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Current Therapy And Protective Potential Of Medicinal Mushroom Cordyceps Militaris Against Alzheimer's Disease

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Abstract
Alzheimer disease is a neurodegenerative disorder which mainly affects older people and effects of quality of life. In this condition, brain cells get degenerated leading to dementia characterized by memory and learning impairment with significant decline in thinking process. It is estimated that around 107 million people will be affected with this disease by the year 2050 worldwide. The current treatment options for this disease are able to provide modest symptomatic relief and most of the drugs act by reducing symptoms by counter balancing neurotransmitter disturbance. The medicinal mushrooms are known to have a number of beneficial effects and are used as a part of traditional medicine system for many years. Medicinal mushroom *Cordyceps militaris* contains a number of bioactive compounds which has tremendous health effects. Cordycepin is the major component of these mushrooms which is well known for its anticancer, antioxidant, anti-inflammatory, immunomodulatory and neuroprotective effects. This compound helps in the improvement of antioxidant enzymes level and demonstrated anti neuroinflammatory effects in various studies. Due to the protective role of *Cordyceps militaris*, this mushroom could help in the development of novel treatment strategies against Alzheimer disease. These review insights the pathogenesis mechanisms, current therapy and protective role of Cordyceps militaris against Alzheimer disease.

Keywords- Alzheimer disease, neurodegenerative, anti-inflammatory, cordycepin.

Introduction

Alzheimer disease is a neurodegenerative disorder and mainly affects people in their older age. Recently, the patients of this disease are increasing rapidly, and it is estimated that around 107 million people will be affected with this disease by the year 2050 (Calabro et al., 2020). The current therapy only provides modest symptomatic relief to the patients. The natural bioactive compound has gained much importance recently due to their anti-inflammatory, antioxidants and anti-amyloidogenic activities (Uddin et al., 2020). A number of studies are still required in order to understand pathogenesis of Alzheimer in relation to β-Amyloid and Tau related mechanics (Calabro et al., 2020). Nowadays, studies are continued on understanding different pathways of this disease such as metabolism of abnormal tau proteins, β-amyloid, inflammatory response and free radical damage along with aim to develop novel treatment agents (Breijyeh et al., 2020). The current treatment drugs are offered to minimize symptoms through counter balancing neurotransmitter disturbance. However, the treatment using disease modifying drugs are still under development. In order to block the disease progression, the drugs are required to interfere with the pathways which lead to disease pathogenesis including deposition of extracellular amyloid β plaques and intracellular neurofibrillary tangle formation, iron deregulation and neuroinflmmation (Yiannopoulou et al., 2013). In Alzheimer's disease, amyloide beta (Aβ) aggregates and get deposited as senile plaques and tau proteins forming neurofibrillary tangles (Calabro et al., 2020). The occurrence of Alzheimer's dementia has been regarded as one of the important health and social issue in industrialized and non industrialized countries (Yiannopoulou et al., 2013). In this condition, brain cells degenerate and lead to dementia which is characterized by decrease in thinking process

and other personal daily works. Alzheimer disease is a multifactorial disease and has several risk factors such as increased age, genetic factors, vascular diseases, infections and head injuries. Presently, there are two classes of drugs which are approved for the treatment of this disease including cholinesterase enzyme inhibitors and antagonists to *N*-methyl D-aspartate (NMDA). However, these drugs do not cure or prevent the disease (Breijyeh et al., 2020).

In recent years, there is an increase in the development of medicines from natural compounds (Jin et al., 2018). Plant based medicines and natural compounds such as flavonoids have significant antioxidant, anti inflammatory and neuroprotective effects against neurodegenerative disorders (Ahmad et al., 2019). Some flavonoids have ability to promote clearance of Aβ peptides along with inhibition of tau phosphorylation by mTOR/autophagy signaling pathway. Flavonoids can be presented as potential anti Alzheimer agents due to their ability to inhibit cholinesterase. More studies are still required in order to understand the interaction of these compounds with various pathways of Alzheimer disease in order to increase cognitive performance and prevention of disease progress (Uddin et al., 2020).

