BIO ACCENT

BAOJ Biotechnology

An Open Access Journal

BAOJ Biotechnol
Review Article
Volume 6

Centella asiatica: Medicinal importance with special emphasis on its role in cancer and neuroprotection

Irfan Bashir Ganie[1]; Anwar Shahzad[1]*; Zishan Ahmad[2,3]

[1]Plant Biotechnology Section, Department of Botany, Aligarh Muslim University, Aligarh 202002, UP, India.

[2]Co-Innovation Centre for Sustainable Forestry in Southern China, Nanjing Forestry University, Nanjing, 210037, China.

[3]Bamboo Research Institute, Nanjing Forestry University, Nanjing, 210037, China.

***Corresponding Author: Anwar Shahzad**

Plant Biotechnology Section, Department of Botany, Aligarh Muslim University, Aligarh 202002, UP, India.

Email: ashahzad.bt@amu.ac.in

Received: Mar 31, 2022

Accepted: Jun 08, 2022

Published: Jun 13, 2022

Keywords: Asiatic acid; Anti-cancer; Radiotherapy; Antioxidant; Anti-inflammatory.

Abstract

Centella asiatica is an important medicinal herb and being utilized traditionally for wound healing, asthma, cough etc. Several studies have emphasized the phytocompounds obtained such as Asiatic acid, and madecosside have potential to become therapeutic alternatives against various kinds of diseases. The plant has shown anticancer activities through the regulation of some of the key pathways involved in apoptosis. The anti-inflammatory and anti-oxidant activities of the plant has further promised its anti-oxidative properties which indirectly contributes in the protection of neurons by maintaining the ATP balance by protecting the mitochondrial embedded proteins from various kinds of inhibitors and ROS. Hence the plant is becoming an important medicinal choice in East Asian countries. The present review aims to provide the broader perspective on the neuroprotective, anti-inflammatory and anti-oxidant potential of the plant. In addition, the review also highlights molecular mechanisms of cancers that are significantly controlled by Centella derived extract and Asiatic acid.

Citation: Ganie IB, Shahzad A, Ahmad Z. Centella asiatica: Medicinal importance with special emphasis on its role in cancer and neuroprotection. BAOJ Biotechnol. 2022; 6(1): 1004.

Introduction

Natural products are a diverse group of metabolites with a huge potential for biological activities particularly against various diseases. Natural products are derived from plants, marine animals, birds etc. However, the natural products that are derived from plant parts are the products of secondary metabolism which are playing a great role in self defence particularly against various abiotic and biotic stresses. Moreover, the discovery of insecticidal, herbicidal and various other pharmaceutical compounds from plant sources have further given impetus to science led discovery among various branches of plant science. Since from ages humans have relied on plants for the treatment of various diseases and it has been reported that the confidence of humans on herbal medicine has expanded over the years and it has reached to about 6 billion people worldwide [1]. The use of plants as a medicine in Mesopotamia have also been reported dating back to 2500 BCE and about 1000 plant based products were in use in those times derived from the plant species like *Commiphora acuminate* and *Cedrus libani* [2]. The use of Chinese system of medicine is also historically very old practice dating back to 2000 years. Various studies have reported that *Centella asiatica* has range of some significant functions such as anti-inflammatory, antiulcer, antifungal, antioxidant, antiviral, insecticidal, cardio-protective and antibacterial which make them a crucial case of research aiming to investigate its therapeutic potential.

The family (Apiaceae) to which *C. asiatica* belongs is both economically and medicinally rich plant family and has almost 3500 species and 400 genera [3,4] and it has been reported that medicinal investigation on 50 species of the family have been conducted [5]. Moreover, over the years *Centella asiatica* as a dietary supplement has increased because of its numerous health benefits and confidence among the public on herbal medicines [6,7]. The plant is reputed to be natural choice of antioxidants and neutralizes some of the dangerous free radicle formations. As we know that free radicles expedite the aging process and affect the brain cells in humans therefore including *Centella asiatica* in the medicinal system would be a best choice to avoid such a damage to take place. Due to huge medicinal value of *Centella asiatica*, the research interest for the plant has constantly grown over the years. As per the one recent report claimed by National Medicinal Plant Board [India] that *Centella asiatica* is included in the list of 178 plant species of medicinal plants which are consumed in tones per year in India [8]. Moreover, the annual trade of this herb under the trade name of Brahmi booti is about 500-1000 million tones. The *Centella asiatica* is one of the most important formulation of several conventional and modern medicines. It has reached to the markets as powder, liposomal tablets, and creams.

