Health gut microbiota-mediated effects of mushrooms: potential in neuroprotection

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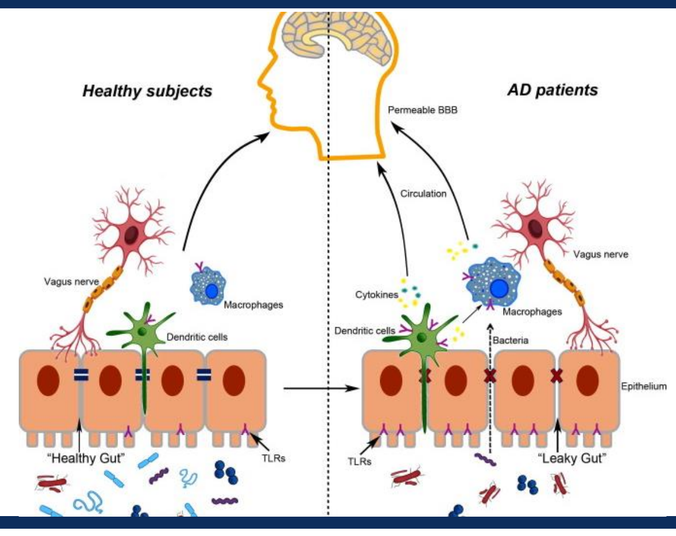
Resume

- Gut microbiota dysbiosis has been directly connected with several clinical conditions, including neurodegenerative disorders. Many neuroactive molecules produced by intestinal flora such as short-chain fatty acids (SCFAs), gamma-aminobutyric acid (GABA), and serotonin, have been shown to contribute to healthy brain function. Alzheimer's disease (AD) has been connected with reduced levels of these metabolites. Intestinal microbiota dysbiosis and aging have been associated with increased permeability of the gastrointestinal tract epithelium and blood-brain barrier, resulting in the alteration of transport mechanisms. Gut microbiota modulation has been suggested as a potential tool for AD and diet is believed to be a powerful driver in this modulation.
- Numerous studies showed the prebiotic potential of mushrooms or mushroom polysaccharide extracts. β-glucans and other mushroom prebiotic molecules strongly stimulate the production of neuroactive metabolites by gut microbiota.
- We aimed to assess the state-of-the-art of mushroom prebiotic potential and their neuroprotective gut microbiota-mediated effects.



Lin et al. (2019)

