A Systemic Review on *Centella asiatica*: Traditional Uses, Phytochemistry & Toxicological Properties

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ABSTRACT:

Centella asiatica (*C. asiatica*), belongs to the Apiaceae family. , grows in moist areas. It is known as Gotu kola, Indian pennywort, Pegaga, Madukaparni for various pharmacological activities like neuroprotective, wound healing activities, memory enhancing, cardioprotective, antioxidant, anticancer, anti-inflammatory. Various phytochemical present in the plant like plant sterols, pentacyclic triterpenoids, flavonoids, isoprenoids like sesquiterpenes, phenylpropanoid and saponins derivatives like caffeoylquinic acids, eugenol derivatives. Literature survey was carried out utilising databases such as PubMed, Google Scholar, SciFinder, Wiley Online, Web of Science, Scopus, Science Direct and Research Gate. Numerous pharmacological characteristics are present in *C. asiatica*, such as antibacterial, anticancer, antidiabetic, anti-inflammatory, memory-enhancing, neuroprotective, hepatoprotective, and anti-ulcer activities. It has been reported that about 70 chemicals have been identified or purified. There have been notable pharmacological effects described for these identified phytochemicals. Therefore, the focus of future studies should be on the biological and pharmacological effects of plant extracts as well as analyses of the bioactive compounds that underlie the activity. This review has the potential to advance knowledge about *C. asiatica* and identify areas that warrant more investigation.

KEYWORDS: *Centella asiatica*, Gotu kola, Pharmacological activities, Anticancer, Phytochemicals

1. INTRODUCTION:

Extensive research is presently being undertaken on several plant species and their medicinal potential, which is revitalizing traditional medicine across [1]. The WHO estimates that approximate 80% of the global population receives their primary care from traditional medicine. The management of various ailments in folklore involves the proficient application of plant extracts and their therapeutic components [2]. The predominant species within this genus, *C. asiatica*, belongs to the Apiaceae (Umbelliferae) family and typically thrives in moist environments [3]. This plant also known as Indian pennywort, Gotu kola, Pegaga,

Madukaparni etc in various region. *C. asiatica* responsible for numerous pharmacological activities like memory enhancing, neuroprotective, antioxidant, anticancer, anti-inflammatory, wound healing and cardioprotective activities [4]. It has historically been used in folk medicine to treat several disease, including cough, fever, elephantiasis, enlarged scrotum, leprosy, scrofula, syphilis, ulcers, and skin diseases. This leafy vegetable juice serves as a tonic beverage, in addition to various other applications. A variety of compounds has been isolated from *C. asiatica*, including diverse plant sterols, pentacyclic triterpenoids, flavonoids, isoprenoids such as saponins, phenylpropanoid derivatives and sesquiterpenes including eugenol derivatives and caffeoylquinic acids [5].

In recent years, several medicinal and bioactive compounds from plant sources have shown therapeutic promise and are now undergoing comprehensive clinical evaluation. The predominant species are indigenous to South Asia, Southeast Asia, Africa. Extracts from diverse plant species, such as those in the Acanthaceae family (Andrographis paniculata and Lepidagathis hyalina), the Gynura genus (Compositae), Syzygium fruticosum, Psychotria calocarp, Boerhavia diffusa, and Molineria capitulata, have demonstrated a variety of ethnopharmacological advantages in treating numerous health issues. Spirulina platensis, acknowledged as a 'superfood' photosynthetic bacteria, and leaves from the medicinal plant Ophiorrhiza rugosa, signify new discoveries in natural anti-inflammatory medicines exhibiting anti-nociceptive properties. The furanocoumarin phytochemical class has shown significant efficacy in augmenting anti-cancer pathways in multiple tumor types, including leukemia, glioma, breast, lung, renal, liver, colon, cervical, ovarian, and prostate cancers, by modulating various cancer-associated cell signaling pathways. Twenty-one Coumarin derivatives have significant anti-cancer efficacy, especially against prostate cancer leukaemia and renal cell carcinoma. Moreover, bioactive substances such flavonoids and metabolites from cruciferous vegetables in the Brassicaceae family have potential anti-tumor actions in colorectal cancer cell lines. Additional plant substances, such as Aglaonema hookerianum and the monoterpenoid alcohol terpineol, have neuroprotective characteristics and are now under investigation for their potential biological benefits in alleviating symptoms of depression and anxiety. Ongoing research is concentrating on nanocarrier systems to enhance the bioavailability of plant-derived medicinal compounds for medical purposes. Improvements in these drug delivery techniques have the capacity to significantly augment the therapeutic use of these natural substances [6-9].

Phytochemical investigations of *C. asiatica* revealed the presence of isoprenoids, including sesquiterpenes, saponins, pentacyclic triterpenoids and plant sterols, along with phenylpropanoid derivatives such as eugenol derivatives, flavonoids, caffeoylquinic acids. Among the discovered substances, flavonoids and their derivatives consistently satisfy several pharmacological criteria. Kaempferol, a prominent phenolic component present in medicinal plants, is found in this plant both in its whole form and as a coumarate derivative. In terms of their structural activity characterisation, the coumarate derivatives of kaempferol, such as castilliferol (3-(4-Hydroxy trans-cinnamoyloxy)-4’,5,7-trihydroxyflavone) and castillicetin ([2-(3,4-dihydroxyphenyl) 5,7-dihydroxy-4-oxochromen-3-yl]E)-3-(3,4-dihydroxyphenyl)prop-2-enoate) have not been sufficiently investigated. Both compounds include a structural framework defined by a core flavonoid skeleton, augmented by a cinnamoyloxy moiety located at position 4 of the C ring. Castilliferol and castillicetin vary in

their hydroxyl group count; castilliferol has four hydroxyl (-OH) groups at C4', C5, C7, and C8(cin), whereas castillicetin includes six hydroxyl groups at C3', C4', C5, C7, C7(cin), and C8(cin) [6, 8, 10].

This review provides a detailed investigation of the morphology, distribution, traditional uses, phytochemistry of the plant. In addition to several bioactive compounds that have been identified and extracted from *C. asiatica* which lead to responsible for various pharmacological activities.

2. METHODOLOGY:

A collection of around 119 published publications that were obtained from several relevant scientific databases on the ethno-pharmacological applications of *C. asiatica*, as well as phytochemical ingredients in various in-vitro and in-vivo biological activity. Wide range of online scientific resources, such as ResearchGate, Science Direct, SciFinder, PubMed, Web of Science, Google Scholar, Wiley Online and Scopus can be used to find relevant studies, research, and investigations. To obtain the necessary information about this plant species, search terms including " *Centella asiatica*", "Gotu kola", "Thankuni", "ethno-pharmacology", "phytochemicals" and "traditional uses" were employed.

