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Ethnomedical, phytochemical and pharmacological insights on an Indian medicinal plant: The balloon vine (*Cardiospermum halicacabum* Linn.)

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ABSTRACT

Ethnopharmacological relevance: Cardiospermum halicacabum Linn. (*C. halicacabum*) is one of the well-known leafy green vegetables in India. It is an herbaceous climber from the Sapindaceae family which is found in almost every Continent and Oceania. In the traditional Indian medicine systems, this plant is used for the treatment of rheumatism, abdominal pain, orchitis, dropsy, lumbago, skin diseases, cough, nervous disorders, and hyperthermia.

Aim of the review: This review presents the current information about ethnomedical uses and progress on geographical distribution, pharmacological activities, phytochemistry, micropropagation, and toxicity of *C. halicacabum*. Also, critically summarizes the relationship between the reported pharmacological activities and the traditional usages along with the future perspectives for research on this medicinal plant.

Materials and methods: The data on *C. halicacabum* were collected using multiple internet sources such as Google Scholar, Science Direct, Taylor & Francis, PubMed, Web of Science, Springer Link, Wiley online, and plant databases.

Results: Chemical characterization using LC-MS/MS, HPLC, and NMR exposed the presence of chlorogenic acid, caffeic acid, coumaric acid, luteolin-7-o-glucuronide, apigenin-7-o-glucuronide, and chrysoeriol in different parts of *C. halicacabum*. Based on the outcomes of this review, the main bioactive compounds found in *C. halicacabum* include phenols, phenolic acids, flavonoids, flavonoid glycosides, and flavonoid glucuronides. Besides the above-mentioned constituents, palmitic acid, oleic acid, stearic acid, linolenic acid, eicosenoic acid, and arachidic acid are the compounds that constitute the fatty acid profile of *C. halicacabum* seeds. Specifically, Cardiospermin, a bioactive compound isolated from the root extract of *C. halicacabum* has been recognized for its anxiolytic activity. Moreover, *C. halicacabum* showed a broad spectrum of pharmacological activities including anti-inflammatory, anti-arthritic, anti-diabetic, anxiolytic activity, antiulcer, apoptotic activity, antibacterial, anti-viral, anti-diarrheal, antioxidant, hepatoprotective, and nephroprotective properties. However, the bioactive compounds responsible for most of the above therapeutic properties have not been elucidated till now.

Conclusion: Phytochemicals from *C. halicacabum* showed noticeable pharmacological effects against plethora of health disorders. Some of the traditional applications were supported by modern scientific studies, however, more pharmacological evaluations should be conducted to validate other traditional uses of *C. halicacabum*. Despite *C. halicacabum's* vast pharmacological activity, additional human clinical trials are needed to determine the potent and safe dosages for the treatment of various health abnormalities. Besides, bioassay-guided isolation of active constituents, pharmacokinetic evaluations and identification of their mode of action are recommended for future investigations on *C. halicacabum* to unveil its therapeutic drug leads. Overall, this review suggests that *C. halicacabum* could be a new source of functional foods.

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Abbreviations

ABTS	2, 2-azinobis-3-ethylbenzothizoline-6-sulphonate
DPPH	1, 1-diphenyl-2-picrylhydrazyl
LC –MS/MS	liquid chromatography –tandem mass spectrometry
COX	cyclooxygenase
HR-MS	high resolution mass spectrum
GC-MS	gas chromatography-mass spectrometry
HPLC-MS	high-performance liquid chromatography-mass spectrometry
AAS	atomic absorption spectrometry
TNF-α	tumor necrosis Factor alpha
IC50	50% inhibitory concentration
MMP	matrix metalloproteinase
NO	nitric oxide
NSAID	non-steroidal anti-inflammatory drug
BHT	butylated hydroxyl toluene
SGOT	serum glutamate oxaloacetate transaminase
SOD	superoxide dismutase
SGPT	serum glutamate pyruvate transaminase
NMR	nuclear magnetic resonance spectroscopy
NF-κB	nuclear factor-kappa B
PTZ	pentazocine hydrochloride
DMARD	disease-modifying anti-rheumatoid drugs
STZ	streptozotocin
ALP	alkaline phosphatase
CFA	complete freund's adjuvant
ChC	*Clostridium histolyticum* collagenase
BAT	bovine achilles tendon
HBV	hepatitis B virus
HIV	human immunodeficiency virus
IFN-γ	interferon –gamma
IL-2	interleukin-2

1. Introduction

Appreciable progress has been noticed in the usage of plants and plant-derived products as drugs against arthritis, diabetes mellitus, cancer, cardiovascular diseases, and neurodegenerative disorders owing to their low toxicity and lesser side effects. Around the world, more than 80% of people are following naturopathic treatments against various diseases (Tugume and Nyakoojo, 2019). This has demanded researchers to identify and explore the phytochemicals with protective effects against emerging diseases. It is a well-known fact that polyphenolic compounds from plants act as antioxidants due to their ability to quench, donate and reduce the free radicals created during several metabolic processes. The family Sapindaceae contains four subfamilies with relatively 1900 species of trees, shrubs, and lianas, broadly distributed throughout the tropical and subtropical regions of the world.

Notably, in the Sapindaceae family, about 16 species of herbs and vines are in existence under the genus Cardiospermum. *Cardiospermum halicacabum* L., an annual or sometimes perennial climber plant, with various vernacular names such as balloon vine, heart pea, and puff-ball. There are eight synonyms are available for Cardiospermum halicacabum, including Cardiospermum corycodes Kunze, Cardiospermum glabrum Schum. Thonn, Cardiospermum halicacabum luridum (Bl.) Adelb., Cardiospermum. luridum Bl., Cardiospermum microspermum E. Mey., Cardiospermum truncatum A. Rich., Corindum halicacabum Medic., Rhodiola biternata Lour. (da Cunha Neto et al., 2017; Cardiospermum halicacabum Linn, 2021).

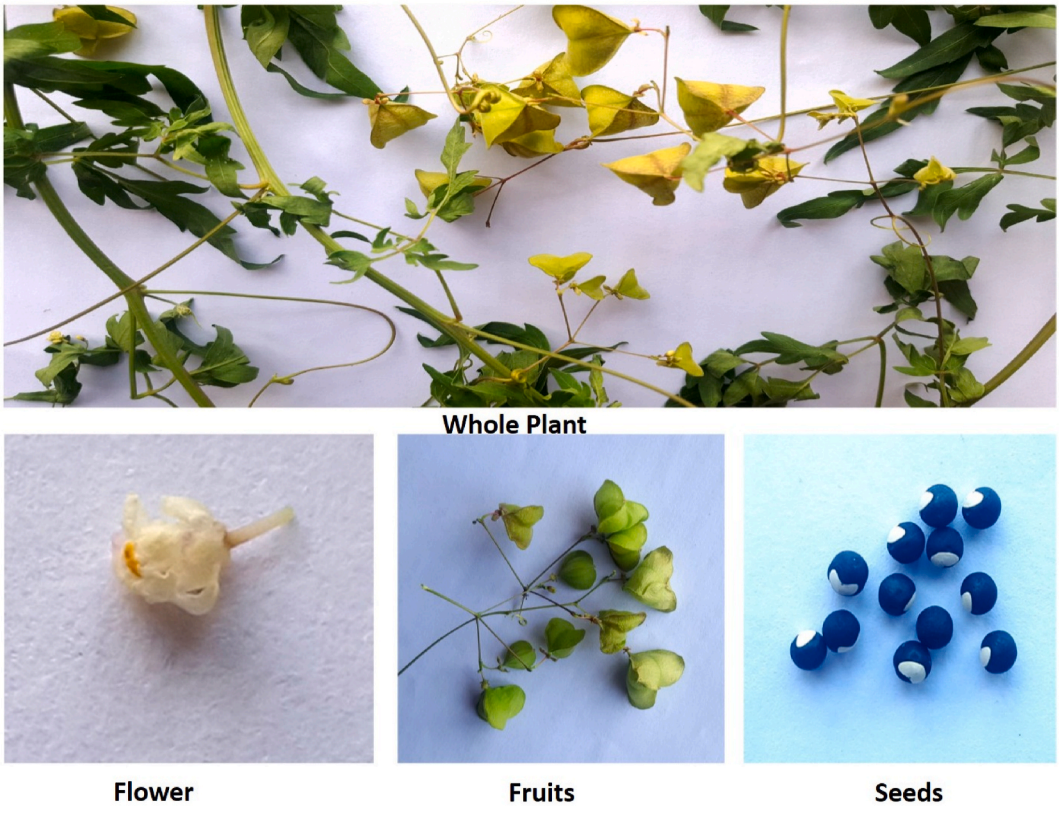


Fig. 1. Aerial parts of *Cardiospermum halicacabum*.

The genus name, *Cardiospermum* was derived by combining the Latin words "Cardio" (heart) and "Sperma" (seed). The name "cardio" reflects the heart-shaped design found on the seeds whereas, the species name was derived from the Latin term "halicacabus" meaning a plant with inflated fruits (Johnston et al., 1979). *C. halicacabum* is a slender herbaceous, more or less hairy plant (Fig. 1) and habitually categorized as a cosmopolitan species with an extensive distribution. The vernacular names of *C. halicacabum* in different countries are given in Table S1. It is not only popular as a healthy green vegetable in rural areas but also in the townships of southern India. Though this plant has been used for the ornamental purpose in some countries, it is mainly used as a medicinal plant in India. The common names used to represent *C. halicacabum* in India are presented in Table S2. The leaves and stems from this plant have been used in Tamil cuisine for preparing curries, lentil crepes, decoctions, sauces, herb purees, and vegetable soups as part of a healthy diet.

C. halicacabum imparts an energizing effect, a nutty flavor, and delectable touch to soups, and thus, it is highly valued in Indian cuisine. Most importantly, *C. halicacabum* has been used in popular medicinal practices like Siddha, Ayurvedic, Unani, and Indian folk medicine in the treatment of rheumatism, lumbago, cough, hyperthermia, nervous diseases, snake bite, stiffness of limbs, and earache (Table 1). It is also used as a demulcent in the cases of orchitis and dropsy (Zalke et al., 2013). Interestingly, many *in vitro* and *in vivo* studies on *C. halicacabum* have revealed its pharmacological properties including anti-inflammatory, anti-arthritic, antioxidant, anticancer, antimicrobial, anti-ulcer, neuroprotective, analgesic, anxiolytic, nephroprotective and anti-diabetic activities (Raza et al., 2013).

Table 1
Reported traditional medicinal uses of *Cardiospermum halicacabum* Linn.

