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An overview of *Centella asiatica* and its therapeutic applications

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ABSTRACT

Globally, medicinal herb intervention has become popular in treating many illnesses. *Centella asiatica* (*C. asiatica*), a plant native to Southeast Asia, is utilized extensively due to its pharmacological and therapeutic benefits attributed by its triterpenoids and saponins. It has been widely researched for a variety of medicinal properties, including antidiabetic, antioxidant, wound healing, reproductive, sedative, anxiolytic, digestive, gastric ulcer, cognitive, antidepressant, and anti-inflammatory effects. The sedative qualities are associated with regulating the HPA axis to mitigate stress and modulate GABAergic activity, while its capacity to promote collagen production, provide antioxidant protection, and lower inflammation aids in the healing of wounds. Owing to a wide range of literature on *C. asiatica,* the significant discoveries about various diseases are occasionally overlooked. Hence, more concise and succinct information is warranted. This review aimed to summarize the potential medicinal aspects of *C. asiatic*a, highlighting the medicinal properties, physicochemical properties and health benefits along with future direction of the therapeutic potential. While many of the well-established properties and effects have been proven, the procurement of further clinical trials must be attended to involving the determination of standardized procedures and investigate the ultimate possible function of *C. asiatica* in treating diverse medical diseases, thus, to fully comprehend the therapeutic benefits of the herb. By possessing numerous pharmacological properties, *C. asiatica* could potentially offer greater assistance in the medical world for treating the patients while minimizing risks and mitigating degenerative effects.

Keywords: *Centella asiatica; antioxidant; antidiabetic; wound healing and sedative*

INTRODUCTION

Centella asiatica (*C. asiatica*) is a medicinal herb from the Umbelliferae family (Idrus et al., 2018), widely known by the locals as "Daun Pegaga". Various studies demonstrated that *C. asiatica* has a wide range of pharmacological effects including wound healing, sedative, anxiolytic properties, antidepressant, cognitive and antioxidant properties. In addition, the herb had therapeutic and relieving effects on common diseases such as dysentery, kidney problems, inflammations, allergic and viral fever (Sun et al., 2020). According to tradition, the herb is practically used as remedies to treat minor scars, wounds, and lesions (Azis et al., 2017; Saeidinia et al., 2017). It is found that *C. asiatica* allows the process of wound healing (Gohil et al., 2010; Khairuddin, 2016) with the aid of structural proteins synthesis stimulation in both of in-vitro and in-vivo (Gohil et al., 2010; Shukla et al., 1999), followed by triggering the new formation of blood vessel (Francis & Thomas, 2016; Gohil et al., 2010), and finally promoting tissue regeneration (Hashim et al., 2011). *C. asiatica* is one of the most multi-functional herbal supplements for various treatments and mechanisms of action in both clinical and preclinical studies. The therapeutic potential of this multipurpose herb is universal in terms of its efficacy and versatility which may lead to more convincing detailed research that appears crucial.

C. asiatica is imperative to heal wounds and acts as a certain medication as it possesses beneficial antioxidant and anxiolytic properties. Previous reports have reported probable actions of this multifunctional herb extract, such as the ability to produce various good properties like sedative agents, antidepressants, and antimicrobial agents (Azis et al., 2017; Somboonwong et al., 2012).

Like any other plants, *C. asiatica* present its pharmacological activities through their main chemical components such as triterpenes glycosides, pectin, volatile oils, alkaloids, amino acids, iron, calcium, vitamins and phosphorus (Gray et al., 2018). Despite that, several of the triterpenoids prove to become the significant ones. They are the madecassoside, asiaticoside, madecassic acid, and asiatic acid as shown in Figure 2. Asiaticoside and madecosside exert biological activity through converted into aglycone; madecassic acid, and asiatic acid (Ruksiriwanich et al., 2020). They have been considered pharmacologically active ingredients which are beneficial to human health. In addition, researchers found out that the effectiveness of the asiaticoside application as wound healing agent which has been tested on injured Sprague Dawley rats (Somboonwong et al., 2012).

With the recent growth in the body of literature for *C. asiatica*, this mini review is needed to give overview of its role to avoid future cross-studies or unnecessary research due to missed reviews of the existing research. In this mini review, relevant studies related to the medicinal properties, health benefits and physicochemical properties of *C. asiatica* were identified and summarised.

BOTANICAL DESCRIPTION OF PLANT

C. asiatica, also known as “pegaga” in Malay, is commonly consumed by local communities of Malaysia and widely used as a medicinal herb in traditional medicine such as Traditional Chinese Medicine and Ayurvedic medicine (Gray et al., 2018). *C. asiatica* has been recognized as a very potent herb belonging to the *Umbelliferae* family plant. It is classified as a perennial herbaceous creeper. *C. asiatica* preferably grows most in a wet, moist environment throughout swamps, rice paddies, and even in uneven, rocky lands, especially at high altitudes (Singh et al., 2010). This plant is recognized with their spade-like shaped leaves and uneven scalloped edges that emerge on a row of petioles clustered around the stem nodes as shown in Figure 1(Gray et al., 2018). Some are observed with green or pinkish-white small flowers which come in a crowd of parts not to mention the seeds are considered as round-shaped, small nutlets having a length of 3-5mm and attaining height up to 15cm (6 inches). It was reported that the fresh leaves of *C. asiatica* contain fiber, calcium, potassium, provitamin A, vitamin B, C and carotenoids (Chandrika & Kumarab, 2015). This herb is a modern and traditional botanical remedy used for health and beauty products worldwide. Malaysia and Indonesia use *C. asiatica* for culinary purposes such as side salads or healthy smoothies (Plengmuankhae & Tantitadapitak, 2015).