3. MORPHOLOGY:

The herbaceous creeper plant *C. asiatica* (Fig. 1) can grow up to 15 cm tall, some enormous varieties reaching up to 25 cm. The plant is made up of shovel- or spade-shaped leaves that are glabrous on both sides, orbicular-reniform, sheathing at the leaf base, with 4-6 cm long and 1.5–5 cm wide. Striated, glabrous and rooted at the nodes is the stem. Nutlets shaped like pumpkins, 3-5 mm in length, bear seeds, while the pinkish-white or green blooms are carried in numerous umbels [5, 11].

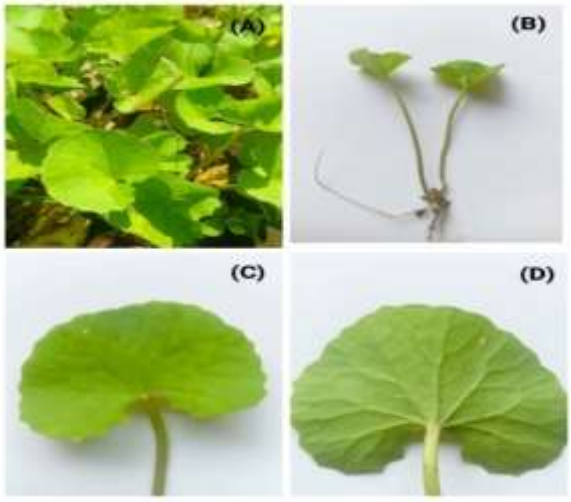


Fig. 1. *C. asiatica* plant (A); stem and root (B); upper surface of leaf (C); lower surface of leaf (D)

4. DISTRIBUTION:

C. asiatica plant grows in marshy places in tropical, subtropical regions of the world [3, 12]. It is indigenous to some areas of East and West Central Africa, as well as some temperate sections of China, Taiwan, Korea and Japan. It is also found in tropical Asian territory of the South East Asia, Solomon Islands, Indian Subcontinent, and Malaysia. It is indigenous to New South Wales in Australia, a few spacific Islands, and several areas of the United States' Southeast [13]. This plant is known as different names in different language which is shown in Table. 1.

Table. 1 List of regional common names for *C. asiatica*

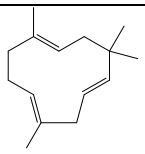
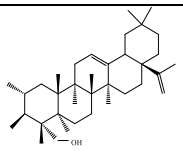
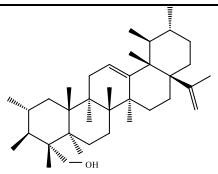
Sl No:	***Language/Region***	***Common Names***	***Ref***
1	Arabic	Artaniyal-hindi, zarnab	[5]
2	Tibetan	Sin-mnar	[5]
3	Chinese	Tungchian, ji xue cao, luei gong gen	[5, 14]
4	Thailand	Bau-bog	[5]
5	English	Indian Pennywort, Indian water navelwort, Asiatic pennywort, sheeprot, pennyweed, marsh pennywort	[5, 14, 15]
6	Swedish	Sallatsspikblad	[5]
7	French	Hydrocotyle Asiatique, e´cuelle d'eau	[5]
8	Sri Lanka	Hingolukola, gotu kola	[5]
9	German	Indischer wassernabel, Asiatisches Sumpfpfennigkraut	[14]
10	Spanish	Sombrerito, hierba de clavo	[5]
11	India (language wise)	Sanskrit- Brahmi, cheka parni, mandukaparni; Hindi- Brahmamanduki, Khulakudi; Marathi- Karivana, undri, karinga; Bengali- brahma-manduki, Thulkuri; Gujarati- karbrahmi; Telegu- saraswathi aku, brahmakuraku, manduka; Tamil- babassa, vellarai; Malayalam- kutakam	[5]
12	Persian	Sard Turkistan	[5]
13	Indonesia	Kaki kuda, tete kadho, pegagan, tete karo, anantan gede, kaki kuta, gagan-gagan, puhe beta, gang-gagan, piduh, kirok gatok, pepiduh, panegowan, calingan rambat, rending, tungke-tungke, pagaga, kos tekosan.	[14]
14	Nepal	Kholachagya	[5]
15	Italian	Idrocotyle	[14]
16	Myanmar	Minkhuabin	[5]
17	Japan	Tsubo-kusa, tsubokura	[5,

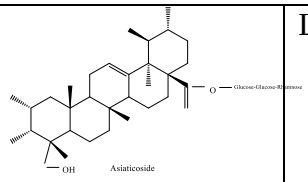
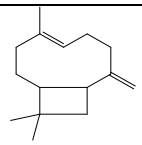
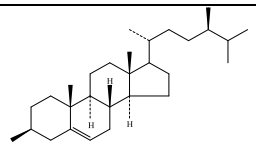
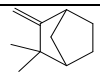
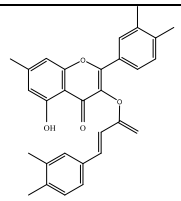
			14]
18	Mauritius	Bavilaaqua	[14]
19	Malagasy	Talapetraka	[16]
20	Malaysia	Dawoopungah-gah, pegaga	[5, 17]

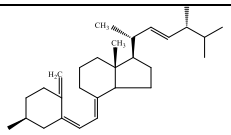
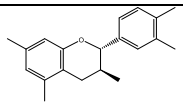
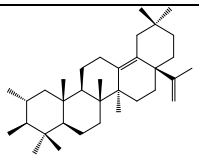
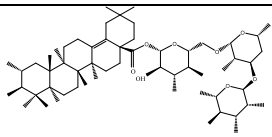
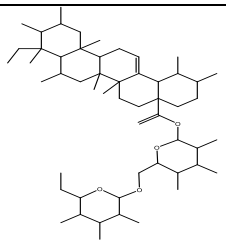
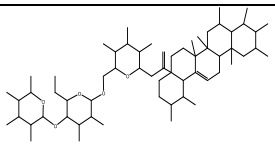
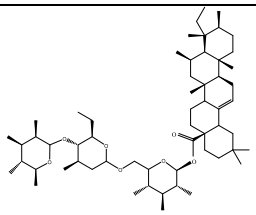
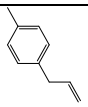
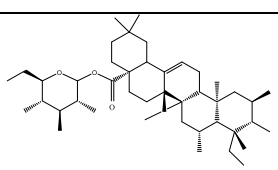
5. PHYTOCHEMISTRY:

