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Immunomodulator Role Of *Coccinia Grandis* (L.) And Their Active Constituents In Hepatocellular Carcinoma Prevention And Treatment

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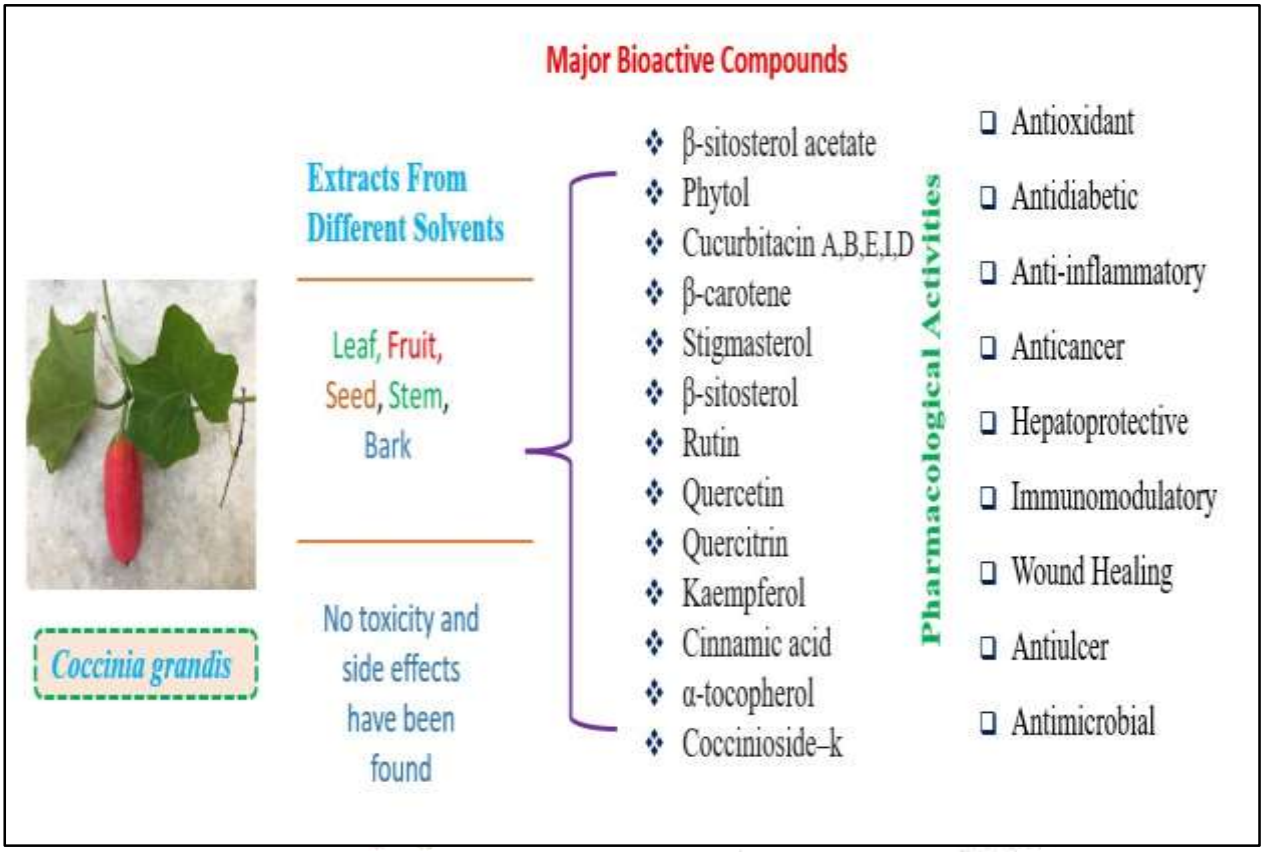
Abstract:

