Phytochemistry and pharmacological properties of *Centella Asiatica:* A comprehensive review

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Abstract

Centella asiatica (L) known as the brahmi plant (Gotu kola) is a therapeutic plant that has been used in traditional folk medicine since ancient literature as well as in methodically oriented medicine. The literature review and experimental studies have reported several important bioactive compounds present in plants and their therapeutic activities. The phytochemicals present in the plant are showing more effect on endocrine diseases, skin diseases, gastrointestinal diseases, neurological diseases, and gynaecological diseases. The major bioactive components that are responsible for their therapeutic activity are asiaticoside, madecassoside, triterpenes, and madecassic acid. The plant extract contains triterpene components that exhibit several pharmacological activities, including cardioprotective, neuroprotective, antidiabetic, wound healing, anti-oxidant, anti-inflammatory, anti-fungal, anti-bacterial, and anti-cancer. This review study explains the importance of bioactive compounds and the medicinal properties of *Centella asiatica (L)* plant extract. In this review, we have focused on *in silico*, *in vitro* and *in vivo*practices of major bioactive compounds and their clinical importance with an update.

Keywords: *Centella asiatica* (L), Phytochemistry, Pharmacology, Therapeutic Applications.

Introduction

Traditional therapeutic plants have been used to heal human diseases for thousands of years [1]. The importance of medicinal plants and ancient medical systems in addressing global health challenges is being recognized more widely [2]. As a result of this enhanced attention, global research on medicinal plants is developing. Herbs with medicinal properties provide essential functions in disease prevention, and their adoption and usage are compatible with all current disease prevention techniques [3]. The research and utilization of herbal medicine in the treatment of diseases are increasing every day because of the availability of natural substances. Medicinal plants are an important source of compounds with therapeutic capabilities [4]. Due to the presence of phytochemical components, medicinal plants are effective for curing diseases in humans and play an essential role in healing [5]. The application of medicinal plants has become an important role in global health systems, this includes not only applying medicinal plants to treat diseases but also as a possible material for sustaining good health and demands [6-7]. In fact, two-thirds of the world's population relies on medicinal plants for essential health care. They are more accepted in culture, have stronger compatibility and adaption with the human body, and have fewer adverse effects [7].

C. asiatica (L) is a medicinal plant also locally known as Asiatic pennywort, gotu kola, and brahmi. It is a member of the Apiaceae (previously Umbelliferae) family and the Mackinlayoideae subfamily. As part of molecular phylogenetic investigations, the plant was relocated from the subfamily Hydrocotyloideae [10].It is an evergreen shrub having leaves and stems that can be used to make a green leafy vegetable and is well-known for its medicinal and nutritional qualities[8].*C. asiatica* (L) is a hairless or partially hairy perennial herb with several horizontal and creeping stems. The leaves are spherical, 2 to 9 cm in diameter, in groups of 4 to

5, and are held by a long petiole (1-10 cm). The purple flowers are very minimal and grouped by 2-5 at the leaf base, and they frequently appear broad and drab in the fields, but they could be thick, fleshy, and shining near the sea [11].

C. asiatica (L) is used as a traditional medicine to treat a variety of moderate and chronic diseases, it is also used as a cerebral rejuvenator, anti-rheumatic, antibacterial, antipyretic, anti-inflammatory and antiviral [12].The pharmacological properties of *C. asiatica* (L) are shown in **Figure**1.*C. asiatica* (L) is useful in the treatment of wounds due to the mechanism responsible for improving fibroblast proliferation and increasing collagen synthesis,the bioactive compounds present in the plants shown numerous therapeutic properties.*Bylkaet.al 2013* described therapeutic role of bioactive compounds includetriterpenes,pentacyclic mainly asiaticoside, asiatic madecassoside and madecassic acids [13].*In vitro* and *in vivo* investigations demonstrated that these plant chemicals have an effect on dermatological illnesses such as atopic dermatitis, acne, burns, and wounds *via* TGF-/Smad, Wnt/β-catenin, MAPK, NF-κB, and STAT signalling. [14].