The medicinal mushrooms are known to have a number of beneficial effects and are used as a part of traditional medicine for many years. Many studies on these mushrooms have been done in order to evaluate the beneficial effects of the bioactive compounds found in them (Wasser et al., 2010). *Cordyceps* is well known medicinal mushroom which contains a number of bioactive compounds having tremendous health effects. Cordycepin is the major component of these mushrooms which is a nucleoside derivative and is low in molecular weight. This compound is well known for anticancer, antioxidant, anti-inflammatory and immunomodulatory effects (Soltani et al., 2019). The studies revealed that *Cordyceps militaris* may be a promising candidate for the neuroprotection of hippocampus and recovery of neuroinflmmation (Kim et al., 2019). The bioactive compound Cordycepin, help in improvement of antioxidant enzymes level and poses anti neuroinflammatory effects. Due to the anti-neuroinflammatory effects of cordycepin, this compound could help in the development of promising novel treatment strategies against neurological disorders like Alzheimer disease (Govindula et al., 2021). This review highlights the pathogenesis mechanisms, current treatment and potential protective role of Cordyceps militaris against Alzheimer disease.

Mechanisms of pathogenesis in Alzheimer's disease

More than 40 million people are affected with this disease all over the world (d'Errico and Meyer-Luehmann, 2020). Alzheimer's disease is characterized by the presence of extracellular amyloid-beta (Aβ) plaques and neurofibrillary tangles in the intracellular region, neural cell death and the loss of synapses leading to cognitive decline. The abnormal neurofibrillary structures may be formed due to faulty tau phosphorylation. Many different structures of the brain are susceptible to the disease such as reticular formation, thalamus, hypothalamus, locus ceruleus, amygdala, substantia nigra, striatum, and claustrum. In the various stages of the disease, various other changes are reported such as premature synaptotoxicity, changes in neurotransmitter expression, neurophils loss, accumulation of amyloid β-protein deposits (amyloid/senile plaques), and neuronal loss (Kocahan et al., 2017).

In the Alzheimer's disease, amyloid-β (Aβ) peptide generated by breakdown of amyloid precursor proteins accumulates along with hyperphosphorylated tau proteins inside the neurons leading to neurofibrillary tangles, neuronal dysfunction and dementia. During the development of disease, firstly tau and Aβ misfolded and get aggregated in one region of brain and get spread to interconnected areas by inducing gradual morphological and functional deterioration (d'Errico and Meyer-Luehmann, 2020). It is evident from recent research that amyloid amyloid β (Aβ), and tau proteins has significant contributions to different cellular and molecular pathways in pathogenesis of the Alzheimer's disease (Guo et al., 2020).

The neuronal death and the loss of synapses lead to cognitive decline. Low level of N-methyl-D-aspartate (NMDA) receptors leads to excitotoxicity and other characteristics such as premature synaptotoxicity, changes in neurotransmitter expression, neurophils loss, accumulation of amyloid β-protein deposits, neuronal loss, and brain atrophy are linked with later stages of Alzheimer's disease. The spine loss induced by amyloid-β (Aβ) is associated with decreased glutamate receptors along with calcium dependent calcineurin which dependent upon calcium dependent phosphate calcineurin which

also associated with long term depression (Kocahan et al., 2017). (Fig-1, 2).

Fig- 1 Characteristics of Alzheimer's disease

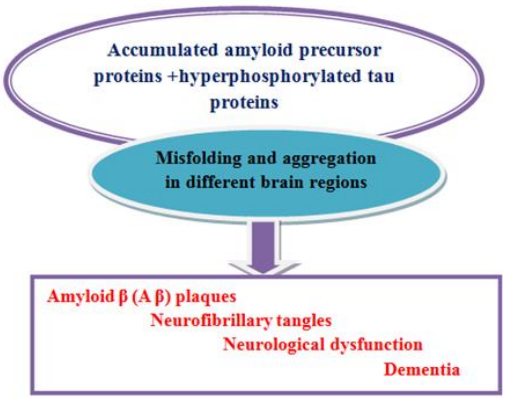

Fig- 2 Mechanisms of pathogenesis of Alzheimer's disease

Current therapy for Alzheimer's disease

There is extensive research undergoing in regard to development of disease modifying treatment strategies. Currently, the treatment available for the symptomatic form of the disease is to manage neurotransmitter disturbance, 3 cholinesterase inhibitors and memantine. In order to stop disease progression, the therapeutic agents are required to interfere with the steps involved with the symptoms appearance, amyloid β plaques deposition and formation of neurofibrillary tangle. Neuroprotective, anti-inflammatory, growth factor promotive, metabolic efficacious agents and stem cell therapy are other treatment strategies which are used to counter the steps involved in disease pathogenesis (Yiannopoulou and Papageorgiou, 2020). (Fig-3). Alzheimer's disease is the one of the most commonly occurring neurodegenerative disorder observed in age-dependent dementia. Due to lack of accurate underlying mechanism, currently there is no treatment for this disease (Guo et al., 2020).