Hepatocellular carcinoma (HCC) is a serious global health concern that is a lethal disease with few viable treatment options. The potential use of natural chemicals in preventing and treating cancer has been brought to light by recent studies. Because of its immunomodulatory qualities, *Coccinia grandis*, an old medicinal herb, is a serious contender. An overview of current research on the functions of *Coccinia grandis* 50 bioactive compounds were listed and its active ingredients in the prevention and management of HCC is given in this article. We look at the plant's bioactive ingredients, like flavonoids and cucurbitacins, which have been shown to have anti-cancer properties through a variety of pathways, including immune response regulation, tumor growth reduction, and apoptosis induction. The review also covers the molecular processes involved, such as

the upregulation of antioxidant defenses and the inhibition of inflammatory cytokines. We also go over *Coccinia grandis's* pharmacological challenges and potential therapeutic applications for the management of HCC. By integrating data from preclinical and clinical trials, this review seeks to provide a comprehensive understanding of the potential applications of *Coccinia grandis* as an additional strategy in HCC therapy. It also highlights the need for more investigation to ascertain this treatment's safety and therapeutic efficacy.

Key words: Hepatocellular carcinoma (HCC), *Coccinia grandis* (L.), Bioactive compounds, Cancer prevention and therapy.



INTRODUCTION

Historically, most civilizations have found that a wide range of illnesses can be effectively treated by combining various culinary ingredients. CAM, or complementary and alternative medicine, is a contemporary field with a large global user base. Among the five recognized classifications of complementary and alternative medicine, the most widely utilized therapy modality is herbal products. Because herbal remedies are believed to be less or non-toxic, there has been a surge in the search for innovative herbal items and medicines to treat a variety of human problems. It is common knowledge that several plants in the Cucurbitaceae family have been used as natural remedies by most civilizations. *Coccinia* plants, also referred to as ivy, are members of the Cucurbitaceae family and are used in traditional medicines like Chinese herbal

medicines, which are used in China, Ayurveda in India, and the Unani school of medicine, which is practiced in Iran and is also known as Greco-Arab medicine [1].

A perennial climber that is edible and native to tropical Asia, *Coccinia grandis* (Linn.) Voigt (Cucurbitaceae) is most usually found in Sri Lanka, India, and Pakistan. Every portion of this plant has medicinal value, and the indigenous medical system of Sri Lanka has made numerous decoctions to treat a variety of skin conditions, diabetes mellitus, bronchitis, urinary tract infections, itchy skin eruptions, and ulcers [2],[3]. Furthermore, C. grandis leaf extract is a common treatment for diabetes mellitus used by Ayurvedic physicians in Sri Lanka [4]. C. grandis leaf extract has been evaluated for its in vivo hepatoprotective, antibacterial, antioxidative, anti-inflammatory, and antihyperglycemic effects [5-8]. Of these, the antihyperglycemic effect is the most obvious. However, nothing is known regarding the toxicological effects of *C. grandis* leaf extract or how well it withstands glucose in scientific studies.

C. grandis is referred to as "kolakochu" in the local dialect in Noakhali, Bangladesh, and a paste made from crushed leaves is used to cure cancer and diabetes [9]. C. grandis is referred to as Telakucha in Pabna, Bangladesh, and is used as a vegetable and herbal remedy by the locals. The juice made from crushed leaves and stems is used by the locals to treat jaundice and diabetes.In 2010, Rahmatullah et al.[10]A mixture of C. grandis root juice and coconut oil is applied externally to the head as a treatment for mental illness in the Comilla district of Bangladesh. The cooked plant is additionally used to treat diabetes [11]. Leaf juice is taken for hypertension, and leaves are chewed every morning to regulate blood sugar levels [12-13]. To manage their diabetes, the Chakma Tribe of Bangladesh's Bandarban District drinks raw leaf juice [14]. To lower blood sugar, the urban residents of Khurda, Odisha, India, drink ivy gourd fruit juice with dried piper nigrum seed powder once a day on an empty stomach [15]. The leaves and fruits of this plant are widely used by local traditional healers in Karela, India, to treat a variety of illnesses, including diabetes, sperm production issues, bodily strength issues, and skin diseases. The locals use fruit paste and leaves of C. grandis with milk to treat diabetes, and with sugar to treat jaundice [16].