Medicine system	Plant part	Formulation name/Method of preparation	Mode of administration	Used against	Country	References
Siddha	Whole plant	Powder and aqueous extraction	Topical and Oral	Inflammatory skin disease, arthritis, constipation, dysentery, infertility, rheumatism, lumbago,	India	Khare et al. (2007); Cardiospermum halicacabum (2019)
	Leaves	Powder, juice, and oil		skeletal fractures, nervous diseases, joint pains,		
	Roots	Aqueous extraction		stiffness, amenorrhea, hemorrhoids, erysipelas, anti-dandruff, alopecia, and hair colorant		
Ayurveda	Seeds	Vasadilepa, Nagaradi Taila Amatisaranasaka Yoga, Lausunadi Kasaya	Oral	Abdominal pain, fever, swellings, anemia, orchitis, osteoarthritis, microbial infections, and hysteria	India	(AYUSH)
	Roots	Aragvadhadi Kvatha Curna		Abdominal pain, fever, anemia, swelling, orchitis, snake bite, liver disorders, jaundice, cough, memory enhancement, tuberculosis, osteoarthritis, rat poison, alopecia, kidney stones, bronchitis, nervous, and psychiatric disorders		
Unani	Seeds	Kushta Zeher mohra	Oral	Refrigerant, cardiac ailments, and palpitations	India	Medicine (2008); Kabir (2003)
		Laboobe Kabir		Aphrodisiac		
		Majun Muravvahul		Cardiavasular disorders, liver ailments, brain health, gastric problems, memory enhancer, and energy booster		
		Arvah		Aphrodisiac		
		Laboobe Sagheer				
Folk medicine	Leaves	Leaf paste	Topical and Oral	Joint pain, arthritis, asthma, swelling, burns, and body pain	India	Chinnasamy et al. (2019)
Local healers	Leaves	Paste with salt	Topical	Swellings	India	Malaviya et al. (2009)
		Juice	Topical	Ear ache and itchy skin		
Indian system of medicine	Leaves	Decoction	Oral	Emetic, stimulant, diarrhea, hemorrhoids, general sores, and obesity	India	Jahan et al. (2014)
Folk medicine	Root	Not mentioned	Not mentioned	Anxiety and epilepsy	India	Venkatesh and Krishnakumari (2006)
Folk medicine	Unspecified	Not mentioned	Not mentioned	Didymitis, hydrocele, asthma, amenorrhea, gonorrhea, nervous diseases, and erysipelas	India	Kukkar et al. (2014)
	Unspecified	Not mentioned	Not mentioned	Laxative and anti-rheumatic		
	Leaves	Crushed leaves	Vapor inhalation	Headache		
Local healers	Unspecified	Not mentioned	Not mentioned	Swelling, gnathostomiasis, and inflammation	Thailand	Khunkitti et al. (2000)
Tribal community	Whole plant	Not mentioned	Not mentioned	Rheumatoid arthritis	India	Ragupathy and Newmaster (2009)
Traditional practitioners	Unspecified	Not mentioned	Not mentioned	Anti-anthelmintic	Sri Lanka	Khunkitti et al. (2000)
Indian Materia Medica	Entire plant	Decoction	Oral	Diuretic, diaphoretic, and laxative	India	Pillai and Vijayamma (1985)
Folk medicine	Root	Hair oil	Topical	Throat infection, and head ache	India	Muthu et al. (2006)
African traditional medicine	Aerial parts	Aqueous extract after 12 h maceration	Oral and Topical	Cough, hyperthermia, rheumatism, lumbago, nervous disorders, and amenorrhea	East Africa	Waako et al. (2005)
	Seeds	Aqueous extract	Oral			
Local healers	Leaves	Mixed with castor oil	Oral	Rheumatism and lumbago	India	Sadique et al. (1987)
Folk medicine	Leaves	Decoction mixed with jaggery and pepper	Oral	Cough and fever	India	Sheeba and Asha (2009)
	Seeds	Tonic	Oral	Fever		
	Roots	Not mentioned	Not mentioned	Emetic, laxative and anti-rheumatic		
Folk medicine	Stalks and leaves	Not mentioned	Not mentioned	Dysentery, diarrhea, and headache	India	Rao and Prakash (2006)
Sri Lankan system of Medicine	Unspecified	Not mentioned	Not mentioned	Skeletal fractures	Sri Lanka	Veeramani et al. (2008)
Sri Lankan system of Medicine	Leaves	Boiled with castor oil	Topical	Rheumatic pain and tumors of different kinds	Sri Lanka	Peiris et al. (2015)
	Leaves	Fresh juice	Oral	Asthma, obesity, and male infertility		

Though several studies reported the phytochemicals content and pharmacological activities of *C. halicacabum,* no review was undertaken to critically analyze these studies and propose the future research prospects of this plant as a cradle of novel drug candidates and as a functional food. Moreover, there is no comprehensive study on the link between the traditional uses and scientifically verified pharmacological activities of *C. halicacabum.* Therefore, this review critically encapsulates the botanical description, geographical distribution, ethnomedical applications, phytochemistry, pharmacological activity, micropropagation and toxicity of *C. halicacabum* along with the research gaps for potential future investigation.

2. Literature review methods

A considerable scientific review of the literature was conducted and the search was limited to English Language articles published up to June 2021. The internet sources including, Google Scholar, Science Direct, Pubmed, Springer Link, Wiley online, Web of Science, Taylor & Francis, and plant databases were utilized to retrieve all the appropriate information about *C. halicacabum*. The keywords employed in this search were *Cardiospermum halicacabum*, Sapindaceae, balloon vine, ethnomedical uses, phytochemistry, pharmacology activities, and micropropagation. All phytochemical compounds discussed in this review were validated using the PubChem database.

3. Botanical description

C. halicacabum is a slender, sparsely hairy plant that climbs on the other plants, and attains 1–3 m in length. The stems of this herbaceous plant are 3 mm in thickness that can reach a height of up to 2 m. The internodal length of the *C. halicacabum* plant is about 5–10. The grooved stem of the plant carries alternate double triad leaves, 3–5 cm long, that are either glabrous or covered in a soft down of hairs. The leaves are trifoliate and 5–9 cm long with small stipules at the base (Ayati et al., 2019). The leaflets are ovate to lanceolate, 1–5 cm long, with coarsely toothed or lobed margins. Just beneath the flower stalks are 2 cm long tendrils, usually in pairs, mostly twisted. The tiny radiate flowers are white, arranged in rolls on long flower stems of 5–10 cm in length. The perianth consists of 4–5 egg-shaped sepals; four petals and 8 stamens. The fruits are inflated, obovoid, 1.5–2.5 cm long, triangular, capsules are 3-celled, papyraceous, and keeled. The seeds are black and rounded with a prominent white heart-shaped aril at the base (Durgesh and Patel, 2019). The seed coat is black, opaque, smooth, thick, and quite hard with a white finely porous, cordate spot at the micropyle (Fig. 1).

4. Geographical distribution

C. halicacabum is a common plant in tropical and subtropical regions throughout the world. It is widespread in South Africa and North American countries (Antigua and Barbuda, Barbados, Dominica, Grenada, Guadeloupe, Martinique, Montserrat, Netherlands Antilles, Saint Kitts, and Nevis, Saint Lucia, Saint Vincent, and the Grenadines). Moreover, *C. halicacabum* has broad occurrence in several Asian countries (26), South African countries (32), European countries (4), and North American (52), and South American regions (32). Further, it extends throughout the different regions of Oceania like Australia, New South Wales, Northern Territory, Queensland, Western Australia, Christmas Island, Cook Islands, Fiji, French Polynesia, Guam, New Caledonia, Niue, Northern Mariana Islands, Papua New Guinea, Solomon Islands, Tonga, Vanuatu, Wallis and Futuna (Cardiospermum). The geographical reports on the origin of *C. halicacabum* worldwide are presented in Fig. 2.

In India, its occurrence is higher in the southern states such as Tamil Nadu, Kerala, Karnataka, and Andhra Pradesh than in the other regions. Apart from this, *C. halicacabum* resides in other Indian states such as Maharashtra, Madhya Pradesh, Rajasthan, Bihar, Punjab, Meghalaya, Assam, Nagaland, and Arunachal Pradesh (Cardiospermum halicacabum Linn, 2021). On the other hand, Gildenhuys et al. (2015) confirmed the alien status of *C. halicacabum* in southern Africa through phylogenetic and biogeographic outcomes acquired by investigating phylogenetic (*C. corindum*, *C. grandiflorum*, *C. halicacabum,* and *C. pechuelii*) relationships within and among ballon vine species. In some regions of the world, it is used for medicinal purposes while the rest consider this, as a weed. Unlike the other medicinal plants,

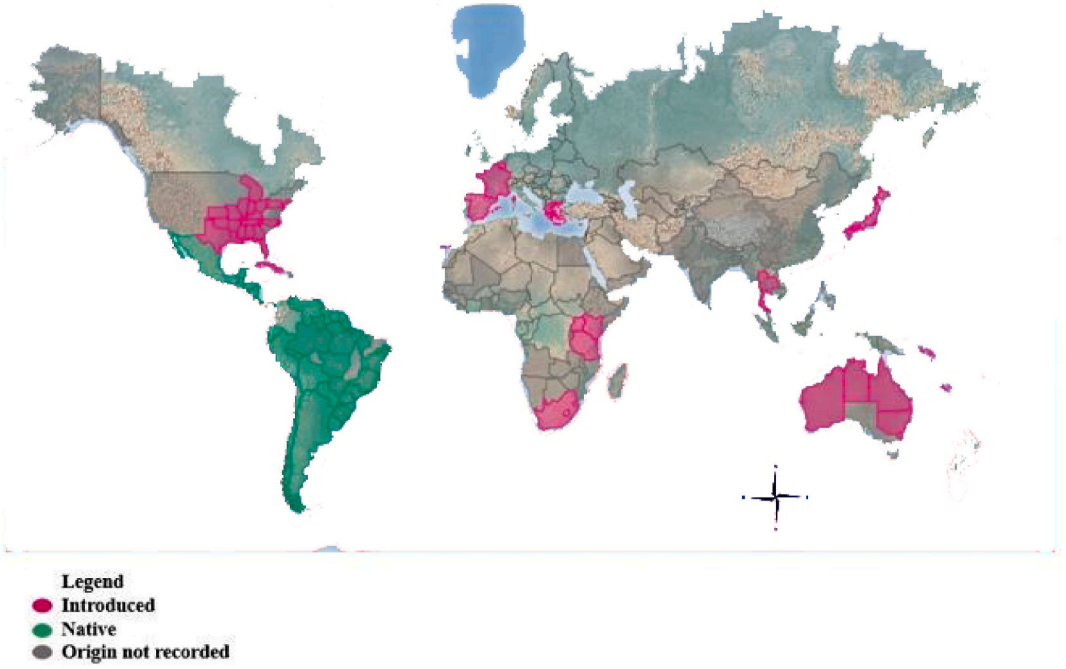


Fig. 2. Global reports on the origin of *Cardiospermum halicacabum* (pink color represents the introduced regions, green color represents the nativity and grey color represents origin not recorded regions). Adapted from CAB International, 2021. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Cardiospermum invasions are perceived as a threat to the natural vegetation because of their capability to conquer the forest lands and crops (Silva et al., 2014). Thus, equal importance should be given to the control, management, and conservation of *C. halicacabum*, globally.

5. Ethnomedical uses

C. halicacabum is one of the widely consumed green leafy vegetables as well as a well-documented medicinal plant in the Indian traditional system of medicines. It is also implemented for various remedial purposes in other parts of the world including China, Sri Lanka, Africa, and Thailand (Raza et al., 2013). All parts of this plant are usually consumed as food as well as medicine. In south India, especially in the Tamil cuisine, pureed leaves are eaten along with rice porridge, spongy lentil pancakes, and steamed rice. Similarly, in most of the south Indian houses and Tamil households, a tangy flavorful soup made out of the aerial parts of *C. halicacabum* makes its presence whenever they are down with flu, especially in the monsoon season. This tangy soup is served with boiled rice as a meal and also consumed as a refreshing and soothing drink to rectify body ache, cold and sore throat (Raman et al., 1998).