TRADITIONAL USES OF *C. ASIATICA*

Widely known for its potential in both medicinal and nutritional purposes, *C. asiatica* is commonly eaten raw as “ulam” or salad and made into supplemental drinks in many countries around the globe. *C. asiatica* has also been used traditionally for the treatment of a variety of disorders, diseases and conditions pertaining to skin and cognitive health, as well as for general well-being. One of its main traditional uses is wound healing (Choi et al., 2017; Hussein et al., 2017). Historically, societies have turned to *C. asiatica* to speed up the healing of wounds and injuries. The plant has gained a reputation for its capacity to promote the production of collagen and aid in tissue regeneration, which has helped previous generations of people heal wounds effectively (Yao et al., 2017). Apart from that, this miracle herb had done wonders where it was used to improve cognitive function in addition to its physical therapeutic properties. It is frequently referred to as a brain tonic , with historical links to better memory, focus, and overall mental performance (Gray et al., 2018). Earlier communities have incorporated this herb into their wellness routines, recognizing its ability to improve cognitive health and energy.

Another traditional application of *C. asiatica* includes skincare, where it has been used to treat a variety of dermatological and skin disorders. The anti-inflammatory characteristics possessed by *C. asiatica* make it excellent for relaxing and treating skin irritations, dermatitis, and eczema (Park, 2021). This traditional wisdom emphasizes its importance in overall well-being, addressing both internal and external health issues. *C. asiatica* has been valued for decades in the field of mental health for its anti-anxiety and stress-relieving effects. Traditional practices frequently include the use of this herb for its adaptogenic properties, which help the body adapt to stimuli and provide a sense of serenity (Jana et al., 2010; Orhan, 2012). This ancient consumption is consistent with recent research on its potential as a natural stress reliever.

Additionally, *C. asiatica* has traditionally been employed as an anti-inflammatory therapy, demonstrating its usefulness in treating inflammation-related illnesses such as arthritis (Dahanukar et al., 2000; Newall et al., 1996). Furthermore, traditional therapies using *C. asiatica* include digestive health, where it has been reported to aid digestion and boost appetite.

Figure 1

C. asiatica plant

Notes: C. asiatica plant, presenting its spade-like leaves and small flowers, which are typically small, rounded, and fan- or kidney-shaped. They grow in clusters along thin-like stems and produce small, inconspicuous flowers that add to its overall aesthetic appeal.

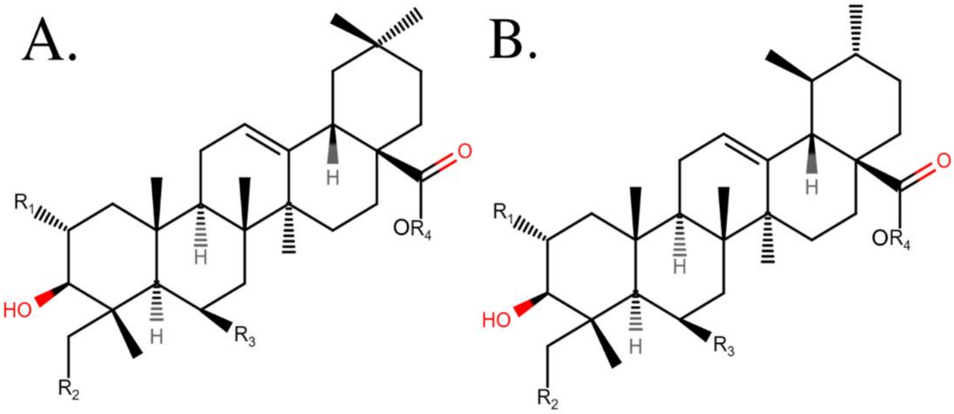
PHYSICOCHEMICAL CHARACTERISTICS OF *C. ASIATICA*

The contents of *C. asiatica* is mainly classified into saponins which include asiaticoside and madecassoside, and their aglycones such as asiatic acid and madecassic acids. Researchers found these compounds to be the most abundant pentacyclic triterpenoids and considered to be the major active constituents in *C. asiatica* plant (Gray et al., 2018). In addition, the total extract contains lignoceric, palmitic, oleic, stearic, linoleic, and linolenic acids (Chandrika & Kumarab, 2015). Gas chromatography-mass spectrometry (GCMS) analysis found that P- cymene was the main constituent in *C. asiatica* pure essential oil (Francis & Thomas, 2016). P-cymene is a monoterpene found in plant species used for medicine and food purposes. It shows a range of biological activity including antioxidant, anti-inflammatory, antinociceptive, anxiolytic, anticancer and antimicrobial effects. The saponins which include asiaticoside are mainly responsible for wound healing and vascular effects.

Several triterpenoid compounds have been isolated from *C. asiatica*. The most important ones are asiaticoside, asiatic acid, madecassic acid and madecassoside (de Padua et al., 1999). They have been considered pharmacologically active ingredients which are beneficial in improving human health. Several studies indicated that *C. asiatica* and its triterpenes were effective in many diseases (Razali et al., 2019; Wu et al., 2020). *C. asiatica* is reported to have a significant level of pentacyclic triterpenoids, which also refer to centelloids. These centelloids as presented in Figure 2, have been widely used as an important biomarker for *C. asiatica*, that act as protective compounds due to their antimicrobial activities (James & Dubery, 2009). Extracts from *C. asiatica* demonstrate a broad range of pharmacological effects through their antioxidant activities in several preclinical models (Buranasudja et al., 2021). As acknowledged in the previous review, the vast physical structure of pentacyclic triterpenoids in *C. asiatica* has been observed (Azerad, 2016). The centelloids are divided into two subtypes; the oleanane and ursine series. Both of these structures can be distinguished by the methyl substitution pattern on C-19 and C-20 (Azerad, 2016).