Scientific classification of *Coccinia grandis*

Many of the plants that nature offers have long been valued for their medicinal qualities. Coccinia grandis, also referred to as the crimson gourd or ivy gourd and a member of the Cucurbitaceae family, is one such medicinal plant [17]. Figure 1 lists the taxonomy and additional binomial names for C. grandis. C. grandis is found in the tropical regions of Southeast Asia and North and Central Africa. It is commonly found in a wide range of countries, including Bangladesh, India, Pakistan, China, Malaysia, Yemen, Senegal, Tanzania, Kenya, Indonesia, Philippines, and Thailand, according to multiple sources [18; 19:20]. Bryonia grandis L., Coccinia cordifolia, Cephalandra indica, Coccinia indica Wight & Arn., and *Coccinia grandis* (L.) Voigt are known by a variety of botanical names. The *Coccinia grandis* species is classified scientifically as Genus: Coccinia; Species: C. grandis; Binomial name: *C. grandis (L)* J. Voigt; Common name: Coccinia; Family: Cucurbitaceae The name "scarlet fruited gourd," sometimes referred to as "ivy gourd," comes from the Latin word coccineus, which means "scarlet," referring to the colour of the fruit [21].

Botanical Description

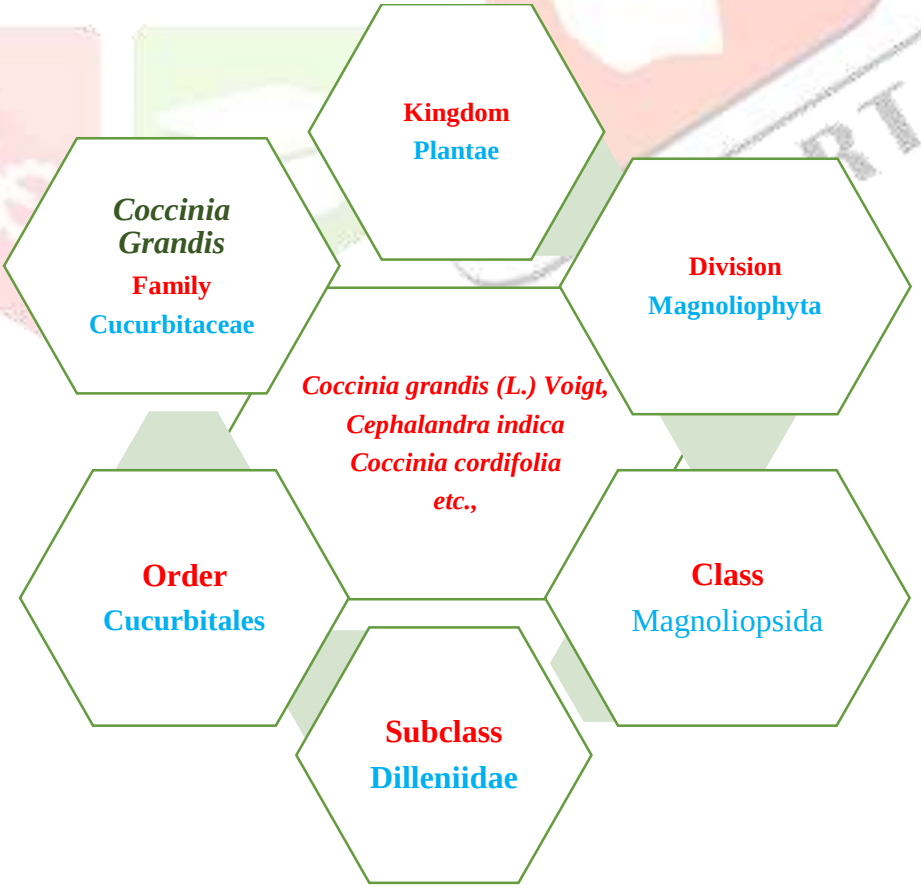


Figure 1 *Coccinia Grandis* scientific classification

C. grandis is described as a perennial herbaceous vine that is dioecious in the botanical description. Simple, glabrous tendrils that sprout yearly from a tuberous base in the stems are called axillary tendrils. Simple, alternating blades that are roughly oval, five-lobed, and measure [(5-9)*(4-9)] cm. At the base, the blades are cordate and have a big sinus; at the apex, they are acute and mucronate. Surfaces are glabrous or scaly, with 3–8 glands near the base and petioles that range in length from 1 to 5 cm and have denticulate margins. An inflorescence usually consists of one axillary bloom. The calyx on the hypanthium is composed of five subulate, recurved lobes that vary in length from two to five millimeters. Peduncle length: 1 to 5 cm. Typically, an inflorescence consists of a single axillary flower. 5 subulate, recurved lobes, ranging in length from 2 to 5 mm, make up the calyx on the hypanthium. Length of peduncle: 1 to 5 cm. The white, campanulate corolla is 3–4.5 cm long and deeply split into five oval lobes. In female flowers, three stamens function as staminodes. Ovarian is subpar. Fruit is an ovoid to ellipsoid fruit that is smooth, bright red, and measures 2.5–6 cm in length [22]. "Cephalandra indica" is another word for the botanical name (ivy gourd).