Figure.1 Therapeutic effect of*Centella asiatica* (L)

Bioactive compounds in present in *Centella asiatica*(L)

C.asiatica (L) contains a number of isoprenoids (plant sterols, sesquiterpenes, triterpenoids, saponins, and pentacyclic compounds) and phenylpropanoid substances (caffeoylquinic acids, eugenol derivatives, and flavonoids) [15]. Preliminary phytochemical analysis revealed the presence of tannins, carbohydrates, terpenoids, steroids, flavonoids, alkaloids, cardiac glycosides, saponins etc. The majority of flavonoids are also found in all parts of the plant, like leaves, stem, and roots [16]. Plant steroids are widely recognized for their cardio tonic properties, as well as insecticidal and antibacterial characteristics; they are used in food, herbal cosmetics, and medicine [17]. Tannins have also been shown to have antiviral, antimicrobial, and anti-tumour properties. It was also found that some tannins could selectively decrease HIV replication and could be utilized as a diuretic [18].

Table No.1. List of bioactive compounds present in *Centella asiatica (L)* plant

Sl.No	Bio-Active compounds Names	PubChem CID	Chemical Formula
1	Asiaticoside	11954171	$C_{48}H_{78}O_{19}$
2	Madecassoside	45356919	$C_{48}H_{78}O_{20}$
3	Asiatic acid	119034	$C_{30}H_{48}O_5$
4	Madecassic acid	73412	$C_{30}H_{48}O_6$
5	Gluconic acid	10690	$C_6H_{12}O_7$
6	Ferulic acid	445858	$C_{10}H_{10}O_4$
7	Kaempferol	5280863	$C_{15}H_{10}O_6$
8	Chlorogenic acid	1794427	$C_{16}H_{18}O_9$
9	Valine	6287	$C_5H_{11}NO_2$
10	Triparanol	6536	$C_{27}H_{32}ClNO_2$
11	Butamben	2482	$C_{11}H_{15}NO_2$
12	Neuraminic acid	441037	$C_9H_{17}NO_8$
13	Aesculin	5281417	$C_{15}H_{16}O_9$
14	Esculetin	5281416	$C_9H_6O_4$
15	Famciclovir	3324	$C_{14}H_{19}N_5O_4$
16	Rhoifoline	97597	$C_{21}H_{17}NO_5$
17	Gentiopicrin	88708	$C_{16}H_{20}O_9$
18	Urocortisone	5866	$C_{21}H_{32}O_5$
19	Pelargonic acid	8158	$C_9H_{18}O_2$

20	Gabapentin	3446	$C_9H_{17}NO_2$
21	Sarmentoside	24836660	$C_{29}H_{42}O_{11}$
22	Khivorin	21596331	$C_{32}H_{42}O_{10}$
23	β-carotene	5280489	-
24	Centellasapogenol A	73196815	$C_{30}H_{48}O_5$
25	Centellasaponin B	85411973	$C_{42}H_{68}O_{16}$
26	Centellasaponin C	85348461	$C_{48}H_{78}O_{19}$
27	Asiaticoside C	101103169	$C_{50}H_{80}O_{20}$
28	Asiaticoside D	102212084	$C_{48}H_{78}O_{18}$
29	Asiaticoside E	102212085	$C_{42}H_{68}O_{15}$
30	Asiaticoside F	53317001	$C_{48}H_{78}O_{18}$
31	Isoasiaticoside	76551298	$C_{48}H_{78}O_{19}$
32	Asiaticoside G	53320941	$C_{48}H_{78}O_{20}$
33	Asiaticoside I	101568838	$C_{48}H_{76}O_{19}$
34	Centelloside E	101568838	C_{48}H76O19
35	Centellasaponin J	56964357	C42H68O16
36	Centelloside D	85348461	C48H78O19

Bioactive compounds and their biological importance

Kaempferol:

