Role of *Centella asiatica* in Alzheimer's Disease: A Comprehensive Review

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurological illness that causes cognitive decline and memory loss and affects millions of people worldwide. As synthetic medications often prove ineffective or cause severe side effects, natural remedies are gaining attention. This review explores the potential of *Centella asiatica*, a herb traditionally used in oriental medicine, in the treatment of Alzheimer's disease. Triterpenoids, asiaticoside, and madecassoside are among the bioactive substances found in *Centella asiatica* that contribute

to its therapeutic qualities. Studies suggest that *Centella asiatica* may enhance cognitive function through multiple mechanisms, such as inhibiting acetylcholinesterase activity, reducing phospholipase A2 activity, protecting against β-amyloid formation, and modulating oxidative stress responses. The plant's effects on neuronal morphology, learning performance, and memory retention have been demonstrated in animal models. *Centella asiatica* extract mitigates oxidative stress generated by Aβ plaques in the hippocampus and cortex. While these results are exciting, more research is needed to fully understand the mechanisms of action of the herb and assess its usefulness in human clinical trials. This review highlights the potential of *Centella asiatica* as a promising natural intervention for Alzheimer's disease and emphasizes the need for continued investigation into its therapeutic applications.

Keywords: *Centella asiatica*, alzheimer's disease, neuroprotection, cognitive enhancement, antioxidant.

INTRODUCTION

Numerous diseases impact bodily functions throughout the human lifespan, and an array of effective remedies is available in the natural world. When synthetic pharmacological agents fail to yield positive outcomes or produce significant adverse effects, these remedies constitute a natural medicinal approach derived from botanical sources, ensuring safety and comfort for patients undergoing therapeutic interventions[1].

Alzheimer’s disease (AD) represents the most prevalent form of dementia. It is characterized as a progressively debilitating neurodegenerative disorder marked by the presence of neuritic plaques and neurofibrillary tangles, which arise from the accumulation of amyloid-beta peptide (Aβ) in the brain's most affected regions, specifically the medial temporal lobe and neocortical structures [2]. Three illustrative cases elucidate the clinical spectrum of AD. Case A underscores a genetically determined variant of AD, Case B depicts a language variant of

AD, typically manifesting in individuals younger than 70 years, while Case C exemplifies a classic amnestic variant, more frequently observed in patients exceeding 70 years of age [3]. Approximately 50 million individuals are afflicted with AD globally; this figure is anticipated to double every five years, potentially reaching 152 million by the year 2050 [2].

Centella asiatica is recognized as a versatile and remarkable herb utilized in traditional oriental medicine [4]. In the Indian medicinal systems, *Centella asiatica* is employed to enhance cognitive functions and address dermatological ailments as well as nervous system disorders [5]. In India, this plant is colloquially referred to as 'Mandukaparni,' whereas in Sri Lanka and Indonesia, it is known as 'Thankuni Sak.' In classical Ayurvedic texts of India, it is regarded as one of the 'Rasayana' (rejuvenating) agents and is reputed to improve skin texture, augment memory, and extend lifespan [6]. This review seeks to elucidate the therapeutic role of *Centella asiatica* in the management of AD. Through the analysis of various datasets, it was determined that *Centella asiatica* significantly contributes to the enhancement of memory capabilities. Furthermore, this article presents an overview of the additional pharmacological properties exhibited by the plant. Plant Centella asiatica are shown in figure 1.