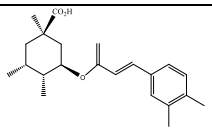
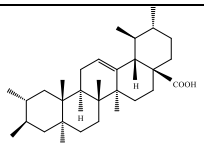
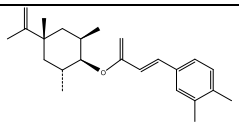
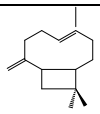
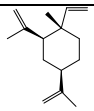
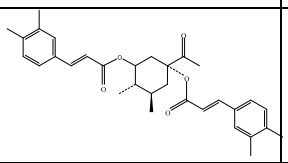
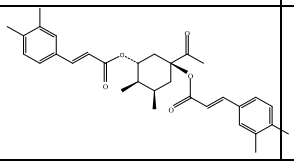
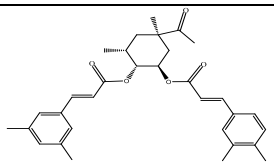
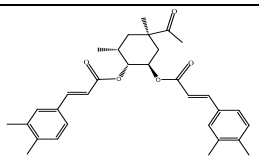
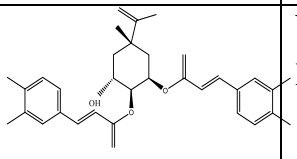
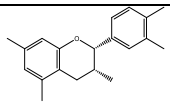
From *C. asiatica*, a number of different chemical compounds have been identified and isolated. Leaves, aerial parts and other parts contain approximately 70 chemicals, which is identified by GC, GC/MS, LC/MS, NMR, HPLC methods (Table 2). Several monoterpenoids and sesquiterpenes, including myrcene, a-humulene, bcaryophyllene, germacrene-D and bicyclogermacrene, were identified by GC-MS analysis of extracts from aerial portions [18]. Other constituents have been identified as oxygenated monoterpenes like menthone, a-terpineol; oxygenated sesquiterpenes like humulene epoxide, caryophyllene oxide and a sulfide sesquiterpenoid like mintsulfide [18, 19]. The most prevalent pentacyclic triterpenoids are saponins, such as madecassoside and asiaticoside, and their asiatic acid, aglycones and madecassic acids [3]. In addition to having a large number of phenolic and flavonoids, such as quercetin, epicatechin, kaempferol and related glycosides, *C. asiatica* is particularly rich in chlorogenic acids, a broad class of substances created when quinic acid is esterified to cinnamic acid derivatives [20].

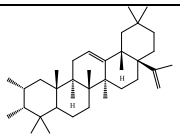
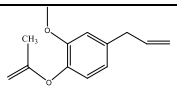
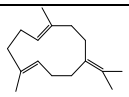
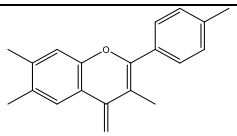
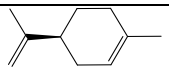
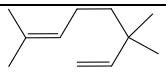
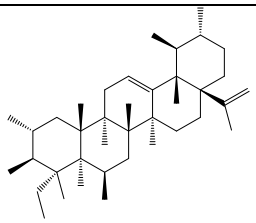
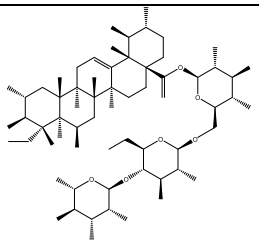
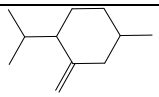
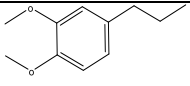
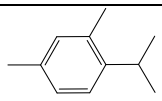
Table. 2 List of Chemical constituents presents of *C. asiatica*

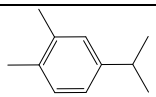
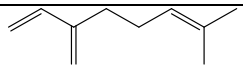
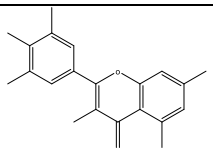
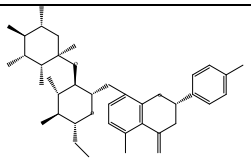
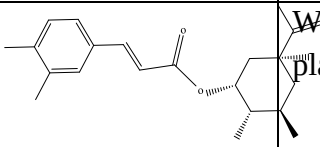
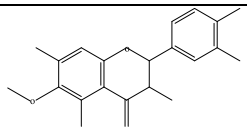
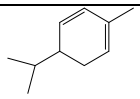
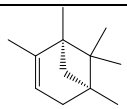
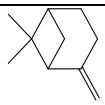
Sl no :	***Chemical compounds***	***Structure***	***Plant part***	***Identification***	***Pharmacological activities***	***Ref***
1	α-Humulene		Aerial parts	GC/MS	Antimicrobial, anti-inflammatory, antitumour .	[18, 21-24]
2	Arjunolic acid		Whole plant		Wound healing, antimutagenic and antimicrobial.	[25]
3	Asiatic acid		Leaves	GC/MS	anti-inflammatory, antioxidant,	[5, 14, 26-29]

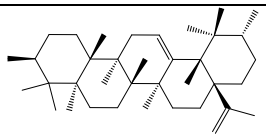
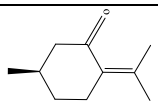
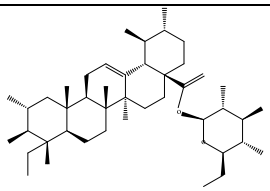
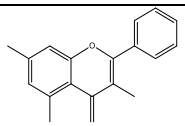
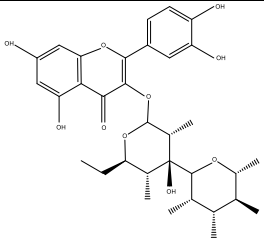
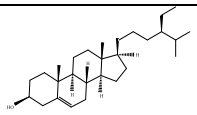
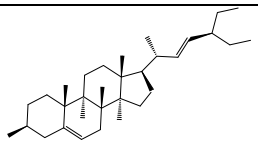
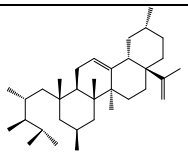
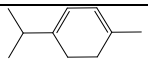
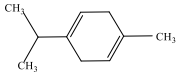
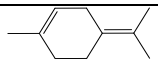
4	Asiaticoside		Leaves	GC/MS	Antioxidant, anti-tumor, anti-inflammatory, antibacterial, antidepressant.	[14, 26, 30, 31]
5	Asiaticoside B		Leaves	GC/MS	anti-inflammatory, antioxidant.	[14, 26]
6	Asiaticoside C		Leaves	GC/MS	Wound healing,anti-inflammatory, antioxidant,anti-allergic.	[3, 26]
7	Asiaticoside D		Leaves	GC/MS	Wound healing,anti-inflammatory, immunomodulatory, anti-fibriotic.	[25, 26]
8	Asiaticoside E		Leaves	GC/MS	Wound healing and enhence new skin formed.	[25, 26]
9	Asiaticoside F		Leaves	GC/MS	Wound healing,anti-inflammatory, immunomodulatory, anti-fibriotic	[25, 26]
10	Asiaticoside G		Leaves	GC/MS	Wound healing,anti-inflammatory, antioxidant,anti-allergic.	[25, 26]
11	Bicyclogermacrene		Aerial parts	GC/MS	Antioxidant, antimicrobial.	[18, 21, 32]
12	Brahminoside B		Whole plant		Anti-tumor, anti-inflammatory, immunoregulatory.	[3, 33]
13	Campesterol		Whole plant		Anti-cancer, reduce cholesterol level, antibacterial, wound healing, blood coagulation.	[34-37]
14	Camphene		Whole plant	GC/MS	Decrease intracellular cholesterol level.	[18]
15	Castillicetin		Whole plant	NMR	Antioxidant, anti-tumor, anti-microbial, anti-inflammatory, anti-obesity, hypotensive effects.	[6, 38-40]