The therapeutic potential of the plant has led to huge exploitation of the herb and severe depletion of its native population. Therefore, the gravity of the situation has led plant to be included in the endangered list of the IUCN. Increasing demand due to its multipurpose nature and reducing population has made scientists to find some alternative approaches to grow the plant at large scale. Therefore in vitro culture and other approaches have been sought to meet the demand of the herb. In addition, some of its compounds like asiaticoside which is turning out to be a very useful against the neurodegenerative disease and its antioxidant nature has led to the growth of the herb under controlled conditions with special focus given to its precious compounds by overexpressing the biosynthetic pathway of asiatic acid, asiaticoside etc. Therefore approaches like precursor feeding and elicitation have been coupled with in vitro culture of the herb to enhance the metabolite production [9].

Chemical constituents

The major principle chemical constituents in the plant are asiatic acid, triterpenes and madecassic acid and their various derivations [10]. Furthermore, the GC-MS analysis of a whole plant has revealed a chemical profile such as diethyl ether has yielded β-pinene, α-terpinene, bornyl acetate, α-copaene, β-elemene, β-caryophyllene, trans-β-farnesene, germacrene-D and bicycloelemen [11]. Similarly, polyacetylenic compounds were isolated from the underground parts of the plant [12].

Phyto-compounds of *Centella asiatica*

Pharmacological properties of *Centella asiatica*

Wound healing: Traditionally the *Centella asiatica* has been used for the wound healing and the investigation havde been increasingly supportive of these claims [13]. Sunil kumar et al. [14] reported that the *Centella asiatica* extract when applied 3 times in a day in the form of ointments and cream to the wounds of a rat has resulted in collagen synthesis and cellular proliferation at the site of the wound indicates the healing power. The wound healing property of *Centella asiatica* was attributed to one of its chemical constituent that is asiaticoside [15]. Scientists have found that the *Centella asiatica* treated wounds epithelialized faster [16]. Apart from its ability to heal up the wounds, the asiaticoside were reported to increase the tensile strength of the skin [17]. World health Organization has described *C. asiatica* as one of the most valuable medicinal plant and held it as the most conserved medicinal plant. An experiment on a rat has a revealed that rats has gained better tensile strength at the site of wound after 7 days of wound infliction however, the control has a failed to generate any positive response [16]. The increase in collagen synthesis was also supported by the increase in the DNA and protein content of the tissue.

Antioxidant properties: Oxidative stress is capable of generating free radicles which poses a serious threat to the biological system of the plant by damaging membranes and various important macromolecules. The Free radicles are usually called Reactive Oxygen Species [ROS] when exceeds in potential than that of antioxidant system of a plant causes a serious damage to the cell, Figure 1 [18]. Oxidative stress has already been involved in some major diseases like cancer, diabetes, inflammation etc [19]. However, an antioxidant system has an ability to protect the cell from ROS by scavenging them. Almost all organisms have the ability to fight against ROS with their own antioxidants however, sometimes the antioxidants are limited in number and do not cover up everything which leads to damage of the cell. Therefore antioxidants from natural sources particularly through dietary source is a good alternative to fight against the ROS. It has been reported that essential oil from *C. asiatica* extracted from the plant through the method of steam distillation has been an excellent choice as an antioxidant and its activity was compared with the butylhydroxyanisole which is a synthetic antioxidant [20]. Similarly, tannin, Vitamin C, Polyphenol, flavonoid, β-caroten and DPPH are significantly found in the extracts of *Centella asiatica* have a higher antioxidant activity [21]. Polyphenols are also critical factor to determine the antioxidant capacity of a plant [22]. The antioxidant potential of Polyphenols is due to their capabilities to act as reducing agents, metal chelators, and hydrogen donors [23]. Vitamin C also terminates