Kaempferol (KP), also known as kaempferide or kaempferol-3, is a flavonoid component that is naturally found in tea, various kinds of vegetables, fruitsand leaves including *C.asiatica (L)*. Studies shown thatKP reduces the levels of pro-inflammatory cytokines while increasing anti-inflammatory cytokines, including IL-10 by inhibiting nuclear transcription factors[19]. Multiple investigations have revealed that reducing IL-1-stimulated inflammatory substances is the first-line therapeutic option for osteoarthritis (OA), increased prostaglandin E2 (PGE2) expression, and nitric oxide (NO) formation, which may be significant contributors to the progression of OA. KP reduced IL-1-stimulated PGE2 and NO production in a concentration-dependent manner, while also enhancing iNOS and Cox-2 expression [20].KP, which has anti-cancer activity, may be used as well on a human Oesophageal adenocarcinoma cell line. Imran et al., 2019. KP has been shown to decrease breast cancer cell invasion by disrupting the protein kinase C

(PKC)/MAPK/activator protein-1 cascade, as well as matrix metalloproteinase activity; it was also found to inhibit TCS-induced MCF-7 breast cancer cells growth [21].

Madecassic acid or Brahmic acid

Madecassic acid is one of the three triterpenes isolated from *C. asiatica* (L). Madecassic acid's wound healing effectiveness has been associated with its capacity for stimulating collagen synthesis [22]. It is a natural immunomodulatory with a diverse profile of anti-inflammatory and anti-diabetic effects. It operates in mice by inhibiting NF-κB activation and macrophage lipid metabolism. Studies are underway to research the metabolism of Madecassic acid [23].

Famciclovir

Famciclovir is one of the active phytocompound identified in*C. asiatica* (L).It is a replacement to acyclovir for treating herpes simplex virus (HSV) first episodes and recurrences, as well as for chronic infection suppression. Famciclovir is effective against both HSV-1 and HSV-2 *in vitro* [24].

Rhoifoline

Rhoifolinis another phytochemical constituent present in *C Asiatica (L). In vivo* studies onRhoifolin showed hepatoprotective, anticancer, anti-rheumatic, antidiabetic, antibacterial, and anti-viral capabilities [25,26,27] Rhoifolin's wound-healing activity was validated by its ability to stimulate re-epithelization, angiogenesis, antibacterial, immunomodulatory, and anti-inflammatory actions [28,29].

Genistein

Genistein has a number of pharmacological effects, including antioxidant activity and anti-carcinogenic activity [30]. Genistein is a glycoside with a high potential for bioactivity.*Lee et., al 2012* study has shown that potential anticancer agent against ovarian cancer, gentiopicrin, a derivative of Genistein effectively inhibited the NF-κB signalling pathway, produced mitochondrial membrane potential loss, and promoted apoptosis in human ovarian cancer cells [31].

Gabapentin

Gabapentin is an anticonvulsant substance utilized for the treatment of seizures caused by epilepsy. It can also be used to reduce nerve discomfort caused by diabetes or shingles, as well as restless leg syndrome (RLS) [32]. Several studies show that diabetes-related nerve pain can be relieved by taking gabapentin orally [33].

Epigallocatechin-3-gallate (EGCG):

Catechins are phenolic molecules with high antioxidant action, particularly. EGCG found in small quantities in *C,asiatica*. Catechins are able to pass the blood-brain barrier and enter the central nervous system, where they regulate the expression of genes and proteins [34]. The properties of catechins in the limbic system have been identified at the molecular level by an increase in BDNF levels. Catechins have the potential to be therapeutic agents for reversing neurodegenerative processes associated with ageing and related disorders [35]. Several clinical trials are being conducted to assess the efficacy of catechins in the treatment or improvement of cognitive abilities in a number of age-related neurological disorders [36].

