

Potential neurological applications of *Centella asiatica*: a brief review

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<https://doi.org/10.22146/ijpther.1693>

ABSTRACT

Submitted: 17/04/2021
Accepted : 15/11/2021

Keywords:

Centella asiatica;
neurological condition;
stroke;
epilepsy;
Alzheimer's disease;
Parkinson's disease;

Centella asiatica (*C. asiatica*) or gotu kola has been used traditionally in many Asian countries as herbal medicines for many conditions, such as headache, asthma and memory enhancement. *Centella asiatica* has been also widely investigated for its neuroprotective effects in animal disease model including epilepsy, Alzheimer's and Parkinson's diseases. A brief review of neurological effects studies of *C. asiatica* in animal model was reported. Eligible studies published through December 2020 from PubMed and EMBASE journal data base were collected. Any keywords related to *C. asiatica* or gota kola AND neurological conditions were used. The results showed that several experimental studies concerning the neuroprotective properties of *C. asiatica* have been reported. Phytochemical studies reported that *C. asiatica* contained many bioactive compounds in which triterpenoids are the most identified. Furthermore, the triterpenoids have proven to have neuroprotective effect due to their effects of anti-inflammatory, antioxidant, improvement of mitochondrial dysfunctions, and increased brain-derived neurotrophic factors. Further studies are needed to investigate the neuroprotective mechanisms of *C. asiatica*. In conclusion, *C. asiatica* might have potential as an alternative medicine for neurological conditions, such as stroke, epilepsy, Alzheimer's and Parkinson's disease.

ABSTRAK

Centella asiatica (*C. asiatica*) telah digunakan secara tradisional di banyak negara di Asia sebagai obat herbal untuk berbagai kondisi, seperti nyeri kepala, asma, serta untuk memperkuat ingatan. *Centella asiatica* juga banyak dikaji efek neuroprotektifnya pada model hewan coba seperti penyakit epilepsi, Alzheimer dan Parkinson. Telaah secara singkat penelitian efek neuroprotektif *C. asiatica* pada hewan coba telah dilaporkan. Penelitian yang memenuhi kriteria yang dipublikasi hingga Desember 2020 dari data base jurnal PubMed dan EMBASE dikumpulkan. Kata kunci *C. asiatica* atau *gota kola* DAN *neurological conditions* digunakan. Hasil telaah menunjukkan penelitian eksperimental mengenai efek neuroprotektif telah dilaporkan. Penelitian fitokimia melaporkan *C. asiatica* mengandung banyak senyawa bioaktif dengan senyawa terpen sebagai senyawa terbanyak. Selanjutnya senyawa triterpenoid terbukti mempunyai efek neuroprotektif karena efeknya sebagai antiinflamasi, antioksidan, perbaikan disfungsi mitokondria dan peningkatan *brain-derived neurotrophic factor* (BDNF). Penelitian lanjut diperlukan untuk mengkaji mekanisme neuroprotektif *C. asiatica*. Dapat disimpulkan, *C. asiatica* mempunyai potensi sebagai obat alternative untuk gangguan saraf seperti stroke, epilepsi, Alzheimer dan Parkinson.

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INTRODUCTION

Centella asiatica, also known as gotu kola or asiatic pennywort or pegagan in Indonesia, is belong to genus *Cetella*, Mackinlayoideae subfamily and Apiaceae family. *Centella* comprises approximately 53 species which is commonly grow in South East Asia regions, India, Japan, China, Taiwan and Korea. *Centella asiatica* is well known as medicinal plant which traditionally used to treat various conditions such as headache, body ache, asthma, memory enhancement and other illness. It also has been used for food as a vegetable salad, or in juices, in several Asian countries.¹

Various active compounds have been isolated from *C. asiatica*. It contains triterpenoids centelloids such as madecassic acid, asiatic acid, madecassoside and asiaticoside. *Centella asiatica* also contains flavonoid derivatives such as quercetin and kaempferol. Other active found in *C. asiatica* are chlorogenic acid, polyacetylenes (e.g. cadinol, acetoxycentellinol, and asiaticin), vanillic acid, p-coumaric acid, o-coumaric acid, and transcinnamic acid, sterols (e.g. 11-oxoheneicosanil-cyclohexane, dotriacont-8-en-1-oic acid), phenolic acids (e.g. p-hydroxybenzoic acid), and polysaccharides (e.g. centellose).^{2,3}

Preclinical studies reported that *C. asiatica* has several biological activities such as anti-inflammatory, antimicrobial, antifungal, antidepressant, antioxidant, anticancer effects.⁴ *Centella asiatica* has been well studied and documented as neuroprotective effects including epilepsy, Alzheimer's and Parkinson's diseases. In this brief review, we reported the neurological effects of *C. asiatica* in animal disease model.