chain reaction caused by free radicles. Similarly, ß-carotene has also displayed a great potential to scavenge singlet oxygen molecules [24]. A work has been conducted Jayaprakasha et al. [25] in which different solvents were used to make 100% ethanol extract, 50% ethanol extract and water extract of *C. asiatica* and to check their antioxidant potential. The results of this work has shown that 50% ethanol extract of *C. asiatica* [63.4 ± 1.7 µg of AE/ml] was higher than total reducing power of 100% of ethanol extract of *C. asiatica* [40.4 ± 0.7 µg of AE/ml] and water extract of C. asiatica [56.3 ± 0.6 µg of AE/ml] Moreover, triterpenes are the most abundant chemical constituents in the chemical profile of *C. asiatica* and among triterpenes, asiaticoside is most prevalent and has been observed to be the first among the antioxidant defense system which act as first responsive element during the early phases of wound healing [26]. Similarly in vitro studies have revealed that leaves are reported to have higher antioxidant activity following a 3 pathway defense system; inhibition of superoxide free radicles [86.4%], inhibition of acid peroxidation [98.2%], and scavenging of free radicles [92.7%] [27]. Error! Not a valid embedded object.

In addition to triterpenes, the flavonoids also contribute to antioxidant activity of *C. asiatica* as evidenced by its ability to induce cell rejuvenation [28]. In vivo studies have revealed that the administration of methanolic extract of *Centella asiatica* to the lymphoma bearing mice [50 mg per day] has significantly increased the activity of some of the key antioxidant enzymes like catalase, superoxide dismutase and glutathione peroxidase [29]. Similarly an another work conducted by Hussin et al. [30] has also observed that oxidative stress significantly got reduced in rats after 25 weeks of *C. asiatica* extract consumption. Furthermore, Ullah et al. [31] has reported increasing antioxidant activity in Centella extract with 4.0 µg/mL IC50 value on chloroform and 7.0 µg/mL in methanol extract.

Antibacterial activity

Bacterial infections are cause of worry as these organisms consume huge number of lives across the world. It has been reported that about 80% population of Africa can't afford to buy conventional medicines. More importantly, although synthetic medicines are having great capacity to deal with bacterial diseases but they are not free from side effects. Therefore, an interest has grown among the public to rely on herbal medicines or ethanomedicinal plants. The interest for herbal medicines has particularly been reported in developing countries which is around 60% in numbers. Moreover, the continuous use of synthetic antibiotics has led to the emergence of large number of antibiotic resistant bacteria [32]. WHO has also stressed on to the need to replace the synthetic drugs with plant based medicines [33] and through its awareness drives many countries have started shifting towards the herbal medicines system and significant responses have been shown by various research and institution established in number of countries in order to ensure better healthcare [34]. More importantly, the bacterial resistance against various antibiotics necessitates the need to advance in the herbal research aiming to find out the true therapeutic solution [35]. The alcoholic extract of *C. asiatica* has shown antiprotozoal activity against *E. histolytica* while as its chloroform extract has shown antibacterial activity against a rage of bacteria [33]. Similarly, methanolic extracts of *C. asiatica* has also shown antibacterial activity against a range of bacteria such as *S. typhi, S. sonnei, E. coli and S. aureus*. In a study conducted on the tetracycline as a positive control and 0.2% DMSO negative. The effect of the tetracycline was higher against all the above mentioned five bacteria species compared with the extract of *C. asiatica* at all the concentrations taken. However the significant effect of the *C. asiatica* extract was observed at a conc. Of 500 mg/ml against all the five bacterial species. Similarly, many plants contain potential compounds which can be used as natural remedies to cure bacterial diseases. More importantly, many plant derived medicines have shown minimal side effects. The methanolic extract of a whole *C. asiatica* plant have shown antibacterial activity against *V. vulnificus* and *Streptococcus sp* [36]. Similarly, ethanolic extract has shown antibacterial activity against bacteria like *Escherichia coli, Propionibacterium vulgaris* and *Staphylococcus aureus* while as the petroleum ether extract has shown moderate response followed by water extract with least effect [37]. The crude extract of *C. asiatica* has shown inhibitory response against the pathogens like *Propionibacterium acnes* and *Staphylococcus epidermidis [*38]. It was further reported that the methanolic extract of *C asiatica* grown in Nepal has shown antibacterial activity against both gram positive and gram negative bacteria [39].

Table 1: Antimicrobial activity of *C. asiatica* extracts obtained by various methods.