The ethnomedical applications of *C. halicacabum* in various traditional systems of medicines are summarized in Table 1. Based on the historical applications by local occupants in traditional medicine, it is evident that the whole plant and the various parts of *C. halicacabum* are used internally and/or externally as a remedy for rheumatoid arthritis, joint pain, body pain, stiffness of limbs, snakebite, stomach pain, microbial infections, neurodegenerative disorders, inflammations, fever, bronchitis, hemorrhoids, skin diseases, dandruff, cough, headache, orchitis, tumor reduction, earache, skeletal fractures, amenorrhea, sprains, swellings, burns, liver and psychiatric disorders (Nandhinipriya and Kumaudhavalli, 2021).

Although there were several scientific facts, various local claims lack meticulous studies. In Unani medicines, only the seeds have been explored whereas in the Ayurvedic medicine, the *C. halicacabum* roots have been principally used as the active parts to manage sicknesses (Table 1). Nevertheless, the outcomes of scientific studies displayed that several bioactive compounds also resided in the aerial parts of the plant. However, the elementarily efficacious segments, constituents, and mechanisms of action of *C. halicacabum* were also unclear. Further, it has been observed that some crucial medicinal data such as dosages, treatment durations, drug preparation procedures, and the name of the specific plant part used in the drug formulations were also vaguely documented.

6. Phytoconstituents

Cyanolipids are the lipid derivatives predominantly found in the seed oils of Sapindaceae plants. A short-chain methyl ester, methyl 4, 4-dimethoxy-3-(methoxymethyl) butyrate isolated from *C. halicacabum* seed oil confirmed the occurrence of cyanolipids which influenced the further investigation of cyanolipids in the seed oils of other Sapindaceous members as well. Furthermore, a GC-MS study on the composition of *C. halicacabum* seed oil resulted in the identification of its chief compound, 11-eicosenoic acid (monounsaturated omega-9 fatty acid). The quantity of eicosenoic acid in the seed oil investigated was found to account for 42% of the total long-chain fatty acids. Additionally, palmitic acid (3%), linolenic acid (8%), linoleic acid (8%), oleic acid (22%), stearic acid (2%), arachidic acid (10%), and small proportions (1–2%) of a low-molecular-weight acid and C_{22} acids were found in the seed oil of *C. halicacabum* (Chisholm and Hopkins, 1958). Likewise, several classes of phytochemicals have been reported in *C. halicacabum* including flavonoids, phytosterols, alkaloids, flavone aglycones, triterpenoids, pentacyclic triterpenes, tannins, glycosides, saponins (Raza et al., 2013).

More than 2500 plants synthesize cyanogenic compounds as part of their defense system. These compounds occur in the form of glycosides that release hydrogen cyanide when degraded by hydrolyzing enzymes. Rajesh Kumar et al. (2011) isolated a cyanogenic compound called cardiospermin, from the root extract of *C. halicacabum* and also demonstrated its anxiolytic activity in rodents using elevated plus-maze (EPM) and light-dark transition model. Among the phytochemicals, phenolic compounds are well-known for their health benefits including the prevention and treatment of various types of diseases such as cancer, cardiovascular disease, diabetes, and obesity.

Later, Jeyadevi et al. (2013) explored the phenolic profile of ethanol extract of *C. halicacabum* leaves through ultra-performance liquid chromatography coupled with quadrupole time-of-flight tandem mass spectrometry (UPLC-Q-TOF-MS/MS) analysis. The results revealed a total of 18 phenolic compounds such as caffeic acid, caftaric acid, methyl salvianolate, protocatechuic acid, 3,4-trihydroxy-(S)-benzenepropanoic acid, phloridzin, chlorogenic acid, coumaric acid, luteolin-7-O-glucuronide, K-hydroxy, benzoyl hexoside isomer, prunin, apigenin -7-O-glucuronide, ferulic acid, ferulic acid glucoside, quercetin, coumaroylquinic acid, coniferaldehyde, and chrysoeriol.

At the same time, Cheng et al. (2013) determined the phenolic profile of Taiwanese C. halicacabum using high-performance liquid chromatography (HPLC) and spectroscopic analyses such as ^{1}H nuclear magnetic resonance spectroscopy (NMR), ^{13}C NMR, ^{1}H–^{1}H correlation spectroscopy (^{1}H–^{1}H –COSY), heteronuclear multiple quantum coherence spectroscopy (HMQC), heteronuclear multiple – bond correlation spectroscopy (HMBC), and nuclear overhauser effect spectroscopy (NOESY). The outcomes of the aforesaid study revealed the presence of 17 phenolic compounds including quercetin-3-O-α-l-rhamnoside, kaempferol-3-O-α-l-rhamnoside, apigenin-7-O-β-d-glucuronide, apigenin-7-O-β-d-glucuronide methyl ester, apigenin 7-O-β-d-glucuronide ethyl ester, chrysoeriol, apigenin, kaempferol, luteolin, quercetin, methyl 3,4- dihydroxybezoate, p-coumaric acid, 4-hydroxybenzoic acid, hydroquinone, protocatechuic acid, gallic acid, and indole-3-carboxylic acid, in the whole parts ethanol extract of Taiwanese C. halicacabum.

In addition, Menichini et al. (2014) showed that the seeds contain β-amyrin (19.3%), β -sitosterol (7.8%), neophytadiene (6.4%), stigmasterol (5.5%), phytol (5.1%), phytol acetate (2.6%), β -Amyrin (14.8%), 8-methoxipsoralen (14.0%), osthol (10.8%), neophytadiene (7.2%), and stigmasterol (5.4%). It is noteworthy that *C. halicacabum* holds several phenolic compounds with various biological activities (Table 2). According to Jeyadevi et al. (2013) the total phenol and flavonoid contents of leaf ethanol extract of *C. halicacabum* were, 17.94 mg gallic acid equivalents/g and 14.97 mg rutin equivalents/g of extract.

Similarly, Mohaddesi et al. (2015) compared the total phenolic and flavonoid contents of different solvent extracts of *C. halicacabum* seeds. The highest phenol (187.37 mg pyrogallol equivalent/g) and flavonoid content (139.26 mg quercetin equivalent/g) were found in the aqueous methanol seed extract of *C. halicacabum*. Whereas the n-hexane extract possessed the lowest amount of phenol (52.17 mg pyrogallol equivalent/g) and flavonoid contents (33.07 mg quercetin equivalent/g). The studies on the phenolics and flavonoid content of roots were rarely elucidated. Until now, more than 60 compounds in this plant belong to various phytochemical classes have been identified among which flavonoids, phenolic acids, glucosides, fatty acids, and volatile esters were proclaimed for the pharmacological activities of *C. halicacabum*.

7. Micropropagation

Micropropagation is an efficient technique not only employed to increase the yield but also to produce the phytochemicals massively under some standard conditions. An earlier study has suggested a method for rapid micropropagation of *C. halicacabum* through plant regeneration from its leaf and nodal explants. Murashige and Skoog (MS) medium supplemented with various concentrations of 2, 4 – dichlorophenoxy acetic acid (0.5–9 μM) had been used for the explants from *C. halicacabum*. It was observed that callus production was

Table 2
Structure, class and biological activity of various compounds identified in Cardiospermum halicacabum.

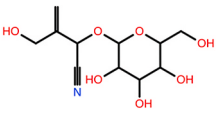
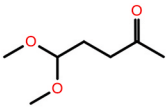
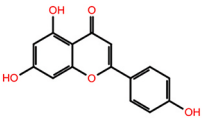
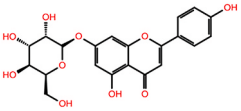
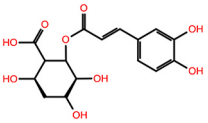
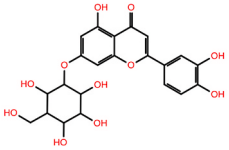
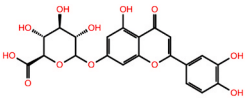
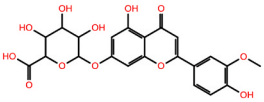
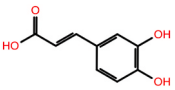
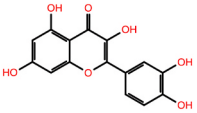
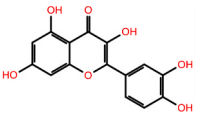
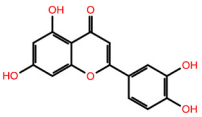
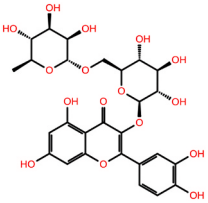
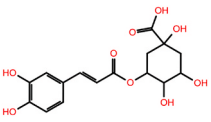
S. No	Compound	Class	Chemical structure	Biological activity	References
1.	Cardiospermin	Cyanoglucoside		Anxiolytic activity	Rajesh Kumar et al. (2011)
2.	Methyl 4, 4-dimethoxy-3-butyrate	Volatile ester		NA	NA
3.	Apigenin	Flavonoid		Neuroprotective properties Anti-cancer activity Anti-inflammatory activity	Nabavi et al. (2018) Ahmed et al. (2021) Ginwala et al. (2019)
4.	Apigenin-7-glucoside	Flavonoid- 7-glycoside		Anxiolytic activity Anti-proliferative activity Induction of human hematopoietic stem cell differentiation	Kumar and Bhat (2014) Nasr Bouzaiene et al. (2016) Samet et al. (2015)
5.	Apigenin-7-O-glucuronide	Flavonoid -7-O-glucuronide		Anti-atherosclerotic activity	Ma et al. (2017)
6.	Luteolin-7-glucoside	Flavone		Induction of human hematopoietic stem cell differentiation Gastroprotective properties Antioxidant activity Anti-cancer activity	Samet et al. (2015) Antonisamy et al. (2016) Song and Park (2014) Chen et al. (2018)
7.	Luteolin-7-O-glucuronide	Flavonoid -7-O-glucuronide		*In vitro* estrogen like activity Anti-inflammatory activity	Wielogorska et al. (2019) Ma et al. (2018)
8.	Chrysoeriol-7-O-glucuronide	Flavonoid -7-O-glucuronide		Anti-cancer activity	Cheng et al. (2013)
9.	Caffeic acid	Polyphenol		Anti-viral activity Anti-cancer activity Cardioprotective properties	Chukwuma et al. (2019) Brautigan et al. (2018) Agunloye et al. (2019)
10.	Quercetin	Flavonoid		Anti-arthritic activity Anti-microbial activity Anti-diabetic activity	Kawaguchi et al. (2019) Zeng et al. (2019) Abdelkader et al. (2020); Beula et al. (2019)
11.	Protocatechuic acid	Phenolic acid		Anti-inflammatory and redox regulatory activity Neuroprotective properties Protective effect on pulmonary toxicity	Adedara et al. (2018) Adedara et al. (2019) Ameeramja et al. (2018)
12.	Luteolin	Flavonoid		Anti-oxidative activity	Song and Park (2014)
13.	Rutin	Flavonoid		Anti-inflammatory and hypolipidemic activity Anti-cancer activity Anti-fungal activity	Manzoni et al. (2019) Deepika et al. (2019) Gaziano et al. (2018)
14.	Chlorogenic acid	Polyphenol		Hepatoprotective and cardioprotective properties Anti-diabetic activity	Agunloye et al. (2019) Bhandarkar et al. (2019)

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Table 2 (*continued*)