MATERIALS AND METHODS

A systematic review concerning the neurological effects of *C. asiatica* in animal disease model was performed.

Eligible studies obtained from PubMed and EMBASE journal database published until December 2020 were gathered. Any keywords related to "*Centella asiatica*" (e.g.: "gotu kola") and neurological conditions (e.g.: stroke, epilepsy, neurodegenerative) were used for literature search. The results were then filtered only included studies in animal model. The process of selecting the studies was plotted in a flow diagram based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.⁵

RESULT AND DISCUSSION

Possible mechanisms for neuroprotective properties of *C. asiatica*

Sun *et al.*⁶ suggested four possible mechanisms of action for neuroprotection properties of *C. asiatica*, based on experimental studies of *C. asiatica* in Parkinson's disease (PD) and Alzheimer's disease (AD). *Centella asiatica* may exert its neuroprotective effects due to its anti-inflammatory effects, reduction of oxidative stress, improvement of mitochondrial dysfunctions, and increased brain-derived neurotrophic factors (BDNFs).

Neuroinflammation processes and inflammatory cytokines have been associated with neurodegenerative lesions. In Alzheimer's disease (AD), neuroinflammatory cytokines induce β -amyloid neurotoxicity through modulating amyloid precursor protein levels and metabolism.⁷ The pathology of AD is characterized by the accumulation of β -amyloid containing neuritic plaques and neurofibrillary tangles.⁸ Neuroinflammation is also the hallmark in the pathogenesis of PD.

Activation of glial cells and increases of pro-inflammatory cytokines has been reported in studies of PD. Activated astrocytes and microglia release pro-inflammatory cytokines that may be detrimental for neurons and exacerbate degeneration of AD

neurons in substantia nigra pars compacta.⁹ Neuroinflammation and neurodegenerative lesions lead to synaptic dysfunction and neuronal death in AD and PD.¹⁰ *Cetella asiatica* has been reported to significantly attenuate NO, TNF- α , and free radicals in LPS-stimulated microglial cells. It is suggested that *C. asiatica* may exert its anti-inflammatory effects through inactivation of PI3K/AKT and ERK1/2 signaling pathway that in turn inhibits NF-kB activation.¹¹

The brain has a high oxygen consumption but poor antioxidant system. Therefore, it is susceptible to oxidative stress, especially the hippocampus and cortical regions. Problems in cholinergic channeling in the cortical areas and regions of hippocampal have been associated with cognitive disorders. Increased AChE activity is associated with increased acetylcholine breakdown, which in turn leads to cholinergic dysfunction that manifests as cognitive deficits. It is postulated that, *C. asiatica* exerts its neuroprotective properties by modifying superoxide dismutase (SOD), reduced glutathione (GSH) and protein carbonyl (PC) activities, as well as lowering the AChE activity which improves cholinergic transmission.¹²

Shinomol *et al.*¹³ evaluated the activity of *C. asiatica* in ameliorate the neuronal oxidative distress in rodents of prepubertal age. Male mice were fed with a *C. asiatica* diet (with a dose of 0.5 and 1%) for 4 weeks, and oxidative stress in brain regions were measured. The mice fed *C. asiatica* showed significant reduction of malondialdehyde (3-50%), reactive oxygen species/ROS (32-42%) and hydroperoxide (30-35%) levels, which was accompanied by increased antioxidant enzyme activities in all brain regions. Furthermore, the aqueous extract of *C. asiatica* showed significant free radical scavenging activity and ameliorated the 3-NPA induced oxidative stress response in brain mitochondria under *in vitro* exposure. Taken together, these data suggest that *C. asiatica* has the propensity to ameliorate oxidative

impairments in the brain and it may have neuroprotective properties in response to oxidative stress.