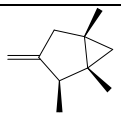
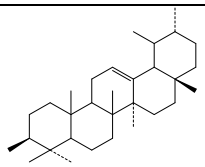
16	Castilliferol		Whole plant	NMR	Antibacterial, anti-inflammatory, Antiosteoporotic, anti-cancer, antioxidant,anthelmintic	[6, 38-40]
17	Catechin		Whole plant		Antitumor, antioxidant, antidiabetic,antimicrobial.	[41-44]
18	Centellasapogenol A		Whole plant		Anti-bacterial, antiinflammatory, antifungal.	[25, 45]
19	Centellasaponin A		Whole plant		Neuroprotective, antibacterial, antifungal.	[25, 45]
20	Centellasaponin B		Whole plant		Antidiabetic, anti-inflammatory, antioxidant.	[25, 46]
21	Centellasaponin C		Whole plant		Antidiabetic, anti-inflammatory, antioxidant	[25, 46]
22	Centellasaponin D		Whole plant		Antidiabetic, anti-inflammatory, antioxidant	[25, 46]
23	Centelloside E		Whole plant	HPLC	Inhibiting the production of collagen at wound site.	[5, 25]
24	Centelloside D		Whole plant	HPLC	Anti-inflammatory, antioxidant, wound healing.	[5, 25]
25	Chavicol		Whole plant		Antinitrosation, antimutagenic,anticarcinogenic.	[14, 46, 47]
26	Chebuloside II		Whole plant		Antibacterial, antioxidant, antidiabetic,anti-HIV,anti-aging	[25]

27	Chlorogenic acid		Whole plant	LC/MS	Antioxidant, antiinflammatory, antiviral,hypoglycemic,antimutagenic, anticardiovascular.	[5, 12, 20]
28	Corosolic acid		Whole plant		Anti-diabetic, anti-inflammatory, antiproliferative,protein kinase C inhibition.	[48, 49]
29	Cryptochlorogenic Acid		Whole plant		Anticancer, antiinflammatory, antioxidant,antimicrobial,antiviral.	[5, 12, 50]
30	β-Caryophyllene		Aerial parts	GC, GC/MS	Gastroprotective, anxiolytic, antibacterial, antioxidant,antiinflammatory	[18, 21, 23]
31	β-Elemene		Whole plant	GC/MS	Trigger cell death, stop cell division, and halt the cell cycle.	[18, 51]
32	1,3-Dicaffeoylquinic acid		Whole plant		Anti-cancer,antiviral,anti-inflammatory.	[12, 52, 53]
33	1,5-Dicaffeoylquinic acid		Whole plant			[12, 53]
34	Isochlorogenic acid B		Whole plant		Antibacterial, antimutagenic, anticardiovascular.	[12, 52]
35	Isochlorogenic acid A		Whole plant		Antioxidant, antiinflammatory,antibacterial,hypoglycemic,antimutegenic,anticancer	[12, 52]
36	Isochlorogenic acid C		Whole plant		Antioxidant, antiinflammatory,antibacterial,hypoglycemic,antimutegenic,anticancer	[12, 52]
37	Epicatechin		Whole plant		Anti-cancer, antihypertensive, antidiabetic.	[41]

38	3-Epimaslinic acid		Whole plant		Anti-tumor, antiinflammatory, antioxidant,apoptosis.	[34, 48, 54]
39	Eugenol acetate		Whole plant		Antimicrobial, antiinflammatory, analgesic and antioxidant.	[14, 55]
40	Germacrene B		Aerial parts	GC/MS	Antibacterial, antifugal.	[18, 56]
41	Kaempferol		Whole plant		Antioxidant, antiinflammatory, antidiabetes, neuroprotective, anticancer.	[57-59]
42	Limonene		Whole plant	GC/MS	Antiinflammatory, anticancer.	[18, 24]
43	Linalool		Whole plant	GC/MS	Antibacterial, antiplasmodial, antidepressant.	[18, 24]
44	Madecassic acid		Leaves	GC/MS	Anti-neural inflammation, anticancer, pulmonary.	[14, 26, 29]
45	Madecassoside		Leaves	GC/MS	Antiinflammatory, antioxidative, collagen synthesis, angiogenesis.	[14, 26, 60]
46	Menthone		Whole plant	GC/MS	Antibacterial, antifungal, antibiofilm,antiinflammatory	[18]
47	Methyleugenol		Whole plant		Antioxidant, anti-inflammatory, antimicrobial,genotoxicity.	[14]
48	Methyl thymol		Whole plant	GC/MS	Anti-inflammatory, antioxidant, antispasmodic, analgesic, antibacterial, antiseptic, antifungal,	[18]

					antitumor.	
49	Methyl carvacrol		Whole plant	GC/MS	Antibacterial, antifungal, insecticidal, antioxidant, antitumor.	[18]
50	Myrcene		Aerial parts	GC/MS	Anxiolytic, antioxidant, anti-aging,anti-inflammatory, analgesic.	[14, 18]
51	Myricetin		Whole plant		Antioxidant, antiinflammatory, anticarcinogen, antiviral,apoptosis.	[38]
52	Naringin		Whole plant		Antioxidant, antiinflammatory, anti-apoptotic, , neuroprotective, anti-asthmatic, anti-diabetic, antitussive, hepatoprotective, anti-obesity.	[43, 61, 62]
53	Neochlorogenic acid		Whole plant		Antioxidant, antiinflammatory, antiviral, antibacterial, anticardiovascular, antimutagenic, immunomodulatory,	[5, 12, 63]
54	Patuletin		Whole plant		Antiinflammatory, cytotoxic, genotoxic, hepatoprotective, antiproliferative, antiplatelet, antinociceptive, antioxidant.	[11, 38]
55	α-Phellandrene		Whole plant	GC/MS	Antitumor, antimicrobial,	[18]
56	α-Pinene		Whole plant	GC/MS	Antimicrobial, apoptosis, antimetastatic, antibiotic.	[18, 21, 24]
57	β-Pinene		Whole plant	GC/MS	Antibacterial, antidepressant, cytotoxic,antimicrobial.	[18, 24]

58	Pomolic Acid		Whole plant		Antitumor, apoptosis.	[48, 64]
59	Pulegone		Whole plant	GC/MS	Antioxidant, antimicrobial, anti-feeding, antifungal, antiviral, pesticide.	[18]
60	Quadranoside IV		Whole plant			[25, 65]
61	Quercetin		Whole plant		Antioxidant, neurological, antiviral, anticancer, cardiovascular, antimicrobial, antiinflammatory, hepatoprotective.	[59, 61, 66]
62	Rutin		Whole plant		Antioxidant, antiinflammatory.	[61, 62]
63	Sitosterol		Whole plant		Anxiolytic, analgesic, immunomodulatory, antimicrobial,anticancer, antiinflammatory.	[3, 36, 48]
64	Stigmasterol		Whole plant		Anticancer, antibacterial,antidiabetic.	[38, 67, 68]
65	Terminolic acid		Whole plant	HPLC	Antiinflammatory, anticancer,antioxidant.	[14, 69, 70]
66	α-Terpinene		Whole plant	GC/MS	Antioxidant, anticancer.	[18, 71]
67	γ-Terpinene		Whole plant	GC/MS	Antioxidant, antidiabetic.	[18, 51]
68	Terpinolene		Whole plant	GC/MS	Antioxidant, anticancer, antibacterial, antimicrobial	[18, 51]