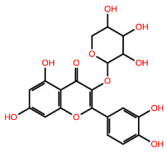
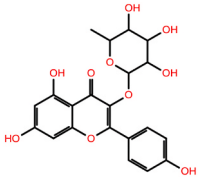
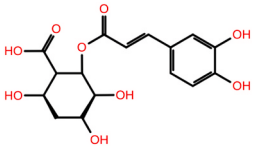
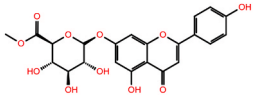
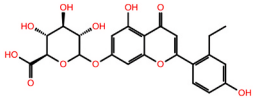
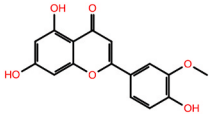
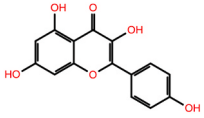
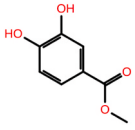
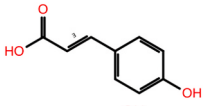
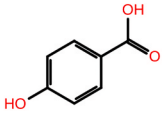
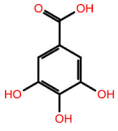
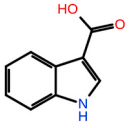
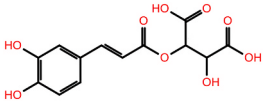
S. No	Compound	Class	Chemical structure	Biological activity	References
15.	Quercetin-3-O-α-l-rhamnoside	Flavonoid glycoside		Anti-oxidative activity	Srinivasan et al. (2015)
16.	Kaempferol-3-O-α-l-rhamnoside	Flavonoid glycoside		NA	NA
17.	Apigenin-7-O-β-d-glucuronide	Flavonoid -7-O-glucuronide		Anti-inflammatory activity	Hu et al. (2016)
18.	Apigenin 7-O-β-d-glucuronide methyl ester	Flavonoid -7-O-glucuronide		Anti-proliferative activity Anti-inflammatory activity	Rao et al. (2018) Ma et al. (2018)
19.	Apigenin 7-O-β-d-glucuronide ethyl ester	Flavonoid -7-O-glucuronide		NA	NA
20.	Chrysoeriol	Flavonoid		Anti-cancer activity	Takemura et al. (2010)
21.	Kaempferol	Flavonoid		Anti-cancer activity	Chen and Chen (2013)
22.	Methyl 3,4-dihydroxybenzoate	Phenol		Neuroprotective properties	Cai et al. (2016)
23.	p-coumaric acid	Phenol		Hepatoprotective properties	Cha et al. (2018)
24.	4-hydroxybenzoic acid	Phenol		Anti-cancer activity	Wang et al. (2018)
25.	Gallic acid	Phenol		Anti-cancer and anti-oxidant activity Anti-inflammatory activity	Kahkeshani et al. (2019) Dludla et al. (2018)
26.	Indole-3-carboxylic acid	Plant growth regulator		Anti-fungal activity Anti-proliferative activity	Szmigiel et al. (2018) Ma et al. (2018)
27.	Caftaric acid	Coumaric acid		Inhibitor of ophidian myotoxicity	Cardoso et al. (2020)

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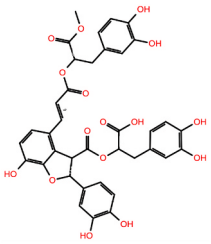
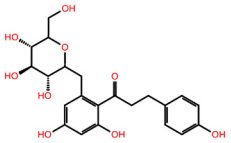
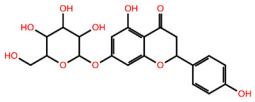
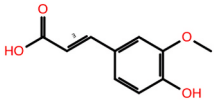
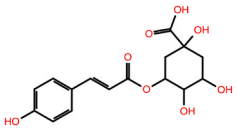
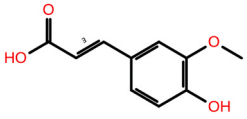
Table 2 (*continued*)

S. No	Compound	Class	Chemical structure	Biological activity	References
28.	Methyl salvianolate	Phenolic acid		NA	NA
29	Phloridzin	Dihydrochalcone glycoside		Hepatoproective Anti-diabetic activity	Khalifa et al. (2017) Kumar et al. (2019)
30	Prunin	Nargenin -7-O-beta-D-glucoside		Inhibition of HMG-CoA reductase	Chang et al. (2011)
31	Ferulic acid	Phenolic acid		Anti-osteoporotic activity Anti-obesity	Hou et al. (2019) Luna-Vital et al. (2020)
32	Coumaroylquinic acid	Quinic acid derivative		NA	NA
33	Coniferaldehyde	Cinnamaldehyde		Anti-inflammatory activity	Kim et al. (2016)

"NA" denotes information is not available.

maximum at 5 μM 2, 4 – dichlorophenoxy acetic acid where 96% and 90% of cultured leaf and nodal explants, respectively. Consequently, the viable calli were sub-cultured on MS medium (half-strength) supplemented with various concentrations of 6-benzyl adenine (2–10 μM) or kinetin (2–10 μM) alone or in combination with indole 3-acetic acid (0.2–1.0 μM) for shoot regeneration. The explants supplemented with 8 μM kinetin showed the maximum number of adventitious shoots (28 per callus).

Later, those shoots were subjected to root generation with various concentrations (1–5 μM) of indole-3-acetic acid (IAA), indole 3- butyric acid, and α-naphthalene acetic acid. Out of three supplementations, indole 3- butyric acid (2.5 μM) was observed to be potent in inducing root generation from the explants. It was found that 91% of the regenerated shoots developed roots with an average of 4.2 roots per shoot within 45 days by way of indole 3- butyric acid supplementation at a concentration of 2.5 μM. Finally, the plantlets raised through this protocol were acclimatized and shifted to soil with 90% success (Thomas and Maseena, 2006).

According to the *in vitro* experiments by Babber et al. (2001) it is evident that different explants like cotyledon, hypocotyl, cotyledonary node, leaf, internode, and node derived from *C. halicacabum* can effectively produce calli on MS medium, supplemented with benzyl amino purine (BAP) and naphthalene acetic acid (NAA), effectively. The results of the above-said study state that among the different explants tested, shoots were favorably produced by the calli obtained from leaf and cotyledon explants. Moreover, the highest number of shoots were formed from calli subcultured on MS medium supplemented with BAP (17.8 μM).

Further, Jahan et al. (2014) devised a plant regeneration protocol for *C. halicacabum* using seven-day-old hypocotyls obtained from the MS medium. The hypocotyl explants were inoculated on the MS medium with five different concentrations of thidiazuron (0.1, 0.3, 0.5, 0.7, and 0.9 μM). Out of the five concentrations tested, hypocotyl explants with 0.7 μM of thidiazuron showed a maximum of 18.20 ± 0.98 number of shoots in 94% cultures in the fourth week. Subsequently, shoots supplemented with 0.7 μM thidiazuron were subcultured five times in a hormone-free MS medium. Notably, the explants displayed a significant increase in the number of shoots and shoot length from the fourth subculture (number of shoots: 40.00 ± 1.15; shoot length: 6.53 ± 0.49 cm).

Although these studies recommend the use of micropropagation for the rapid multiplication of *C. halicacabum* from its explants, they did not demonstrate the vital qualities that can be improved through the micropropagation of *C. halicacabum.* Tissue culture offers numerous advantages by enhancing the secondary metabolites production, propagating large-scale plants in controlled environmental settings, manipulating the metabolic pathways, and optimizing growth conditions etc. None of these were demonstrated in the micropropagation studies of *C. halicacabum.* Therefore, future studies should utilize the benefits of tissue culture in terms of biotechnological production of therapeutic compounds and compare the products of conventional breeding approaches and *in vitro* culture techniques to confirm the improvement in their qualities.

8. Pharmacological actions of C. halicacabum extracts

As an Indian traditional medicine, *C. halicacabum* is widely used for treating rheumatic pain and inflammation of joints. Inflammation is a primary physiologic defense mechanism that helps the body to protect itself against infection, burn, toxic chemicals, allergens, or other noxious

stimuli (Chen et al., 2017). Uncontrolled and persistent inflammation could act as an etiologic factor for many of the chronic illnesses that human beings encounter in their lifetime. Despite being a defense mechanism, it acts as a central executor in the pathogenesis of many diseases such as rheumatoid arthritis, arteriosclerosis, myocarditis, infections, cancer, and metabolic disorders (Furman et al., 2019). The advancement of several side effects following the consumption of anti-inflammatory drugs has led to the search for natural anti-inflammatory products.

In recent years, several studies have confirmed the effects of *C. halicacabum* against inflammation via *in vitro* and *in vivo* models. Implementation of the carrageenan-induced rat paw edema and cotton pellet granuloma models of experimental inflammation had led to the innovation of many clinically valuable anti-inflammatory compounds. Those models were applied to study the anti-inflammatory activities of *C. occidentalis* leaves and the aerial parts of *C. halicacabum*. Researchers have compared the anti-inflammatory effects of the fine powder from *C. occidentalis* (1000 mg/kg) and *C. halicacabum* extract (250 mg/kg) after a seven-day oral treatment in male Wistar rats. Phenylbutazone (100 mg/kg) and hydrocortisone (15 mg/kg) were the reference drugs used in the Carrageenan paw edema and cotton pellet granuloma, respectively. They used three concentrations of *C. halicacabum* (100, 250, and 500 mg/kg) and two higher doses of *C. occidentalis* (1000 and 2000 mg/kg) for the carrageenan paw edema model.

Interestingly, they found that the anti-inflammatory activity shown by the *C. halicacabum* (100 mg/kg- 41%; 250 mg/kg −64.6%; 500 mg/kg −69.4%) was quite higher than phenylbutazone (44.0%) and *C. occidentalis* (1000 mg/kg – 48.2; 2000 mg/kg - 63.0%) in the carrageenan paw edema model. A single dose for each plant has been used in the cotton pellet granuloma model (*C. occidentalis* -1000 mg/kg and *C. halicacabum* -250 mg/kg). The percentage of inhibition found in the group administered with *C. halicacabum* (42.3%) was higher than the *C. occidentalis* (27.4%) and hydrocortisone (29.4%) treated groups. As per their findings, *C. occidentalis* was maximally active at a dose of 2000 mg/kg, while the *C. halicacabum* extract was maximally effective at a dose of 500 mg/kg itself (Sadique et al., 1987).

Ethanol leaf extract of *C. halicacabum* inhibited NO production (IC_{50} = 90 μg/ml) in the Lipopolysaccharide (LPS) stimulated macrophages cell line RAW 264.7 and TNF-α production (IC_{50} = 17 μg/ml) in the L929 tumorigenic murine cells (Venkatesh and Krishnakumari, 2006). TNF-α is an inflammatory cytokine that arbitrates a wide array of biological functions through the initiation of the TNFR1 receptor. Meanwhile, Sheeba and Asha (2009) investigated the anti-inflammatory effect of C. halicacabum through studying the expression of COX-2, COX-1, iNOS, and TNF-α using mouse macrophage cell line (RAW264.7 cells) and the regulation of NFκB activation on Jurkat T cells. C. halicacabum extract at a concentration of 200 μg/ml showed a 72.52% reduction in the mRNA expression of COX-2 which was comparable with the inhibition exhibited by the non-selective inhibitor, indomethacin (72%) at a concentration of 5 μg/ml.