Figure 2

Chemical structure of centelloids



Notes: Chemical structure of centelloids; A. Ursane-type centelloids, B. Oleane-type centelloids. R_1 to R_{-3} = H or OH, R_4 = H or oligosaccharide.

C. ASIATICA PROPERTIES AND ITS EFFECTS

Antioxidants properties

Oxidative stress is one of the most common phenomena involving the accumulation of reactive oxygen species (ROS) and free radicals, for instance, superoxide (O^2•), hydroxyl (OH), and peroxyl (ROO) which causes various major pathological conditions. An antioxidant is a molecule stable enough to donate an electron to a rampaging free radical and neutralize it, thus reducing its damage effects. These antioxidants delay or inhibit cellular damage mainly through their free radical scavenging property. *C. asiatica* has been proven for its ability to scavenge free radicals and have potential to counteract the oxidative damage done to the body. *C. asiatica* contains various phenolic compounds as well as flavonoids, which are considered to be the most potent scavengers of free radicals (Zainol et al., 2003). Moreover, analysis by using ultra-high performance liquid chromatography–mass spectrometer has identified major components such as kaempferol, ferulic acid, asiatic acid, chlorogenic acid and gulonic acid which might be responsible for the antioxidant activity of the *C. asiatica* (Kumari et al., 2016; Razali et al., 2019). These studies had successfully demonstrated that the extracts from *C. asiatica* pertains to a broad range of pharmacological effects through their antioxidant activities.

Free radical damage contributes to the aetiology of many chronic health problems such as cardiovascular and inflammatory disease, cataract, and cancer. Imbalances between free radicals and antioxidant defence caused a phenomenon called oxidative stress which leads to oxidative damage that involves the macromolecules such as nucleic acid, proteins and lipids. Centelloids including asiatic acid, madecassic acid, asiaticoside, and madecassoside are the most important constituents isolated from *C. asiatica* have been shown to decrease oxidative stress of Parkinson's model induced-mice via an enhancement of cellular antioxidant enzyme activities (Bhatnagar et al., 2017). Classified to be under age-related skin disorder, callus extract of this herb was able to reduce this contingency, more likely to enhance the capacity of fibroblasts and ameliorate the H_2O_2-induced-cytotoxicity (Buranasudja et al., 2021).

At this time, the utilisation of *C. asiatica* has become a common practice all around the globe in treating other illnesses and diseases. Occasionally, the aqueous extract would also be an attractive approach for its cheap, non-toxic, non-flammable and holds the highest polarity (Das et al., 2010) compared to other solvents (Abubakar & Haque, 2020). The aqueous extract can be safely used for oral consumption or administration treatments, although that its non-volatile and the constituents of the herb were still extractable. A study involving amyloid beta (Aβ)-induced hippocampal neurons that triggered oxidative stress and mitochondrial dysfunctions have been reversed by the treatment of *C. asiatica* aqueous extract (Gray et al., 2017). Similar extract form could also suppress lipid peroxidation that is caused by several liver toxic injuries (Intararuchikul et al., 2019; Kumari et al., 2016). Active constituents presented in the extract are postulate to be responsible for enhancing parameters such as body weight, antioxidant enzymes, and serum lipid levels in high cholesterol-fed rats (Kumari et al., 2016).

Evidently, this herb has passed to become a natural agent in the diet as well as a promising traditional medicine in various types of disorders. Many studies have presented different perspectives and findings of the active constituents' responsibilities, yet *C. asiatica* has undertaken to become a useful plant in both pharmacological and therapeutic treatments. It ought to be noted that every antioxidant/phytochemical is a redox (reduction-oxidation) agent that protects against ROS generation while also promoting free radical/ROS generation in some cases. Excessive antioxidant activity may have a negative impact on some physiological mechanisms.

As various disease originates from the redox imbalances particularly in generation of reactive oxygen species, the antioxidant property of *C. asiatica* ought to give beneficial therapeutic effects. Summarize in this paragraph, by its antioxidant properties, *C. asiatica* able to ameliorates Parkinson's, obesity and diabetes mellitus to name a few.

The valuable antioxidant properties of *C. asiatica* have been recognized in preventing and mitigating various types of diseases, especially those linked with oxidative stress and chronic inflammation. This perineal herb became apparent in its potential to fight against cardiovascular diseases. Oxidative stress is the primary cause in the progression of cardiovascular symptoms such as atherosclerosis, hypertension and coronary artery disease (Bunaim et al., 2021). Due to the ability of *C. asiatica* to scavenge harmful free radicals, it aids in maintaining the health of the blood vessels while lowering the risk of inflammation, thus supporting the overall health of the heart. Additionally, Utami and Farida claimed that the future could depend on the herb as an alternative for a plaque stabilizer, which may serve as a preventive therapy option for cardiovascular treatment (Utami & Farida, 2019).

According to previous research studies, *C. asiatica* has also been associated in giving promising effects in neuroprotection (Rajakumari, 2010). Generally, the pathogenesis of the certain diseases like Alzheimer's and Parkinson's have been implicated by the occurrence of oxidative stress. The capability of this herb is to counteract the oxidative damage in the brain, which helps in slowing down or possibly halt further impairment (Haleagrahara & Ponnusamy, 2010; Soumyanath et al., 2005). Another research suggested that the antioxidant of the *C. asiatica* may improve the cognitive function while protecting the neurons, hence, mitigating the risk of neurodegenerative effects.