Phytochemical Constituents

C. grandis has a variety of pharmacological effects due to its abundance of bioactive compounds. A broad spectrum of chemical classes is represented in the bioactive compounds that have been extracted from various plant sections. Alkaloids such as 1-tert-Butyl-5,6,7-trimethoxyisoquinolene and lucianol have been detected in methanolic leaf and aqueous fruit extracts [23-24]; Senecionine, Cathinone, Camptothecin, (S)-Norlaudanosoline, Trachelogenin, and (6S)-Hydroxyhyoscyamine were detected in ethyl acetate fruit extract [25]. Alkanes including tricontane, heptacosane, and others were extracted using petroleum ether callus and leaf extracts, as well as ethyl acetate callus extract [26]. The petroleum ether leaf extract contained octadecane,1-(ethenyloxy), an alkyl ether. Pentadecanoic acid, octadecanoic acid, and other fatty acids were present in a variety of extracts, including petroleum ether callus, ethyl acetate leaf, and methanolic fruit extracts [24]. Additionally, a wide range of alkenes, esters, aldehydes, alcohols, terpenoids, steroids, phenols, benzoic acid derivatives, glycosides, amines, ketones, and phenolic compounds were identified using different plant components and solvent extracts.

Collection of bioactive compounds from *Coccinia grandis* through online database:

Through an extensive review of available online bioinformatics tools such as the Indian Medicinal Plants, Phytochemistry and Therapeutics 2.0 (IMPPAT 2.0) and the NPACT (Naturally occurring plant based Anti-cancerous compound-activity-target database), a total of 50 bioactive compounds were identified and collected from the *Coccinia grandis* plant. These compounds were gathered based on their known pharmacological activities, relevance in traditional medicine, and potential therapeutic applications. The identified bioactive compounds play a crucial role in the medicinal properties attributed to *Coccinia grandis*, such as antioxidant, anti-inflammatory, antidiabetic, antimicrobial, and hepatoprotective activities. These compounds have been subjected to further analysis for their potential in drug development and other biomedical applications. The complete list of these bioactive compounds is presented in **Table 1** below, which includes the compound names, their molecular formulas, and their known or proposed biological activities.

