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Review

Ethnomedicinal Uses, Phytochemistry, Pharmacological Activity, Therapeutic Potentials, and Functional Foods of *Coccinia grandis* (L.) Voigt: An Updated Review

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Abstract

Coccinia grandis (L.) Voigt (ivy gourd) is popularly consumed in South Asia for food and therapeutic purposes. *C. grandis* acts as a remedy for various ailments, such as hypertension, diabetes, cancer, ulcers, diarrhea, jaundice, inflammation, fever, bronchitis, burns, skin eruptions, insect bites, allergies, eye infections, and urinary disorders. Researchers have identified phytoconstituents in diverse chemical classes from this species, including alkaloids, flavonoids, coumarins, esters, ethers, fatty acids, fatty alcohols, terpenoids, and phenolic compounds. Comprehensive research conducted *in vitro* and *in vivo* has confirmed the properties of the plant as antidiabetic, anticancer, antiparasitic, antimicrobial, hepatoprotective, analgesic, antipyretic, anti-Alzheimer's, anticataract, antileishmanial, anti-anaphylactic, anti-histaminic, and wound-healing agent, as well as being advantageous for cardiovascular health. Most pharmacological findings are derived from studies on the extracts and the subsequent phytoconstituents from this plant species. Nevertheless, the specific phytoconstituents underlying these biological effects and the mechanisms of action involved are yet to be fully identified. Toxicological evaluations indicate that *C. grandis* is generally safe, although high doses can cause dose-dependent hepatotoxicity. Moreover, the clinical trials focusing on the antidiabetic effects of *C. grandis* demonstrate promising effects in managing glucose dysregulation. This review aims to provide a comprehensive update on *C. grandis*, expanding on previous studies by incorporating a broader ethnomedicinal scope, a more extensive phytochemical profile with detailed chemical structures, and additional clinical trial data. Unlike prior publications, this review emphasizes *C. grandis* as a functional food, highlighting its potential in chronic disease management. By integrating these aspects, this study offers a more in-depth analysis of the therapeutic potential and future applications of this plant. The functional food aspect of *C. grandis*, rich in bioactive compounds, supports its role in preventing and managing chronic diseases as a regular vegetable.

Keywords: *Coccinia grandis*; pharmacological activity; phytoconstituents; functional foods; ethnomedicinal

1. Introduction

Coccinia grandis (L.) Voigt, commonly known as Ivy gourd, belongs to the Cucurbitaceae family and is consumed as both food and a medicinal herb in South Asia [1]. It is widespread across tropical Asia, Central America, and Africa but is particularly prevalent in India, Bangladesh, Pakistan, Indonesia, Malaysia, the Philippines, Cambodia, Vietnam, Myanmar, Thailand, and Sri Lanka, where it is commonly utilized as a vegetable [2–4]. In Bangladesh, Ivy gourd is known by various vernacular names, such as Telakucha [5]. The tender, young, and elongated stems, leaves, and tuberous roots of *C. grandis* are used in culinary preparations or as seasoning, while its youthful fruits are incorporated into salads. Across various traditions, every part of this plant is believed to possess medicinal properties [6].

The World Health Organization (WHO) estimates that 80% of residents in developing nations rely primarily on traditional remedies for their basic healthcare needs [1]. *C. grandis* holds significant importance in traditional medicine. Almost all parts of *C. grandis*—fruits, leaves, and roots—are used for remedies like wound healing, ulcers, jaundice, diabetes, and fever [2,3]. Traditionally, it has been employed for its hypoglycemic, digestive, carminative, laxative, and analgesic properties. Additionally, it exhibits antimicrobial effects against syphilis, leprosy, gonorrhea, urinary tract infections, eye infections, bronchitis, and abscesses. It is also used for skin problems (burns, skin eruptions, psoriasis, allergies) and inflammatory conditions such as fever, asthma, joint pain, and stomach pain, as well as for other ailments, including vertigo, ulcers, insect bites, filarial swelling, and snake poisoning [4–6].

Scientific studies, both *in vitro* and *in vivo*, have validated the efficacy of *C. grandis* in addressing these conditions. Research findings suggest that this plant species helps relieve pain, relax muscles, protect the liver, reduce fever and inflammation, and manage blood sugar, dyslipidemia, ulcers, malarial infections, and even cancer [7–9]. The leaves of this species are a rich source of secondary metabolites such as flavonoids, alkaloids, triterpenoids, glycosides, saponins, and carotenoids.

Table 1. Vernacular names of *C. grandis* in various countries.

Country	Vernacular names	Ref.
Bangladesh	Telakucha, kawajhinga	[10]
India	Tindora, tondli, parval, tindora, tinda, kundru, golenda, kaage thonde, theekkuduru, covel, aracanviroti, araiyanviroti, attarittan, katutumpi, korutan, periyakovai, perunkovai, dondatheege, rattakkovai, nallakovai	[11]
Malaysia	Pepasan, papasan	[12]
Chinese	Hong gua	[12]
Denmark	Skariagenagurk	[12]
Indonesia	Boluteka, papasan	[13,14]
Thailand	Tåḷụng, Tam Lueng, p̄hạk Tåḷụng, Phak Tam Lueng	[12,13]
Spain	Pepino cimarrón	[15]
Germany	Scharlachranke, tindola	[15]
Vietnam	Hoa bát, rau bát	[15]
Japan	Yasai karasu uri	[16]
SriLanka	Kowakka	[17]
Myanmar	Kin pone, Taw-kinmon, Kinmon, Hla cawi bactine (mon)	[18]
Cambodia	Sleuk bah	[19]
Saudi Arab	Mogad	[20]
Tanzania	Lukewja, pondwa	[20]
Nepal	Gol kankri, Ngadha	[20]
Iran	Kabare-hindi	[20]
Somali	Masskar	[20]
Nigeria	Lombaria	[20]
Singapore	Aroi papassang	[20]
Mali	Seff	[20]
Senegal	Barbouf	[20]
Ethiopia	Gale	[18]
Franch	Gourde Écarlate De L´Inde Tindola, Courge Écarlate	[18]
Kenya	Nyamutu Kuru	[18]
Niger	Magaro	[18]
Pakistan	Kanduri, Kundur	[18]

This review provides a comprehensive update on *C. grandis*, expanding on previous studies by incorporating a broader ethnomedicinal scope, a more extensive phytochemical profile with detailed chemical structures, and clinical trial. Unlike prior reviews, it emphasizes *C. grandis* as a functional food, highlighting its potential in chronic disease management. By integrating these aspects, this study offers a more in-depth analysis of the plant's therapeutic potential and future applications.