69	α-Thjuene		Whole plant	GC/MS	Antiinflammatory, antibacterial.	[18]
70	Ursolic acid		Whole plant		Anti-inflammatory, antioxidant, antimicrobial, hepatoprotective, anticancer,.	[48, 72, 73]

6. TRADITIONAL USE:

C. asiatica has historically been widely used to treat a many types of diseases. In many countries, the plant is traditionally used in preparing juice, tonic drink, and leafy vegetable [11]. In the past, the herb was also used to treat cough, fever, elephantiasis, enlarged scrotum, leprosy, scrofula, syphilis, ulcers and as well as skin disease. Coughs are treated using a syrup made from the plant's leaves, ginger, and black pepper. Women are given leaf juice and palm jaggery as a tonic after childbirth. Intermittent fever is treated using pills made from a paste of the plant's leaves, *Ocimum sanctum* Linn, and black pepper. Clarified butter or vaseline are used to manufacture an ointment made from powdered leaves, which is used to cure elephantiasis, enlarged scrotums, and other affected areas. For syphilis, ulcers, scrofula, and leprosy, three to five grain dosages of the plant's leaf powder are used three times a day. In the meantime, a poultice prepared from freshly ground leaves pasted may be placed, or a small amount of the powder put to the ulcers [74]. Herbal preparations were administered topically to cure infectious skin conditions and hasten the healing of wounds [5]. In Sri Lanka, the herb is frequently used to make porridge for children as a way to address nutritional deficiencies [75].

7. PHARMACOLOGICAL ACTIVITIES:

7.1. Antioxidant activity

Antioxidants are substances that can protect your cells from free radicals, which can damage DNA, proteins, lipids, and various human cell types [76]. In a study, the oxidative stress caused by *C. asiatica* powder and extract was successfully decreased in Sprague-Dawley rats. The rats' levels of SOD, oxidative stress, and ROS production all decreased when the powder and extract were used, demonstrating their excellent antioxidant potential [77]. According to a different study, a standardised plant extract from China was compared with plant extracts from Turkey and India. Using the DPPH assay, the three extracts at concentrations of 250, 500, 1000, and 2000 µg/mL demonstrated radical scavenging activity. Where they found that both extract has prominent antioxidant activity but sample extract of Turkey has more antioxidant property than Indian extract [78]. Another study revealed that mice with lymphomas showed lowering levels of ascorbic acid and rised levels of antioxidant enzymes after receiving a 14-day methanolic extract supplementation [79]. In a different study, three

different solvent extracts (ethanol, light petroleum, and water) of all plant parts were evaluated using the thio barbituric acid test and a linoleic acid model system. The results showed that the light petroleum ether had very little antioxidative activity, and the water extract had lower antioxidative activity than the ethanol extract of any part. Both the water and ethanol extracts' antioxidative activity increased when the extract concentration was raised to 1000–3000 ppm [80]. Every research indicates that *C. asiatica* has prominent antioxidant activity in both in-vivo and in-vitro study.

7.2. Anticancer activity

The uncontrolled growth and proliferation of abnormal tissues is the hallmark of a large class of disorders known as cancer [81]. A study was performed to evaluate the anticancer activity of isolated asiatic acid from *C. asiatica* plant. The finding showed that cell line inhibitory concentration (IC_{50}) values of methanolic solution of asiatic acid on cancerous lung cell A549 and PC9/G, were 26.03±2.47 and 25.57±0.51 respectively [82]. According to Pittella et al., the aqueous extract showed good inhibitory activity against the mouse melanoma (B16F1), rat glioma (C6), and breast cancer cell lines (MDA MB-231) of humans [83]. Another study reported that the methanolic extract inhibited MCF-7 cell lines and caused MCF-7 cells to undergo apoptosis through increased annexin staining, nuclear condensation, induction of DNA breaks and loss of mitochondrial membrane potential [84]. All findings point to *C. asiatica*, has promising anticancer activity but future research is require to discover the lead molecules except asiatic acid.

7.3. Antidiabetic activity

Diabetes is a chronic illness characterised hyperglycemia caused by either insufficient pancreatic manufacture of insulin or inefficient body utilisation of insulin [85]. Rahman et al. evaluated antidiabetic effect of ethanolic extract of *C. asiatica* and they found that, dose of 500 mg/kg extract has shown the highest antidiabetic activity against adult wister albino rats [86]. Another research study was conducted to evaluate the antidiabetic effects of ethanolic extract in rats. They have demonstrated that extract prevent intestinal α-amylase and disaccharidase enzymes from binding to glucose fibres, hence preventing the absorption of glucose [87]. Invitro study of α-amylase inhibitory activity found that, ethanolic extract had prominent antidiabetic activity when compared with standard acarbose [88]. Another study reported that ethanolic extract was administered on obese diabetic rat over a lengthy period of time, after that rat's blood glucose level returned to normal [89]. Above the all data we conclude that the ethanolic extract of *C. Asiatica* is capable to reduce blood glucose level but it is yet unknown which molecule is causing the antidiabetic effect.

7.4. Anti inflammatory activity

Inflammation is the vascularised tissue's reaction to pathogens and damaging stimuli. It happens when host defence molecules and cells are taken from the circulation and sent to the areas where they are required to eliminate the toxic substances [90]. An investigation into the

anti-inflammatory properties of *C. asiatica* aqueous extract revealed that intraperitoneal injection of the extract (2 mg/kg) significantly reduced prostaglandin E2-induced paw edema in mice [91]. An additional investigation was conducted to assess the anti-inflammatory properties of asiatic acid, a compound present in *C. asiatica*. Asiatic acid successfully decreased the paw edema in mice at the 4th and 5th h after λ-carrageenan administration by lowering the level of iNOS, NF-κB, MDA and COX-2 in the edema paw via increasing the activities of SOD, GPx and CAT in the liver [92]. A research was performed to evaluate the carrageenan induced paw edema of chloroform and methanolic extract at 100 and 200 mg doses in Wistar albino rat. They found that 200 mg doses of methanolic extract has promising anti-inflammatory activity by inhibiting the release of histamine or kinins [93]. George et al. (2009) conducted an anti-inflammatory assay using an alcoholic and aqueous extract of *C. asiatica* in a distinct investigation. They discovered that both had anti-inflammatory properties and might be possible both extracts contain terpenes and luteolin [94]. Taking into account all the data, it can be concluded that *C. asiatica'*s aqueous, methanolic, and alcoholic extracts all exhibited anti-inflammatory action. Asiatic acid, terpenes and luteolin are responsible chemical which are present in that plant.