Further, selective inhibitor, CAY10404 (5 μg/ml) showed an 80.8% reduction in the expression of the COX-2. In contrast, mRNA expression of the COX-1 gene was not affected in LPS activated RAW264.7 cells. The extract at a concentration of 200 μg/ml inhibited the mRNA expression of iNOS by 66.3% at the same time reduced the expression of TNF-α by 51%. Likewise, the Western blot analysis also revealed the down-regulation of COX-2 protein (70%) at 200 μg/ml in the LPS treated RAW264.7 cells. Again, at 200 μg/ml concentration, the extract prevented 87% of NFκB activation in Jurkat T cells. Hence, the authors concluded that the ethanol extract of C. halicacabum could potentially inhibit the over expression of COX-2, iNOS, and TNF-α by blocking NFκB activation. COX-2 is an enzyme that is necessary for the production of pro-inflammatory prostaglandins (PGE2) and thus has been a target for many modern anti-inflammatories and cancer-preventive drugs (Chavan et al., 2017).

Moreover, nitric oxide (NO) is a free radical derived from the oxidation of the terminal guanidine nitrogen atom of L-arginine by nitric oxide synthase (iNOS) that mediates many physiological processes, including neurotransmission and inflammation (Ostojic et al., 2021). NFκB is a key mediator of inflammation that triggers inhibitor of kappa B (IκB) kinase in the cytosol upon being induced by inflammatory stimuli. Consequent signaling pathways via a canonical or non-canonical lead to migration of NFκB toward the nucleus and hence activates the targeting gene such as macrophages, monocytes, pro-inflammatory cytokines (IL-1β, IL-6, IFNα, and TNF-α), mast cells, T-cells, and B-cells (Choy et al., 2019). Thus inhibition of the NFκB signaling cascade could be one of the tactics to reduce the progression of disease in inflammatory conditions.

In another study, treatment with ECH (100, 200, and 400 mg/kg) significantly reduced serum nitric oxide (18.84%, 38.81% and 53.85%), TNF-α (7.41%, 25.88%, and 42.69%), and MDA (33.04%, 43.05%, and 54.29%) levels in the experimental mice in a dose-dependent manner. Specifically, ECH (400 mg/kg) significantly inhibited the progression of carrageenan-induced paw edema after 5 h ($p < 0.001$) of treatment. Oxidative stress is associated with the origin of numerous diseases such as arthritis, cancer, atherosclerosis, diabetes, hypertension, cardiovascular problem, intestinal disease, and aging. Free radicals released from the damaged cells are indicators of inflammatory response. An increase in the level of oxidative stress can stimulate the generation of free radicals, malondialdehyde, 8-hydroxy-2′-deoxyguanosine (8-OHdG), and isoprostanes, each of which can induce many transcription factors, such as NFκB, AP-1, p53, and STAT (Chen et al., 2017).

Similarly, the antioxidant activity of ECH [CAT- 4.07 ± 0.10, SOD – 22.09 ± 0.13, and GP_X – 2.19 ± 0.13 U/mg protein] was equal to the reference standard, indomethacin [CAT- 4.01 ± 0.63, SOD – 21.20 ± 0.27, and GP_X – 2.15 ± 0.19 U/mg protein] and higher than the other two doses of ECH (100 and 200 mg/kg). The same study also reported the inhibition of LPS-induced NO production in the RAW 264.7 cell line by ACH (IC_{50} = 407.82 ± 3.82 μg/ml), ECH (IC_{50} = 104.06 ± 2.38 μg/ml), luteolin (IC_{50} = 38.47 ± 1.32), and apigenin (IC_{50} = 27.36 ± 1.5 μg/ml). ECH was able to mitigate the inflammation by increasing the enzymatic antioxidants (CAT, SOD, and GP_X) and suppressing the activities of NO, TNF-α, and MDA (Huang et al., 2011). However, all the above studies did not examine the effect of C. halicacabum on the important inflammatory agents such as proinflammatory cytokines (e.g. IL-8, IL-10, IFN-γ), prostaglandin E2, high sensitivity C-reactive protein (hs-CRP), matrix metalloproteinases (MMPs), intracellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM-1), etc.

As per the outcomes of this review, *C. halicacabum* decreases inflammation via the inhibition of COX-2, TNF-α, iNOS, NO, and by blocking NFκB activation (Fig. 3.). In inflammation, inducible nitric oxide synthase (iNOS) activates NO, which alters the immune response. Compounds that suppress iNOS activity have anti-inflammatory properties (Choy et al., 2019). Based on these observations, it is evident that bioactive compounds present in *C. halicacabum* contain anti-inflammatory properties. Numerous *in vitro* and *in vivo* studies have demonstrated the other therapeutic activities of *C. halicacabum* against oxidative stress, arthritis, diabetes, collagen degradation, cancer, anxiety, ulcer, microbial infections, liver disorders, neurological problems, and kidney diseases. Those scientific studies on various pharmacological activities of *C. halicacabum* are summarized in Table 3. Additionally, the antibacterial activity of different solvent extracts of *C. halicacabum* against human pathogenic bacterial species is depicted in Fig. 4 as reviewed by Gaziano et al. (2019).

9. C. halicacabum based nanoparticles and its pharmacological applications

Green synthesize of nanoparticles from medicinal plants is considered as an effective strategy in the field of drug designing. Plant based nanoparticles are preferred over chemical methods since it deals with simple, rapid, cost-effective and eco-friendly approaches (Ahmed and

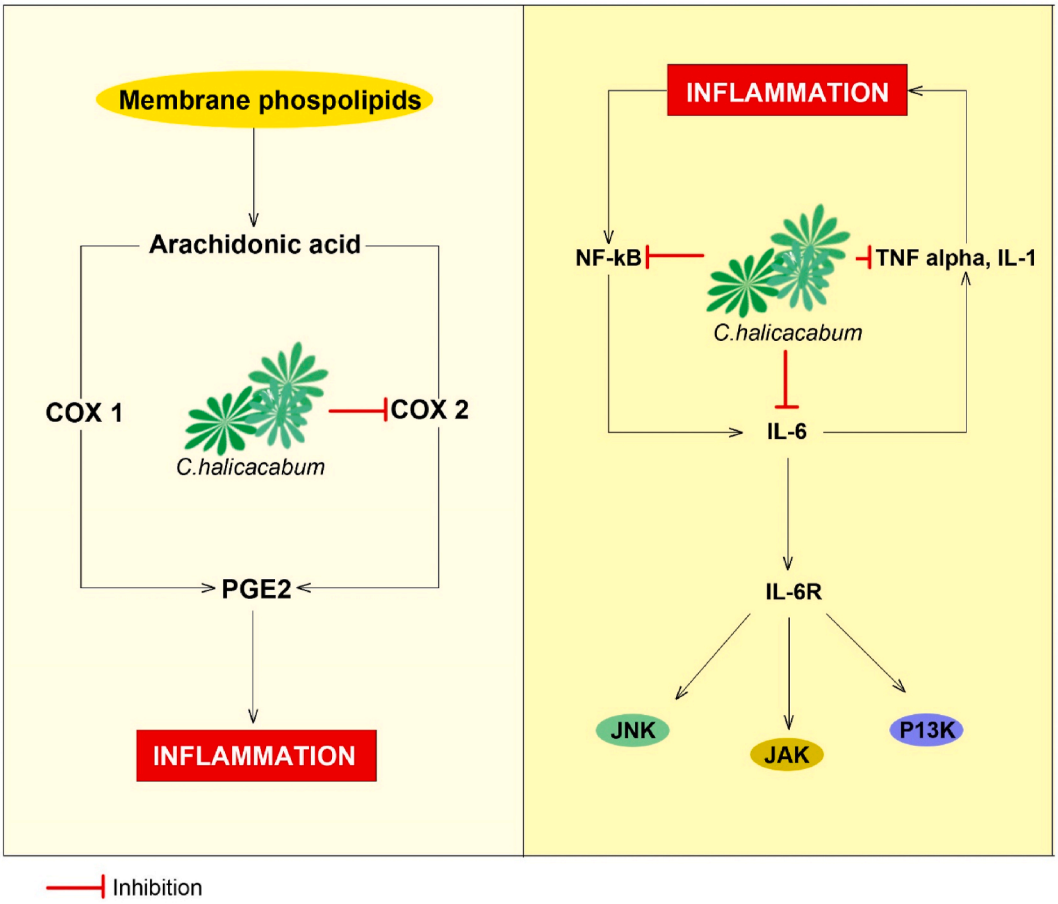


Fig. 3. Anti-inflammatory mechanism of *Cardiospermum halicacabum*. Inhibition of the inflammatory mediators COX 2, NF-κB, TNF alpha, IL-1 and IL-6 by *Cardiospermum halicacabum*. COX 2: Cyclooxygenase; NF-κB (nuclear factor kappa B); TNF alpha: Tumor Necrosis Factor Alpha; IL-1: Interleukin 1; IL-6: Interleukin 6.

Mustafa, 2020). A comparative study analyzed the antibacterial efficacies of biosynthesized ZnO nanoparticles from *C. halicacabum* leaf ethanol extract (Bio-ZnO NPs) and chemically synthesized (Chem-ZnO NPS). Three concentrations of Bio-ZnO NPs (0.2, 0.4 and 0.6 mg/ml) and a single concentration of Chem –ZnO NPS (50 μg/ml) were assessed against Gram-positive bacteria (*S. saprophyticus*, *B. subtilis*) and gram-negative bacteria (*Escherichia coli* and *P. aeruginosa*) along with the positive control ciprofloxacin (5 μg/disk). Bio-ZnO NPs at the highest concentration (0.6 mg/ml) displayed the highest zone of inhibition (21 mm) against *Escherichia coli* whereas the control was highly active against *Staphylococcus aureus* with a zone of inhibition (27 mm). Likewise, among the four bacterial species tested, the maximum inhibition exerted by Chem-ZnO NPS was also against *Staphylococcus aureus* but comparatively with a small zone of inhibition (13 mm). This study proved that the antibacterial activity of biosynthesized zinc oxide obtained from the aqueous leaf extract of *C. halicacabum* was better than the chemically synthesized zinc oxide nanoparticles (Nithya and Kalyanasundharam, 2019).

Li et al. (2019) confirmed the biosynthesis of gold nanoparticles from the leaf extract of *C. halicacabum* by Energy Dispersive X-Ray Analysis (EDAX) and used eight different concentrations of CH–AuNP (0, 5, 7.5, 10, 25, 50, and 100 μg/mol) against three different gastric carcinoma cell lines AGS, SNU-5, and SNU-16. The authors have demonstrated the biosynthesis of gold nanoparticles from *C. halicacabum* through various characterization studies (UV–visible spectroscopy, DLS, FTIR, SAED, EDAX, AFM, and TEM). For the MTT analysis, they had used eight different concentrations of CH–AuNP against three different gastric carcinoma cell lines AGS, SNU-5, and SNU-16, and found that AGS cell lines were more sensitive to CH–AuNP compared to SNU-5 and SNU-16 because about 50% of cells were dead in AGS cells treated with 25 μg/mol.

Hence, for the further assessment of anticancer activity of CH–AuNP in the AGS gastric cell line, a dosage of 25 μg/mol was selected. Also, reported that CH–AuNP can suppress the growth of gastric carcinoma cell line, AGS at a dose of 25 μg/mL. The authors have noticed a significant number of apoptotic cells (92.5%) in 24 h treatment with CH–AuNP (25 μg). They have also identified that CH–AuNP (25 and 50 μg/mol) was able to upsurge the expression of pro-apoptotic protein Bcl-2 associated protein (Bax), the initiator caspase-3, and executor caspase-9, as well as down regulate the expression of anti-apoptotic proteins, B-cell lymphoma 2 (Bcl-2), and B-cell lymphoma-extra-large (Bcl-XL). Even though the authors had displayed the increase of ROS content in the cells treated with CH–AuNP, the oxidant/antioxidant status was not clear.