2. Literature Search Strategy

Information for this article was gathered from Web of Science, PubMed, Science Direct, and Google Scholar employing specific keywords related to *Coccinia grandis*, *Coccinia indica*, *Cephalandra indica*, and Telakucha. The search spanned various periods, with approximately 1% of the data retrieved predating the year 2000, 19% falling within the range of 2001 to 2012, and the remaining 80% from the past decade, specifically from 2013 to 2024. Data collection occurred between January to July 2024, during which around 600 papers were reviewed to locate relevant information. Following initial screening, 209 papers were selected for thorough examination and summarization in this current review.

3. Vernacular Names

Vernacular names or local names are essential to biodiversity, showcasing the deep connection between people, language, and the natural world (Table 1, Ref. [10–20]). They serve as a valuable addition to scientific names, preserving local knowledge and cultural heritage. The local names of this species across the world are summarized in Table 1.

4. Taxonomy and Distribution

The *Coccinia* genus includes 30 species found exclusively in tropical Asia and Africa. This common dioecious plant is widely grown across Asia, from India to Indonesia, including Bangladesh, Nepal, Sri Lanka, Pakistan, Malaysia, Myanmar, Thailand, and Vietnam [21]. *C. grandis* is a trailing, dioecious, perennial climber, reaching lengths of up to 20 to 30 meters, with tuberous rootstock.

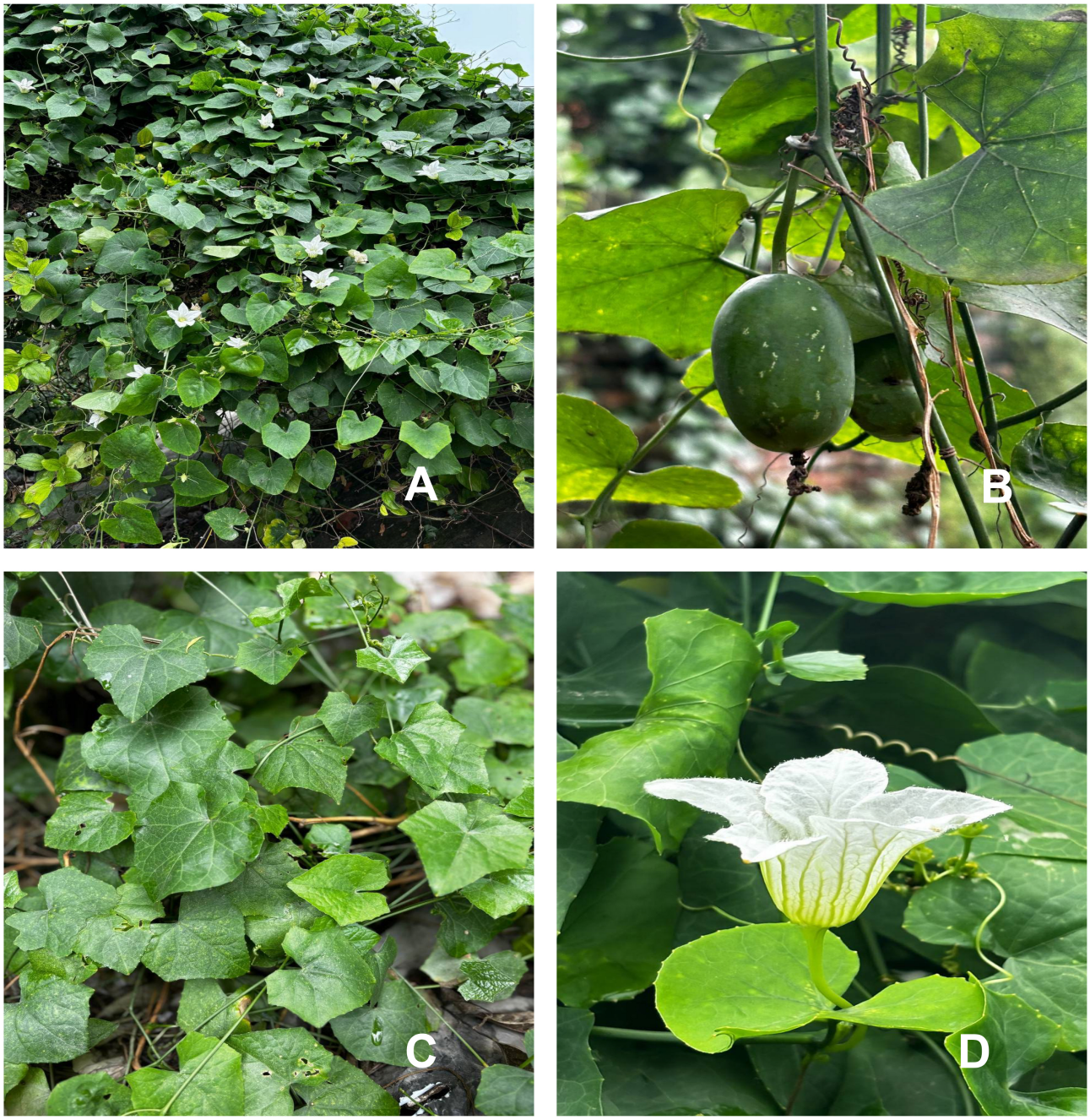

Fig. 1. *Coccinia grandis*. (A) Full plant. (B) Fruit. (C) Leave. (D) Flower.