In terms of dermatological-wise, anti-aging and other skin issues has been commonly triggered by oxidative stress. While scavenging these harmful radicals, *C. asiatica* boosts the natural defence mechanism of the skin by promoting the production of collagen and reducing the appearance of wrinkles (Buranasudja et al., 2021). Additionally, the rich-profile of antioxidant possessed by the herb has been include widely as part of the skincare ingredients and formulations. It is believed that the contents of *C. asiatica* may help to improve overall skin health, thus presenting its utmost potential to mitigate the effects of oxidative stress.

Antidiabetic properties

Recent scientific studies have presented evidence supporting the potential advantages of *C. asiatica* extracts in managing diabetes mellitus, (DM). Furthermore, experimental models have demonstrated the significant antidiabetic properties of triterpene compounds derived from *C. asiatica,* with asiatic acid identified as the most potent among them (Oboh et al., 2021; Ramachandran & Saravanan, 2015).

In diabetes, hyperglycaemia caused and exacerbate the elevation of free radicals and oxidative stress along with inflammatory reactions. Treatment of *C. asiatica* aqueous extract for 28 days shown to improved hippocampal superoxide dismutase (SOD), gluthathione peroxidase (GPx) and catalase and decrease the lipid peroxidation (Giribabu et al., 2014). Similar finding was reported in the liver as *C. asiatica* methanol extract shown to reduce the hepatic lipid peroxidation by-products, MDA and increased GST & GPx activities as well as FRAP and GSH values (Oyenihi et al., 2017). They also reported reduction in its inflammatory cytokine such as IL-1β, MCP-1 and TNF-α levels. Its active compound Asiatic acid increased SOD activity and reduced MDA (Chen et al., 2018), whereas the madecassic acid shown to cause reduction in ROS and improvement in oxidized ratio (Hsu et al., 2015). Asiaticoside, another active compound also observed to caused reduce ROS and decreased levels of TNF-α & IL-1 in the cell culture study in human neuroblastoma SHSY5Y cells chronically exposed to high glucose (Yin et al., 2015). Similarly, *C. asiatica* also shown to reduce inflammation in diabetic experimental studies. Masola et al reported *C. asiatica* methanol extract administration for 14 days restore the brain and renal inflammatory cytokines namely TNF-α, & IFN-γ levels (Masola et al., 2018). Its triterpernes, madecassic acid also reported to cause reduction IL-1β, IL-6, TNF-α and MCP-1 level (Hsu et al., 2015). By ameliorates both oxidative stress and inflammation*, C. asiatica* and its active compound shows great potential as antidiabetic agent.

C. asiatica also reported to have direct stimulatory effect on the β-cells in the pancreas to release more insulin (Oyenihi et al., 2019; Rahman et al., 2012). The enhancement of the glucose uptake by glucose transporter 4 (GLUT4) and upregulation the peroxisome proliferator-activated receptor-γ (PPAR-γ) level contribute to improvement in the insulin sensitivity (Fitriawan et al., 2019). As insulin resistance is one of the hallmarks of type 2 diabetes mellitus, improvement of the insulin resistance signifies *C. asiatica* potential role to be utilise as hypoglycaemic agent. Study utilising gene modified rat, Goto Kakizaki also reveal to improve insulin resistance utilising *C. asiatica* active compound, asiatic acid (Wang et al., 2015a). In another study, asiatic acid also shown to cause improvement in insulin signalling pathway the IRS-1/2, PI3K, Akt (Ramachandran & Saravanan, 2015). The overall improvement in regulation of insulin signalling and its release further potentiates its role as hypoglycaemic agent. The improvement in the insulin release translated to better glucose, lipid and glycogen metabolism. Interestingly, the *C. asiatica* also plays a role in carbohydrate metabolism. Kabir et al reported ethanol extract of *C. asiatica* caused and inhibition of intestinal disaccharidase and α-amylase enzymes (Kabir et al., 2014). This will prevent the rapid spike in blood glucose level especially in post prandial state.

Various studies have shown the potential phytochemical compounds responsible for *C. asiatica* antidiabetic potential which includes asiaticoside, brahmoside and brahminoside (Yanti et al., 2020). This is in the agreement with other studies which reveal, plant extracts with high content of flavonoids (Hussain et al., 2020; Rasouli et al., 2019), tannins (Ajebli & Eddouks, 2019), glycosides (Bundgaard Anker et al., 2019) have high antidiabetic potential. In brief, available evidence showed that the *C. asiatica* extract could lower blood glucose level potentially by improve insulin resistance which is the hallmark for T2DM. Additionally, by amelioration oxidative-inflammatory reactions, *C. asiatica* and its related compounds could mitigate the progress of DM. This give cues that *C. asiatica* or its isolated compounds can be incorporated as alternative or complementary to management of DM and its complications

Effect on reproductive system

Infertility is defined as not being able to get pregnant after one year (or longer) of unprotected sex (CDC) (Wamser-Nanney, 2022). This condition is mainly associated with environmental factors or health problems like diabetes (Stefan & Temidayo, 2018), and infections such as chlamydia, gonorrhoea or mumps to name a few. Male population is considered more vulnerable to the problem compared to women. The common causes of infertility in the male are abnormal sperm production which could be due to varicocele, an enlarged vein within the testes (Practice Committee of the American Society for Reproductive Medicine, 2014), problems with sperm delivery, overexposure to radiation or chemicals (Okonofua et al., 2022). Oxidative stress is also one of the contributors to infertility due to the testicular artery debility. In such condition during cell division, the testicular cells would require higher consumption of oxygen to undergo spermatogenesis, hence there is a risk of excess production of the reactive oxygen species (ROS) in the mitochondria. This could elevate the level of ROS within the normal range (Asadi et al., 2017). The testes are rich in polyunsaturated fatty acids (PUFAs) but, the presence of high PUFAs is vulnerable to ROS damage particularly during the transportation of spermatozoa from the germ cells to the epididymis (Asadi et al., 2017).