In brief, both the mitochondria-mediated intrinsic and death receptor-mediated extrinsic pathways, i.e. the up-regulation of pro-apoptotic proteins/enzymes such as (caspase8, p53, BAK, and BH3-only proteins), the down regulation of anti-apoptotic members (FAS, FADDR, TRAIL, BCL-W, MCL-1, and A1/BFL-1), death receptor signaling, regulation of c-Flip by metabolic inhibitors should be studied in detail to know the signaling pathways that get modulated by *C. halicacabum in vivo*. Specifically, long-term studies on CH–AuNP *in vivo* are essential to assess its potency and toxicity. However, an in-depth study will be required to comprehend the actual mechanism behind the anticancer activity of *C. halicacabum*. Recently, Duan et al. (2020) found that CH-ZnONPs (*Cardiospermum halicacabum*-zinc oxide nanoparticles) at 12.5 μg/ml induced apoptosis in human melanoma cells (A375), through up-regulating the expressions of caspase 3, 8, and 9. However,

Table 3
Pharmacological activities of different parts of *C. halicacabum*.

Plant part	Extract/ fraction	Experimental model/assay	Pharmacological activity	Effect (s)/active concentration (s)/ Inhibition	Positive control	Reference
Leaf	Ethanol	*In vitro*	Antioxidant	Nitric oxide: IC_{50} value - 83 μg/ml ABTS: IC_{50} value - 58 μg/ml DPPH: IC_{50} value - 29 μg/ml Reducing power – 0.4074	Butylated hydroxyl toluene (20–100 μg/ml)	Jeyadevi et al. (2013)
Leaf	Ethanol	*In vitro*	Antioxidant	EC_{50} value: DPPH -198.26 ± 4.62 g/ml TEAC value: ABTS - 166.98 ± 2.07 g/mg	Butylated hydroxyl toluene (100 μg/ml)	Huang et al. (2011)
Leaf	Aqueous	*In vitro*	Antioxidant	EC_{50} value: DPPH- 357.18 ± 2.58 g/ml TEAC value: ABTS - 126.52 ± 1.60 g/mg	Butylated hydroxyl toluene (100 μg/ml)	Huang et al. (2011)
Seed	Methanol	*β*-carotene bleaching *(in vitro)*	Antioxidant	Inhibited lipid peroxidation: IC_{50} value - (6.5 μg/ml)	Propyl gallate (10–100 μg/ml)	Menichini et al. (2014)
Leaf	Methanol	*In vitro*	Antioxidant	EC_{50} value: DPPH - 67.55 μg/ml SOD -145.51 μg/ml *β*-carotene–linoleate −70.62% at 200 μg/ml	Butylated hydroxyl toluene (50–200 μg/ml)	Kumaran and Karunakaran (2006)
Aerial	Ethanol	Carrageenan paw edema (*in vivo*) Cotton pellet granuloma (*in vivo*)	Anti-inflammatory	Percentage of inhibition: (500 mg/kg - 69.4%) Percentage of inhibition: (250 mg/kg - 42.3%)	Phenylbutazone (100 mg/kg) Hydrocortisone (15 mg/kg)	Sadique et al. (1987)
Leaf	Ethanol	LPS stimulated macrophages cell line RAW 264.7 (*in vitro*) L929 tumorigenic murine cells (*in vitro*)	Anti-inflammatory	Inhibition of TNF-α: (90 μg/ml – 50%) Inhibition of NO: (17 μg/ml – 50%)	None	Venkatesh and Krishnakumari (2006)
Whole plant	Ethanol	LPS treated RAW264.7 cells (*in vitro*)	Anti-inflammatory	Inhibition of COX2: (200 μg/ml −72.52%)	Indomethacin (10 mg/ml)	Sheeba and Asha (2009)
Leaf	Ethanol	Carrageenan paw edema (*in vivo*)	Anti-inflammatory	Inhibition of TNF-α; (400 mg/kg - 42.69%) Inhibition of NO: (400 mg/kg - 53.85%) Inhibition of NF-κB: (200 μg/ml – 87%)	Indomethacin (10 mg/kg)	Huang et al. (2011)
Aerial	Methanol	Cholinesterase inhibitory assay (*in vitro*)	Neuroprotective	Inhibition of butyrylcholinesterase: IC_{50} value – 59.8 μg/ml	Physostigmine (0.9 mg/ml)	Menichini et al. (2014)
Whole plant	Methanol	Hot plate (*in vivo*) Tail immersion test (*in vivo*)	Analgesic	Increased latency time at 150 mg/kg Increased latency time at 350 mg/kg	Pentazocine hydrochloride (6 mg/kg)	Shabi et al. (2009)
Leaf	Ethanol	CFA- induced (*in vivo*)	Anti-arthritic	Decreased rheumatoid factor: 500 mg/kg - 5.58 ± 0.31 U/ml Decreased C- reactive protein: 500 mg/kg - 29.24 ± 0.58 mg/l	Diclofenac sodium (0.3 mg/kg)	Jeyadevi et al. (2013)
Leaf	Ethanol	CFA- induced (*in vivo*)	Anti-arthritic	Reduced paw volume: 200 mg/kg - 152.23 mm	Indomethacin (45 mg/kg)	Padmini et al. (2016)
Root	Ethanol	Light-dark transition model (*in vivo*)	Anxiolytic	Increased the time of locomotion (200 s) at 30 mg/kg	Diazepam (1.0 mg/kg)	Rajesh Kumar et al. (2011)
Leaf	Ethanol	STZ-induced (*in vivo*)	Anti-diabetic	Decreased blood glucose and increased insulin levels (200 mg/kg)	Glibenclamide (600 μg/kg)	Veeramani et al. (2008)
Leaf	Flavonoid fraction	STZ-induced (*in vivo*)	Anti-diabetic	Decreased total cholesterol and LDL (100 mg/kg)	Glibenclamide (500 μg/kg)	Babu and Sekar (2015)
Whole plant	Ethanol	Ethanol-induced (*in vivo*)	Anti-ulcer	Decreased ALP: 600 mg/kg- 25.54 ± 2.39 IU/L Increased GSH: 600 mg/kg- 1.45 ± 0.01 μg/mg protein	Omeprazole (20 mg/kg) and ranitidine (150 mg/kg	Sheeba and Asha (2006)
Whole plant	Ethanol	Indomethacin-induced (*in vivo*)	Anti-ulcer	Reduced the gastric juice pH (6.33 ± 0.02) and ulcer index at 600 mg/kg	Omeprazole (20 mg/kg)	Sheeba et al. (2016)
Whole plant	Alcohol Petroleum ether Aqeous	Castor oil-induced, prostaglandin E2- induced-enter pooling, and gastro-intestinal motility model	Anti-diarrhea	Reduced the cumulative fecal mass and decreased the frequency of defecation at 400 mg/kg	Atropine sulphate (5 mg/kg) and loperamide (3 mg/kg).	Rao et al. (2006)
Whole plant	Methanol	CTX-induced (*in vivo*)	Immunomodulatory	Increased total bone marrow cellularity and α-esterase positive cells (20 mg/kg)	None	Pratheeshkumar and Kuttan (2010)
Stem	Ethyl acetate	CCl_4-induced (*in vivo*)	Hepatoprotective	Decreased liver biomarkers (SGPT, SGOT, ALP) - 400 mg/kg	Silymarin (100 mg/kg)	Ara et al. (2009)
Leaf	Ethanol	CCl_4-induced (*in vivo*)	Hepatoprotective	Decreased liver biomarkers (SGPT, SGOT, ALP) and increased antioxidant levels at 500 mg/kg	Silymarin (50 mg/kg)	Jeyadevi et al. (2013)
Whole plant	Methanol	Acetaminophen-induced (*in vivo*)	Nephroprotective	Renal biomarkers (blood urea nitrogen, uric acid and creatinine) at 400 mg/kg	None	Parameshappa et al. (2012)

(*continued on next page*)

Table 3 (*continued*)

Plant part	Extract/ fraction	Experimental model/assay	Pharmacological activity	Effect (s)/active concentration (s)/ Inhibition	Positive control	Reference
Leaf	Ethanolic aqueous	Hydroxyproline assay (*in vitro*)	Anti-collagenolytic	Protected against collagen degradation Inhibition of ChC activity: (80 μg - 86.66%)	None	Ganesan et al. (2011)
Leaf	Methanol	HIV-1RT activity inhibition assay (*in vitro*) Hepatitis B surface antigen-binding assay (*in vitro*) HBV DNA polymerase inhibition (*in vitro*)	Antiviral	Anti-HIV-RT at 200 μg/ml Anti-HBV at 5 mg/ml Anti-HBV effect at 400 μg/ml	Lamivudine (CNM)	Murugan et al. (2011)
Leaf	Ethanol	Well diffusion assay (*in vitro*)	Anti-bacterial	Maximum inhibition against- *Staphylococcus aureus*- zone of inhibition 18 mm (MIC – 80 μg/ml)	Chloroamphenicol (10 μg)	Jeyadevi et al. (2013a)
Seed	Methanol	Antifungal activity assay (*in vitro*)	Antifungal	Maximum inhibition against- *Aspergillus flavus* (86%) at 3000 ppm	Thiram (2 g/l)	Girish et al. (2011)
Whole plant	Ethanol	Disc diffusion assay (*in vitro*)	Antibacterial	*Pseudomonas aeruginosa* (MBC: 116.7 ± 14.4 μg/ml) and *Streptococcus pyogenes* (MBC: 125.0 ± 25.0 μg/ml)	Tetracycline (CNM)	Beula et al. (2019)
Leaf	Ethanol	Well diffusion assay (*in vitro*)	Antifungal	*Candida albicans* [MIC - 190 μg/ml (ZOI - 15 mm)]	Nystatin (20 μg)	Jeyadevi et al. (2013a)
Leaf	Aqueous and alcohol	*In vitro*	Antiplasmodial	Aqueous extract at 2 mg/ml rapidly decreased the larval motility (*Strongyloides stercoralis)*	Ivermectin (250 μg/ml) and piperazine (2 mg/ml)	Boonmars et al. (2005)
Whole plant	Ethanol	Yeast-induced (*in vivo*)	Antipyretic	Controlled pyrogenesis at 400 mg/kg	Paracetamol (100 mg/kg	Asha and Pushpangadan (1999)
Leaf	Aqueous	*In vitro*	Antifilarial	Reduced the motility of adult worms (*Brugia pahangi)* and the release of microfilariae from females at 0.5 mg/ml	None	Khunkitti et al. (2000)
Leaf	Aqueous	*In vivo*	Fertility augmenting effect	Increased total sperm count, testosterone level and impregnation at 200 mg/kg	None	Peiris et al. (2015)
Root	Ethanol	Electroshock and chemical induction -strychnine, pentylenetetrazol, picrotoxin (*in vivo*) Neurotransmitter test (*in vivo*)	Anti-epileptic	Anticonvulsive effect at 300 mg/kg Enhanced GABA activity in cerebellum at 200 mg/kg	Diazepam 10 mg/kg and	Dhayabaran et al. (2012)

EC_{50}: Half maximal effective concentration; IC_{50}: Half maximal inhibitory concentration; MIC: minimum inhibitory concentration; ZOI: Zone of inhibition; MBC: minimum bactericidal concentration; CNM: Concentration not mentioned.