Taxonomy of Centella asiatica [7]

Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Order	Apiales
Family	Apiaceae
Genus	*Centella*
Species	*asiatica*

Fig.1: *Centella asiatica* Plant

DESCRIPTION OF PLANT

Centella asiatica is a clonal, perennial herbaceous creeper prevalent throughout the Indian subcontinent, typically flourishing in moist habitats at altitudes reaching up to 1800 meters. This species is distributed across numerous tropical and subtropical nations, thriving in swampy ecosystems, which include regions of India, Pakistan, Sri Lanka, Madagascar, as well as South Africa, the South Pacific, and Eastern Europe. The plant exhibits diminutive, fan-shaped green leaves alongside inflorescences that range in color from white to light purple or pink, ultimately producing small, oval-shaped fruits [8]. The stems are characterized by slender, creeping stolons that manifest a green to reddish-green pigmentation, thereby facilitating interconnection among individual plants. The long-stalked, green leaves possess a reniform shape with rounded tips, exhibiting a smooth texture and palmately netted venation. These leaves are attached to pericladial petioles that typically measure around 20 centimeters in length. The rootstock is comprised of rhizomes that grow vertically downward, presenting a creamish hue and are enveloped in root hairs [7]. This

species is naturally found in wet, shaded environments up to elevations of 7000 feet and is commonly observed along the banks of rivers, streams, ponds, and cultivated fields. Approximately 20 species of Gotu kola have been documented to thrive in various tropical or moist pantropical settings, including rice paddies as well as rocky terrains and elevated regions [9].

CHEMICAL CONSTITUENTS

The primary chemical components identified within *Centella asiatica* consist of triterpenoids, vallarine, asiaticoside, sitosterol, tannin, and oxyasiaticoside (figure.2) [10]. The species *C. asiatica* exhibits a high concentration of pentacyclic triterpene glycosides, and the therapeutic properties of the plant are predominantly ascribed to these principal bioactive constituents, namely asiaticoside and madecassoside, alongside their corresponding aglycones (sapogenins), which are asiatic acid and madecassic acid. Additional phytochemical entities originating from the herb encompass phenolic acids, triterpene steroids, volatile oils, flavonoids, tannins, phytosterols, vitamins, essential oils, amino acids, and carbohydrates [11]. Moreover, *C. asiatica* displays the presence of isoprenoids, including sesquiterpenes, plant sterols, pentacyclic triterpenoids, and saponins, as well as phenylpropanoid derivatives such as eugenol derivatives, caffeoylquinic acids, and flavonoids [12]. The foliar structures of *C. asiatica* encompass a variety of terpene types, including monoterpenes, sesquiterpenes, and triterpenes. The aerial portions of *C. asiatica* are characterized by triterpenes, phenols, and cadiyenol, whereas the root system also harbors monoterpenes, sesquiterpenes, and triterpenes, in conjunction with several mineral elements [13].

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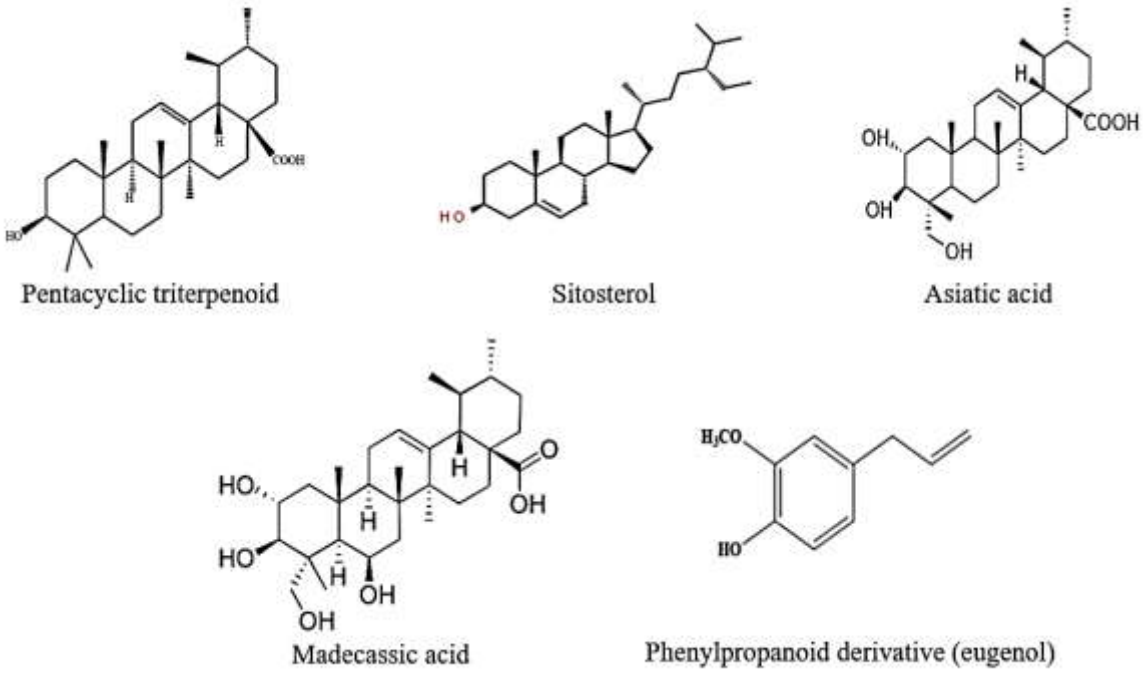