Extraction Method	Solvent	Antimicrobial Method	Bacteria	Effect	References
Maceration	Methanol	Open hole diffusion method	*Bacillus subtilis, Citrobacter freundii, Escherichia coli*	Postive	[40]
Maceration	Ethanol	Agar diffusion method	*Bacillus cereus, Listeria monocytogenes*	Positive	[41]
Maceration	Ethanol	Disc diffusion Method	*Vibrio cholera, Shigella sonnei, Shigella dysenteriae*	Positive	[42]
Maceration	Chloroform	Broth dilution, agar well diffusion method	*Edwardsiella tarda, Aeromonas hydrophila*	Positive	[43]
Maceration	Acetone	Microplate dilution assay,	*Enterococcus faecalis, Enterococcus gallinarum, Bacillus cereus, Pseudomonas aeruginosa*	Positive	[44]
Soxhlet	Methanol	Disc Diffusion Method	*Klebsiella pneumonia, Pseudomonas aeruginosa, Escherichia coli, Methicillin-resistant Staphylococcus aureus [MRSA].*	Positive	[45]
Soxhlet	Aqueous	Agar well diffusion	*Bacillus megaterium, Shigella boydii, Bacillus cereus, Salmonella Paratyphi, Sarcina lutea, Vibrio parahaemolyticus.*	Positive	[46]
Soxhlet	Petroleum ether	Disc diffusion Method	*Streptococcus pyogenes, Curvularia lunata, Serratia marcescens, Proteus vulgaris, Proteus mirabilis, Alternaria alternate*	Positive	[47]
Soxhlet	Ethanol	Disc diffusion Method	*Acinetobacter baumannii, Klebsiella pneumonia*	Positive	[48]

There is huge search going on to find out the promising medicinal treatment to various life threatening diseases like HIV AIDS, cancer etc [49]. Various studies have claimed that compounds obtained from plants has shown cytotoxic and anti-proliferative effect against various types of cancer cells [50]. Most cancer patients are often given chemo treatment which doesn't differentiate between normal and abnormal cells and therefore leads to the development of weak immune system often called immunosuppression. Therefore there is a need to find an alternative with zero or least side effects and plants are said to be the right source of medicines.

Asiatic acid one of the main compound of *Centella asiatica* has multiple properties like anti-cancer, anti-inflammatory, and antioxidant. Chaloangiocarcinoma [CCA] is a type of cancer specifically effecting the epithelium of bile duct. This is one of the leading cancer disease is Southeast Asia. Many studies have revealed that oxidative stress is involved in causing CCA. Lot of evidences has shown that Asiatic acid has been quite effective against various kinds of cancers such as colon cancer, breast cancer, hepatoma and ovarian cancer. Moreover, it has been reported that Asiatic acid causes arrest of S-G2/M phase cell cycle and apoptosis of breast cancerous cells by activating P-38 mitogen activated kinase pathway [51]. Similarly another study has reported that methanolic extract has shown dose dependent inhibitory effect of breast cancer cells, MCF-7. A concentration dependent decrease in the cell viability was observed. However, several types of cells such as HeLa, SW 480 and HepG2 nothing like concentration dependent decrease in cell viability was observed. The decrease in cell viability was confirmed by Ethidium Bromide/Acridine Orange staining upon the treatment of cells with methanolic extract of *C. asiatica* Furthermore, the Apoptosis pathway features were reported to be induced by an extract as the key proteins involved in apoptosis like Annexin V and phosphatidyl serine were observed to be binding on the cell membrane which is a usual phenomenon during the initiation of apoptosis. However, more concrete evidences were supported by the loss of mitochondrial membrane which suggests that an intrinsic pathway has undergone in the cell. Besides, DNA strands breaks were also observed to be caused by the methanolic extract of *C. asiatica* [52,53].