Epicatechin

Epicatechin is a vitamin that is hypothesized to promote health by preventing or decreasing cardiovascular disease (CVD). In humans, epicatechin gets absorbed from the intestine, as well as having bioavailability and being bioactive [37]. In addition to basic antioxidant activity, recent investigations show that the metabolism of nitric oxide and reactive nitrogen species is altered, resulting in the maintenance and enhancement of endothelial function in arterial blood vessels.

Epicatechin metabolic conversion products such as glucuronidated and methylated species could contribute to understanding its protective effect on the vascular endothelium [38].

Quercetin

Quercetin is a flavonoid with antioxidant properties. Quercetin has been reported to have a variety of beneficial effects on human health, including protection against diseases including osteoporosis, lung cancer, and cardiovascular disease [39].Quercetin is found in more than twenty plants and is widely recognized for its anti-inflammatory, antihypertensive, anti-obesity, vasodilator, anti-hypercholesterolemia, and anti-atherosclerotic properties [40].

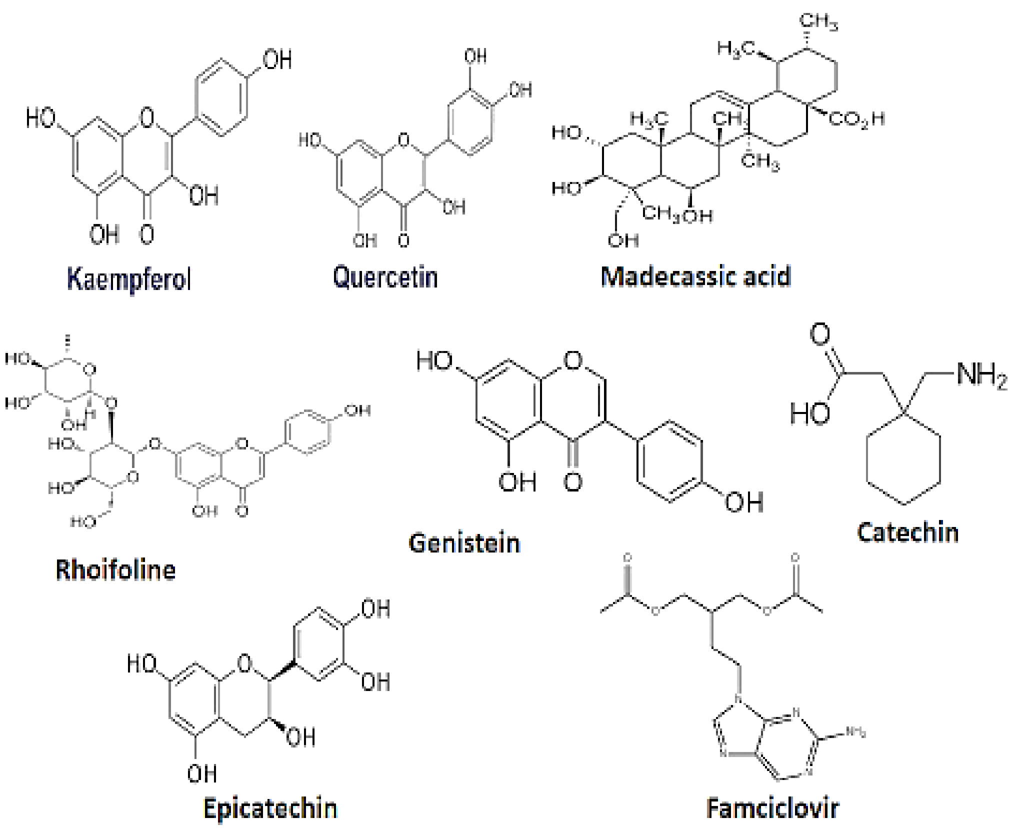

Figure:2. Structure of Bioactive compounds

In vitro **studies of** ***Centella asiatica (L)*** **plant**

The main components of *C. asiatica* (L) include triterpene compounds such as asiatic acid, madecassic acid, asiaticoside, and madecassoside, which are responsible for wound healing [41].According to numerous research studies, the physiologically active components of glycosides are asiatic acid and madecassic acid. Although their low concentration in tissues and plasma, they can be found in faeces 48 hours after oral administration of *C. asiatica* (L) extract. This indicates that triterpenoid glycosides are primarily metabolized in the intestine [42]. A partially purified portion of *C. asiatica*(L)methanol extract reduced tumour cell proliferation while having no adverse impacts on lymphocytes. Water extract possesses chemopreventive properties against colon carcinogenesis. Asiatic acid was discovered to have anticancer properties in skin cancer [43].*C. asiatica* (L) extract from leaves exhibit antibacterial action against *Escherichia coli* as well as many other bacteria and fungi. The volatile extract has antibacterial activity against both Gram-positive and Gram-negative organisms [44].Human dermal fibroblasts were used in the majority of *in vitro* experiments. *C. asiatica* (L) has been shown to have a significant impact on the deposition of extracellular matrix proteins [45]. It improves fibroblast proliferation, activates the Smads signaling pathway, enhances collagen synthesis, lowers metalloproteinase activity, and increases collagen deposition [46].According to study, the substances found in *C. asiatica* (L) may have antioxidant, anti-cellulite, anti-inflammatory, and anti-aging activities [47]. It has been used to treat varicose veins, psoriasis, small lesions,chronic venous insufficiency, and has analgesic and