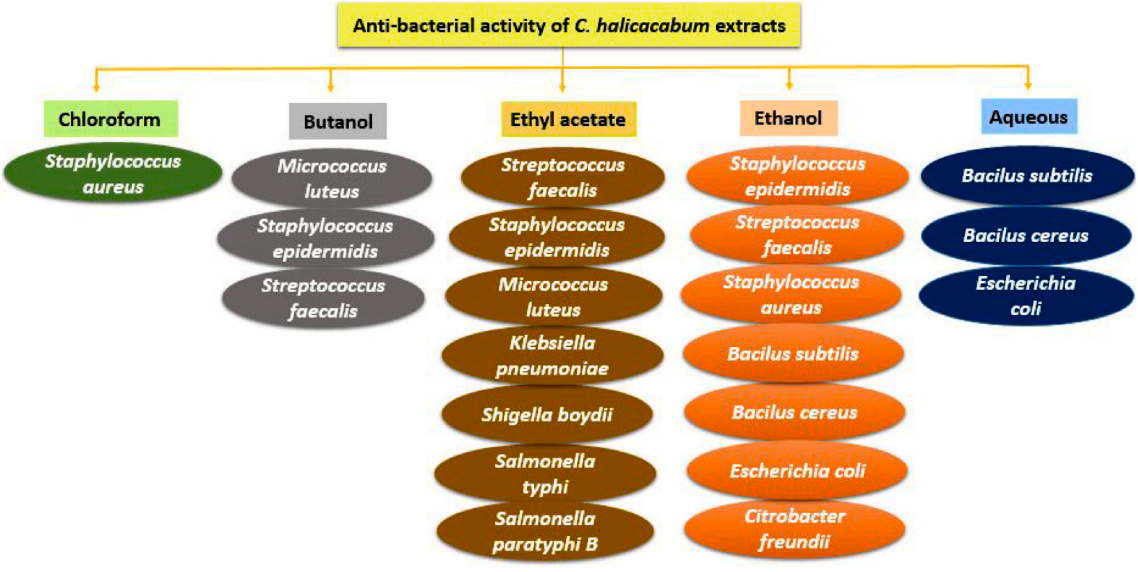


Fig. 4. Antibacterial activity of different solvents extracts of *Cardiospermum halicacabum*.

meticulous studies on the ROS levels and apoptosis related proteins such as Bid, Bax, and Bcl-2 should be performed to confirm the apoptotic property of CH-ZnONPs.

10. Toxicity studies

C. halicacabum leaves have well-established traditional application in folk medicine and in general, are believed to be safe. Even so, it is essential to experiment with its safety level for long term usage. The oral acute toxicity study of the ethanol extract of *C. halicacabum* was carried out using Swiss albino rats (150–200 g). The animals were administered with different doses of leaf ethanol extracts (0.5, 1.0, 1.5, 2, 2.5, and 3.0 g/Kg body weight). Each animal was carefully observed for 72 h for behavioral signs of toxicity (tremors, lethargy, salivation, convulsion, diarrhea, changes in hair, skin, eyes, motor activity, circulatory, respiratory, autonomic, and central nervous system) and mortality. It has been reported that the extract was safe up to the dose of 2000 mg/kg b. w. p.o. and did not show any acute toxicity signs (Jeyadevi et al., 2013). Likewise, a couple of studies have reported the absence of toxic signs up to a dose of 2000 mg/kg of *C. halicacabum* extracts in the acute toxicity tests conducted on rats and mice, respectively (Padmini et al., 2016; N. V. Rao et al., 2006).

On the contrary, an acute toxicity study indicated that no toxic effects were observed after oral administration of 5000 mg/kg of whole plant methanol extract of *C. halicacabum* (Shabi et al., 2009). Thus far, sub-acute, sub-chronic, and chronic toxicological studies have not been carried out on various parts and solvent extracts of *C. halicacabum*. Unfortunately, very little amount of work has been conducted on the safety profile of *C. halicacabum*. Hence, a thorough toxicological evaluation on the safety level of the extracts is required for consideration of *C. halicacabum* as an innocuous herbal drug.

11. Validation of traditional uses of C. halicacabum

Traditional knowledge about herbal plants aid in accelerating the drug discovery process since it has been accepted and followed by the local communities. In India, it is widely eaten and prescribed in various traditional systems of medicine like Ayurveda, Homeopathy, Siddha, and Unani for alleviating several illnesses. Even though *C. halicacabum* has been used in many drug formulations or concoctions corresponding to a wide spectrum of inflammatory disorders, traditionally, it was mainly used as a remedy for arthritis and rheumatism. It is interesting to note that scientific research has verified its therapeutic effect on rheumatic disorders and divulged its hidden pharmacological properties such as antioxidant, anti-diabetic, anti-ulcer, nephroprotective, immunomodulatory, antiviral activity, and collagen protection.

However, a cluster of ethnomedical applications of *C. halicacabum* in the treatment of alopecia, earache, amenorrhea, hemorrhoids, erysipelas, dandruff, alopecia, skin disease, grey hair, hysteria, osteoarthritis, snake bites, cardiac problems, anemia, memory complications, tuberculosis, cognitive problems, rat poison, urolithiasis, bronchitis, jaundice, orchitis, stomach ache, gnathostomiasis, asthma, obesity, male fertility, cognitive impairments, palpitations, urine retention, constipation, depression, neurobehavioral and psychiatric disorders that have not been inspected to date. On the other hand, some of its therapeutic properties were investigated by modern science which includes anti-arthritic property, antimicrobial, anxiolytic anti-inflammatory, analgesic, anticonvulsive, hepatoprotective, antimicrobial, antipyretic, antidiarrheal, and infertility. Among the research works that have been conducted on the pharmacological properties of *C. halicacabum*, the majority of them have correlations with its traditional uses. Indeed, well-designed experimental and clinical studies are required to illuminate the above-mentioned traditional uses.

a) Links between ethnomedical uses and scientific studies

The relations between the traditional uses of *C. halicacabum* and the pharmacological activities reported by scientists have been analyzed and the findings are compiled in this section. *C. halicacabum* decoctions have been known to act as a gentle sedative by the local people as part of its alleviating actions in conditions like lumbago, spasms, skeletal fractures, abdominal pain, headache, joint pains, arthritis, body pain, and rheumatism. Allegedly, *C. halicacabum* has been proven to hold anti-arthritic, immunomodulatory, collagen degradation protection, and analgesic activity by various researchers. Two important pharmacological properties namely, antioxidant and anti-inflammatory activities of *C. halicacabum* expound the usage of this plant by many medicinal practitioners for the treatment of cardiac ailments, abdominal pain, liver damage, swellings, inflammatory skin diseases, and different kinds of tumors. At the same time, Ayurvedic medicine has used the roots and seeds of *C. halicacabum* for the reduction of abdominal pain, inflammations, bronchitis, muscle wasting associated with tuberculosis, cough, fever, sores, microbial infections, and swellings. On the contrary, later research on the above said infirmities had used the whole plant extracts, leaves, and stalks in the investigations.

Likewise, the anti-ulcer activity of *C. halicacabum* has been studied using the whole plant extract by Sheeba and Asha (2006). In the Unani system of medicine, seeds are employed against gastric problems. Hence, comparative studies on the performance of different plant parts as well as the whole plant will help identify the active part (s) of the plant against those illnesses. Peiris et al. (2015) showed the improvement of male reproductive parameters in the *C. halicacabum* leaf extract treated rats. According to the Unani system, male infertility and potency-associated complications can be cured by consuming a drug preparation that uses *C. halicacabum* seeds. As it can be seen from Table 1, other naturopathic treatments also recommend the use of this plant to treat orchitis. This indicates that this plant might have potent compounds associated with male reproductive health.

Unfortunately, some of the ancient prescriptions followed by the traditional therapists and local practitioners mention the maladies in general terms like liver problems, psychological complications, nervous diseases, bone disorders, respiratory illnesses, and cardiac ailments, and so on. For instance, research has shown the anti-ulcer activity of *C. halicacabum* via animal experiments. As per traditional medicine, this plant has been used to treat abdominal pain. However, the specific condition and incident of complaints such as pain caused by bloating, allergens, menses, gastritis, stress, toxins, indigestion, and infections for which it can be used are indistinct. Altogether, the pharmacological activities such as anti-arthritic, anti-microbial, analgesic, anxiolytic, anti-diarrheal, anti-inflammatory, anticonvulsive, anticancer, antipyretic, and hepatoprotective activities reported in various research works concur with the traditional prescriptions in different medicinal systems followed in India.

b) Correlations between the ethnomedical uses, phytochemical and pharmacological properties

Investigation of the interplay between the of phytochemical contents *C. halicacabum* and their pharmacological actions in connection with its traditional usage could revamp our understanding of how those phytoconstituents act and overlap to exert their functions in disease conditions. The presence of antimicrobial compounds such as quercetin, rutin, and caftaric acid in *C. halicacabum* is in accordance with its traditional practice against microbial infections, hyperthermia, skin diseases, dandruff problem, and other diseases caused by microbial infections like tuberculosis. In this manner, *C. halicacabum* could be an assuring candidate to derive natural antimicrobial compounds against a wide range of microorganisms including both gram-positive and gram-negative bacterial and fungal pathogens. Consequently, the tradition of scalp massage using hair oil prepared from *C. halicacabum* might be the reason behind its usage against dandruff, premature greying, and hair fall.

Besides, it is used by traditional practitioners and local residents to cure several kinds of pain including headache, joint pain, sprains, stomach ache, inflammations abdominal pain, lumbago, and earache (Table 1). It is important to point out that studies have reported the presence of anxiolytic compounds, cardiospermin, and apigenin-7-glucoside in the root and leaf extracts of *C. halicacabum,* respectively. Furthermore, flavonoid compounds found in *C. halicacabum* such as apigenin-7-glucoside, apigenin, apigenin-7-O-glucuronide, luteolin-7-glucoside, luteolin-7-O-glucuronide, chrysoeriol-7-O-glucuronide, quercetin, luteolin, chrysoeriol, kaempferol, quercetin-3-O-α-l-rhamnoside, apigenin-7-O-β-d-glucuronide have been reported for a range of pharmacological activities like anti-arthritic, anticancer, anxiolytic, anti-proliferative, anti-atherosclerotic, gastroprotective, anti-microbial, anti-inflammatory, and neuroprotective activities (Table 2).

It is worth noting that the antioxidant capacity of *C. halicacabum* is attributed to its active constituents including quercetin, apigenin, and luteolin which scavenge reactive oxygen and nitrogen species. Since ancient times, this plant is used in different forms to treat cough, bronchitis, throat infection, fever, inflammation, microbial infections, erysipelas, asthma, and other respiratory illnesses (Table 1). This can be linked with the *in vitro* antiviral activity of *C. halicacabum* exposed by Murugan et al. (2011). Based on molecular docking observations, it was found that two compounds (benzene dicarboxylic acid and eicosanoic acid) identified from the methanol extract of *C. halicacabum* had a relatively different interactive relationship with the viral receptors (Fig. 5). Given this notable result, further *in vivo* studies could confirm the antiviral action of *C. halicacabum* against HIV and HBV. Recent studies have described the antiviral activity of flavonoids including quercetin, kaempferol, apigenin, luteolin, and rutin against SARS –CoV-2 (Badshah et al., 2021; Khan et al., 2021). Additionally, quercetin was reported for its strong inhibitory activity toward infectious viruses such as influenza-A virus, dengue virus (DENV-2), hepatitis C virus (Badshah et al., 2021; Kukkar et al., 2014).