Antioxidant properties of *C. asiatica* may due its effect on glutathione level. Glutathione is an antioxidant and found as reduced forms intracellularly. Glutathione is a free radical scavenger and reacts with a wide variety of free radicals. Lower GSH level and glutathione-S-transferase has been associated with the increase of free radical levels and weaker glutathione systems in face of oxidative stress. Administration of *C. asiatica* may restore GSH level that in turn increase glutathione-S-transferase activity.¹⁴ A study found that treatment with *C. asiatica* was associated with increased glutathione level compared with controls in rats of an AD model.¹⁵

Another *in vitro* and *in vivo* study were performed to assess the effect of ethanolic extract of *C. asiatica*. SH-SY5Y cells treated with cent *C. asiatica* showed significant reduction in the AChE activity in a dose-dependent manner. A similar result was also found in an experimental study of neuroinflammation with Sprague Dawley rats' model.¹⁶

Centella asiatica may also modify mitochondrial function. Mitochondria are organelles that perform aerobic respiration to generate energy for cellular functions. Mitochondrial dysfunction has been associated with the development of neurodegenerative diseases. Previous studies reported that mitochondrial dysfunction is a trigger or propagator of neurodegenerative processes. Therefore, it can be postulated that treatments that target mitochondrial dysfunction may prevent *C. asiatica* may modify mitochondrial activity, increase the expression of mitochondrial enzymes and increase its content. These results suggested the possibility of *C. asiatica* having beneficial effects on mitochondrial activity. It is noteworthy that *C. asiatica* also had beneficial effects on mitochondrial function in the absence of A β , suggesting broader potential application of *C. asiatica* outside AD and PD.¹⁷

BDNF plays important roles in neuron maintenance, survival, and neurotransmitter regulation. BDNF promotes synaptic growth and is involved in learning and memory processes. Its level is reduced in the brain of neurodegenerative disease patients. It is suggested that abnormal BDNF levels may be the result of chronic inflammation in the brain.¹⁸ *Centella asiatica* increased the BDNF concentration in the hippocampal region. *Centella asiatica* treatment may up-regulate BDNF protein and mRNA expression.¹⁹

Jiang *et al.*²⁰ speculated that asiatic acid and madecassic acid had significant effect of induction on both neurofilament expression of NF68 and NF200 neurite outgrowth. NF68 is a representative marker for the early stage of differentiation neurons, while NF200 is a marker for neuron differentiation of the latter stage. They also suggested that the combination of asiatic acid and madecassic acid induces neuronal differentiation partially through mediating the MEK signaling pathways.

Experimental models of neuroprotective effects

Cognitive impairment

Rao *et al.*²¹ investigated the nootropic effect of *C. asiatica* in mice. Administration of *C. asiatica* for fifteen days in 3-months old mice was associated with better learning and memory performance. Results from the radial arm maze test showed an increased number of correct entries in a dose-dependent manner. They also treated another group of newborn mice with *C. asiatica* for 15 days [from day 15 to day 30 postpartum (p.p.)] and were compared with a control group after 1 and 6 months p.p. The treatment group had significantly better results in hole board tests and radial arm maze, but not in locomotor activity. Administration of *C. asiatica* was also associated with increased hippocampal acetylcholine esterase activity. Histologic

studies found increased arborization of hippocampal CA3 neurons at one month and 6 months time points. Taken together, these results suggested that *C. asiatica* treatment during the postnatal developmental stage may affect the neuronal morphology and promote higher brain function.

Another study reported that *C. asiatica* extract improved age-related cognitive impairment in mice. In the study, 20 month-old CB6F1 mice were treated with *C. asiatica* extract (2 mg/mL) for 2 weeks before behavioral testing. The authors found better performance in memory and executive function. Histology examination revealed increased synaptic density in the hippocampus, increased expression of NRF2 and porin as antioxidant and mitochondrial markers, respectively.²²

Thong-asa *et al.*²³ studied cognition and its relation to the effect of *C. asiatica*. They studied hippocampal pathology as a model of dementia in mild chronic cerebral hypoperfusion (CCH). CCH was induced by permanent right common carotid artery occlusion (RCO). *Cetella asiatica* ameliorate learning ability deficit in 2 and 12 months after CCH. They also found that *C. asiatica* ameliorated damages in neuron of the dorsal hippocampus at 2 months after CCH if treatment started 24 hours post-CCH. After 12 months, improvement in memory and learning were reported, as well as reduction in dentate gyrus neuronal damage.