The young stem is green, longitudinally ribbed, and eventually becomes woody [22]. The leaves are roughly oval-shaped with a central indentation at the base. Leaf measures 310 cm length, and width ranging from 4 to 10 cm, displaying five angles and typically having 3–7 lobes branching out from the center. The edges of the leaves are finely toothed, and the tips are blunt with a small point. The leaf stems are 1–3 cm long, and the tendrils are not divided into smaller branches [23]. The flowers are sizable, star-shaped, and white. The calyx comprises five recurved lobes, approximately 25 mm in length, situated on the hypanthium with a peduncle ranging from 1 to 5 cm. The corolla is white, bell-shaped, 34.5 cm in length, and consists of five ovate lobes. Individual flowers contain three stamens, and the ovary of the flower is located below the other floral parts. The fruit is either ovoid or elliptical, length of 25 to 60 mm, a diameter of 15 to 35 mm, with a smooth surface and hairless stalks (Fig. 1) [24]. The full taxonomic classification of *C. grandis* is outlined below [25]: Kingdom: Plantae; Division: Magnoliophyta; Class: Magnoliopsida; Order: Violales; Family: Cucurbitaceae; Genus: *Coccinia*; Species: *grandis*.

Table 2. Ethnomedicinal uses of *C. grandis* in various countries.

Country	Parts used	Preparation & method of extraction	Ethnomedicinal uses	Ref.
Bangladesh	Root	Juice used topically	Moisturizer (for dry skin)	[26]
		Roots of macerated	Osteoarthritis and joint pain	[27]
	Leaf	Paste prepared from leaves (topical use)	Scabies	[27]
	Fruit	Flowers of *Lagenaria siceraria* and *Zingiber officinale* are pasted in combination	Infertility of women	[27]
	Whole plant		Diabetes	[28]
Cambodia	Stem	Decoction	Hepatoprotective activity	[29]
Ethiopia	Leaf	Decoction	Diabetes	[30]
	Fruit	Consumption of Fruits	Diabetes	[30]
	Root	Dry, grind into powder, & mix with water	Stomachache, Headache, Fever	[31]
India	Fruit	Orally administered	Antidiabetic	[32]
	Leaf	A blend of black pepper & decoctions of the leaves from both *C. grandis* & *Acalypha indica*	Anti-ulcer	[33]
		Juice is mixed with honey	Diabetes and bronchitis	[34]
			Dysuria	[35]
Indonesia	Leaf	Infusion (Orally administered)	Fever, Malaria	[36]
	Fruit	Pound	Diabetes	[37]
	Stem	Infusion	Diabetes	[38]
Kenya	Leaf	Made into decoction or consumed as a vegetable	Heavy snoring	[39]
Malaysia	Leaf	Infusion (Orally administered)	Diabetes	[40]
	Fruit	Infusion (Orally administered)	Diabetes	[40]
Myanmar	Root	Apply crushed root	Stomachache	[41]
Nepal	Fruit	Juice used topically	Dysentery, body pain & syphilis	[48]
	Root	Juice used topically	Dysentery, body pain & syphilis	[48]
Nigeria	Leaf		Depression	[42]
	Fruit		Venereal diseases	[42]
Pakistan	Leaf	Made into decoction from fresh leaves (Orally administered)	Antidiabetic	[43]
	Fruit	Orally administered	Antidiabetic	[43]
	Root	Juice extracted from the roots	Antidiabetic	[44]
Saudi Arabia	Fruit	Consumed when fresh ripe & tastes mildly sweet	Antioxidant & antidiabetic	[44]
Sri Lanka	Leaf	A decoction made from fresh leaves (Orally administered)	Antidiabetic	[43]
Thailand	Stem	Made into decoction (Oral ingestion)	Antidiabetic	[45–47]
Uganda	Fruit	Consumed as fruits	Bedwetting	[49]
	Root	Made into decoction	Antivenom	[50]

5. Ethnomedicinal Uses

C. grandis is widely utilized as a traditional medicine, particularly in Southeast Asia and Africa. Its uses differ, with some being common, like those for diabetes, whereas others are limited to specific regions (Table 2, Ref. [26–50]). In Bangladesh, the plant is popular for its antidiabetic, antioxidant, osteoarthritis, joint pain, antihyperlipidemic, anti-diarrheal, anti-dyslipidemia, and anti-inflammatory properties [26–28]. In Cambodia, the stems are used to treat hepatoprotective activity [29]. In Ethiopia, leaves, fruits, and roots are employed for diabetes, stomachache, headache, and fever [30,31]. In India, infusions made with entire plants or their stems are used to treat diabetes mellitus, hypertension, cardiovascular diseases, bronchitis, anti-ulcer, dysuria, itch, cough, emaciation, fever, and skin infections [32–35]. In Indonesia, the stems, fruits, and leaves are used to cure fever, malaria, and diabetes [36–38]. The leaves are employed in Kenya for heavy snoring [39]. In Malaysia, the fruits and leaves of the plant serve as therapeutic options for diabetes and hyperlipidemia [40]. In Myanmar, roots are employed in treating stomachaches [41].

In Nigeria, leaves and fruits are used to treat depression, and venereal diseases [42]. In Pakistan, Saudi Arabia, and Thailand leaves, fruits, and stems are employed to manage diabetes, respectively [43–47]. In Nepal, roots and fruits are utilized for dysentery, body pain, and syphilis [48]. In Sri Lanka, the leaves are made into powder for the treatment of hyperglycemia, hyperlipidemia, and diabetes [43]. In Uganda, the fruits and roots are employed for their antivenom properties [49,50].

6. Phytoconstituents

Nuclear magnetic resonance (NMR) analysis of isolated pure bioactive compounds from *C. grandis* has confirmed the structure and purity of several key phytoconstituents. Extensive phytochemical investigations on the aerial parts of *C. grandis*, as well as its components such as leaves, stems, roots, and fruits, have led to the identification of over 31 distinct compounds across various chemical classes. Flavonoids are the most abundant phytochemicals in this species, with several bioactive flavonoids identified in the leaves and fruits. A significant number of alkaloids, phenolic acids, and glycosides have also been reported, particularly in the roots and leaves, highlighting their diverse pharmacological potential. Other classes of secondary metabolites present to a lesser extent include terpenoids, lignans, and miscellaneous aromatic compounds.

