Review Article

Neuropharmacological and Cognitive Effects of *Celastrus paniculatus* – A Comprehensive Review

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ABSTRACT

Celastrus paniculatus (CP) has been used for thousands of years in Indian system of medicine, Ayurveda. It is referred to as *Jyotishmati* and as the name suggests, boosts intelligence. Seed and seed oil are the most used parts of this deciduous plant and oral and intranasal routes are most preferred for delivering this drug in Ayurveda. Studies in laboratory animals have shown CP improves intellect and memory and is beneficial in neurodegeneration. Clinical studies in mentally retarded children have also shown that it enhances the Intelligence quotient. CP also ameliorates stress associated cognitive dysfunctions. The herb possesses antioxidant, free radical scavenging and neuroprotective activity. This manuscript reviews current information on the neuropharmacological effects of *Celastrus paniculatus* (CP) in different neuropsychiatric conditions.

Keywords: Antioxidant, *Celastrus paniculatus*, Cognition, Neurodegeneration.

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INTRODUCTION

Natural compounds have been used abundantly since prehistoric times to treat a range of diseases, more so in India with its vibrant holistic system of Ayurveda. With its repertoire of more than 1500 botanical species of medicinal value, Ayurveda has the potential to provide a wide variety of herbs for prospective drug development for most disease conditions. One such important medicinal herb used in Ayurveda is *Celastrus paniculatus* (CP), also known as '*Jyotishmati*' in Sanskrit and Intellect tree in English. *Celastrus paniculatus* Willd. a woody climber belongs to the Celastraceae family and grows throughout India. While it is widely used in Ayurveda for different conditions, it is most famous as a '*medhya rasayana*' meaning intellect enhancer/ rejuvenator.[1-2] '*Medhya*' is also another name for '*Jyotishmati*'.[3] Different parts of the plant are used for medicinal purposes including bark, leaf and most importantly seed and seed oil.[4] *Jyotishmati* is also used by different tribal communities to treat variety of conditions including wound healing, sedative, abortifacient, bronchodilator and antidote for opium poisoning.[5]

In this review, we selected relevant articles in English language from biomedical databases PubMed and Google scholar till May 2020 using keywords '*Celastrus paniculatus*'; '*Celastrus paniculata*' and 'neuro'; and '*Celastrus paniculatus*' and 'memory'; and other related terms. The titles and abstracts were screened for relevance. The screened articles were imported to Mendeley reference software and duplicates were removed. The articles selected thus have been reviewed and summarized.

Ayurveda pharmacology of CP

Ayurveda describes pharmacokinetics and pharmacodynamics of a herb in terms of taste (*rasa*), potency (*virya*), post-digestive effect (*vipaka*), qualities (*guna*) and special effect (*prabhava*) (Charaka Samhita, Sutra sthana, Chapter 26, Verse 71-73).[6] These are unique concepts in Ayurveda which can potentially be applied to all living things that are a source of food and medicine in this world.[7] CP is described as being pungent (*katu*) and bitter (*tikta*) in taste, piercing in quality (*teekshna*), hot in potency (*ushnaveerya*), pungent post-digestion (*katuvipaka*), with special effect of boosting the intellect (*medhya*). It improves cognition, memory, digestion, relieves constipation, aids wound healing and is also prescribed for anemia like conditions, liver disorders, certain skin diseases and arthritis.[4] A wealth of new information may be revealed by integrating these ethnopharmacological concepts into current herbal drug discovery research.

Photochemistry of CP

The chemical constituents of *Celastrus paniculatus* include triglycerides palmito oleo palmitin, palmito oleo stearin, palmito diolein, palmito oleo linolein, stearodiolein, triolein and dioleolinolein; sesquiterpene alkaloids celapanin, celapanigin, celapagin; quinone-methide and phenolic triterpenoids celastrol, pristimerin, zeylasterone

and zeylasteral.[8-12] Previous studies have demonstrated the beneficial effects of *Celastrus paniculatus* in different diseased condition. The neuropharmacological effects of CP include *in-vitro* and *in-vivo* studies; behavioral, neurochemical, cellular and molecular studies are covered in this review.