As *C. asiatica* possess antioxidant property, it can ameliorate the oxidative stress and minimize the ROS damage that could lead to infertility. *C. asiatica* inhibits lipid peroxidation by scavenging free radicals, preserving the integrity of the testicular cell membrane and protecting against oxidative damage (Oyenihi et al., 2020). It also restores depleted antioxidant enzymes such as SOD and GPx, which are critical for neutralizing free radicals and reducing oxidative stress. Another study conducted by Sainath et al. reported a significant increase in epididymal sperm count, sperm viability, and motility in rats that received co-administration of *C. asiatica* extract (Sainath et al., 2011).

However, despite the antioxidant property of *C. asiatica*, its effect on the testes remains controversial. Various other study found that *C. asiatica* administration caused a reduction in sperm count and sperm quality (Yunianto et al., 2010; Yunianto, 2017). Damage to Leydig and Sertoli cells involved in spermatogenesis also reported to cause decrease in sperm count (de Kretser, 2004). Heidari et al. reported, the ethanol extract of *C. asiatica* induced apoptosis of spermatogenic cells in normal rats, with an increase in the number of apoptotic germ cells and a marked decrease in the hormones FSH, LH and testosterone indicating the direct toxic effect of *C. asiatica* in male reproductive system(Heidari et al., 2012).

As for females, infertility is commonly linked with endometriosis, an inflammatory disease on the uterus lining and ovarian dysfunction which is triggered by the increase of AGEs which accelerates ovarian oxidative stress and changes the levels of ovarian steroid hormones (Merhi, 2014). *C. asiatica* reported to improve some disease related to female reproductive function. Its active compound, asiatic acid reported to be effective in treating pelvic inflammation, endometriosis and ovarian cancer (Cao et al., 2018; Kong et al., 2019; Ren et al., 2016) Asiatic acid inhibits the NF−κB signaling pathway along with amelioration of the inflammatory markers such as IL−1 β, IL−6 and TNF−α which improves pelvic inflammation. In vitro study done on endometrial epithelial cell reveals similar finding in which asiatic acid inhibit the NF-κB pathway to reduce the production of inflammatory factors namely, TNF-α , IL-1β , p-IκBα and p- p65 (Cao et al., 2018). Additionally, the role of asiatic acid in ovarian cancer also reported by suppressing the of PI3K/Akt/mTOR signaling pathway (Ren et al., 2016). The reported studies on female reproductive function are mainly utilizing asiatic acid. But Fard et al has reported the *C. asiatica* plant extract cause an increased in caspase 3 and 9 in breast cancer cell line (Fard et al., 2018)

Wound healing properties

C. asiatica extract and its triterpenoids are also reported to possess wound-healing properties and alleviate skin inflammation (Choi et al., 2017; Hussein et al., 2017; Ju Ho et al., 2018; Sawatdee et al., 2016; Shen et al., 2019). The phases of wound healing comprise of inflammation, proliferation, epithelialization, angiogenesis, remodelling, and scarring (Sorg et al., 2017) which reported to be alleviated by the treatment of *C. asiatica.*

C. asiatica prepared in electrospun gelatin nanofibers reveal enhancement of the wound healing process (Yao et al., 2017). It also activates the fibroblast action and collagen synthesis which promotes tissue repair and regeneration, positively improving wound healing (Yao et al., 2017). Similarly, a study showed that the crude methanol extract of *C. asiatica* enhance the wound-healing in experimental animals (Sh Ahmed et al., 2019). Asiaticoside, one of the herb's main bioactive compounds, demonstrated to promote fibroblast migration and promotes thick epithelial layer and keratin formation which could facilitate the wound healing process (Sh Ahmed et al., 2019).

C. asiatica and its triterpenoids also reveal to improve the degree of re-epithelialization, increased collagen synthesis, reduced inflammation around wounds, and caused no obvious skin irritation (Ghiulai et al., 2020). A good pre-clinical study that involves any natural or chemical formulation of the herb extract and applied to open wounds in rats is suggested by successfully developing cellular proliferation and promoting collagen synthesis (Chandrika & Kumarab, 2015; Sunilkumar & Shivakumar, 1998). *C. asiatica* extract has also been shown to be effective for tissue regeneration of the oral mucosa (Camacho-Alonso et al., 2019).

C. asiatica showed potential for treating burns (Park, 2021) and scars formation with the aid of fibroblast proliferation, stimulating the synthesis of collagen and guarding the phase of inflammation to take part on particular types of scars; hypertrophic and keloids (Bylka et al., 2013; Prakash et al., 2017). Practically proven, the herb gives out the best results to cure wounds and counteract the pain (Yasurin & Pitinidhipat, 2012) simultaneously escalating the tissue cell regeneration which results in a complete process of wound healing (Saeidinia et al., 2017).