Fig.2: Chemical constituents of *Centella asiatica*

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

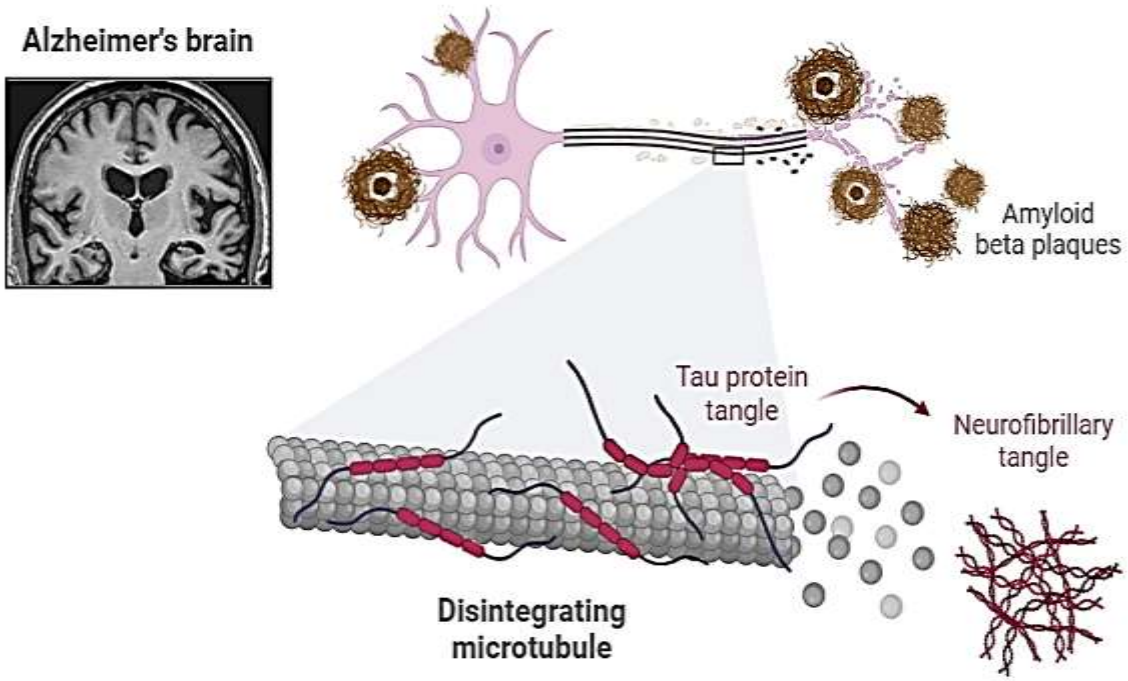

Fig.3: Pathophysiology of Alzheimer's disease

Alzheimer's disease (AD) is attributable to the pathological accumulation of aberrant neuritic plaques and neurofibrillary tangles within the cerebral context. Pathophysiology of Alzheimer's disease are shown in figure 3. These neuropathological alterations are concomitant with a significant loss of neurons, particularly affecting cholinergic neuronal populations situated in the basal forebrain and the neocortex [14]. The clinical presentation of AD manifests predominantly as dementia, which characteristically initiates with subtle and often unrecognized memory impairments, gradually intensifying to a more profound and ultimately debilitating state [15]. In the context of Alzheimer's disease, however, aberrant biochemical transformations precipitate the detachment of tau protein from microtubules, leading to its aggregation with other tau molecules, thereby forming filaments that eventually coalesce into tangles within neurons. These neurofibrillary tangles obstruct the transport mechanisms of neurons, consequently impairing synaptic communication among neuronal entities [16]. There exists a widespread atrophy of the cerebral cortex accompanied by secondary dilation of the ventricles. The pathological deposits are predominantly localized within the hippocampus, temporal cortex, and the nucleus basalis of Meynert. The neuronal loss associated with these pathological transformations culminates in diminished neurotransmitter levels, particularly acetylcholine, thereby precipitating cognitive deficits in affected individuals [15].

Two principal hypotheses have been postulated to elucidate the etiology of AD, namely the cholinergic and amyloid hypotheses [2]. The Cholinergic Hypothesis posits that the diminished concentrations of acetylcholine (ACh) within the brain, consequent to neuronal degeneration in the Nucleus Basalis of Meynert, are pivotal in the pathogenesis of AD. The amyloid hypothesis asserts that amyloid beta (Aβ) peptide is generated from amyloid precursor protein (APP) via the enzymatic activities of β- and γ-secretase. Typically, APP is

cleaved by either alpha or beta-secretase, yielding fragments that lack neurotoxic properties. Conversely, sequential cleavage by beta followed by gamma-secretase culminates in the production of 42 amino acid peptides (Aβ42). An increase in Aβ42 levels fosters the aggregation of amyloid, which subsequently induces neurotoxicity [14].