Neuroprotective activity

Parkinson's neurodegenerative is still a cause of worry across medical specialists as the disease is yet to find its ultimate solution. It is caused by the loss of dopaminergic neurons of the substantia nigra part of the brain. There is now huge emphasis to find out how could the dopamine levels of the brain be increased in order to improve the motor functions [54]. However, various studies have revealed that several phytocompounds have shown neuroprotective effect in Parkinsons's disease [55]. Although the mechanism that leads to Parkinson's disease is quite elusive but the events suggest that disease is borne out of a cascade of events. Mitochondrial dysfunction and reactive oxygen species are reported to be the main constituents that led to Parkinson disease [56]. Since mitochondria regulates energy reactions, immune response and apoptotic pathways so therefore any damage in the mitochondria would result in the weakening of immune system, neurodegeneration and a cause for other diseases [56]. The inhibition of mitochondrial dependent electron transport chain reactions also leads to the low pool of ATPs and generation of ROS and both are reported to lead to Parkinson's disease [57]. Similarly, several protein aggregates that bind to mitochondria during its biogenesis are also reported to be one of the causes of fragmentation of mitochondria which leads to the generation of ROS. Alzheimer's beta amyloid [Aβ] protein aggregates has been observed to be causing such binding with mitochondria at the time of its biogenesis [58]. The oxidative damage caused by the overproduction of ROS further effects the respiratory pathway and therefore ATP formation is impaired which takes place through oxidative phosphorylation [59]. The brain is highly prone to oxidative stress as the neurotransmission requires much energy therefore the damage to the mitochondria effects the functioning of the brain. However, the use of antioxidants has been reported to be quite useful against neuro-degeneration caused by oxidative stress. The *Centella asiatica* extract studies have revealed that it has a potential to improve memory loss [60]. Further studies have claimed that the *Centella asiatica* confers protection against hippocampal dysfunction, the part of the brain which has a major role in memory and learning process [61]. Similarly, asiaticoside has been reported to enhance cognitive learning particularly in aged animals [62]. Furthermore, in rat models it has been reported that Asiatica acid prevents mitochondrial abnormalities [63]. In a separate study, asiaticoside has been found to inhibit Aβ-induced apoptosis by restoring the mitochondrial membrane potential [64].

Mitochondrial dysfunction is also one of the mechanism that leads to neurodegeneration in Parkinson's disease [65]. The disturbance in mitochondrial driven ATP synthesis particularly when the mitochondrial complex I is inhibited by inhibitors like rotenone causes the generation of reactive oxygen species. These factors collectively leads to neurodegeneration by causing the dopaminergic neural death [66]. The inhibition in Mitochondrial complex I has been reported to significantly affect the substantia nigra part of the brain [67]. Active compounds of C. asiatica such as Asiatic acid and madecassoside have been reported to have potential to protect the mitochondrial membrane damage by reducing the impact of rotenone and ROS [68]. Recent research conducted on animal model of Parkinson's disease have shown that Centella asiatica extract ECa233 significantly controls oxidative stress led damage to mitochondria and contributes in a protective mechanism for Parkinson's patients [69].Furthermore, ECa233 further decreases lipid peroxidation and increases antioxidant activity in rotenone models.

***Centella asiatica* offers an alternative choice against radiotherapy**

Radiotherapy has become a most preferred choice in treating the patients suffering from various types of cancers. However, various studies have revealed that radiotherapy treatment can itself become a deadly choice to go with as it induces malignant cancer cell movement and therefore leads to metastasis. Lung cancer is most prevalent and accounts for a high rate of annual deaths globally. Lung cancers have two subtypes- non-small cell lung cancer and small cell lung cancer [70]. The option for the treatment of lung cancers are chemotherapy, surgical operations and radiotherapy. However, in case of late stages [III and IV] the chemotherapy and radiotherapy are most preferred choices [71]. Radiotherapy is a type of treatment in which cancer cells are exposed to ionizing radiations in order to kill them. However, it can promote metastasis [72]. Therefore, is necessary to find an alternative with almost no side effect on human cells. Although the anticancer effect of *Centella asiatica* has been reported but its inhibitory impact on the metastasis and cancer cell migration caused by ionizing radiations are yet to be investigated [73]. The three compounds of Centella – asiatic

acid, asiaticoside and medecassic acid have been reported to having anticancer activity [74]. Asiatic acid has shown anticancer activity in a number of cancer cells, lung cancer, breast, by way of regulating the apoptosis [75] and madecassic acid has also shown anti-proliferative activity by apoptotic regulation in mouse colon cancer [76]. Similarly, asiaticoside has also shown anticancer activity by inhibiting the cell migration and invasion caused by an ionization reaction. The START 3 gene regulation at the cell membrane was reported to be regulated by asiaticoside in myeloma cancer [77].