Firdaus *et al.*¹² analyzed the neuroprotective effect of *C. asiatica* against the D-gal-stimulated aging rat model. They found that *C. asiatica* improved behavioral and cognitive functions, and prevented neurodegeneration in these animal subjects. *Centella asiatica* supplementation may counter behavioral deficits through several possible mechanisms, either by improving spatial memory, reducing anxiety, or improvement in coping behavior and locomotor activity.

Epilepsy

Epilepsy is a common burden on chronic neurological disorder. It is characterized by unprovoked and spontaneous seizures. A study used pentylentetrazol (PTZ) in rats to cause epileptic seizures, as well as increase ACh and inhibit AChE in all brain regions. They reported anticonvulsant effects of *C. asiatica* against PTZ-induced seizures. Increased acetylcholine content and reduced acetylcholinesterase activity were recorded in a number of brain regions during PTZ-induced seizures. Meanwhile, animals pretreated with *C. asiatica* extracts had higher acetylcholine and acetylcholinesterase levels. These findings suggested that *C. asiatica* may have beneficial effects in the cholinergic system that explained its anticonvulsant.²⁴

Stroke

A study conducted by Lee *et al.*²⁵ using multiple stroke models in rats suggested that asiatic acid caused significant reduction in infarct volume and improved neurological outcome. Similar results were still found even when *C. asiatica* was administered up to 12 hours after ischemia onset. The treatment was reported effective against multiple focal ischemia models. It was also suggested that treatment with *C. asiatica* had a long therapeutic time window. The beneficial effects of asiatic acid in post-ischemic lesion may be mediated through its protective effects on mitochondria and inhibition of matrix metalloproteinase-9 induction and activation.

Tabassum *et al.*²⁶ investigated the effects of *C. asiatica* on ischemic stroke. They used Wistar rats treated with transient focal middle cerebral artery occlusion (MCAO). Before occlusion, these rats were pretreated with *C. asiatica* extract for 21 days. The animals were then subjected to right MCAO for 2 hours, followed by 22 hours of reperfusion. Rats pretreated with *C. asiatica* had better neurobehavioral activity and reduced infarction volume

as well as better histological brain morphology, compared to control animals. Furthermore, supplementation with *C. asiatica* in the MCAO group was associated with lower thiobarbituric acid reactive species, higher glutathione content and antioxidant enzymes in a dose-dependent manner.

Alzheimer's and Parkinson's disease

The AD and PD are the two most common neurodegenerative disease, characterized by cognitive and motoric function degeneration due to loss of neuronal cells. Asiatic acid, a triterpenoid component of *C. asiatica*, may have potential for treatment of AD. Asiatic acid may have protective effects against various pathological features of AD. A study of AD model, using aluminum chloride (AlCl₃)-induced amyloid pathology, found that AlCl₃ treatment for 6 weeks was associated with significant reduction in spatial memory performance, anxiety, and motor dysfunction, as well as reduced expression of cyclin-dependent kinase 5 (a marker of tau proteins phosphorylation), pTau, oxidative stress, and apoptosis. Pretreatment with asiatic acid for 7 weeks resulted in attenuated AlCl₃-induced cognitive impairment, Aβ burden, oxidative stress, cholinergic deficits, Tau pathology, inflammation, and apoptosis in these rats. It is suggested that asiatic acid ameliorated AlCl₃-induced pathological alterations in hippocampus and cortex regions.²⁷

A study of the AD model in rats using intracerebroventricular injection of streptozotocin reported that *C. asiatica* was effective to prevent cognitive deficits in rats. Pretreatment with aqueous extract of *C. asiatica* resulted in improved cognitive behavior in a dose-dependent manner.¹⁵

Centella asiatica may exert its neuroprotective properties through a number of possible mechanisms. Studies suggested that *C. asiatica* has anti-inflammatory effects, ameliorates oxidative stress, improves mitochondrial

dysfunctions, and increases brain-derived neurotrophic factors. Results from experimental studies should be interpreted cautiously and cannot be extrapolated directly for clinical routines. Therefore, human studies should be performed to confirm the findings of these phytochemical experimental studies.

CONCLUSION

Evidence from experimental animal studies suggest the potential of *C. asiatica* as alternative treatment for neurological conditions, such as stroke, epilepsy, Alzheimer's and Parkinson's disease.

ACKNOWLEDGEMENTS

The authors would like to thank Ismail Setyopranoto, MD, PhD, Head of Department of Neurology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.

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