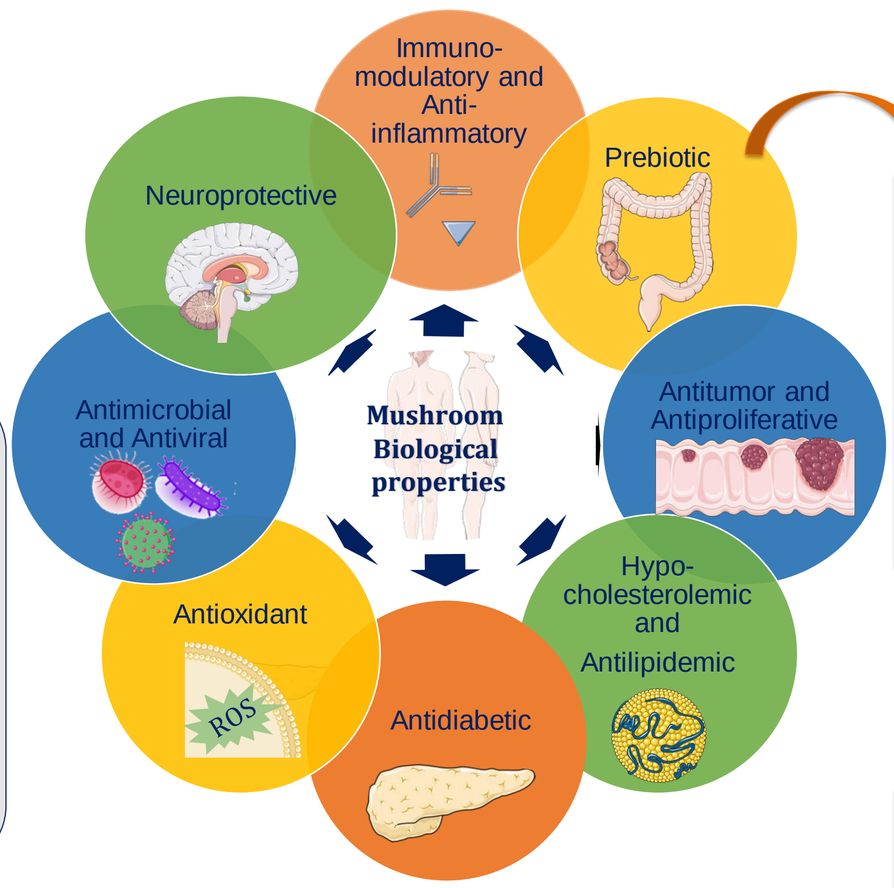
Results and discussion

Some mushroom species

Agrocybe bisporus
Coriolus versicolor
Flammulina velutipes
Hericium erinaceus
Ganoderma lucidum
Grifola frondosa
Lentinula edodes
Pleurotus spp.
Sparassis crispa
Poria cocos

Some bioactive molecules

Polysaccharides:
•α-, β-glucans, chitin
Proteins:
•Lectins, FIPs, enzymes
Fatty acids:
•Oleic and linoleic acids
Terpenes:
•Mono/Diterpenoids
Phenolic compounds:
•Caffeic and ferulic acid
Minerals and vitamins:
•K, P, Mg
•B-complex, C, A, E, D2



Prebiotic Studies

"a substrate that is selectively utilized by host microorganisms conferring a health benefit" (Gibson, 2017)

Entire or extract (polysaccharide)

***In vitro* fermentation with single strains**

Healthy donors

GIT simulation

Human fecal fermentation

Oral/ Gavage/ Intragastric

Fecal and blood analysis

Clinical trials

Main approaches

- Microbiota Dynamics (RT-PCR or 16S rRNA sequencing)
- SCFA quantification
- mRNA expression and anti-inflammatory and pro-inflammatory markers

Some key findings

- Reshape the gut microbiota diversity
  ↑ Firmicutes/Bacteroidetes ratio; ↑ *Lactobacillus* and *Bifidobacterium;* ↓ Pathogenic
- ↑ SCFA (e.g., acetic, propionic and butyric acid)
- ↓ Proinflammatory cytokines
- ↓ Oxidative stress
- ↑ Colon tight junction protein expression

→ ↑ Intestinal barrier integrity

Neuroprotective and gut-brain axis studies

Or
Entire or extract (polysaccharide)

Oral/ Gavage/ Intragastric

And/or

Fecal and blood analysis

Brain biochemical assays

Mushroom species	Main results	Reference	
Hericium erinaceus *Coriolus versicolor*	↑ Lipoxin A4 ↑ Stress responsive vitagene proteins (Hsp72, Heme oxygenase-1 and Thioredoxin)	Trovato et al. (2016) [1, 2]	Brain
Coriolus versicolor	↑ β-catenin ↑ Dendritic length and branching and total dendritic volume of immature neurons ↑ Hippocampal neurogenic reserve	Ferreiro et al. (2018)	
Agaricus bisporus, Agaricus bisporus brunnescens	↑ Il-6, Nox-2, Hmox-1 ↑ Lipid peroxidation ↓ Catalase and superoxide dismutase	García-Sanmartín et al. (2022)	Gut-brain axis
Sparassis crispa	↓ Proinflammatory cytokines (IL-6, TNF-α, IL-1β) ↓ Glial activation ↓ TLR4 and NF-κB ↑ Neurotransmitters level ↓ Neuropathological changes	Zhang et al. (2023)	

Conclusions

- The underlying mechanisms by which the gut microbiota affect AD are unknown. However, is believed that gut-brain crosstalk is mediated through gut-derived signaling molecules such as cytokines, neuroactive molecules and microbial metabolites. Microbiota transplantation, probiotics and prebiotics supplementation seem to have therapeutical potential for AD treatment.
- SCFA are involved with gut homeostasis, promoting the control of gene expression, cell signaling pathways, decrease in intestinal cell permeability and increase mucus thickness.
- SCFA also play important role in gut-brain axis crosstalk. These metabolites increase tight junction protein expression and modulate the blood-brain barrier.
- Some studies suggested an increase in neurotransmitter levels produced by gut microbiota, which positively affect normal brain function (e.g., GABA - synaptic plasticity).
- Neuroinflammation is a key driver in AD. The vitagen system (heat shock proteins 70, heme oxygenase-1, thioredoxin and Lipoxin A4) is an intracellular redox system involved in neuroprotection. For instance, in some reported studies, an increase in lipoxin A4 during mushroom consumption is reported. Also, a reduction in proinflammatory cytokines and glial activation is suggested.
- Mushroom diet showed a reduction of some neuropathological changes, mainly by modulation of neurotransmitter levels and brain oxidative stress markers reduction.

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