In old age people, Alzheimer's disease (AD) is mainly characterized by continuous impairment in cognition, emotion, language and memory. Pharmaceutical formulations and cholinesterase inhibitors has been endorsement by FDA as a part of treatment for this disease. However, these medicines were found to be ineffective in removing pathogenesis of the disease and only improve patient's cognitive outcome. Therefore, the studies are required to search for better disease modification strategies. Clear knowledge of neuroprotective mechanisms, specific genes, antibodies and nanoparticles is required in order to design novel therapeutic options for Alzheimer's disease (Thoe et al., 2021). Recently, the development of novel treatment strategies for the disease is on increase with major emphasis on neuropsychiatric symptoms along with treatment of insomnia, psychosis, apathy and agitation. Many novel mechanisms are studied for designing treatment options targeting cognitive and behavioural targets (Cummings, 2021).

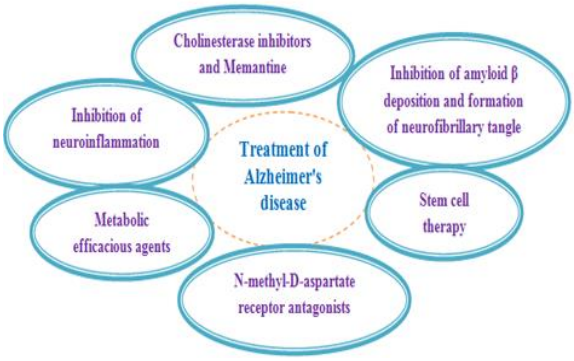

Fig-3 The treatment design to stop Alzheimer's disease progression.

Recent therapeutic options have incorporated many novel characteristics such as new biomarkers, neuropsychological outcomes and innovative trial designs. In future, various specific agents might be used for every patient in a manner where particular biomarkers containing a specific pattern of neuropsychological and neuroincomaging results will be used to design a highly specific treatment regimen within a customized therapeutic framework (Yiannopoulou and Papageorgiou, 2020).

The pharmacological therapy for Alzheimer's disease can be categorized into two categories viz; symptomatic and etiology based treatment. The symptomatic treatments include acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists. Etiology based treatments includes secretase inhibitors, tau and amyloid binders. There are several other nonphamacological ways such as exercise, mental challenges and socialization and balanced diet which can also be used for disease prevention (Mendiola-Precoma et al., 2016).

A cascade of pathophysiological events involves cellular signalling leading to various symptoms of

the disease. In United States, cholinesterase inhibitors are the main treatment options for mild to moderate state of disease while memantine has been recently approved in Europe for severe to severe cases of the disease. Other agents which have shown beneficial effects in clinical trials include, vitamin E, selegline, *Ginkgo biloba* extracts. The potential possible treatment options for future targeting multiple aspects of pathophysiological cascades include neurotrophic function and processing of amyloid and tau proteins (Tariot and Federoff, 2003). The cholinesterase inhibitors and memantine, do not change disease progression, but can be beneficial with some symptoms. However, the quantification of benefits of currently available treatments on cognition is difficult due to the associated unidentified adverse effects (Marasco et al., 2020).

Medicinal plants have been used in various medicine systems from ancient times for the treatment of a number of diseases. A number of herbs and herbal formulations have shown significant potential in improving brain functions and symptoms of Alzheimer's disease (John et al., 2022). The herbal therapy could be a novel treatment strategy for Alzheimer's disease as per the results obtained from clinical trials. The recent studies suggest that single herbs or herbal formulations may provide some complementary cognitive benefits to the approved drugs. Herbal formulations have several advantages with multiple target regulations as compared to single target antagonists. Several clinical trials using herbal formulations are being conducted in China for treating Alzheimer's disease (Tian et al., 2010).

The products based on herbal formulations have been used to treat behavioral and psychological symptoms of dementia. Based on the research studies, the herbs beneficial for Alzheimer's disease such as *Melissa officinalis*, Yi-Gan San, *Salvia officinalis* and *Ginkgo biloba* were identified. These were found useful for cognitive impairment and demonstrated good therapeutic efficacy (Santos-Neto et al., 2006). Some phytocompounds such as natural flavonoids have significant antioxidant, anti inflammatory and neuroprotective effects against neurodegenerative disorders. Ahmad and co-workers (2019), investigated the beneficial effects of fisetin against neurodegenerative diseases in animals. These results demonstrated that fisetin significantly reversed the LPS induced apoptotic neurodegeneration and improved hippocampal-dependent synaptic and memory functions in LPS treated mice (Ahmad et al., 2019).