Effect of *Coccinia grandis* as Immunomodulator

The immune system can be strengthened or weakened by immunomodulatory medications, which may aid the body in fending against infections, cancer, and other diseases. In a recent study [27], a crude extract of C. grandis showed immunomodulatory effects on many pathways of human monocytic THP-1 cells, including phagocytosis, migration, death, and the generation of inflammatory cytokines. THP-1 cells showed significant downregulation of Bax, ERK5, Cyclin D, BCL2, ERK1, NF-κB, p-NF-κB, p-IκBα, and p-p38, as well as molecular signaling pathways (ERK1/2, NF-κB, p38 MAPK, and IL-6/JAK/STAT3 signalling cascades) after treatment with phorbol-12-myristate 13-acetate and exposure to lipopolysaccharide (LPS) with or without 50 g/mL or 100 g/mL of C. grandis extract [27]. A recent in vivo study showed that C. grandis (L.) Voigt (Cg-Ex) leaf extract is a potent ($P < 0.05$) immunomodulator against visceral leishmaniasis via inducing pro-inflammatory responses in parasite-infected BALB/c mice. The findings demonstrated that, in response to a decline in the parasite load, there was a decrease in the creation of ROS and NO as well as in the production of disease-suppressive Th1 cytokines. Furthermore, compared to the infected control, Cg-Ex-treated mice produced a considerable amount of IgG2a antibody [28].

Indian medicinal plant	Plant part	IMPPAT Phytochemical identifier	Phytochemical name	References
Coccinia grandis	aerial part	IMPHY001896	Heptacosane	ISBN:9788171360536, ISBN:9788172360481
Coccinia grandis	aerial part	IMPHY001953	Isomultiflorenol	ISBN:9788172362133
Coccinia grandis	aerial part	IMPHY003952	Cycloartanol	ISBN:9788172362133
Coccinia grandis	aerial part	IMPHY009483	Tritriacontane	ISBN:9788171360536, ISBN:9788172360481, ISBN:9788185042053
Coccinia grandis	aerial part	IMPHY011393	24-Methylenecycloartanol	ISBN:9788172362133
Coccinia grandis	aerial part	IMPHY011619	alpha-Amyrin	ISBN:9788172362133
Coccinia grandis	aerial part	IMPHY012223	beta-Amyrin	ISBN:9788172362133
Coccinia grandis	aerial part	IMPHY012473	Lupeol	ISBN:9788172362133
Coccinia grandis	aerial part	IMPHY014836	beta-Sitosterol	ISBN:9788171360536, ISBN:9788172360481, ISBN:9788185042114
Coccinia grandis	fruit	IMPHY000846	Riboflavin	ISBN:9788171360536
Coccinia grandis	fruit	IMPHY004039	beta-Amyrin acetate	ISBN:9780387706375
Coccinia grandis	fruit	IMPHY004645	beta-Cryptoxanthin	ISBN:9770972795006, ISBN:9788185042084
Coccinia grandis	fruit	IMPHY007426	Taraxerone	ISBN:9788171360536, ISBN:9788172362133, ISBN:9788185042114
Coccinia grandis	fruit	IMPHY008915	(all-E)-6'-Apo-y-caroten-6'-al	ISBN:9770972795006, ISBN:9788171360536, ISBN:9788185042084