Sedative and anxiolytic properties

Because *C. asiatica* has strong antioxidants that prevent oxidative damage to the central nervous system, it has sedative and anxiolytic effects (Rocha et al., 2011; Wijeweera et al., 2006). Oxidative stress, defined as an imbalance between free radicals and antioxidants, has been linked to neurological illnesses such as anxiety. *C. asiatica*, by scavenging free radicals and minimizing oxidative damage, may preserve neural structures and control neurotransmitter release, contributing to a sedative effect (Flora & Gupta, 2007; Orhan, 2012). Furthermore, both adaptogenic characteristics and its antioxidant effects, may help the body adapt to stress and maintain equilibrium in the neuroendocrine system, enhancing its potential to treat anxiety and stress-related disorders (Jana et al., 2010; Orhan, 2012). These findings imply that the antioxidant properties of *C. asiatica* play a critical role in its sedative and anxiolytic effects, making it a promising natural approach for stress management.

According to a previous study by Ramaswamy, the triterpene derivatives brahmoside and brahminoside were identified as the primary compounds responsible for the sedative effect of *C. asiatica*, while the interaction with cholecystokinin receptors (CCKB), a class of G protein-coupled receptors thought to play a role in the modulation of anxiety, nociception, and memory, was thought to contribute to the anxiolytic activity (Gohil et al., 2010; Ramaswamy, 1970). *C. asiatica* has demonstrated anxiolytic properties in healthy rodents (Wijeweera et al., 2006) and in chronically stressed mice and mice with sleep-deprived anxiety (Chanana & Kumar, 2016). This study proves that the herb reduces oxidative damage and lowers anxiety among the mice in both conditions. Additionally, oral administration of *C. asiatica* ethanol extract has been shown to cause a decrease in the infarct volume in the middle cerebral artery, which caused drastic neurobehavioral improvements in the subjects (Tabassum et al., 2013).

The proposed mechanism for these effects is postulated to be due to the antioxidant potential of *C. asiatica* which reduces the reactive oxygen species (ROS), lipid peroxidation markers, and improves antioxidant enzymes. Researchers also reported improvement in the behaviour which coincides with the oxidative damage markers in the brain (Doknark et al., 2014).

Antidepressants properties

C. asiatica generally protects the brain structures from depression-related damage by acting as an antioxidant, neutralizing reactive oxygen species and mitigating oxidative stress in the brain, factors associated with depression (Jagadeesan et al., 2022). The herb demonstrate various mechanisms in improving the cognitive function such as the inhibition of acetylcholinesterase activity, reduction of phospholipase A2 (PLA2) activity, protection against the ß-amyloid formation, and protection from brain damage (Gupta et al., 2003; Soumyanath et al., 2012). Furthermore, in preclinical studies, *C. asiatica* has also shown anti-stress, antidepressant, anxiolytic, and anti-seizure properties. It is suggested that *C. asiatica* can potentially possess antidepressant properties, subject to anti-stress supplements (Nik, 2015). In animal models, asiatic acid showed neuroprotective, anti-depressive, and anxiolytic effects (Sabaragamuwa et al., 2018). Learning and memory improvements facilitated by asiatic acid have been observed in passive and active avoidance tests (Puttarak et al., 2017). These data conclude that *C. asiatica* can be one of the potential active ingredients in nutraceutical products for improving brain function.

C. asiatica is believed to modulate neurotransmitter levels, particularly serotonin and dopamine, which are vital for mood regulation (Subaraja & Vanisree, 2019). According to recent research, asiaticoside generates an antidepressant-like effect in a chronic unpredictable mild stress model of depression in mice, involving reversion of inflammation and the cAMP-response element binding protein (CREB) signalling pathway (Wang et al., 2020). The administration of asiaticoside triggers the elevation of monoamine neurotransmitter, halts the inflammation of the hippocampal, and significantly enhances the levels of pNF-κBp65 and nucleotide-binding domain (NOD)-like receptor protein 3 (NLRP3) inflammasome in the experimental rats. In many of the research studies relating both inflammation and depression, its anti-inflammatory properties may also help reduce the symptoms of depression. It was more likely that the antidepressant-like effect of asiaticoside could be triggered via modulation of the CREB signalling pathway (Wang et al., 2020). The role of monoamine neurotransmitters in the antidepressant effects is observed, which suggests the involvement of total triterpenes of *C. asiatica* in improving the function of the hypothalamic-pituitary-adrenal axis (HPA) and elevating the monoamine neurotransmitter contents (Shamsi & Jabin, 2018). Based on the therapeutic implications of these findings, *C. asiatica* may be a viable natural supplement for depression sufferers, providing a comprehensive strategy that focus on inflammation, neurogenesis, oxidative stress, and neurotransmitter balance. In order to confirm these effects and establish the best dose and treatment plans for those with depressed symptoms, more clinical study is necessary.

Cognitive properties

C. asiatica is known to restore the brain and nervous system, increase attention span and combat ageing. Imbalances between oxidative and antioxidant defence mechanisms in the body lead to ageing. Increased reactive oxygen species (ROS) production can directly affect neuronal synaptic activity and neurotransmission, leading to cognitive dysfunction. Pre-clinical studies have shown that *C. asiatica* improved cognitive impairments and oxidative stress (Gray et al., 2018). Several studies have demonstrated that *C. asiatica* enhances learning and memory deficits, which are associated with hippocampal neurogenesis to increase cell proliferation in the hippocampus and stimulate spatial working memory (Gray et al., 2018). Asiatic acid prevents neurogenesis and spatial memory impairment caused by valproic acid (VPA) (Umka Welbat et al., 2016). In addition, asiatic acid has been reported to prevent and restore cognitive deficits and decrease hippocampal cell proliferation and survival induced by 5-FU chemotherapy in a rat model (Chaisawang et al., 2017).