The Nasopharyngeal carcinoma [NPC] is another deadly cancer consuming so many lives in Eastern Asia. The etiological factors of the disease vary from human papilloma infection to salted fish consumption. The only treatment for such a cancer is radiotherapy. However sometimes a chemotherapeutic agents are used as adjuvants [78]. Previous studies have reported that Asiatic acid derived from *C. asiatica* has shown wide range of activities such as antioxidant, anticancer, neuro-protective and anti-diabetic [75]. It has been reported that Asiatic acid inhibit growth factor-beta1 [TGF-beta1] which has a role in inducing epithelial mesenchymal into lung cancer [79]. Cisplatin based chemotherapy is mostly used against the NPC, however its curative potential has been limited by Cisplatin resistance by NPC cells. Therefore to find a solution to this problem studies were conducted in which it was reported that NPC cells resistant to cisplatin have undergone apoptosis when the cells were treated with Asiatic acid. The apoptosis were particularly reported in cisplatin-resistance NPC-039 and NPC- BM cell lines via the p38 and ERK signaling transduction pathway [75]. Moreover, Asiatic acid induces apoptosis via decreasing the Bcl-2 proteins and increasing the proteins that causes the deasth of cells such as caspases-3 and 9, Bax in a rat model [80].

The regulation of Apoptosis by Asiatic acid derived from *Centella asiatica*

It was reported that in case of cancer cells that undergo apoptosis upon treating them with different doses of *Centella asiatica*, underwent two pathways of apoptosis- intrinsic and extrinsic pathway. In case of Asiatic acid treated cells, it was observed that both the mitochondrial dependent pathway and death receptor dependent pathway are activated. More studies have reported that apoptosis induced by Asiatic acid in lung cancer cells occurs due to the change in mitochondrial membrane potential which leads to an activation of Caspase proteins and PARP pathway [81]. Similarly, Asiatic acid regulates BCL 2 family proteins which leads to increase in Bax protein and eventually contributes to apoptosis in cancer cells [82]. Various studies have reported that Asiatic acid causes apoptosis by activating the Mitogen Activated protein kinase [MAPK] [51]. The inhibition of ERK and p38 phosphorylation in the cancer cells treated with Asiatic acid has also been observed [81].

Recently the cancer cell (nasopharyngeal carcinoma) resistant to cisplatin were treated with Asiatic acid and the results claimed that Bax proteins were increasingly produced and Phosphorylation of p38 was upregulated which significantly contributes to apoptosis of nasopharyngeal carcinoma cells. Earlier studies reported that the excision repair cross complementation 1 (ERCC1) was increasingly getting expressed in cisplatin resistant nasopharyngeal carcinoma cells [83]. However, in asiatic acid treated cisplatin-NPC cells the ERCC1 was down-regulated as the protein has a potential to repair DNA in cancer cells which would further deteorioite the problem. Therefore, the potential of asiatic acid to down-regulate the expression of ERCC1 could become a formulation for various anti-cancer medicines. Some others studies have reported that Asiatica acid cause the downregulation of p38 MAPK pathway which further decreases the expression of ERCC1 proteins [84].

These studies suggest us that natural products could provide an efficient cure against diseases like cancer with least or no side effects. Otherwise, the chemotheraphy based treatment is no free from side effects such as, mucositis, xerostomia, loss of taste, dysphagia, skin damage, skull bone damage, sensorineural hearing loss, and osteoradionecrosis. The Asiatic acid is a pentacyclic compound derived from *C. asiatica*. Previously various studies have reported that the plant has demonstrated anti-inflammatory and anti-oxidant activities, more importantly has been involved in many molecular mechanisms and signaling pathways [75]. More research have reported the anticancer effect of Asiatic acid in breast cancer by using the mitochondrial type of apoptotic pathway and cell cycle arrest [51].

Cachectic syndrome is a kind of cancer which is characterized by abnormal weight loss due to the depletion of adipose tissue and skeletal muscle [85]. Two hormones are reported to be response for the syndrome - lipoprotein lipase [LPL] and Hormone sensitive lipase [HSL] [85]. The LPL breaks down fatty acids and transports them into adipose cells for the production of triglycerol while as another enzyme HSL contrary breaks down triglycerol into fatty acids and glycerol [85] Figure 2. Studies have reported that decreased levels of LPL enzymes and increased levels of HSL are associated with the cachectic syndrome. Moreover increased proteolysis has also been reported in the patients and studies revealed that the ubiquitin mediated pathway of proteolysis is a major cause of excessive proteolysis in cachectic patients [86].