Considering the current pandemic situation, investigation of the inhibitory activity of *C. halicacabum* both *in vitro* and animal models infected with coronaviruses and the highly contagious viruses like COVID-19, Ebola virus, Zika virus, hepatitis B virus, HINI influenza, and respiratory syncytial virus might help in finding the antiviral metabolites since it has the immunomodulatory property as well. On the whole, among the research works that have been conducted on the pharmacological properties of *C. halicacabum*, the majority of them have correlations with its traditional uses. It was noted that the results of the pharmacological evaluations such as anti-arthritic, anti-inflammatory, anti-cancer, anti-pyretic, fertility, hepatoprotective, anti-diarrheal, anxiolytic, anti-bacterial, anti-fungal, anti-epileptic, and analgesic properties tested via preliminary research works correspond to the ones applied traditionally.

12. Future directions

The present review highlighted the important areas of investigation being performed on *C. halicacabum* with particular emphasis on crude extracts and identified compounds. It is apparent that the pharmacological properties of *C. halicacabum* reported via various *in vitro* and *in vivo* studies are in agreement with its traditional uses. Moreover, every part of this plant is useful, as food and as a remedy for various diseases. It should be noted that inflammation has been linked to almost all major diseases such as arthritis, cancer, diabetes, cardiovascular, psoriasis, Parkinson's, Alzheimer's, dementia, and irritable bowel syndrome. In general, several inflammatory conditions are characterized by high levels of inflammatory molecules like cytokines and prostaglandins. On the other note, *C. halicacabum* is rich in antioxidants and phytochemicals that protect cells and DNA. They help support the immune system and reduce inflammation throughout the body. The findings of this review, suggest that consuming *C. halicacabum* can help regulate the anti-inflammatory molecules and reduce inflammation.

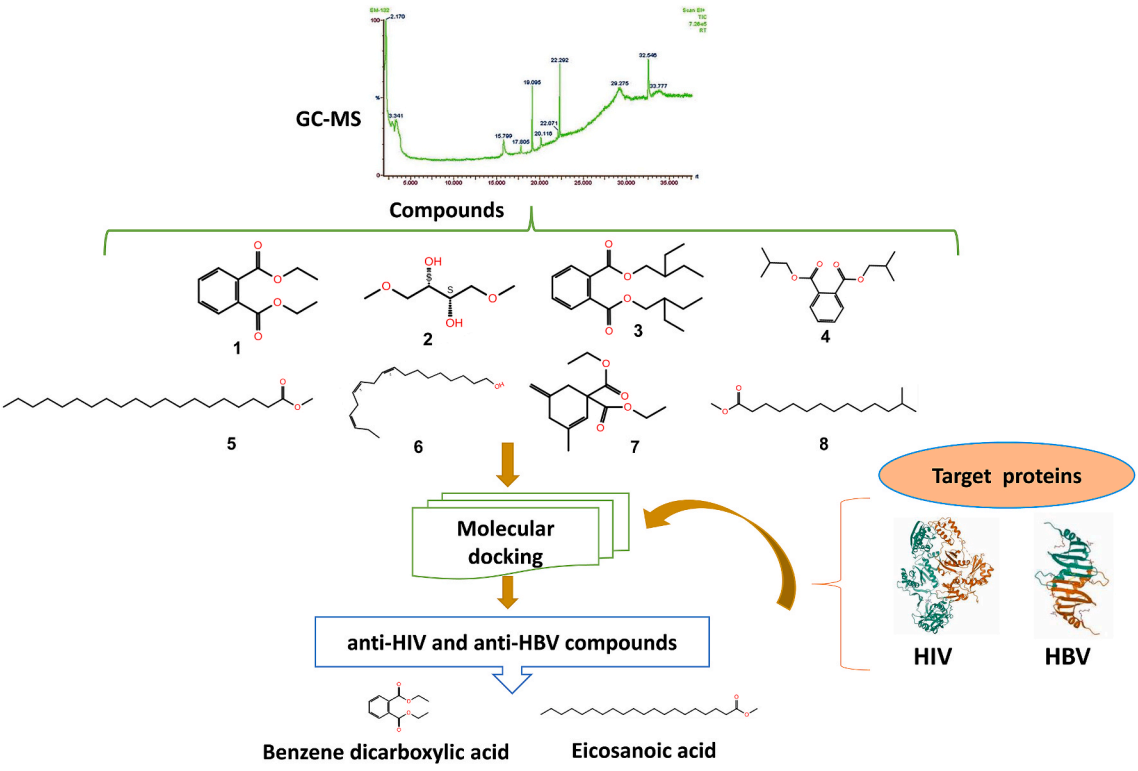


Fig. 5. Identification of antiviral compounds from *Cardiospermum halicacabum* leaves by GC-MS analysis and molecular docking: (1) 1, 2 – benzene dicarboxylic acid diethyl ester, (2) 1, 4 butandiol, 2, 3-dimethoxy, (3) 1, 2 – benzene dicarboxylic acid bis (2 –ethylhexyl), (4) 1, 2 – benzene dicarboxylic acid bis (2-methylpropyl), (5) eicosanoicacid methyl ester, (6) 3,4 epoxy –6,9 – octadecadiene, (7) diethyl 4 methyl- 5-methylene cyclohe -3- ene –1,1 –dicarboxylate, (8) methyl 13- methyl tetradecanoate

From the present review, it is clear that *C. halicacabum* encompasses a large number of flavonoids and its derivative compounds that have been reported for several medicinal qualities namely anti-arthritic, anti-osteoporotic, anti-oxidative, anti-inflammatory, and anti-cancer activities. Hence, the isolation and characterization of the identified flavonoid compounds, as well as their mode of action, warrant further attention in future studies. Furthermore, in Indian traditional medicine, *C. halicacabum* is primarily used for the treatment of arthritis and other joint disorders. Remarkably, the available pharmacological studies on *C. halicacabum* provide support for its traditional practices. Moreover, as mentioned in this review, *C. halicacabum* has an excellent anti-arthritic property which is not only evident through the anti-arthritic rodent studies but also by the positive effects of *C. halicacabum* on inflammatory conditions and immunomodulation in various research models. Therefore, further studies are needed to discover the bioactive phytochemicals responsible for its anti-arthritic activity and to determine the exact mechanistic pathways of *C. halicacabum* that can be used in developing safe and potent anti-arthritic drugs.

Although there has been substantial progress in the phytochemistry and pharmacology of *C. halicacabum,* the current review recognized several drawbacks which are as follows:

(1) A few studies have employed the commercial powders of *C. halicacabum* as plant material or sample for the solvent extractions in the experiments. Consequently, it creates ambiguity in pinpointing the part of the plant that is responsible for the particular pharmacological activity.
(2) Studies were conducted with very high doses (above 400 mg/kg, b.w.) of plant extracts without verification of their toxicities and justification for the dose ranges
(3) The information on quantitative determination phenolic compounds in the crude extracts of various parts are limited.
(4) Despite attaining decent results in both *in vitro* and *in vivo* experiments, the studies concerning the effect of metabolites obtained from *C. halicacabum* and their therapeutic effect on human well-being are still uninvestigated.
(5) Very little attention has been paid to qualitative and quantitative determination of secondary metabolites through assays as well as robust analytical techniques like LC-MS/MS, HR-MS, preparative HPLC, AAS, etc.
(6) In many *in vivo* studies the photomicrographs of histological assessments of animal tissues were indistinct.
(7) Regarding the traditional claims of *C. halicacabum*, a systemic compilation of exact dosages, drug forms, drug preparation protocols, time and duration of intake, and applicable disease names is needed since a great proportion of rural population depend on this plant due to healthful traditional practices and economic reasons.
(8) The choice of animal models will influence the expression of a specific disorder. Therefore, the selection of animal model requires careful attention to the particular disease investigated since a single experimental model cannot emulate every characteristic of human diseases.
(9) *C. halicacabum* is combined with other medicinal plants in traditional healthcare practices. The interactions and safety levels of the herbal combinations should be clarified.
(10) The optimal and effective concentration range remains inconclusive since the diversified usage of crude extracts *in vitro, in vivo,* and *ex vivo.*

Other major drawbacks observed through the current literature review include data insufficiency, incoherence, inarticulacy, inaccessibility, inappropriate investigational models, and poor quality control. In addition, queries continue concerning ideal pharmacological dosage in humans. Regardless of these inadequacies, it is worth noting that there are still scientific gaps in the experimentation of *C. halicacabum* in the areas such as quantification of compounds, nutritional values, isolation of active principles, pharmacokinetic studies, cytotoxic activities, clinical trials that remain open for investigations. Especially, more experiments are required on the scientific evaluation of the safety and toxicity of *C. halicacabum.* As documented in this present review, a substantial amount of work has been performed on the leaves of *C. halicacabum* than the other parts such as fruits, seeds, stalks, and roots. Hence, more studies have to be conducted on the aforesaid parts of *C. halicacabum* as well. Pharmacological properties of *C. halicacabum* namely antimicrobial, anti-ulcer, anti-epileptic anti-diabetic, anticancer, nephroprotective, hepatoprotective, and analgesic activities should be studied further since these studies are still at a very preliminary phase.

Additionally, this review finds the immunomodulatory property as one of the prominent pharmacological properties of *C. halicacabum* since its other significant medicinal properties like anti-inflammatory, anti-oxidant, anti-arthritic, anticancer, antiviral activities directly or indirectly impacts the immune system. In this sense, extensive research is required to tap the potential of *C. halicacabum* against human immune disorders. Additionally, the role of *C. halicacabum* in hair care treatments such as anti-hair fall, antidandruff, and hair color darkening as well as the antivenom activity against rat and snake poisons remains unexplored. In the same way, the potential of *C. halicacabum* to improve memory power, cognitive functions, neuropsychiatric, and associated neuromuscular problems have not been scientifically proved. Based on the ancient medicinal practices, *C. halicacabum* is consumed popularly as an herbal tea or soup to relieve fatigue, and lethargy and enhance energy level. Especially, explorations into the calming effects of *C. halicacabum* on behavior, mood disorders, cognitive deficits, and psychological stress may give clues about its brain-boosting ingredients. Physicochemical properties, fatty acid profile, nutritional and mineral composition of the whole plant need to be done in order to know about its applications in the food and pharmaceutical industries. Holding a multitude of therapeutic properties, *C. halicacabum* can be utilized in food fortification upon determining its nutritional ingredients.

13. Conclusion

From the results of this review, *C. halicacabum* appears to contain promising effects in numerous neurological, immunological and inflammatory disorders. More robust, standardized clinical trials and molecular studies should be carried out to ascertain the anti-arthritic potential and the other remedial effects of *C. halicacabum* on humankind. The accessible data on *C. halicacabum* shows a wide set of ethnomedical as well as reassuringly new therapeutic applications in the field of functional food research.

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CRediT authorship contribution statement

Abbirami Elangovan: Conceptualization, Writing – original draft, Data curation, Visualization. **Jeyadevi Ramachandran:** Conceptualization, Data curation. **Dinesh Kumar Lakshmanan:** Data curation, Software. **Guna Ravichandran:** Resources, Data curation. **Sivasudha Thilagar:** Writing – review & editing, Supervision.

Declaration of competing interests

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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Appendix A. Supplementary data

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