7.5. Memory enhancing and neuroprotective activity

Neurodegenerative disease rise in inflammation, oxidative stress and excitotoxicity that results in amnesic cognitive impairment which lead to basic neuronal cell death and a decrease in neurotransmitters response [95]. A study was conducted to assess their passive avoidance (PA) and active avoidance (AA) of isolated asiatic acid on male Spraque-Dawley rats. They discovered that asiatic acid at a level of 30 mg/kg considerably enhanced memory in both the PA and AA tests [96]. Another study shows that *C. asiatica* has neuroprotective potential against cognitive impairment and mito-oxidative damage caused by aluminium. This led to a significant increase in the quantity of aluminium, acetylcholine esterase activity, and caspase-3 activity in the cerebral cortex and hippocampus of the rat brain. Additionally, aqueous leaf extract at the dose at 150 and 300 mg/kg significantly improved memory function, oxidative defence decreased aluminium levels, caspase-3, acetylcholinestrease activity, and reversal of mitochondrial enzyme activity in mice compared to those treated with aluminium [97]. Based on the available information, we conclude that the isolated asiatic acid and the aqueous extract of *C. asiatica* have the potential to improve memory and protect neurones.

7.6. Hepatoprotective activity

The purpose of hepatoprotective agents is to protect the liver from harm, promote the regeneration of hepatic cells, and enhance liver functioning [98]. In a study conducted by P. Duggina et al. (2015), the protective properties of centella triterpene saponins extract were examined in relation to cyclophosphamide-induced hepatotoxicity in rats. They discovered that the extract therapy dramatically reduced the hepatic mRNA level of TNF-α, which had been raised after CYP administration. It also decreased the levels of mRNA expression of other cytokines, such as IFN-γ, IL-2, and GM-CSF. The liver's histopathological analysis

revealed that the extract restored the rats' hepatic system function [99]. The hepatoprotective effects of the C. asiatica extract on rats with type 2 diabetes were assessed in another investigation. After receiving a 500 mg/kg body weight extract treatment for 14 days, diabetic rats showed a decrease in MDA, a rise in FRAP and GSH levels, and an increase in GST and GPX activities. The control group experienced a reduction in hepatic concentrations of TNF-a, IL-1b, and MCP-1 to 63%, 68% and 75%, respectively [100] Hepatoprotective effect against galactosamine and CCl4 induced hepatotoxicity by Asiatic acid was assessed by research, and it was found to be significantly active [101]. We may conclude that *C. asiatica* possesses a considerable amount of hepatoprotective activity; however, other than Asiatic acid, the compounds causing this activity still need to be explored.

7.7. Anti ulcer activity

A rupture or discontinuity in a body membrane that prevents an organ from functioning normally is called an ulcer [102]. The antiulcer qualities of *C. asiatica* are evaluated by numerous researches. Cheng et al. (2003) used male Sprague-Dawley rats to investigate the anti-ulcer effects of various concentrations of C. asiatica aquous extract and extracted asiaticoside. At days 3 and 7, they demonstrated promising action against ulcers in a dose-dependent manner by decreasing myeloperoxidase activity and promoting angiogenesis and the proliferation of epithelial cells. Additionally, the expression of essential angiogenic factor and basic fibroblast growth factor was elevated in the rat ulcer tissues [103]. Another study was conducted to explore the gastriculceration effects of *C. asiatica* extract in Charles-Foster rats. It was shown that a dose-dependent elevation of GABA levels in the brain was linked to a dose-dependent decrease in stomach ulcers [104]. The plant's fresh juice significantly protected against the experimental ulcer models; this protective effect against ulcers may have resulted from the mucosal defensive elements being improved [105]. Abdulla et al, revealed that plant extract is capable to protecting gastric mucosa and inhibiting of leucocyte infiltration of the gastric wall in rats [106]. Considering all the information, we conclude that the aqueous extract of *C. asiatica* can prevent rat ulcers. Asiaticoside is the primary ingredient that has the anti-ulcer properties. There is a need to investigate other chemicals that might have anti-ulcer properties.

7.8. Antibacterial activity

The term "antibacterial" describes materials or activities that either kill bacteria or stop them from growing. In a study, the hydrodistillated essential oil from dried *C. asiatica* plant was used to measure the antibacterial activity using a Clevenger apparatus. The isolated essential oil demonstrated broad-spectrum antimicrobial activity against Gram-positive (*Bacillus subtilis, Staphylococcus aureus*) and Gram-negative (*Escherichia coli, Shigella sonnei, Pseudomonas aeruginosa*) species, with minimum inhibitory concentrations (MIC) ranging from 1.25 to 0.039 mg/ml [18]. A different study found that methanolic extract have antibacterial properties against Methicillin-Resistant S. Aureus (MRSA) and Gram-positive S. aureus ATCC 25923 [107]. Taking into account all the data we conclude that methanolic

and aqueous extract of *C. asiatica* have strong antibacterial action against bacteria, both gram-positive and gram-negative

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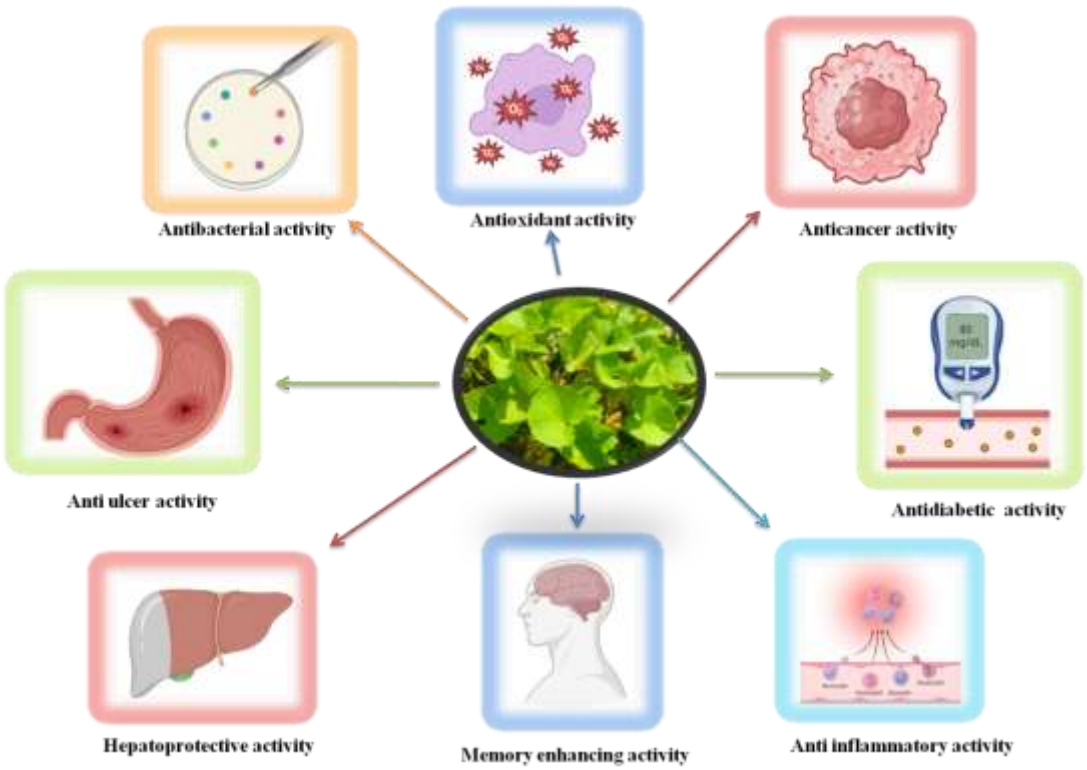