MECHANISM OF ACTION OF *Centella asiatica* IN ALZHEIMER'S DISEASE

Centella asiatica, a botanical entity utilized for several centuries, has been recognized for its potential to significantly enhance cognitive functions, particularly memory [17]. Within the framework of Ayurvedic medicine, *C. asiatica* is prominently indicated for its cognitive-enhancing properties, serving not only as a brain tonic but also playing a crucial role in the therapeutic management of various mental disorders. It is also characterized as a potent memory-enhancing agent. Numerous studies have demonstrated that *C. asiatica* improves neuronal morphology, optimizes learning performance, and contributes positively to memory retention in various animal models subjected to experimental conditions. A multitude of mechanisms through which *C. asiatica* exerts its beneficial effects on cognitive function have been elucidated, including the inhibition of acetylcholinesterase activity, reduction of phospholipase A2 (PLA2) activity, protective effects against beta-amyloid formation, and safeguarding neuronal integrity from damage induced by various pathological processes [18]. Empirical studies indicate that administering extracts derived from *Centella asiatica* may enhance both learning and memory functions by promoting neuronal dendrite growth in rats undergoing growth spurts, while also modulating the pathological landscape associated with amyloid beta in the brain. Additionally, *C. asiatica* influences oxidative stress responses in neurodegenerative models, particularly in mice [19].

The signaling pathways associated with NRF2 are integral to a cellular response aimed at counteracting oxidative stress, regulating reactive oxygen species (ROS), with superoxide

dismutases (SOD) as a key player in this context. The elevation in SOD expression serves as an indicator of heightened oxidative stress, commonly associated with amyloid beta plaques in the brains of individuals with Alzheimer's disease. Detailed analyses have revealed that treatment with *Centella asiatica* water (CAW) extract significantly reduces oxidative stress linked to amyloid beta plaques, particularly in the hippocampus and cortex regions of the brain. The neuroprotective effects of CAW against amyloid beta toxicity are believed to be mediated through the attenuation of oxidative stress, alongside potential mechanisms mitigating neuritic dystrophy near these plaques, contributing to its overall neuroprotective profile [18].