Coccinia grandis	fruit	IMPHY011677	Taraxerol	ISBN:9788171360536, ISBN:9788172360481, ISBN:9788172362133, ISBN:9788185042084, ISBN:9788185042114
Coccinia grandis	fruit	IMPHY011707	beta-Carotene	ISBN:9770972795006, ISBN:9788171360536, ISBN:9788185042084
Coccinia grandis	fruit	IMPHY011913	Cucurbitacin B	ISBN:9780387706375, ISBN:9788185042053
Coccinia grandis	fruit	IMPHY012223	beta-Amyrin	ISBN:9780387706375, ISBN:9788172360481, ISBN:9788185042053
Coccinia grandis	fruit	IMPHY012473	Lupeol	ISBN:9780387706375, ISBN:9788172360481, ISBN:9788185042053
Coccinia grandis	fruit	IMPHY012567	Lycopene	ISBN:9770972795006, ISBN:9788185042114
Coccinia grandis	fruit	IMPHY014836	beta-Sitosterol	ISBN:9788171360536, ISBN:9788172360481, ISBN:9788172361792, ISBN:9788172362133, ISBN:9788185042114
Coccinia grandis	leaf	IMPHY009413	Triacontane	ISBN:9788190595216
Coccinia grandis	leaf	IMPHY014836	beta-Sitosterol	ISBN:9788190595216
Coccinia grandis	root	IMPHY005823	Stigmast-7-en-3-one	ISBN:9788171360536, ISBN:9788172361792, ISBN:9788185042053
Coccinia grandis	root	IMPHY012223	beta-Amyrin	ISBN:9770972795006, ISBN:9788171360536
Coccinia grandis	root	IMPHY012473	Lupeol	ISBN:9770972795006, ISBN:9788171360536
Coccinia grandis	root	IMPHY014836	beta-Sitosterol	ISBN:9770972795006, ISBN:9788171360536
Coccinia grandis	root	IMPHY014893	D-Glucose	ISBN:9789327275590

Coccinia grandis	seed	IMPHY000060	Myristic acid	ISBN:9770972795006
Coccinia grandis	seed	IMPHY003016	Lauric acid	ISBN:9770972795006
Coccinia grandis	seed	IMPHY003448	Desmosterol	ISBN:9770972795006
Coccinia grandis	seed	IMPHY004631	Stearic acid	ISBN:9770972795006
Coccinia grandis	seed	IMPHY004645	beta-Cryptoxanthin	ISBN:9788171360536
Coccinia grandis	seed	IMPHY007327	Palmitic acid	ISBN:9770972795006, ISBN:9788171360536, ISBN:9788172361792, ISBN:9788185042084
Coccinia grandis	seed	IMPHY009542	24-Ethylcholesta-7,22-dienol	ISBN:9770972795006
Coccinia grandis	seed	IMPHY011394	Arachidic acid	ISBN:9770972795006
Coccinia grandis	seed	IMPHY011545	delta7-Avenasterol	ISBN:9770972795006
Coccinia grandis	seed	IMPHY011613	Fucosterol	ISBN:9770972795006
Coccinia grandis	seed	IMPHY011797	Oleic acid	ISBN:9770972795006, ISBN:9788171360536, ISBN:9788185042084
Coccinia grandis	seed	IMPHY012723	Linolenic acid	ISBN:9770972795006
Coccinia grandis	seed	IMPHY014634	24-Methylcholesta-5,22-dienol	ISBN:9770972795006
Coccinia grandis	seed	IMPHY014886	[(E,6R)-6-[(2S,9R,13R,16R,17R)-2,16-dihydroxy-4,4,9,13,14-pentamethyl-3,11-dioxo-2,7,8,10,12,15,16,17-octahydro-1H-cyclopenta[a]phenanthren-17-yl]-6-hydroxy-2-methyl-5-oxohept-3-en-2-yl] acetate	ISBN:9788171360536

Coccinia grandis	seed	IMPHY014990	Linoleic acid	ISBN:9770972795006, ISBN:9788171360536, ISBN:9788185042084
Coccinia grandis	stem	IMPHY001953	Isomultiflorenol	ISBN:9770972795006
Coccinia grandis	stem	IMPHY002139	(-)-Butyrospermol	ISBN:9770972795006
Coccinia grandis	stem	IMPHY003952	Cycloartanol	ISBN:9770972795006
Coccinia grandis	stem	IMPHY004039	beta-Amyrin acetate	ISBN:9770972795006
Coccinia grandis	stem	IMPHY009342	Multiflorenol	ISBN:9770972795006
Coccinia grandis	stem	IMPHY009413	Triacontane	ISBN:9788190595216
Coccinia grandis	stem	IMPHY011393	24-Methylenecycloartanol	ISBN:9770972795006