Fig. 2. *C. asiatica* plant's various pharmacological activities

8. CLINICAL TRIALS:

Gotu kola, or *Centella asiatica*, is a medicinal herb used in traditional medicine for a number of ailments, including skin disorders, wound healing, and cognitive improvement. To assess its safety and effectiveness, numerous clinical trials have been carried out. This is a summary of the main fields in which Centella asiatica has been investigated. Patients having a history of type II diabetes, a stable HbA1c level, and a total symptom score (TSS) of ≥4 indicating symptomatic symmetrical diabetic neuropathy were recruited for the trial. *Centella asiatica* chosen triterpenes (CAST), a standardized extract made from the CA herb, are said to help lessen diabetic neuropathy. CAST dosage was increased from 120 mg to 240 mg daily. The initial daily dose of 120 mg was increased by 60 mg every 4 weeks for the first 12 weeks on 43 patients in order to reach the maximum dose. The researchers discovered improved neurological state and increased oxidative status after 52 weeks [108]. In Eastern medicine, *Centella asiatica* is said to enhance human cognitive performance. In preclinical research, *C. asiatica* aqueous extracts enhance cognitive function in animal models of aging and Alzheimer's disease (AD) by modifying genes involved in the antioxidant response that are dependent on nuclear factor-erythroid-2-related factor 2 (Nrf2) and mitochondrial biogenesis. According to Kirsten M. Wright et al. (2022), 185 participants received two acute dosages (2 g and 4 g) of CAP (*C. asiatica* aqueous extract product) for 14 days in a single-center, randomized, double-blind, crossover research that may have improved cognitive

performance. Consequently, it was discovered to enhance the expression of the NRF2 (nuclear factor-erythroid-2-related factor 2) gene, which aids in the treatment of cognitive decline [63]. Preclinical research on a *Centella asiatica* water extract (CAW) and its bioactive constituents provides compelling evidence of its potential as a phytotherapeutic agent for Alzheimer's disease and cognitive loss in aging by influencing synaptic density, mitochondrial activity, and antioxidant response. Here, 33 individuals in a 60-day clinical trial by Wright Kirsten M. et al. (2022) received a 70% hydro-ethanolic extract of C. asiatica (500 mg/capsule), which may assist to reduce anxiety. After 60 days, researchers discovered that all of the patients had decreased stress, lessened anxiety, and eliminated despair [109]. In order to determine which treatment best addresses healing time, bleeding, and discomfort in the treatment of chronic anal fissures (AF), Chiaretti Massimo et al. (2018) tested and compared the effects of flavonoids (Fs) and *Centella asiatica* (Ca) with the conventional approach. In order to determine whether *C. asiatica* capsules were appropriate for healing chronic anal fissures, 98 volunteers were given 60 mg tablets twice a day. After eight weeks, it was discovered to be effective in reducing pain and bleeding in the treatment of chronic anal fissures [110]. *Centella asiatica* extract capsules are a Thai herb preparation that helps diabetic wound patients heal their wounds more quickly and reduce scarring. 200 participants were given two 50 mg extracted asiaticoside capsules three times a day in order to determine whether *C. asiatica* extract capsules were efficient in healing diabetes patients' wounds, according to Paocharoen MD Veeraya et al. (2010). It was discovered after 21 days that it speeds up the healing process of wounds by promoting the production of human collagen I, collagen matrix remodeling, and glycosaminoglycan [111]. For many years, *Centella asiatica* has been used as a medicinal plant to help cure wounds. It is ineffective at accelerating the healing of wounds caused by laser resurfacing. According to DamkerngsuntornWilawan et al. (2019), 30 participants were given *C. asiatica* extract (0.05% w/w gel) four times a day for seven days and twice a day for thirty days to see if it had an impact on facial wound healing over a ninety-day period. Following the completion of these periods, it was determined that topical use of 0.05% w/w ECa 233 could enhance wound appearance and skin erythema following Er:YAG (erbium-doped yttrium aluminum garnet) 2940 nm laser resurfacing for acne scars [112]. Burns occur frequently and are linked to a high rate of fatalities, disabilities, and expensive expenses. A common therapeutic herb that promotes wound healing in humid regions of various tropical nations is *Centella asiatica* (L.). We evaluated Centiderm's and silver sulfadiazine's (SSD) effectiveness in treating individuals with partial thickness burning based on prior research. According to MD Amin Saeidinia et al. (2017), 75 participants received Centiderm ointment, a derivative of C. asiatica, for 14 days in order to assess its impact on burn patients' wound healing. Centiderm ointment was found to increase re-epithelialization and full healing without infection, in addition to improving objective and subjective signals [113]. More local studies are being conducted these days on herbs that may offer a healing environment for effective wound care. In place of those foreign dressings, herbal wound products are currently being introduced. This study sought to document the therapeutic effectiveness of bandages made of polyester with plant extracts in the treatment of second-degree burns. According to Muangman, MD Pornprom et al. 2016, Herbal dressing: gauze dressing impregnated with lipidocolloids, 5% Centella asiatica, and 2.5% *Aloe vera* extract (changed the dressings every 3 days) on 35 participants for evaluate its

effectiveness towards Wound healing. The findings of this study allow for the conclusion that, in comparison to normal wound dressings, herbal dressings containing 2.5 percent Aloe vera and 5 percent Centellica asiatica healed burn wounds more quickly and were linked to shorter hospital admissions after 21 days. After 21 days, the study's findings allow for the conclusion that, in comparison to conventional wound dressings, herbal dressings containing 2.5% aloe vera and 5% centellica asiatica accelerated the healing of burn wounds and were linked to shorter hospital admissions [114].

Considering all the information, we conclude that aqueous extract, hydroethanolic extract capable to reduce diabetic neuropathy, anxiety and also improve the cognitive function, chronic anal fissure, wound healing. Another side extract mediated ointment or dressing gauze help to improve wound healing on burn patients. Many pharmacological activities like antiulcer, anticancer, memory enhancing and other activities show promising effect but clinical trials on this topic not performed till now, so still need to be explored.