Around 158 compounds have been identified by chromatographic and spectrometric methods from various parts of *C. grandis* (Table 3, Ref. [4,10,51–63]). These studies employed advanced analytical techniques such as Ultra-High-Performance Liquid Chromatography (UHPLC), Liquid Chromatography-Mass Spectrometry (LC-MS), Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS), and Gas Chromatography-Mass Spectrometry (GC-MS), which have successfully characterized a diverse array of phytoconstituents within the plant. However, NMR analysis has not yet been conducted to confirm the structural details of these compounds. Structures of the compounds analyzed using NMR have been illustrated in Fig. 2.

6.1 Alkaloids

The alkaloids identified from *C. grandis* demonstrate remarkable structural diversity and notable pharmacological potential. Five alkaloids (**1–5**) have been isolated from the fruit, contributing significantly to the diverse alkaloidal profile of the species [51]. Alkaloids derived by isolated compounds (**6**, **7**) from leaf callus, highlight the efficacy of plant tissue culture techniques in facilitating the production of secondary metabolites. Moreover, the leaf has yielded compound (**8**), along with two isoquinoline alkaloid compounds (**9**) and (**10**), emphasizing the structural complexity and chemical diversity inherent in the plant's alkaloidal constituents [52–54].

6.2 Flavonoids

The flavonoids identified in this plant reflect significant structural diversity. Eight flavonoids (**11–18**) have been isolated from the leaf, comprising glucosides (**11–14**), rutinosides (**15, 16**), and complex conjugates (**17, 18**), showcasing the chemical diversity of the leaf constituents [61]. The fruit, on the other hand, contains a broader array of flavonoids, with 13 compounds (**21–33**) identified. These include glucosides (**22–24**), galactosides (**25**), rhamnosides (**26, 29**), and rutinosides (**28**), as well as acetyl derivatives (**31**) and simple flavonoids (**27, 32**). Notably, compound **33**, a coumarin, further expands the fruit's phytochemical profile, underlining its pharmacological potential [51,52,56].

6.3 Iso-Flavonoids

Three iso-flavonoids (**34–36**) have been isolated from the fruit of *C. grandis* [51].

6.4 Lignans

Different parts of the plant have been characterized by the presence of several lignans (**37–42**). From the stem, two compounds (**37**) and (**38**), have been isolated [57]. The fruit contains a broader range, with four compounds (**39–42**) identified, contributing to the plant's lignan profile [51, 56,58].

6.5 Phenolic Compounds

Twentynine phenolic compounds (**43–71**) have been isolated from *C. grandis*. The leaf contains six phenolic constituents (**43–48**) emphasizing its diverse bioactive profile [55]. In the stem, compound (**49**) has been identified as a sterol [52,58], while compound (**50**) is a tocopherol derivative, with additional phenolic compounds (**51**) and

Table 3. A list of chemical compounds present in *C. grandis*.

SI.	Class	Chemical compounds	Parts	Ref.
1	Alkaloids	(6S)-Hydroxyhyoscyamine	Fruit	[51]
2		(S)-Norlaudanosoline		
3		Camptothecin		
4		Cathinone		
5		Senecionine		
6		Canadine	Leaf	[52]
7		Protopine		
8		Clonitazene		
9		1-tert-Butyl-5,6,7-trimethoxyisoquinolene		[53]
10		1-tert-butyl-5,6,7-trimethoxyisoquinolin-3 (4H)-one		[54]
11	Flavonoids	Kaempferol-3-*O*-glucoside	Leaf	[55]
12		Kaempferol-3-*O*-neohesperidoside		
13		Quercetin-3-*O*-neohesperidoside		
14		Rutin		[4]
15		Kaempferol-3-*O*-rutinoside (or nicotiflorin)		
16		Kaempferol 3-*O*-robinobioside		
17		Quercetin 3-*O*-robinobioside		
18		Quercetin 3-*O*-β-D-apiofuranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→6)]-β-D-glucopyranoside (or CTN-986)		
19		Kaempferol 3-*O*-β-Dapi-furanosyl-(1→2)-[α-L-rhamnopyranosyl-(1→6)]-β-D-glucopyranoside		
20		Kaempferol 3-*O*-β-D-apiofuranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→6)]-β-D-galactopyranosid		
21		(-)-Sophorol	Fruit	[51,52,56]
22		Esculetin		
23		Hyperoside		
24		Isorhamnetin 3-glucoside		
25		Isorhamnetin 3-*O*-galactoside		
26		Isorhamnetin 3-*O*-glucoside 7-*O*-rhamnoside		
27		Isorhamnetin		
28		Isorhoifolin		
29		Kaempferol 3-*O*-rutinoside		
30		Luteoside/Luteolin 7-*O*-glucoside		
31		Quercetin 3-*O*-acetyl-rhamnoside		
32		Quercetin		
33		Scopoletin		
34	Iso-flavonoids	2,7-Dihydroxy-4-methoxyisoflavanone	Fruit	[51]
35		7,2-Dihydroxy-4-methoxyisoflavanol		
36		Isoformononetin		
37	Lignans	Medioresinol	Stem	[57]
38		5-(Hydroxymethyl)-2-(dimethoxymethyl) furan		
39		Lukianol	Fruit	[51,56,58]
40		Coniferin		
41		Pinoresinol		
42		1-Acetoxypinoresinol		
43	Phenolics	Methyl caffeate	Leaf	[55]
44		Trans-p-coumaric acid		
45		Ferulic acid		
46		Kaempferol-3-*O*-β-D-glucoside		
47		Ligstroside		
48		Oleuropein		
49		Campesterol		[52,58]

Table 3. Continued.