Rejuvenative activity

Ageing is a natural, unavoidable and permanent loss of capability to combat diseases with progressive reduction in both physiological and cognitive functions which leads to death.[13-14] Ayurveda recommends *Rasayana*, rejuvenative measures to impart nourishment in geriatric problems.[15] A recent study indicated that CP acts as rejuvenator by extending lifespan in *Caenorhabditis elegans*. New polyesterified dihydro-β-agarofurans, celaspaculins from seeds of CP remarkably enhanced the average survival time of *C.elegans*.[16]

Neuroprotective activity

Neurodegenerative diseases are characterized by gradual loss of neuronal structure and function.[17-18] Excitotoxicity due to disruption of glutamate transmission through NMDA receptors increases Ca^{2+} influx which in turn activates number of molecular mechanisms. This includes mitochondrial membrane depolarization, caspase activation, generation of reactive oxygen and nitrogen species, and finally neuronal death.[18] CP along with other herbs like *Centella asiatica* and *Curcuma longa* have been reviewed for their neuroprotective effect.[19] Godkar and colleagues demonstrated that CP treatment protected primary forebrain culture against glutamate-induced neuronal toxicity by inhibiting NMDA receptor activated whole cell currents.[20-21]

Kainic acid is a glutamate receptor agonist and potentially causes neurotoxicity.[22-23] *Celastrus paniculatus* treatment for two weeks protected rats from kainic acid induced neurodegeneration. Treatment resulted in behavioral recovery in shuttle box and Morris water maze tests. In addition, corticosterone and cholinesterase levels were restored.[24] Methanolic extract of CP whole plant showed antiepileptic activity in mice. Both isoniazid and pentylenetetrazole induced epileptic seizures reduced after CP treatment.[25] Cholinergic neurotransmission plays an important role in memory formation.[26-27] Scopolamine, a muscarinic cholinergic receptor antagonist, causes learning and memory impairment by modulating cholinergic neurotransmission in brain.[28-29] Spatial navigational memory impairment in Morris water maze task induced by scopolamine in rats was alleviated by CP treatment.[30] The water extract of CP seed protected sodium nitrite induced amnesia by improving the animal's performance in passive avoidance and elevated plus maze tests. This memory enhancement was correlated with altered cholinergic activity in the brain.[31]

Substantial evidence indicates increased oxidative stress, neuronal degeneration and neuronal death in neurodegenerative diseases including Alzheimer's disease.[32-33] Methanolic extract of CP seeds exhibited powerful antioxidant activity in DPPH radical scavenging assay, by inhibiting total reactive oxygen species. The extract also significantly inhibited the activity of both acetylcholinesterase and butylcholinesterase enzyme *in vitro*, thus showing anti-cholinesterase activity.[34-35] Water soluble extracts from CP seeds protected enriched forebrain primary neuronal cell cultures from H_2O_2 induced neuronal death. The extract decreased lipid peroxidation, increased catalase activity and showed antioxidant activity against reactive oxygen species.[36]

Environmental stress like hypobaric hypoxia causes spatial memory impairment, hippocampal neuronal dendritic atrophy and oxidative stress.[37-38] Interestingly, CP treatment restored spatial working memory impairment in T-maze task in hypoxic animals (Vijaykumar, Bhagya, and Shankaranarayna Rao, 2020, Unpublished data). 3-nitropropionic acid (3-NP) produces Huntington's disease like symptoms in animals by lipid peroxidation and increasing free radical generation in the brain which results in neuronal toxicity.[39] CP treatment improved cognitive function as indicated by decreased transfer latency and increased time spent in quadrant in 3-NP rats. Behavioral improvement was substantiated with improved antioxidant status and reduced lipid peroxidation.[40]

Ageing is also accelerated by exposure to different environmental neurotoxic agents like aluminium. Aluminium poisoning resulted in memory impairment and dementia with neurological decline.[41-43] *Celastrus paniculatus* seed extract counteracted aluminium induced neurotoxicity in the hippocampus, cerebral cortex and cerebellum. Treated group showed a significant decrease in the level of lipid peroxidation and enhanced antioxidant activities of superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase when compared with aluminium exposed group.[44] CP oil treatment prevented aluminium-induced spatial memory decline in Morris water maze task and restored retention memory in passive avoidance test. Memory improvement was associated with restoration of acetylcholinesterase activity and neurodegeneration in the hippocampal neurons.[45]

Ageing is associated with altered trace elements like copper, zinc and iron in the brain and is hypothesized to precipitate neurodegeneration and thereby, related diseases.[46-49] Treatment with CP resulted in restoration of these trace elements in aged rats. CP significantly enhanced the activity of copper, zinc and iron in late-aged animals.[50] Crude oil extract of CP seed also showed significant increase in phospholipids and proteins, possibly contributing to the increase in myelination in the cerebellum of healthy Wistar rats.[51]