Mitochondrial dysfunction and oxidative stress increase with age and contribute to cognitive decline and neuronal cell death (Agnihotri & Aruoma, 2020). Mitochondrial dysfunction causes lower ATP production, calcium mishandling, and increased reactive oxygen species (ROS). Previously, aqueous extract of *C. asiatica* has been shown to decrease the intracellular ROS and calcium levels in response to Aβ, thus inducing the expression of antioxidant response genes that help to neutralise calcium reproduction or homeostasis (Gray et al., 2015). These results suggest the neuroprotective extract of *C. asiatica* extract against Aβ-induced mitochondrial dysfunction which is consistent with a recent study showing a mitoprotective effect of *C. asiatica* in a model of aluminium neurotoxicity (Prakash & Kumar, 2013).

Potential uses in the treatment of age-related cognitive decline are suggested by the positive effects of *C. asiatica* on cognitive function, which have been shown. These effects include reduction of PLA2 activity, protection against ß-amyloid formation, inhibition of acetylcholinesterase activity, and prevention of brain damage (Gupta et al., 2003; Soumyanath et al., 2012). These methods demonstrate the broad influence of the herb on brain health, as well as its neuroprotective, anti-depressive, and anxiolytic benefits seen in preclinical research. An ingredient called asiatic acid, in *C. asiatica* has been demonstrated to particularly aid learning and memory as well as have neuroprotective properties (Krishnamurthy et al., 2009). The antioxidant qualities of *C. asiatica* may further add to its possible therapeutic uses in treating age-related cognitive decline, given the established links between oxidative stress, neurodegenerative disorders, and cognitive decline.

Effects on digestive disease and gastric ulcer

The results of oral treatment with *C. asiatica* extract are promising towards protection against Indomethacin-induced (IND) gastric mucosal lesions and lipid peroxidation in rats (Vyawahare et al., 2009). In addition, this research proves the extract protective effect is controlled by a sub-suppression of the elevated inducible nitric oxide synthase (iNOS), proinflammatory cytokine tumour necrosis factor (TNF-a), and cyclooxygenase (COX-2) levels triggered by IND (Vyawahare et al., 2009). Produced by the macrophages, TNF-α acts as an inflammatory cytokine that is responsible for signalling pathways between cells during gastric ulcer induction. It has been shown that IND administration significantly increased the TNF-a expression in gastric tissues, which is one of the aggressive factors in ulcerogenesis (Abbas & Sakr, 2013). The present findings are in agreement with a previous study which demonstrated the ulcer healing efficacy of asiaticoside component on acetic acid-induced chronic gastric ulcers in Sprague-Dawley rats (Wannasarit et al., 2020).

The antiulcer mechanisms could be attributed to promote the formation of new vessels (angiogenesis) and stimulation of epithelial proliferation. Besides, the reduction of the myeloperoxidase (MPO) enzyme activity, along with the up-regulation of protein basic fibroblast growth factor (bFGF) expression at the ulcer tissues might also facilitate the recovery of gastric wounds. Other researchers also have encountered the outcome presenting the efficacy of *C. asiatica* extract via preclinical and clinical studies for the treatment of gastric ulcers (El-Ashmawy et al., 2016; Sengul & Gelen, 2019).

Through a variety of methods, the extract from *C. asiatica* has shown protective properties against lipid peroxidation and stomach mucosal diseases (Wang et al., 2015b). Firstly, its antioxidant qualities are essential for scavenging free radicals and reactive oxygen species, which helps shield stomach tissues from oxidative damage. The stomach mucosa is protected from harm by this antioxidant activity, which also serves to preserve its integrity. Furthermore, it has been demonstrated that *C. asiatica* inhibits the synthesis of inflammatory mediators such as COX-2, which lower down the inflammation in the stomach lining and enhances mucosal defence (Thirza et al., 2021). The capacity of the herb in improving blood flow and encourage the production of growth factors could also contribute to the stomach mucosa's recovery and regeneration. Furthermore, the anti-inflammatory properties of *C. asiatica* can prevent the inflammatory pathways connected to stomach lesions from being activated.

Anti-inflammatory properties

C. asiatica, anti-inflammatory effect is considered as one of its pharmacological highlights as they possess promising positive effects on such cascades. Generally, the occurrence of inflammation involved exacerbation of pro-inflammatory cytokines generation such as; interleukin-1 and interleukin-6 (IL-1 and IL-6) (Legiawati et al., 2018). Cytokines are known to be intracellular proteins that are produced by nucleated cells (Kumar, 2020). They are responsible for binding with the receptor and signal between targeted cells, hence it has the immunomodulatory effect that controls gene expression leading to an inflammatory cascade process (Yahfoufi et al., 2018). Such cytokines are the mediators of lung inflammation, fever and fibrosis, to name a few (Hyun-Young et al., 2020).