SI.	Class	Chemical compounds	Parts	Ref.
50		Stigmatosterol		
51		(+/–)-alpha-Tocopherol acetate		
52		2,4-ditertiary butyl phenol	Stem	[59]
53		Gamma-sitosterol	Stem callus	[57]
54		3,4′-*O*-dimethylcedrusin9′-*O*-glucopyranoside		
55		Syringaresinol		
56		Vanillic acid		
57		α-Tocopherol		[58]
58		β-sitosterol	Bark	[60]
59		4-Feruloylquinic acid	Fruit	[51,58]
60		5-Hydroxyferulic acid		
61		Caffeic acid		
62		Cinnamaldehyde		
63		Cinnamyl alcohol		
64		Coniferyl alcohol		
65		Feruloyl glucose		
66		p-Coumaroyl glucose		
67		Phenol, 2,4-bis(1,1-dimethyethyl)		
68		Phenol-2-methoxy-5(1-propenyl)		
69		2-Methoxy-4-vinylphenol		[52]
70		3,5-bis(1,1-dimethylethyl)-4-hydroxy-methyl ester		
71		Benzenepropanoic acid		
72	Polyprenols	C_{60}-polyprenol	Leaf	[10]
73		2-Methyl-Z, Z-3,13-Octadecadienol	Stem	[51,58]
74		3,7,11,15-Tetramethyl-2-hexadecen-1-ol		
75		Carnosic acid		
76		Cucurbitacin E		
77		Isosteviol		
78		Rosmadial		
79	Sterols	Cholesta-8,24-dien-3-ol,4-meth, (3-beta., 4-alpha.)	Leaf	[52]
80	Steroidal compounds	Olean-12-en-3-ol acetate (3-beta)	Leaf callus	[10]
81		Farnesol	Fruit	
82	Terpenoids	Betulin	Bark	[60]
83		Oleanolic	Leaf	[61]
84		Cucurbitacin B		[51,52]
85		Cucurbitacin D		
86		Cucurbitacin I		
87		Phytol		
88		Neophytadiene	Fruit	
89		Lup-20(29)-ene-3, 28-diol, (3-beta)		
90		β-Amyrin		
91	Glycosides	3β, 25-dihydroxy-24-methyl-30-carboxy methyl cucurbita-5-en-3-*O*-β-d-glucopyranoside	Fruit	[62]
92		3β, 25-dihydroxy-24-ethyl-30-carboxy methyl cucurbita-5, 22-dien-3-*O*-β-d-glucopyranoside		
93		3β-hydroxy-24-(1-butanol-4-yl)-30-carboxy methyl cucurbita-5, 7, 22-trien-3-*O*-β-d-glucopyranoside		
94		Ethyl-α-D-glucopyranoside	Stem	
95		Methyl-β-D-gluco hexodialdo-1,4-furanoside		
96	Fatty acids	9-Octadecynoic acid	Leaf	[52]

Table 3. Continued.

SI.	Class	Chemical compounds	Parts	Ref.
97		Palmitic acid		
98		9,12,15-Octadecatrienoic acid		
99		Oleic acid		
100		9,10,12,13-Tetrabromo-octadecanoic acid	Leaf callus	[58]
101		9,12-Octadecadienoic acid;	Fruit	
102		N-Pentadecanoic acid;		
103		Linoleic acid		
104	Fatty acid derivatives	11-Octadecanoic acid, methyl ester	Leaf	[52]
105		8,11,14-Eicosatrienoic acid, methyl ester (Z, Z, Z)		
106		9,12-Octadecadienoyl chloride (Z, Z)		
107		9,12-Octadecanoic acid, methyl ester		
108		Cyclopentaneundecanoic acid, methyl ester		
109		Hexadecanoic acid, ethyl ester		
110		Pentadecanoic acid, 14-methyl-, methyl ester		
111		Pentadecanoic acid, 2-hydroxy-(hydroxymethyl) ethyl ester		
112		Hexadecanoic acid	Leaf callus	[58]
113		Octadecyl ester		
114		Isopropyl linoleate		
115		Hexadecanoic acid methyl ester	Fruit	
116		Hexadecanoic acid methyl ester	Stem	[59]
117		Methyl stearate		
118		Eicosanoic acid, methyl ester		
119		Decanoic acid, methyl ester	Stem callus	[58]
120		Phosphonic acid, dioctadecyl ester		
121	Fatty alcohols	Behenic alcohol	Leaf	
122		1-Octadecanol	Leaf callus	
123		Undecanol	Fruit	
124		1-Heptacosanol	Stem	[59]
125		1-Eicosanol		
126	Anthocyanins	Cyanidin 3-*O*-sambubioside 5-*O*-glucoside	Fruit	[51]
127		Cyanidin 3-*O*-xyloside		
128	Lactones	Benzofuranone	Fruit	[58]
129		2(3H)-furanone		
130	Aldehydes	4-hydroxybenzaldehyde	Stem	[57]
131		Syringaldehyde		
132	Miscellaneous	2E,4E,6E)-5-methyl-7-(2,6,6-trimethylcyclohexa-2,4-dien-1-yl) hepta-2,4,6-trien-1-o	Aerial parts	[63]
133		9-(furan-3-yl)-4-hydroxy-1,5,6,6a,9,10,10a,10b-octahydro-3H,7H-pyrano[3,4-f] isochromene-3,7-dione		
134		Docosan-1-ol	Bark	[60]
135		Docos-10-one		
136		Cyclohexane, 1,5-diethyl-2,3-dimethyl-	Stem	[59]
137		3-Tetradecene (E)		
138		Cyclohexane,1,1′-(1,2-dimethyl-1,2-ethanediyl) bis-		
139		Cyclohexane, hexyl-		
140		2,2-Dicyclohexylbutane		
141		1-Pentadecene		
142		1,7-Dimethyl-4-(1-methylethyl) cyclodecane		
143		Cyclohexane, octyl-		
144		Cyclohexane, 1,2,4,5 tetraethyl		
145		Cyclohexane, undecyl-		

Table 3. Continued.

