epileptic focus, a technique known as convection-enhanced delivery (CED). The results indicated that this method did not cause damage to the surrounding brain parenchyma and did not adversely affect outcomes following epilepsy surgery. Notably, only one patient experienced a reduction in seizure frequency; this patient had a seizure focus located in the neocortex. In contrast, the other two patients, whose seizure foci were in the hippocampus, did not see any decrease in seizure frequency.[-] Further studies in adult female Wistar rats demonstrated that microinjections of muscimol into the subthalamic nucleus at doses of 30 ng and 60 ng per hemisphere could elevate the threshold for both myoclonic and clonic seizures. Continuous administration of muscimol at a dose of 300 ng per hemisphere per day significantly increased the threshold for myoclonic seizures over a two-week period. Moreover, doses of 300 ng and 600 ng per hemisphere per day enhanced the threshold for clonic seizures for one week. However, following this duration, no significant difference was observed between the seizure thresholds before and after treatment. This finding suggests the development of tolerance to muscimol in the study subjects.[-]

Pleurotus ostreatus

P. ostreatus, commonly known as the oyster mushroom, is found in various regions around the globe, including the United Kingdom, Ireland, North America, Japan, and several other Asian and European countries.[-] This fungus is highly versatile and can thrive on a range of substrates. Due to its popularity as a food source, oyster mushrooms are frequently cultivated on various media, such as corncob, finger millet straw, bamboo waste, and their combinations, each exhibiting different growth performances.[-]

One notable component of this mushroom is chrysin, which demonstrates both cardioprotective and neuroprotective properties. Research conducted on the *Oroxylum indicum* plant indicates its potential benefits in treating epilepsy. Additionally, oyster mushrooms possess antioxidant properties and can inhibit proteases.[8] Their antioxidant effects are attributed to the presence of phenolic compounds, β-D-glucan (pleuran), lectin, and ergothioneine.[-] Furthermore, the anti-inflammatory effects of *P. ostreatus* are evidenced by the reduction in the secretion of TNF-α, IL-6, IL-12, and other cytokines, which inhibits the production of prostaglandins E2 and nitric oxide by down-regulating the expression of COX-2 and iNOS.[-] While these properties warrant further investigation, particularly concerning epilepsy, to the author's knowledge, no additional experiments exploring the effects of *P. ostreatus* on epilepsy have been conducted to date.

Conclusion

Mushrooms hold significant promise as an alternative therapy and adjunct treatment for epilepsy. Their high levels of anti-inflammatory and antioxidant properties are crucial in decreasing seizure frequency, slowing the progression of epilepsy, and enhancing the quality of life for patients. Utilizing this natural adjuvant therapy is anticipated to be more cost-effective and to have fewer side effects compared to traditional synthetic antiepileptic medications.

Competing Interests

The author has no competing interests to declare.

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