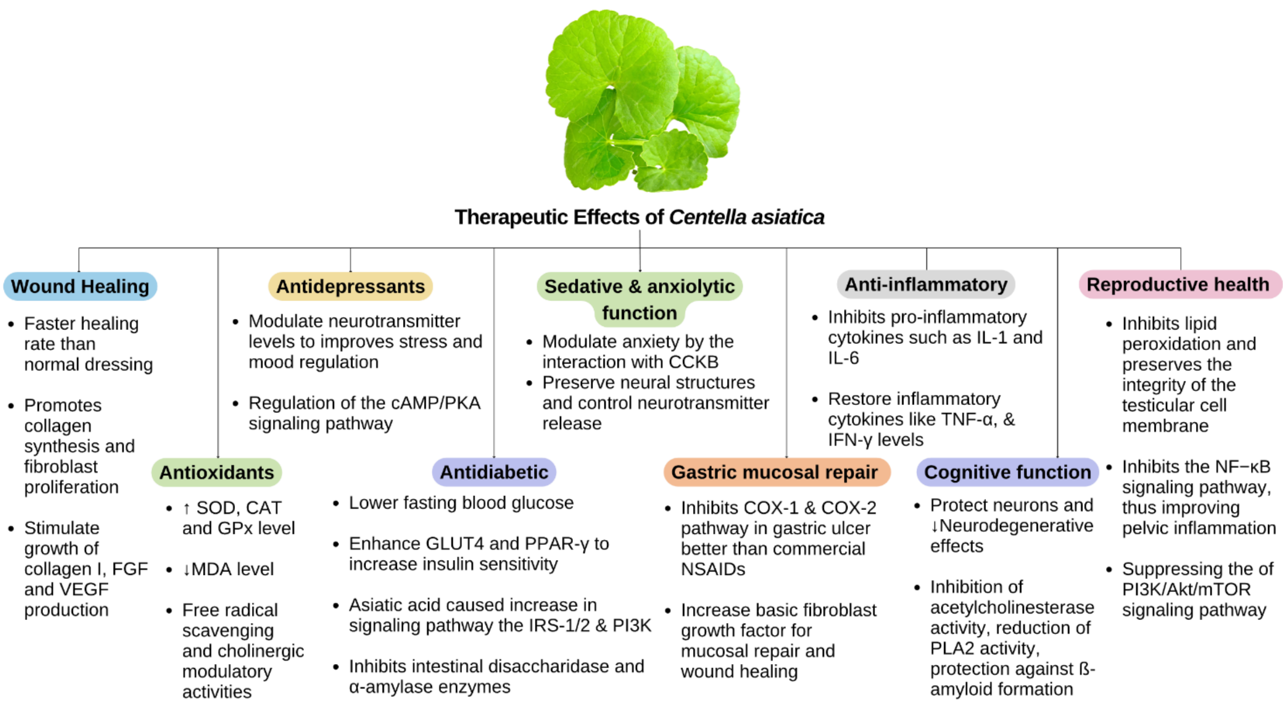
In-vitro studies have shown the active constituents of *C. asiatica*; madecassic acid and asiatic acid, are held responsible for having the anti-inflammatory effect due to the inhibiting enzymes (Prakash et al., 2017; Sabaragamuwa et al., 2018). In conjunction with that, the herb has contributed to the study of neuroprotective and anti-inflammatory effects together with the increased expression of proteins essential for mitochondrial bioenergetics and antioxidant genes (Gray et al., 2018). *C. asiatica* treatment was discovered in multiple ways of extract preparation methods, hence the number of bioactive contents extracted from the plant varied, giving different forms of results. Previous study comparing ethanol and aqueous extracts reveals more abundant bioactive contents in the ethanol extract. Evidently, that particular extract showed better evidence of halting the IL-6 and IL-8 production than the aqueous extract, which signify a better control on skin inflammation (Hyun-Young et al., 2020).

Overall, *C. asiatica* has proven potent in having anti-inflammatory properties. The collection of studies under this subtopic is vital as it contributes to the benefits of natural plant potential to be an alternative treatment.

Figure 3 summarised some of *C. asiatica* theraupetic effects which include antioxidants, antidiabetic, antidepressants, anti-inflammatory, its effect on cognitive function, reproductive health, gastric mucosal repair and wound healing.

Figure 3

Summary of therapeutic effects of C. asiatica



Notes: Therapeutic effects of C. asiatica. SOD: superoxide dismutase; CAT: catalase; GPx: glutathione peroxidase; MDA: malondialdehyde; PLA2: phospholipase A2; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K: phosphatidylinositol 3-kinases; Akt: protein kinase B (PKB); mTOR: mammalian (or mechanistic) target of rapamycin; COX-1 and COX-2: cyclooxygenases 1&2; NSAIDs: non-steroidal anti-inflammatory drugs; IL-1: interleukin-1; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha; IFN-γ: interferon-gamma; cAMP/PKA: cyclic adenosine monophosphate dependent protein kinase; CCKB: cholecystokinin B receptor; GLUT4: glucose transporter type 4; PPAR-γ: peroxisome proliferator-activated receptor gamma; IRS1/2: insulin receptor substrate 1/2; FGF:

fibroblast growth factor; VEGF: vascular endothelial growth factor.

CONCLUSION

Based on this review, *C. asiatica* reveals to possess various health benefits across diverse diseases and physiological systems. However, the imperative for future clinical trials remains undeniable. Establishing an understanding of the underlying mechanisms in each pharmacological effects is pivotal for integrating *C. asiatica* into clinical practice. The current review reveal the need for well-designed clinical trials to validate and refine the therapeutic potential reported on *C. asiatica*. Furthermore, further exploration is warranted to unravel specific molecular pathways and optimize formulations for supplementary or alternative treatment which could benefit humanity.

AUTHOR CONTRIBUTIONS

Farashakira Najiah Aszrin, Siti Hajar Adam, and Hooi Chia Tang were responsible for the conceptualization of the study. The methodology was developed by Maisarah Abdul Mutalib and Shirley Gee Hoon Tang. The original draft of the manuscript was prepared by Farashakira Najiah Aszrin, Siti Hajar Adam, Hooi Chia Tang, and Maisarah Abdul Mutalib. Farashakira Najiah Aszrin also contributed to the illustrations. The manuscript underwent review and editing by Farashakira Najiah Aszrin and Siti Hajar Adam. Supervision of the project was provided by Siti Hajar Adam, Hooi Chia Tang, and Maisarah Abdul Mutalib. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL

Not applicable.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest in this work.

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