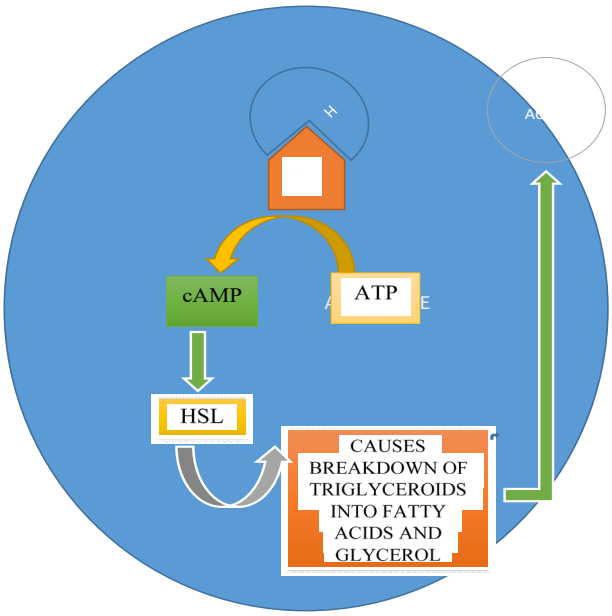

Figure 1: Mechanism of hydrolysis of triglycerides and fatty acid synthesis in adipocyte H-Hormone; HR-hormone receptor; HSL-Hormone sensitive lipase.

Inflammatory cytokines and oxidative stress have a critical to play in tumor induction. It has been reported that ethanolic extract of *C. asiatica* suppressed the production of TNF-α in mouse model [87]. Further studies have revealed that Asiatic acid significantly reduces the IL-6 production [88]. The phenomenon of apoptosis lies at the core of the syndrome. How apoptosis is regulated in this syndrome is important to understand in order to deal with the problem. As said earlier apoptosis is reg-

ulated by two pathways- extrinsic and intrinsic. The activation of caspases- 8, 9 which are called initiator caspases cause the activation of caspase- 3, 7 which in turn activates cytoplasmic endonuclease enzymes [89]. Several studies have reported that the ethanolic extract of *Centella asiatica* has suppressed TNA-α in mouse macrophages. Similarly, Asiatic acid and asiaticoside were reported to significantly decrease cell viability in cancer cells and reduces the level of IL-6 production. Furthermore, methanolic extract has been reported to significantly inhibit the production of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β which are produced by macrophages [90].

It has been reported that TNF-α inhibits the gene expression of LPL thereby controlling the storage or reducing the storage of lipids. However, other enzymes is activated which causes further reduction of lipids and increases proteolysis [91]. Furthermore, IL-6 decreases the activity of LPL in adipose tissue [in vivo], therefore leading to tissue wasting in patient's suffering from cachectic syndrome [92].

It has been reported that ethanolic extract of *Centella asiatica* significantly reduces the concentration of IL-6 and IL-1β in THP-1 and PBMC cells and decreases the activity of HSL and minimizes the inhibition in LPL ezyme. Therefore, the ethanolic extract of *Centella asiatica* maintains the lipogenesis and reduces lipolysis. Furthermore, the IL-6 and TNF- α contributes to cachexia syndrome by activating the ubiquitin mediated proteolysis [93]. Moreover, the activation of NF-κB by pro-inflammatory cytokines leads to inhibition of tumor cells apoptosis by suppressing the expression of genes. NF-κB promotes invasion, tumor progression, metastasis and angiogenesis [94]. Therefore by decreasing the activation of IL-6 and IL-1β in PBMC cells, the ethanolic extract can significantly decreases the activation of NF-κB and ubiquitin mediated proteolysis. In conclusion, the *C. asiatica* has a potential to decrease te cases of tissue wasting by down-regulating the pathways involved for the activation of various pro-inflammatory cytokines [95].