OTHER PHARMACOLOGICAL ACTIONS AND TRADITIONAL USE

WOUND HEALING ACTIVITY

The investigation revealed that the application of ethanolic extract derived from the leaves of *Centella asiatica* significantly accelerated the healing process associated with excision wounds, particularly evident following the administration of the extracts at varying concentrations to experimental Wistar rats with inflicted wounds [20]. Wound healing is an intricate and multifaceted process that initiates immediately after injury and encompasses several distinct phases, including inflammation, proliferation, maturation, and re-epithelization. *Centella asiatica* has gained widespread recognition for its efficacy in treating various infectious skin diseases and its ability to expedite the healing of skin ulcers and wounds. The plant's composition includes pentacyclic ursane-type triterpenoids known as centellosides, specifically madecassic acid, asiatic acid, asiaticoside, and madecassoside. Madecassoside is particularly recognized for its potent anti-inflammatory properties,

enhancing the secretion of collagen type III, while asiaticoside promotes wound healing by stimulating fibroblast proliferation and collagen type I synthesis [21].

ANTIFUNGAL ACTIVITY

Numerous studies have demonstrated that extracts from *C. asiatica* have been rigorously evaluated against a variety of microorganisms, including *Aspergillus niger*. The results indicated that *C. asiatica* extracts exhibited significant preservative effects against the growth of *A. niger* at concentrations of 5% and 1%. The 5% extract showed the maximum inhibitory effect compared to the control group and the 1% solution, highlighting the extract's efficacy in combating this microorganism [22].

IN SKIN DISEASES

Atopic dermatitis, also known as atopic eczema, is one of the most prevalent allergic inflammatory skin diseases encountered in clinical practice. The effects of *C. asiatica* on skin inflammation induced by 2,4-dinitrochlorobenzene (DNCB) have been meticulously tested in both in vitro and in vivo models of atopic dermatitis. The results elucidated the strong protective activity conferred by *C. asiatica* extract, which operates by inhibiting pro-inflammatory cytokines to alleviate and suppress the symptoms of dermatitis [11].

TRADITIONAL USES

The utilization of *Centella asiatica* in culinary applications, including food and beverages, has increased over the years, indicating a growing recognition of its versatility. In addition to its use as a traditional and alternative medicinal herb, *Centella asiatica* is commonly employed in various culinary preparations such as vegetables and beverages, including tea and juice. Due to its mild bitterness, it is often cooked with coconut milk or shredded coconut

and, on occasion, with sweet potatoes or regular potatoes. In Sri Lanka, the leaves of *Centella* are traditionally used to prepare a curry called “mallung” and a porridge known as “kola kenda” [23,24]. Beyond culinary applications, *C. asiatica* extract is used for its anti-aging properties [25]. It is recognized for enhancing skin hydration, contributing to a plumper appearance around the eyes while reducing the visibility of dark circles and fine lines [26]. Furthermore, the dried leaves of Brahmi are processed into powdered form and used as a nutritional supplement, enhancing the nutritional value of consumed foods [27].

FUTURE DIRECTIONS

Future research endeavors focusing on *Centella asiatica* should aim to comprehensively elucidate its precise mechanisms of action, particularly its interactions with the NRF2 signaling pathway and its role in mitigating oxidative stress responses at the cellular level. This would provide valuable insights into how *C. asiatica* enhances cognitive function. To rigorously establish the efficacy and safety of this botanical in human subjects diagnosed with Alzheimer’s disease, large-scale, methodologically sound clinical trials are essential. These trials would offer robust data and contribute to understanding the plant's potential as a treatment for neurodegenerative conditions. Additionally, significant efforts should focus on isolating and identifying the most potent bioactive compounds within *Centella asiatica*, while developing advanced drug delivery systems to improve their bioavailability and therapeutic impact. Exploring potential synergistic effects when used alongside conventional pharmacological treatments is also vital to maximize its therapeutic potential.