anti-inflammatory properties. Triterpene saponins and sapogenins are primarily responsible for wound healing and vascular effects, which function by preventing collagen formation at the wound site [48]. Further, *in vitro* examinations demonstrated that *C. asiatica* (L) has the possibility to be used to treat burns, acne, atopic dermatitis, and wounds [49].It was previously proposed that NF-B, TGF-/Smad, MAPK, Wnt/β-catenin, and STAT signalling are possible molecular mechanisms involved in *C. asiatica (L)* pharmacological activities on skin disorders[50].*Rashid et., al 2023*explained the significance of phenolic and flavonoids in cytotoxicity, antioxidant, antibacterial, and thrombolytic activities. They have done DPPH free radical scavenging activity and concluded flavonoids and phenolics are major bioactive compounds categories with antioxidant and other biological properties [51].Studies revealed that*C.asiatica (L.)*helps in the neuronalcell proliferation from human mesenchymal stem cells [52].

***In vivo*studies of *Centella asiatica (L)* plant**

In vivo investigations revealed that *C. asiatica*(L) entire extract and individual components have a therapeutic effect against a number of neurological disorders. The majority of *in vivo* investigations on neuroprotective effects have been on Alzheimer's disease and Parkinson's diseases[53].In a glucose tolerance test performed on alloxan-induced diabetic rats, ethanolic and methanolic extracts of *C. asiatica* (L) showed substantial protection and decreased blood glucose to normal level [54]. *Chauhan et al., (2010)* studies using rats revealed that plant extract of *C. asiatica(L)*showed anti-inflammatory properties by reducing the acute radiation reaction [55].*Mohandas et., al*(2012) published a research article about the bioactive components present in fresh leaf extract and these compoundshave the ability to stimulate neuronal dendritic cell growth and also improved neuronal dendrites in anxiety and other neurodegenerative and cognitive diseases[56].*C. asiatica* (L) is a commonly used in Chinese traditional medicine due to its strong antioxidant effects.*In vitro* and *in vivo*studies on *C. asiatica* (L)by*Zhaoet., al 2014* showed an influence on lipid metabolism. The active compounds asiatic acid and madecassic acid are responsible for the regulation of lipid metabolism through their strong.antioxidant capabilities and also modulate the degradation of lipids *via* LCAT and scavenger receptor class B type I (SR-BI) augmentation.Taken together, the plant extracthas the potential to be used for lipid regulation [57].Multiple research studies revealed that *C. asiatica*(L) extract has a significant radical scavenging activity with a low IC_{50} value [58-59]. Free radicals and hydroxyl radicals are the primary active oxygen species that cause lipid peroxidation (LPO) and massive cellular damage. LPO plays an important role in cardiovascular disease and cancer by creating malondialdehyde (MDA)-like molecules *via* a variety of chemical reactions [60].