SI.	Class	Chemical compounds	Parts	Ref.
146		Spiro [4.5] dec-6-en-8-one, 1,7-dimethyl-4-(1-methylethyl)		
147		1-Nonadecene		
148		7,9-Di-tert-butyl-1-oxaspiro (4,5) deca-6,9-diene-2,8-dione		
149		Heneicosane		
150		Cyclononasiloxane, octadecamethyl-		
151		Phnol,4-ethenyl-, acetate		
152		9-Methyl-Z, Z-10,12-hexadecadien-1-ol acetate		
153		2,6-Octadiene, 1-(1-ethoxyethoxy)-3,7-dimethyl		
155		9-Octadecynoic acid		
156		9,12,15-Octadecatrienoic acid		
157		Palmitic acid		
158		1-(4-Isopropylphenyl)-2-methylpropyl acetate		

(**52**) further contributing to its chemical complexity. The stem callus adds to this diversity with the presence of a compound (**53**). The fruit has been characterized with four notable phenolic compounds (**54–57**) significantly expanding the plant's repertoire of bioactive compounds [57]. Furthermore, the bark contains a compound (**58**), while the fruit is enriched with an array of phenolics, including isolated compounds (**59–71**), collectively contributing to the comprehensive phenolic profile [51,58,62].

6.6 Polyprenol

Seven polyprenol compounds (**72–78**) have been identified across various parts of *C. grandis*, emphasizing its remarkable chemical diversity. Among these, compound (**72**), identified as C_{60}-polyprenol, was isolated from the leaf [10]. Six polyprenol compounds, including (**73-78**), isolated from the stem each enriching the chemical complexity [51,58].

6.7 Sterol and Steroidal Compounds

Three compounds, including one sterol (**79**) and two steroidal derivatives (**80, 81**), have been identified in *C. grandis*. Specifically, compound (**79**) was isolated from the leaf [52] compound (**80, 81**) have been isolated from the leaf callus, and fruit of *C. grandis*.

6.8 Terpenoids

The terpenoids identified in *C. grandis* showcase a diverse range of chemical structures. Nine terpenoids (**82–90**) have been isolated from different parts of the plant, highlighting its chemical complexity. Specifically, compound (**82**) was isolated from the bark [60] and compounds (**83–87**) have been isolated from the leaf [60,61]. The fruit is rich in additional terpenoids, including compounds (**88–90**) were also isolated, expanding the plant's chemical repertoire.

6.9 Glycosides

Five glycosidic compounds (**91–95**) have been isolated from various parts of *C. grandis*, compounds (**91–93**) have been isolated in the fruit, contributing to the glycosidic profile of the plant [62]. Additionally, compounds (**94**, **95**) were isolated from the stem, further enriching the plant's glycosidic composition.

6.10 Fatty Acids

A diverse array of fatty acids (**96–103**) has been identified across different parts of *C. grandis*, further enriching its chemical profile. From the leaf, compounds **96**, **97**, **98**, and **99** were isolated, significantly contributing to the plant's fatty acid composition [52]. Compound (**100**) was discovered in the leaf callus, introducing a distinctive aspect to the plant's lipid profile. Additionally, the fruit was found to contain compound (**101–103**) thus broadening the fatty acid spectrum and enhancing the plant's potential for diverse pharmacological applications [58].

6.11 Fatty Acids Derivatives

Different parts of *C. grandis* have been characterized by the presence of seventeen fatty acid derivatives (**104–120**). From the leaf, eight compounds (**104–111**) have been identified, reflecting significant chemical diversity [52]. The leaf callus has yielded three additional compounds isolated (**112–114**), further enriching the plant's lipid profile. The fruit has been found to contain a compound (**115**), highlighting its contribution to the fatty acid derivative spectrum [58]. The stem also exhibits considerable diversity with the isolation of three compounds (**116–118**), while the stem callus features two unique derivatives (**119–120**) that have been isolated [59].

6.12 Fatty Alcohols

Five fatty alcohols (**121–125**) have been isolated in various parts of *C. grandis*, compounds (**121**) and (**122**) were isolated from the leaf and leaf callus. The fruit was found to contain a compound (**123**) [58]. Furthermore,

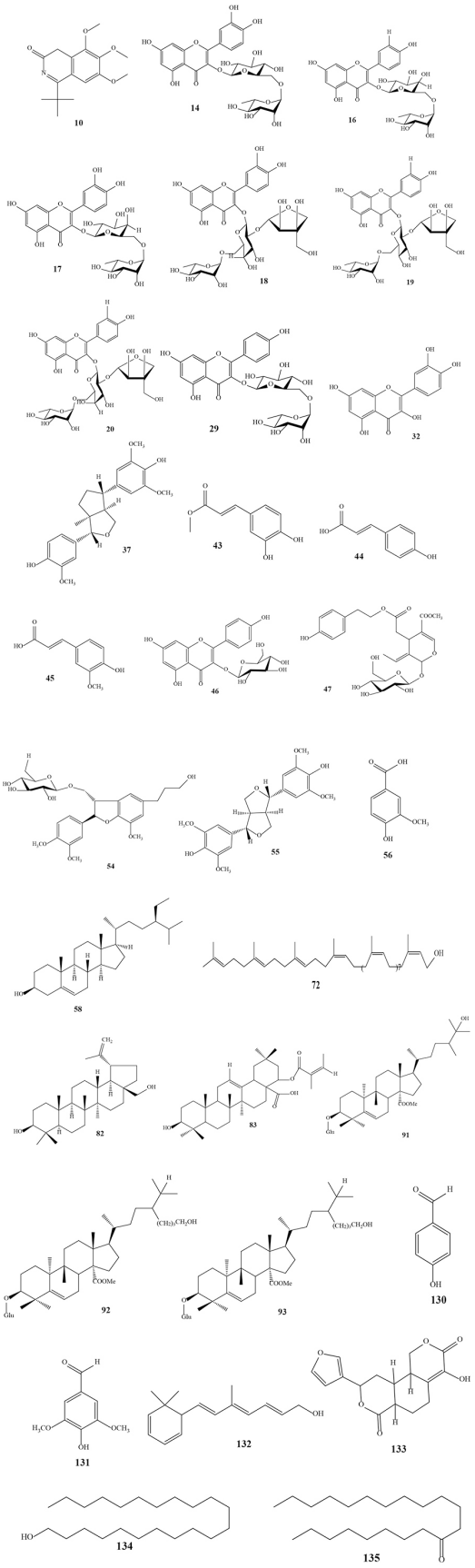

Fig. 2. Chemical structure of bioactive phytoconstituents of *Coccinia grandis*.