The protective effect of natural compound fisetin has also been evaluated against d-galactose-induced oxidative, memory impairment and neuroinflammation in mice. These workers used natural compound against different models of neurodegenerative disorders. They found that this compound has prevented d-galatose mediated ROS accumulation by regulating Sirt1/Nrf2 signalling and suppressing activated *p*-JNK/NF-kB pathway. The study suggests that fisetin may be beneficial in neurodegenerative diseases (Ahmad et al., 2021). Worldwide the people's interest has increased towards complementary and alternative medicines (Jin et al., 2018). In conclusion, there are significant evidences on the use of single and complex herbal formulations for the treatment of Alzheimer's disease but still need further development in this area. There are various issues regarding the trial design in clinical studies of herbal medicines for dementia (Chang et al., 2016). (Table-1).

Table-1 Current therapy for Alzheimer's disease

Sr. No.	Treatment for Alzheimer's disease	Mechanism	References
1	Cholinesterase inhibitors and memantine	Management of neurotransmitter disturbance	(Yiannopoulou and Papageorgiou, 2020; Mendiola-Precoma et al., 2016).
2	Neuroprotective agents, anti-inflammatory agents, metabolic efficacious agents and stem cell therapy	Interfere with steps involved in disease progression	Yiannopoulou and Papageorgiou, 2020)
3	Secretase inhibitors, tau and amyloid binders. Exercise, socialization and balanced diet	Interfere with steps involved in disease progression Nonphamacological ways for disease prevention	(Mendiola-Precoma et al., 2016)
4	Vitamin E, selegline, *Ginkgo biloba* extracts	-	(Tariot and Federoff, 2003).
5	*Melissa officinalis*, Yi-Gan San, *Salvia officinalis* and *Ginkgo biloba*	Improvement of cognitive impairment	(Santos-Neto et al., 2006).
6	Fisetin	Prevention of d-galatose mediated ROS accumulation Reversal of LPS induced apoptotic neurodegeneration	(Ahmad et al., 2021) (Ahmad et al., 2019)

Therapeutic potential of *Cordyceps militaris* against Alzheimer's disease

The medicinal mushrooms are well known their tremendous health benefits and are used as a part of traditional medicine for many years (Wasser et al., 2010). These mushrooms contain various bioactive components which are known for their potential health benefits including immune-modulatory, hepatoprotective, antifibrotic, anti-inflammatory, antidiabetic, antiviral and antimicrobial effects (Asatiani et al., 2018). The very first study published on *in vivo* antitumour activity of fruiting bodies of the mushroom

belonged to Polyporaceae family (Ikekawa et al., 2001).

Cordyceps militaris is a type of medicinal fungi which is consumed by people all over the world and known for its nutritional benefits. The herbal formulations of this mushroom promote health and longevity (Kim et al., 2019). *Cordyceps militaris* is an overall tonic to the whole body as many studies revealed the effectiveness of this mushroom in boosting immunity, stamina, rapid recovery in bronchitis, and anticancer effects (Wu et al., 2020). These mushrooms are used as medicinal food in China and Southeast Asian countries for many years (Soltani et al., 2019).

Cordyceps militaris is known to exhibit anti-oxidant, and neuroprotective activities. He and co-workers (2018), evaluated the efficacy of this mushroom against Alzheimer's disease by administering ethanol extracts in $A\beta_{1-42}$-induced AD mice models. These workers observed that *Cordyceps militaris* extract supplementation has increased new route consciousness and novel object recognition, and taken less time to reach to hidden platform as compared to control group. Also the *Cordyceps militaris* extracts inhibited nitric oxide production and lipid peroxidation in the liver, kidney and brain of the mice. Therefore, their results demonstrated the protective role of *Cordyceps militaris* from cognitive impairment and progression of Alzheimer's disease (He et al., 2018).

In the another study conducted by Kim and co-workers (2019), the therapeutic and neuroprotective potential of *Cordyceps militaris* was investigated along with its promising benefits in ischemic brain neuronal injury, impairment of memory and learning in experimental rats Their findings revealed that *Cordyceps militaris* may be a promising mushroom for the neuroprotection of hippocampus and recovery of neuroinflmmation (Kim et al., 2019).