According to research findings, *C. asiatica (L)* extract has high quantities of phenolic antioxidants, specifically chlorogenic acid, gulonic acid, kaempferol, ferulic acid, and asiatic acid [61]. Furthermore, plant extract components can show considerable anti-hyperlipidemic effects in high cholesterol fat-induced rats by improving indicators such as antioxidant enzyme, body weight, blood lipid levels, and hepatic structure regeneration [62]. *Magaa et al*., (2018) reported that the bioactive compound madecassoside significantly reduced mouse CIA and may be the main active component of *C. asiatica (L)* responsible for its clinical uses in rheumatoid arthritis, with its basic mechanisms of action primarily through regulating abnormal humoral and cellular immunity as well as protecting against joint destruction [63].

Clinical studies of *Centella asiatica* (L)

Constituents of *C. asiatica (L)* have been found in a variety of skin care cosmetic products around the world [64]. The plant leaves have been utilized in dermatological treatments, mainly to improve the healing process of burns, skin, wounds, and venous ulcers [65]. Paocharoen et al. (2010) conducted clinical investigations on wound healing utilizing*C. asiatica (L)* extract aids wound healing in diabetes individuals. The participants in the trial were 200 diabetics who were given two capsules of *C. asiatica (L)* extract (50 mg asiaticoside/capsule) three times each day. Wound contraction outperformed the placebo group, according to the data [66]. Belgium, Greece, France, Portugal, Italy, and Spain are among the European countries that have approved and commercialized*C. asiatica (L)* [67].Skin cream 1% and powder 2% are advised from the outside for local therapy of moderate or benign wound development problems, as well as the local treatment of cutaneous ulcerations. Clinical trials could be suggested to determine the impact on wound healing [68]. However, additional clinical trials are required to show the therapeutic benefit of *C. asiatica (L)* in patients with a variety of wound types and extents, as well as the impact on skin illnesses other than wounds, such as burns, acne, and atopic dermatitis [69]. *Grey et al.'s 2018* review emphasises the extraordinary potential of *C. asiatica (L)* preparations and derivatives for use in the medical management of neurological illnesses, as well as the additional study required to make this a reality. Caffeoylquinic acids, triterpenes, and flavonoids found in *C. asiatica* (L) have been examined in humans and animal models, as have the chemicals or metabolites detected in the brain [70].

In silico* approach of *Centella asiatica (L)

In-silico method is machine learningtechnique,themethod indicates the computational structures that explore pharmacological effects using different methods like homology model, databases pharmacophores, and data analysis tools [71].The computational analysis is performed to analyse the toxicity profiles, pharmacodynamics, biological properties of bioactive compounds extracted from medicinal plants. Molecular docking is a technique used in the development of novel drugs (72). Molecular docking studies allows explain the analyzing molecule in the binding site of the receptor target. The docking technique having the ability to expect the useful binding affinity between the receptor and ligand complex [73].The studies reveals about the bioactive compounds present in *C. asiatica* (L), which showed good binding affinity between receptors and ligands. *Jusrilet., al 2020* reported acetylcholinesterase (AChE) inhibitor against bioacive compounds present in the *C.asaitica*(L). The docking study showed good binding interactions with the active sites of receptor. This study reveals the bioactive compounds present in the plant extract madecassic acid and asiatic acid are showing binding affinity so based on the results, this compounds studied on *in vitro* studies and it for could be used as markers to guide further studies on *C.asaitica*(L) as potential natural products for the treatment of Alzheimer's disease [74].*Jamil et., al 2023* reported the work according analysis performed molecular docking studies between xanthine oxidase enzymes and bioactive compounds from *C.asaitica*(L) such as Madecassic acid, Centellin, Isothankunicacid, Pomolic acid, 2 alpha-Hydroxyursolic acid, Kaempferol and Quercetin are found in the plant extract showing potential to be anti- hyperuricemia and its inhibition the activity of inhibitors of Xanthine oxidase enzymes [75]. *Macalaladet., al 2022*performed *in silico* screening to identify potential SGLT-2 inhibitors from the 21 phytochemicals from *C.asaitica*(L). Docking experiments revealed eleven compounds with binding affinity predicted to be comparable to recognized inhibitor medications [76]. The result exhibits *C.asaitica*(L) as potential inhibitors of sodium-glucose co-transporter 2 for treating diabetes and Betulinic, Centellasapogenol and Methyl brahmate are recommended for *In vivo* and *in vitro* studies.*Mawaddani et.al 2020* the studies shows Beta amyloid precursor protein cleavage enzyme 1 (BACE1) inhibitor in Alzheimer's disease used *in silico*studies against the *C.asaitica*(L) bio active compounds. The results shown effectiveness of binding affinity Sitosterol and Flavonol had ability to reduce BACE1 activity but not directly inhibit BACE1 activity [77]. *Yuliantiet., al (2017)* had been reported the molecular docking study on phytochemicals from C.asiatica (L) active compounds against Aquaporin-3. The Asiaticosside and Madecasosside having good binding energydue to their glucose chain can make some additional bonds to the protein. Hence further research studies are required to find the potential ability of compounds present in plant [78].