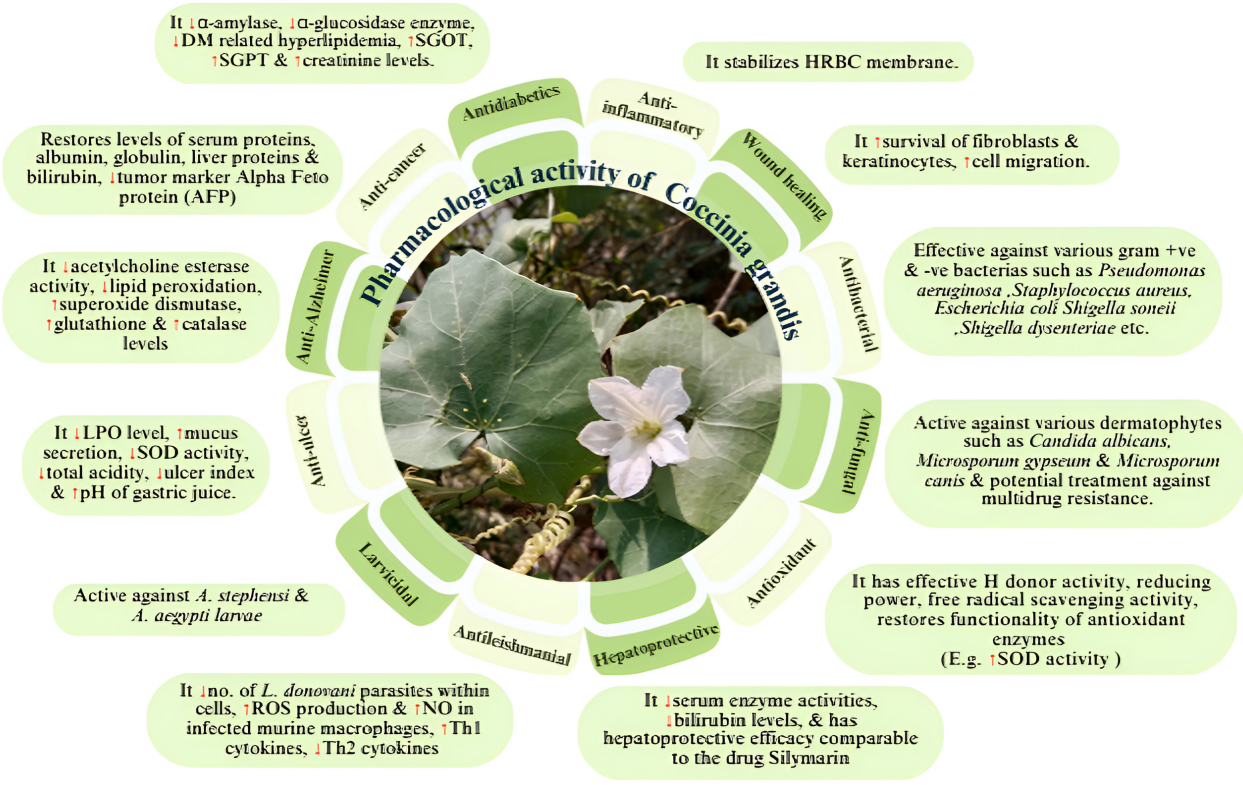

Fig. 3. Pharmacological activities of *Coccinia grandis*. Upward (↑) and downward (↓) arrows represent increases and decreases in activity or levels, respectively. Created using canva.com.

compounds (**124**) and (**125**) were isolated from the stem [59].

6.13 Anthocyanins, Lactones, and Aldehydes in C. grandis

Two anthocyanins (**126, 127**) have been identified in the fruit of *C. grandis* [51]. Among the lactones, two compounds (**128, 129**) were isolated in the fruit, highlighting the plant's lactone diversity [58]. Additionally, the stem yielded two aldehydes (**130**, **131**) further expanding the chemical constituents of the plant [57].

6.14 Miscellaneous Compounds

The phytochemical profile of *C. grandis* also encompasses various miscellaneous compounds. These include two complex cyclic structures (**132, 133**) isolated from the aerial parts [63], along with two docosane derivatives (**134, 135**) from the bark [60]. Furthermore, the stem has yielded a range of diverse compounds, including cycloalkanes, alkenes, and other unique structures (**136–158**) [59].

7. Pharmacological Activities

A variety of *in vitro*, *in vivo*, and *in silico* studies validated the traditional therapeutic uses of *C. grandis*. Most studies have concentrated on its antidiabetic [64] and cardiac activities [65], particularly exploring the molecular mechanisms of extracts and phytoconstituents. There is considerable evidence suggesting that the plant possesses anticancer [66], immunomodulatory [67], anthelmintic [68], antioxidant [69], antidiabetic [70], and antimicrobial effects [71]. Additionally, preliminary studies showed that it has hepatoprotective [72], woundhealing [51], anticataract [73], anti-Alzheimer [74], and larvicidal [75] effects. The pharmacological properties of the plant are outlined in Table 4 (Ref. [9,51,55,64,65,67–111]) and demonstrated in Fig. 3. In addition, researchers unveil the mechanism of actions of some activities, particularly antidiabetic, anticancer, anti-inflammatory, antiulcer, hepatoprotective, and anti-Alzheimer effects. Compared to its traditional uses and beneficial effects, there is still a scope to perform in-depth research to find out the pharmacological activities as well as the precise mechanism of action of those effects [91]. A concise mechanism of action for various pharmacological effects is summarized in Fig. 4.