Moreover, long-term studies are necessary to assess the preventive effects of *Centella asiatica* in aging populations. Standardization of extracts, dose-response investigations to determine optimal concentrations, and research into its applications in other neurodegenerative disorders should be prioritized. Sustainable cultivation practices must also

be developed to meet the growing demand for this promising therapeutic agent, ensuring its future availability for clinical use.

Collectively, these approaches will advance our understanding of the therapeutic potential of *Centella asiatica* and pave the way for its development as a viable treatment option for Alzheimer's disease and related cognitive disorders affecting millions worldwide.

Conclusion

In conclusion, *Centella asiatica* shows promising therapeutic potential for Alzheimer's disease (AD) due to its neuroprotective, antioxidant, and anti-inflammatory properties. The bioactive compounds in *C. asiatica*, such as triterpenoids, asiaticoside, and madecassoside, are reported to enhance cognitive functions through mechanisms like inhibiting acetylcholinesterase, reducing oxidative stress, and protecting neurons from beta-amyloid toxicity. While current studies, particularly in animal models, underscore its ability to improve learning, memory, and neuronal morphology, more comprehensive human trials are necessary. Future research should focus on isolating key bioactive compounds, optimizing dosage, and exploring possible synergistic effects with conventional AD therapies to fully harness *C. asiatica*'s therapeutic potential in AD management.

REFERENCES

1. Sharma D, Tyagi S, Dan S, Pant M, Kumar A. Indigenous therapeutics of Alzheimer: A review of ayurvedic herbs from its ethnobotany to phytotherapy. Lett. Appl. NanoBioSci.. 2021;11(4):4178-91.
2. Bhat R, Hemalatha CH, Shabaraya AR. Exploring the protective effects of aqueous extracts of *Ruta chalepensis* Linn. on drug-induced seizures in animal models. Indian J Pharm Drug Stud. 2023;2(3):113-7.

3. Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, et.al., Alzheimer's disease. Lancet. 2021; 397:1577–90.
4. Golla P, Tirupathi H. To evaluate and compare antidepressant activity of *Centella asiatica* in mice by using forced swimming test. Int J Basic Clin Pharmacol. 2016;5(5):2017-20.
5. Prakash V, Jaiswal N, Srivastava M. A review on medicinal properties of *Centella asiatica*. Asian J Pharm Clin Res. 2017;10(10):69-74.
6. Jayashree G, Kurup Muraleedhara G, Sudarslal S, Jacob VB. Anti-oxidant activity of *Centella asiatica* on lymphoma-bearing mice. Fitoterapia. 2003;74(5):431-4.
7. Widgerow AD, Chait LA, Stals R, Stals PJ. New innovations in scar management. Aesthetic plastic surgery. 2000 May;24:227-34.
8. Gohil KJ, Patel JA, Gajjar AK. Pharmacological review on *Centella asiatica*: a potential herbal cure-all. Indian J Pharm Sci. 2010;72(5):546-56.
9. Sharma K. Gotu kola (*Centella asiatica*): Amazing medicinal plant. Sci Info. 2024.
10. Shastry RA, Habbu PV, Smita DM, Iliger SR, Kulkarni VH. Isolation, characterization and evaluation of endophytic fractions of *Centella asiatica* Linn. (Leaves) for in vitro antioxidant activity. *J Nat Remed*. 2020;20(1):2320-3358.
11. Bandopadhyay S, Mandal S, Ghorai M, Jha NK, Kumar M, Radha, et.al.,. Therapeutic properties and pharmacological activities of asiaticoside and madecassoside: A review. J Cell Mol Med. 2023;27(5):593-608.
12. Kandasamy A, Aruchamy K, Rangasamy P, Varadhaiyan D, Gowri C, Oh TH, et.al., Phytochemical analysis and antioxidant activity of *Centella asiatica* extracts: An experimental and theoretical investigation of flavonoids. Plants. 2023; 12:3547.
13. Chong NJ, Aziz Z. A systematic review on the chemical constituents of *Centella asiatica*. Res J Pharm Biol Chem Sci. 2011;2(3):445.