Oxidative stress is induced by over production of reactive oxygen species (ROS), hydroxyl (·OH), nitric oxide (NO) and hydrogen peroxide (H_2O_2). The oxidative stress created by reactive oxygen species may damage glial cells of nervous system. He and co-workers (2019), investigated antioxidant and neuroprotective effects of *Cordyceps militaris* extract in H_2O_2-induced C6 glial cells. These workers revealed that *Cordyceps militaris* has significant free radical scavenging activity and protective effect against (H_2O_2) (He et al., 2019).

The main bioactive compound cordycepin found in this mushroom is an adenosine analogue and is known to improve cognitive function. This compound and its receptors such as A1 and A2A receptors also reported to have role in learning and memory. Cao and co-workers (2018), investigated the beneficial effects of cordycepin in short term spatial memory through spontaneous alternation behaviour test. These workers found that oral dosages of cordycepin significantly enhanced the relative alteration of mice without changing hippocampal denosine level, body and hippocampus weight. Their study suggested that cordycepin exhibited nootropic effects via A2A receptor modulation in hippocampus and therefore this compound may be helpful in improvement of cognitive function (Cao et al., 2018).

Lee and co-workers (2011), evaluated the beneficial effects of Cordyceps militaris on neurite outgrowth in neuro2A mouse neuroblastoma cells and scopolamine induced memory and learning impairment in rats. These workers found that pre-treatment with Cordyceps militaris was effective to stimulate primary neurite sprouting and extention of 2A cells in a dose dependent manner. Cordyceps militaris was also found to increases choline acetyltransferase expression in differentiated Neuro 2A cells. It has been observed that this mushroom significantly reversed the scopolamine induced memory impairment and effective in protection against memory related neuronal degeneration in brain (Lee et al., 2011)

Yuan and co-workers (2018), explored the mechanisms via which *Cordyceps militaris* improve memory and learning in mouse model. The gene involved in signalling pathways were also screened by using an mRNA expression profile chip. These workers suggested that polypeptide found in *Cordyceps militaris* may help in the improvement of learning and memory in scopolamine induced mouse model (Yuan et al., 2018). The possible protective effects of *Cordyceps militaris* has been summarized in Table-2.

Table-2 Protective effects of Cordyceps militaris against Alzheimer's disease

Sr. No.	Protective mechanisms of *Cordyceps militaris*	References
1	Increased new route consciousness and novel object recognition Inhibition of nitric oxide production and lipid peroxidises	(He et al., 2018)
2	Benefits in ischemic brain neuronal injury Improvement of learning and memory impairment	(Kum et al., 2019)
3	Free radical scavenging activity	(He et al., 2019)
4	Nootropic effects via A2Areceptor modulation	(Cao et al., 2018)
5	Stimulation of primary neurite sprouting and extention of 2A cells Increased Choline acetyltransferase expression	(Lee et al., 2011)
6	Improvement of learning and memory by peptides and polypeptides of *Cordyceps militaris*	(Yuan et al., 2018; Wu et al., 2022).

It is demonstrated by several workers that the management of neuroinflammation related Alzheimer's disease can be regulated by gut microflora. Wu and co-workers (2022), obtained new selenium peptides (Se-Ps), VPRKL (Se) M (Se –P1) and RYNA(Se)MNDYT (Se-P2) which have neuroprotective effects were obtained from Se enriched *Cordyceps militaris.* These Se-Ps peptides exerted significant antioxidant, anti-inflammatory and regulating properties on gut microflora and therefore, this peptide could be an effective dietary supplement in prevention of Alzheimer's disease (Wu et al., 2022).

In a study conducted by He and co-workers (2021), the neuroprotective mechanisms of *Cordyceps militaris* was investigated in the brain of $A\beta_{1-42}$–injected AD mice. These workers observed that oral administration of *C. militaris* inhibited acetylcholinesterase activity at 100 and 200 mg/kg concentrations. Amyloid precursor protein levels were also down regulated with a decrease in β-secretase activity by this treatment. Also, the treated mice demonstrated inactivated inflammatory responses via downregulation of inducible nitric oxide synthase and expression of cyclooxygenase-2 protein (He et al., 2021).

Nallathambya and co-workers (2015), evaluated the solvent extracts of *Cordyceps militaris* stroma powder for cell viability and inhibition of nitric oxide production in LPS triggered BV2 microglia cells. These workers observed that BV2 cells demonstrated no cytotoxicity with the treatment of ethyl acetate fraction and sub fraction CE3 at 0.1µg/mL–100 µg/mL concentrations. It has been found that ergosterol was the major compound in sub fraction CE 3 (Nallathambya et al., 2015).