Anti-ulcerogenic activity

The indomethacin-induced stomach ulcer was significantly avoided by the ethanolic C. grandis leaf extract. According to Datchanamurty et al.[29], the leaf extract contained a few amino acids, including asparagine, arginine, glutamine, glycine, threonine, and proline, in addition to terpenoids, flavonoids, phenols, cardiac glycosides, tannins, polysaccharides, sterols, and saponins. By producing prostaglandin, the flavonoids fortify the mucosal barrier and reduce the production of stomach acid [30]. Furthermore, leaf extract counteracts the inhibitory impact of indomethacin on the release of pro-inflammatory prostaglandins, hence stimulating mucus formation and facilitating ulcer healing [29]. According to Datchanamurty et al. (2019), the inhibition was statistically significant ($P < 0.05$). Rats with stomach ulcers caused by pylorus ligation exhibit notable anti-ulcer activity when exposed to 400 mg/kg of an ethanolic extract of C. grandis. In comparison to conventional omeprazole (85.7%), it exhibits observable inhibition (78.57%) [31]. At dosages of 250 mg/kg and 500 mg/kg, respectively, the leaf extract's anti-ulcer effectiveness was tested in rats

using pylorus ligation and ethanol-induced ulcer models. The results demonstrate a significant ($P < 0.05$) decrease in stomach ulcers [30].

Antiulcerogenic effects of *Coccinia grandis* (Linn.) Voigt leaves powder, its methanol, and aqueous extracts was investigated on an Aspirin-induced gastric ulcer model in rats, on the basis of results, the leaf powder showed a significant increase in mucus secretion and decrease in level of lipid peroxidation (LPO), and Superoxide dismutase (SOD) activity. Methanol extract at an equivalent dose to that of the powder also showed a significant decrease in ulcer index with significant changes in mucus secretion, LPO, and SOD anti-ulcerogenic potential of this plant due to increased gastric mucus secretion and has antioxidant activity [32].

Effect of *Coccinia grandis* as Hepatocellular carcinoma

Tumor growth and survival are critically dependent on telomerase activity (Jafri et al., 2016). Studies show that fruit of C. grandis. cucurbitacin B has been shown to downregulate both c-Myc and hTERT expression, inhibiting telomerase activity in many breast cancer cell lines and causing both apoptosis and cell cycle arrest in G2/M. The most significant growth suppression was seen in the ER-negative breast cancer cell line SK-BR-3 (Kumari et al., 2016). Hepatocellular carcinoma is the fifth most common type of cancer and ranks third globally in terms of cancer-related mortality (Sampath Kumar et al. (2008)). Sampath Kumar et al.suggest that the preventive effectiveness of C. grandis extract against benzidine-induced hepatocellular carcinoma could be attributed to the inclusion of flavonoids and other phyto components. From C. grandis root extract, kaempferol (KP), a naturally occurring aglycone dietary flavonoid, was extracted.

Conclusion:

Scientific research has substantiated the broad pharmacological properties of *Coccinia grandis*, affirming its traditional use as a medicinal remedy. Both preclinical studies and clinical trials have demonstrated the plant's significant properties against Hepatocellular carcinoma, among other therapeutic benefits. As no adverse effects or toxicity have been reported to date, Coccinia grandis shows promise as a natural source of therapeutic compounds. However, further research is necessary to confirm its safety profile and to elucidate the molecular mechanisms underlying its pharmacological actions. Isolating and examining the compounds responsible for specific activities could lead to the development of new drugs.

CRediT authorship contribution statement

Mr. Vino Udappusamy was responsible for conceptualization, data curation, formal analysis, drafting communication, reviewing and editing the manuscript**. Dr. Nirmal Kumar Ramasamy** was responsible for conceptualization, data curation, formal analysis, drafting, supervising, validating, reviewing and editing the manuscript. **Dr. Shalini Ganeshan** was responsible for conceptualization, data curation, formal analysis, drafting, supervising, validating, reviewing and editing the manuscript.

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