14. Kumar A, Sidhu J, Lui F, Tsao JW. Alzheimer Disease [Internet]. PubMed. Treasure Island (FL): StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499922/#:~:text=Alzheimer%20disease%20is%20characterized%20pathologically
15. Bhat R, Varshini, Himasvi, Shabaraya R. Pharmacogenomic approaches in Alzheimer's disease: a comprehensive review. Int J Pharm Phytopharmacol Res. 2023;13(4):7-13.
16. National Institutes of Health. What happens to the brain in Alzheimer's disease. 2017. https://www.nia.nih.gov/health/alzheimers-causes-and-risk-factors/what-happens-brain-alzheimers-disease#:~:text=In%20Alzheimer
17. Gray NE, Zweig JA, Caruso M, Martin MD, Zhu JY, Quinn JF, et.al., *Centella asiatica* increases hippocampal synaptic density and improves memory and executive function in aged mice. Brain Behav. 2018;8(7)
18. Matthews D, Caruso M, Murchison CF, Zhu JY, Wright KM, Harris CJ, et.al., *Centella asiatica* improves memory and promotes antioxidative signaling in 5XFAD mice. Antioxidants. 2019;8(12):630.
19. Shanbhag P, Bhat R, Mestha SV, Nagesh S, Nayak DR. Investigation of Anti-anxiety Activity of Hydroalcoholic Extract of Plectranthus scutellarioides Leaves in Experimental Animal Models. Int. J. Pharm. Sci. Rev. Res. 2022;76(1):115-8.
20. Mgonja F, Lusekelo M, Mohamed A. Excision wounds healing activity of *Centella asiatica* (Gotukola) extract on laboratory rats. Tanzan J Health Res. 2022;23(1).
21. Manasa R, Santosha DU, Meghana HD, Naik SR, Shivananjappa M. Wound healing activity of *Centella asiatica*. IP J Nutr Metab Health Sci. 2023;6(1):1–6.
22. Akter N, Hye MA, Rahman MN. Antifungal activity of *Centella asiatica* on radial growth of Aspergillus species. Lett Appl NanoBioSci. 2020;9(4):1467–73.

23. Bhat R, Shanbhag P. Evaluation of anticonvulsant activity of *Bixa Orellana* Linn. seed. J Pharmacovigil Drug Res. 2023;4(3):34-9.
24. Bhat R, Shanbhag P, Shabaraya R. A comprehensive review of anti-CD20 monoclonal antibodies in multiple sclerosis. Int J Pharm Phytopharmacol Res. 2023;13(3):16-21.
25. Buranasudja V, Rani D, Malla A, Kobtrakul K, Vimolmangkang S. Insights into antioxidant activities and anti-skin-aging potential of callus extract from *Centella asiatica* (L.). Sci Rep. 2021;11.
26. Buranasudja V, Rani D, Malla A, Kobtrakul K, Vimolmangkang S. Insights into antioxidant activities and anti-skin-aging potential of callus extract from Centella asiatica (L.). Scientific Reports. 2021 Jun 29;11(1):13459.
27. Amaravathi T, Geetha PS, Murugan M, Selvam S, Kanchana S. Traditional value-added products from Indian pennywort (*Centella asiatica*) and water hyssop (*Bacopa monnieri*) to alleviate ADHD. Pharma Innov J. 2020;9(7):432–41.