Antioxidant activity

The oxidative stress often occurs when there is imbalance between antioxidants and oxidants, which eventually leads to membrane damage by producing reactive oxygen species (ROS). Superoxide radicals, peroxide, nitric oxide and hydroxyl ions are the most predominant form of ROS agents and causes diseases like cancer, aging, inflammatory conditions. On the contrary, antioxidants are radicle scavenging agents and protect the cells from oxidative stress [96]. The *Centella asiatica* is one of the best source for antioxidants as it contains various polyphenol compounds especially in the leaves of the plant [97]. Moreover, the extraction methods also have an influence on the compound properties. In case of *Centella asiatica*, ethanol extraction was reported to have highest antioxidant properties than water, methanol, and chloroform solvents [22]. Further studies have reported that by dissolving the sample in 40% ethanol for at least 60 minutes an optimum level of an extraction was obtained [98]. Moreover, the leaves of *Centella asiatica* have been reported to have higher antioxidant activity than any other part of the plant and works optimally against superoxide free radicals and linoleic acid peroxidation [98]. The antioxidant potential of *C. asiatica* has been compared with the plants like rosemary [99]. More importantly, the *C. asiatica* has been reported to have a potential to repair DNA damages caused by an exposure to γ-radiation [100]. The antioxidant potential of C. asiatica leaves were tested against superoxide free radicals, 2,2-diphenyl-1-picryl-hydrazyl [DPPH] and inhibition of linoleic acid peroxidation, and the results suggest that Centella leaves are having higher natural antioxidant potential [101]. The higher antioxidant potential of *C. asiatica* leaves are believed to be due to higher content of phenolic compounds in a leaf extract of *C. asiatica* [102]. Statistically, the antioxidant activity of various extracts of *C. asiatica* was attributed to polyphenols and flavonoids. Moreover, the methanolic extract of *C. asiatica* was reported to have DNA damage protective activity [103]. Therefore, this important property of *C. asiatica* is a very crucial step towards finding a solution to various underlying causes of cancer.

Anti-inflammatory activity

Upon the entry of the foreign material in the body the immune system gets triggered and causes damage to the cells. The external agents whether pathogen or toxic compounds trigger signaling pathways such as MAPK, JAK-STAT and NF-kB. The anti-inflammatory case of *Centella asiatica* can be understood by taking the case of Atopic dermatitis [AD]. AD is a kind of skin inflammation with symptoms like dry skin, itching and lesions [52]. This disease has been treated with immunosuppressive drugs and corticosteroids due to their anti-inflammatory drugs, however these drugs have side effects [104]. Natural products like herbs, plants, flowers, fungi etc with low molecular weight can pass through skin barrier and therefore are very much effective against AD when such formulations are applied to skin sites [105]. Various genetic, environmental factors and immunological abnormalities cause AD.

The NF-kB is a main protein in the signaling pathway that plays a key role in the upregulation of various pro-inflammatory cytokines which cause advancement in AD disease [106]. The NF—Kb is itself triggered by factors like TNF-α and IL-6 in mast cells. Once the NF-kB is activated various inflammatory cytokines and chemokines are activated which cause tissue destruction and loss of function [107]. Many studies have reported the compounds inhibiting the activity of NF-kB could be choice to treat the AD disease AD. It has been reported that Centella asiatica phytosomes reduced the effect of NF-kB by reducing the levels of inducers such as TNF-α. The treatment of CA was given to the skin lesions through phytosomal bodies which permeate through the lipid layers while maintaining the originality of the compound [108].

Conclusion

The therapeutic potential of major compounds of the plant is over-arching as various kinds of cancers such as colon, lung etc are regulated by the compounds significantly as we discussed above in detail. Therefore, the research on this plant is very crucial to carry forward. Its potential to regulate some of key mechanisms of apoptosis and cytokines production need to be further explored and subjected to clinical trials as this research could help us to stop many of the life threatening diseases. Moreover, many of the reports have suggested that plant needs to be conserved as its faces human exploitation due to its huge profits in the markets, however, we believe seldom using in vitro approaches for its micro-propagation would not be fair enough for its conservation rather various biotechnological approaches such as elicitation, cryopreservation, Agrobacterium mediated transformation, stress tolerant studies need to be employed in the strategy for its conservation in order to conserve the plant while keeping the market demand and climatic changes into the consideration.

Declarations

Conflict of interest: No.

Author contributions: All the authors contributed equally.

Acknowledgment: Author IBG wants to acknowledge the University Grant Commission, India for financial assistance in the form of non-net fellowship.

Funding: No external funding received.

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