Table: 2. The bioactive compounds in *in silico* studies

Sl.No	*Centella asaitica* (L) Phytochemicals	Bioactive targets	References
1.	Madecassoside Asiaticoside Madecassic acid Asiatic acid Eserine	Acetylcholinesterase (AChE)	*Jusril et., al 2020*
2.	2 alpha-Hydroxyursolic acid Kaempferol Madecassic acid Madasiatic acid Isothankunic acid Centellin Pomolic acid Quercetin	Xanthine oxidase enzymes SLC22A12 and ABCG2	*Jamil et., al 2023*
3.	Asiatic acid Asiaticoside Betulinic acid Centellasapogenol Castilliferol Empagliflozin Isothankunic acid Madasiatic acid Madecassoside Methyl brahmate Myricetin Quercetin Rutin	SGLT-2 Sodium-glucose co-transporter 2	*Macalalad et., al 2022*
4.	Flavonol Germacrene Sitosterol Lanabecestat	Beta amyloid precursor protein cleavage enzyme 1BACE1 Inhibitor in Alzheimer's Disease	*Mawaddani et.al 2020.*
5.	Asiatic acid Madecassic acid Asiaticoside Madecassoside	Aquaporin-3(AQP3)	*Yulianti et., al (2017)*

Future prospective

Most of its pharmacological activity is attributed to asiaticoside, saponins, triterpenoid, asiatic acid, madecassoside, and madecassic acid, which have been employed as biomarkers to test the quality of the *C. asiatica* (L) plant.Other components of *C. asiatica* (L) include steroids, flavonoids, phenolic acids, amino acids, vitamins, and essential oils, which have wound-healing and skin smoothening characteristics.To meet the demand of the herbal sector, there is a need for continuous production of *C. asiatica* (L) established in vitro cultures on a big scale. Until recently, there was little to no information on using *C. asiatica* (L) in cell suspension cultures under different circumstances to increase the production of metabolites essential for commercial productivity.The increasing number of different natural therapies on the market, including *C. asiatica* (L), enhanced the potential of difficulties due to inappropriate use of these products or a lack of medical guidance, as well as the possibility of interactions between medications and medicines when used simultaneously. As a result, additional clinical research is needed to identify achievable therapeutic medications to treat a wide range of disorders.This review attempts and concludes about provide comprehensive information on plant introduction and bioactive components importance. Various biological activities of phytochemicals present in the *C. asiatica* (L) plant, and *in vitro* and *in vivo* investigation on bioactive components of plant. Various clinical studies to understand the current research prospective of the plant.

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Conflict of Interest statement

None

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