Neurobehavioral activity

Jyotishmati has been analysed early on for its phytochemical constituents and effect in treating different brain disorders.[52-55] *Celastrus paniculatus* had also shown sedative and tranquilizing activity.[56-58] *Celastrus*

paniculatus plant extract shortened onset of action in pentobarbitone induced sleeping time, extended the total duration of sleep and showed anxiolytic activity in staircase test in mice.[59] Gaitonde and colleagues discussed the use of CP seed and seed oil in Ayurveda for improving intelligence and enhancing memory.[57] *Celastrus* oil improved cognitive function and memory process in rats.[60-62] CP enhanced passive avoidance learning and memory, decreased biogenic amines noradrenaline, dopamine and serotonin levels in brain.[63] In mentally retarded children, CP oil administration improved their intellectual quotient (IQ).[64] CP oil improved spatial learning and memory performance of male Wistar rats in partially baited radial arm maze.[65] *Jyotishmati* oil treatment resulted in antidepressant activity in mice, reduced monoamine oxidase activity and corticosterone levels.[66] Petroleum ether extract of CP seeds reduced immobility time in forced swim and tail suspension tests. The extract reversed reserpine-induced catalepsy behavior and improved grooming, rearing behaviour in rodents.[67-68]

Petroleum ether extract of CP seeds at dose level of 3.2 g/kg/day for 5 days showed anti-anxiety activity and significant inhibition of punishment related and reward related suppression of operant behavior in rats.[69] *Celastrus* oil displayed significant anti-anxiety activity in rats and reversed anxiolytic effect of buspirone, a 5 HT1A receptor partial agonist in the open field test. This indicates the mechanism of CP oil on anxiety may be through the modulation of serotonergic neurotransmission.[70] CP oil mixed with equal amounts of ghee showed significant enhancement of spatial and fear memory as assessed by elevated plus maze and passive avoidance tests in scopolamine induced amnesia in rats.[71]

Recent *in-silico* study demonstrated that bioactive components from CP has better biological, pharmacokinetic and molecular dock score against selected dihydroxyphenylalanine (DOPA) genes involved in the Schizophrenia compared to clozapine.[72] New chemical entity 3-(3,4-dimethoxy phenyl)-1-4(methoxy phenyl) prop-2-en-1-one extracted from *Celastrus paniculatus* has highest binding score for dopamine and serotonin receptors. Ketamine-induced increase dopamine, serotonin and norepinephrine levels in the hippocampus, cerebral cortex and cerebellum restored by this bioactive compound.[73-74] These studies show that *Celastrus paniculatus* has neuroprotective activity schizophrenia conditions.

Prolonged stress results in behavioral depression.[75-76] *Celastrus paniculatus* showed adaptogenic activity in different animal models. CP oil showed antidepressant activity in chronic unpredictable mils stress model by reducing immobility time in forced swim test and restoring sucrose preference in stressed animals. This behavioral recovery was associated with reduction in monoamine oxidase-A (MAO-A) activity and corticosterone levels in whole brain.[77] Previously, we have shown that CP ameliorated chronic restraint-induced spatial learning and memory impairment in partially baited radial arm maze and T-maze tests. Also, CP reduced anxiety-like behavior in these stressed rats.[78] *Celastrus paniculatus* treatment for two weeks completely restored hippocampal dendritic atrophy, acetylcholinesterase activity and synaptic plasticity in stressed rats. CP restored acetylcholinesterase levels in frontal cortex, hippocampus, septum and hypothalamus. At cellular level, CP improved hippocampal CA1 long-term potentiation in stressed rats. Stress-induced dendritic atrophy in hippocampal neurons are restored by CP treatment (Bhagya, Sneha and Shankaranarayana Rao, 2020, Unpublished data). Lekha and colleagues demonstrated antioxidant effect of *Jyotishmati* oil in immobilization stress induced oxidative stress. Treatment restored the antioxidant activities of superoxide dismutase, catalase and glutathione S-transferase enzymes.[79]

Summary

Herbs sourced from nature are an important source for drug development and offer unlimited prospects for treating neuropsychiatric and neurodegenerative diseases. *Celastrus paniculatus* is an herb used to treat various neuropsychiatric conditions in Ayurveda. This review summarizes current evidence on the beneficial effects of CP on the central nervous system. This herb acts at multiple levels and improves neuronal function by enhancing antioxidant status, modulating neurotransmitter levels, and promoting neuronal plasticity. It warrants further exploration into its potential for preventing and managing diverse neuropsychiatric conditions.

Ethical consideration

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Conflict of interest

None.

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