Govindula and co-workers (2021), highlighted the neuroinflammatory targets of bioactive compound cordycepin in depression, Alzheimer's and Parkinson's disease. Cordycepin acts by inhibition of microglial activation, down regulation of adenosine A2 receptor and subsequent inhibition of several neuroinflammatory markers such as NF-κB, NLRP3 inflammasome, IL-1β, iNOS, COX-2, TNF-α, and HMGB1. Cordycepin decrease LPS-mediated toll-like receptor activation by activating adenosine receptor A1 and hence improve level of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase. These possible anti-neuroinflammatory mechanisms of cordycepin could help in the development of novel therapeutic strategies against neuroinflammation associated central nervous system disorders (Govindula et al., 2021). The inhibitory adenosine A1 receptor (A1R) and excitatory A2A receptor (A2AR) are generally expressed in the brain. The A2AR are mainly implicated in normal aging and has a role in enhancing neurotoxicity in multiple neurodegenerative disorders. The adenosine 1 receptor signalling increases A2AR-mediated neurodegeneration and therefore it may be a great target for the future development of neuroprotective drugs (Stockwell et al., 2017). (Fig-4).

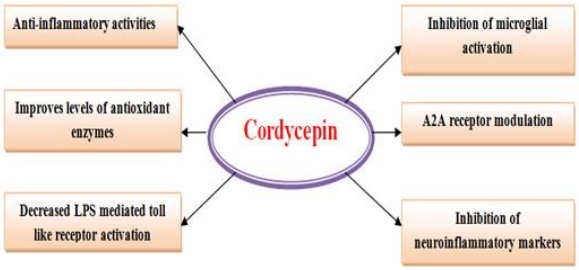

Fig-4 Anti-neuroinflammatory mechanisms of cordycepin.

The traumatic brain injury (TBI), is highly sensitive to neuroinflammation. Wei and co-workers (2021), demonstrated that cordycepin administration ameliorated long term neurological deficits and minimized tissue loss in TBI mice. It has been reported that cordycepin can inhibit TBI-induced neuroinflammation. These workers revealed that cordycepin treatment inhibited microglia/macrophage proinflammatory polarization and triggered anti-inflammatory polarization after traumatic brain injury. Their results demonstrated significant potential of cordycepin in improvement of quality of life of patients with traumatic brain injury (TBI) (Wei et al., 2021).

Cordycepin have shown neuroprotective effects against excitotoxic neuronal death. Although the direct electrophysiological evidence in support of cordycepin's benefit in Alzheimer's disease (AD) is unclear. Li-Hua and co-workers (2019), studied the electrophysiological mechanisms associated with the potential protective effect of cordycepin against the excitotoxic neuronal insult in Alzheimer's disease with whole-cell patch clamp techniques. Their results

revealed that cordycepin delayed AβAβ + IBO-induced excessive neuronal membrane depolarization. The inhibitory effect of cordycepin against the AβAβ + IBO-induced excitotoxic neuronal insult through attenuating excessive neuronal activity and membrane depolarization also strengthen the protective and therapeutic potential of cordycepin in Alzheimer's disease AD (Li-Hua et al., 2019).

Summary and Conclusion

There is continuous increase in the cases of Alzheimer disease which is a neurodegenerative disorder and mainly affects old age individuals. The current therapies available for the treatment of this disease are capable of providing only symptomatic relief. Therefore, there is a great requirement of designing treatment strategies which can help to stop disease progression via targeting pathways involved in pathogenesis of the disease. Recently there is an increase in the development of novel drugs based on herbal formulations due to their bioavailability and lesser side effects. *Cordyceps militaris* is a medicinal mushroom which contains a number of bioactive compounds having tremendous health benefits. Cordycepin is one of the main bioactive compounds found in these mushrooms which in various studies demonstrated anticancer, antioxidant, anti-inflammatory, immunomodulatory and neuroprotective effects. *Cordyceps militaris* helps in the improvement learning and memory impairment in the patients of Alzheimer disease. The recent studies revealed that cordycepin has free radical scavenging activity, exerts nootropic effects via A2A receptor modulation and benefits in ischemic brain neuronal injury. This compound also found to stimulate primary neurite sprouting along with increased choline acetyltransferase expression. Therefore, due to the significant protective potential of *Cordyceps militaris* against this neurodegenerative disorder, this mushroom could help in the development of novel treatment strategies.

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