Table.3 List of reported *C. asiatica* mediated clinical trails

Sl no.	***Material tested***	***Purpose activity***	***Duration***	***Number of patients***	***concentration***	***Effect***	***Ref***
1	*C. asiatica* selected triterpenes	Reduce Diabetic neuropathy	52 weeks	43 patients	240 mg/day	Improving in neurological status and may increasing oxidative status.	[108]
2	*C. asiatica* aqueous extract	Improve cognitive function	14 days	185 participants	2 g and 4 g	increases NRF2 gene expression	[63]
3	70% hydro-ethanolic extract of *C. asiatica*	Reduce anxiety	60 days	33 participants	500 mg/capsule	Reduced stress, attenuated anxiety, negated depression	[109]
4	*C. asiatica* capsule	healing of chronic Anal Fissure	8 weeks	98 participants	60 mg tablets twice per day	Reduce the bleeding and pain in treatment of chronic Anal Fissure	[110]

5	*C. asiatica* extract capsule	Wound healing of diabetic patients	21 days	200 participants	Two 50 mg of extracted asiaticoside capsules three times/ day	Increase wound healing process by stimulate human collagen I synthesis, enhance collagen matrix remodelling and promote the synthesis of glycosaminoglycans	[111]
6	*C. asiatica* extract	Wound healing on the face	90 days	30 participants	0.05% w/w gel applied 4 times for 7 days per day and 2 times per day for 30 days	After Er:YAG 2940 nm laser resurfacing for acne scars, topical administration of 0.05% w/w ECa 233 may improve skin erythema and wound look.	[112]
7	A centiderm ointment derived from *C. asiatica.*	Wound healing on burn patients	14 days	75 participants		Centiderm ointment enhanced re-epithelialization and full healing without infection in addition to improving objective and subjective signs.	[113]
8	Herbal dressing: a gauze dressing infused with 2.5% Aloe vera extract, 5% *Centella asiatica,* and lipidocolloids.	Wound healing on burn patients	21 days	35 participants	changed the dressings every 3 days	The study's findings support the notion that, in comparison to conventional wound dressings, herbal dressings containing 2.5 percent Aloe vera and 5 percent *Centellica asiatica* tended to heal burn wounds more quickly and were	[114]

						linked to shorter hospital stays.	

9. TOXICITY STUDIES:

Toxicity is the process by which specific toxicants interact with live cells to assess the degree of harmful health effects on living things. The toxicity of plant extracts must be experimentally screened in order to guarantee the samples' efficacy and safety [115]. A few writers have examined the level of toxicity of C. asiatica extract, but to date, no significant negative impacts on living things have been reported. Using a model of Swiss mice, Chauhan P.K. et al. assessed the acetone extract of *Centella asiatica's* acute and subacute toxicity. Numerous biochemical markers were assessed following administration of the extract for one day (acute model) and for fifteen days (subacute model). According to this experiment, the extract's LD50 is greater than 4000 mg/kg, and subacute therapy did not alter haematological markers or corporal weight. Nevertheless, there was a shift in liver weight but not in hepatic enzyme levels. This implied that *Centella asiatica* does not affect liver function. Although some variations in the creatinine content were noted, they were not related to the extract dosage [116]. Another study was conducted to evaluate the safety levels of *Centella asiatica* (aerial pars) in albino rats during a 30-day oral dosing period. Test groups II, III, and IV were given graded dosages of 250, 500, and 1,000 mg/kg, whereas control group I was given distilled water. The whole blood was utilised for haematological investigations, the DNA fragmentation assay, and the measurement of marker enzyme levels in serum after blood samples were taken on the thirty-second day. Serum biomarkers (AST, ALT, BUN, and creatinine) and the apoptotic index were significantly elevated in rats in groups III and IV. When compared to the control group, the viability count in the treatment groups decreased statistically significantly. Additionally, histopathology showed mild renal tissue alterations and severe liver damage [117]. A research was performed to investigate the acute toxicity of *Centella asiatica*, Swiss mice were given oral doses of 3, 5, and 7 g/kg body weight. Swiss mice were exposed orally using water as a vehicle for a single delivery of the whole plant powder in the form of aqueous slurry. They keep an eye on variations in body weight, food and water consumption, and cage side conditions. Even at the maximum dosage level, 7 g/kg body weight, no mortality was observed, demonstrating that *Centella asiatica* plant powder has no discernible harmful effects on mice [118]. Another toxicity investigation examined the effects of 2000 mg/kg body weight of *Centella asiatica* extract-mediated iron oxide nanoparticles (CAIONPs) on Swiss mice. Over the course of 14 days, mice were monitored for clinical, behavioural, and mortality indicators of toxicity. Mice were killed by cervical dislocation after two weeks, and their tissues were taken, preserved in 10% formalin solution, and then used for histopathological investigations. Both the control and CAIONP-treated tissues showed no appreciable physiological alterations. No demyelination or anomalies in the grey or white matter of the brain were found. The myocardial and pericardium of the

Control and CAIONP-treated hearts were both normal. In both groups, the adrenal gland displays a normal adrenal cortex and medulla. Both the control and CAIONP-treated mice's liver hepatocytes showed no symptoms of inflammation or necrosis. During the course of treatment, this investigation verified that CAIONPs were safe and nontoxic to the liver, heart, brain, and adrenal gland [119].

Based on all the information, it can be said that while acetone extract, aqueous slurry, and iron oxide nanoparticles mediated by *Centella asiatica* extract do not exhibit any toxicity to Swiss mice, extract of *C. asiatica* at doses of 500 and 1,000 mg/kg is responsible for histopathological modification. To accurately determine the range of toxicity of the *C. asiatica* plant, more research will be required.

10. CONCLUSION:

The investigation outlines the phytochemical properties, traditional uses and pharmacological use of *C. asiatica* by evaluate the provided results. The vast majority of published research has concentrated on the various pharmacological characteristics of plant extracts. It is reported that about seventy chemicals have been isolated or identified from *C. asiatica*. There have been documented strong pharmacological effects for the majority of these recognised phytochemicals. The phytochemicals included in this plant provide a range of benefits, including anti-inflammatory, antioxidant, and anti-ulcer effects. Further research is needed in a number of domains, such as hepato-protective, anti-diabetic, and anticancer actions, in order to identify and examine the lead compounds. The majority of research on pharmacological activity has been found to be restricted to in vitro and in vivo screening, which does not clearly offer a chance to investigate the pharmacokinetics, bioavailability, and mechanisms of action. Even though *C. asiatica* has a lot of medical potential, no clinical trials are carried out. Thus, to expedite the development of a novel medication derived from this plant, clinical investigations must be conducted. The extraction and separation of phytochemicals under the guidance of bioassays has likewise seen very little research. Future studies should examine and substantiate the conventional claims of *C. asiatica* by concentrating on bioassay-guided drug development.

DECLARATION OF COMPETING INTEREST:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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