7.1 Antidiabetic Properties

Non-insulin-dependent diabetes mellitus (NIDDM), commonly known as Type 2 Diabetes Mellitus (T2DM), accounts for approximately 90% of diabetes cases globally, affecting around 9% of the population, or about one in eleven individuals worldwide. T2DM is marked by persistent hyperglycemia, disrupted protein, carbohydrate, and lipid metabolism, and an elevated risk of vascular compli-

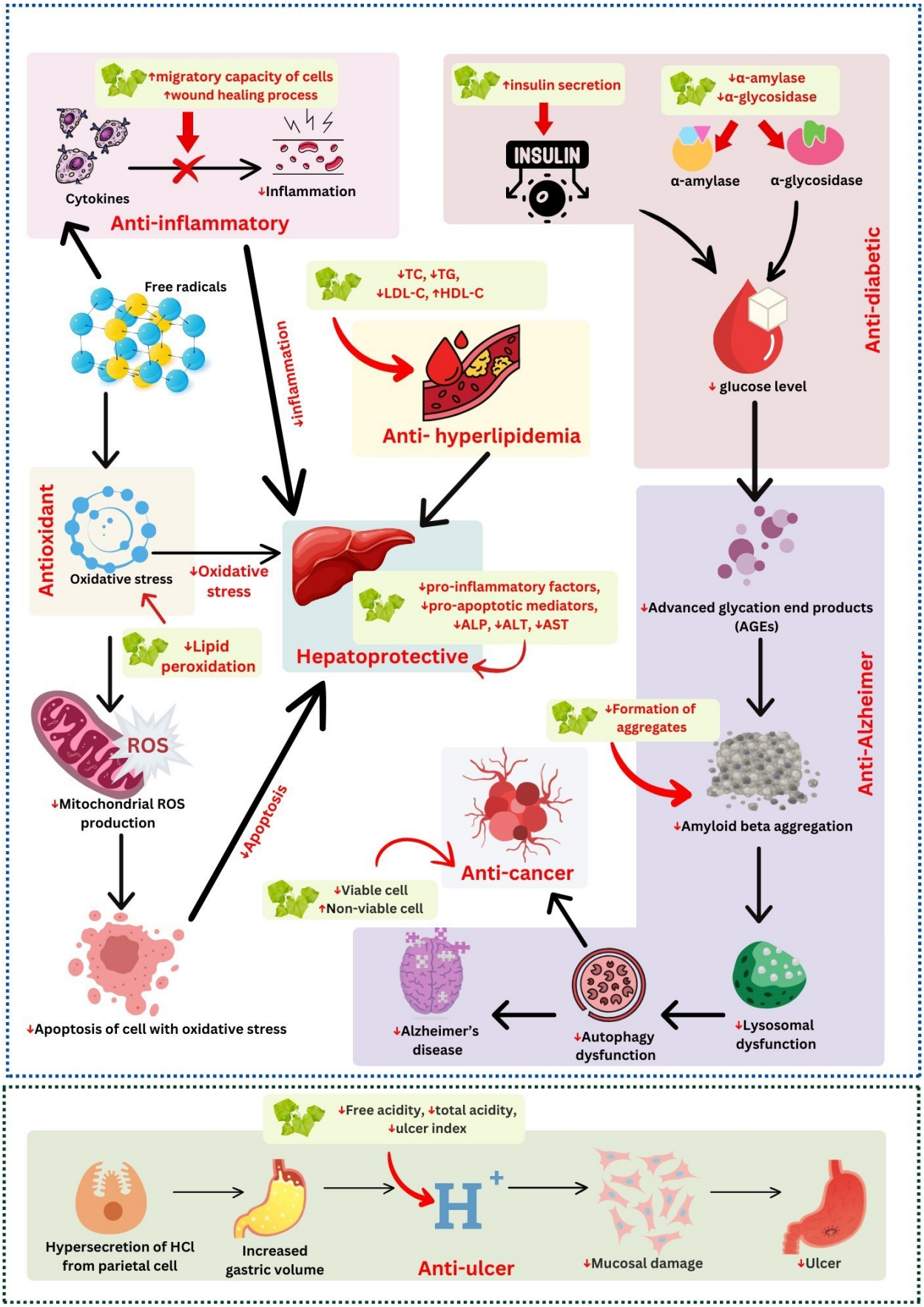

Fig. 4. The diverse effects of *Coccinia grandis* and the underlying mechanisms. The small red upward arrows (↑) indicate an increase or upregulation of the respective biological activity, level, or process, whereas red downward arrows (↓) indicate a decrease or downregulation. Created using canva.com.

Table 4. Pharmacological effects of *C. grandis* extracts observed in various experiments.

Activity	Type of preparation	Study type	Study models/methods	Administered dosage	Biological effects	Ref.
Antidiabetic	Methanolic extract of leaves	*In vivo*	Diabetic mice	100 mg/kg	It ↓TG, ↓blood glucose levels, ↓low-density lipoprotein cholesterol (LDL-C), ↓TC, & ↑high-density lipoprotein cholesterol (HDL-C)	[76]
	Ethanolic extract	*In vitro*	α-glucosidase inhibitory assay	12.5–250 µg/mL	It ↓α-amylase enzyme activity & ↓α-glucosidase enzyme activity	[64,91]
	Ethanolic extract	*In vivo*	Wistar rats (male)		Antihyperlipidemic activity	[77]
	Methanolic extract	*In vitro*	RINm5F cells	0.250 mg/mL & 0.50 mg/mL	It stimulated 1.28 & 1.71-fold ↑insulin secretion	[78]
	Aqueous extract	*In vivo*	Wistar rats with diabetes	0.25–2.00 g/kg	Optimum effectiveness in antihyperglycemic activity	[9]
	Aqueous extract from leaves	*In vivo*	Albino rat models	50 mg/kg body weight	It ↓glucose levels in the blood	[79]
	Methanolic extract	*In vitro*	Murashige & Skoog medium	1.0 mg/L	It ↓α-amylase & ↓α-glucosidase enzyme activity	[80]
	Methanolic extract (leaves, fruits, root & aerial parts)	*In vivo*	Albino mice models	150 mg/kg	After 8 hours, it ↓glucose levels in the blood to 7.87 ± 0.35, 17.9 ± 12.18, 19.5 ± 7.04 & v23.7 ± 7.23 respectively	[70]
				300 mg/kg	After 8 hours, it ↓glucose levels in the blood to 18 ± 12, 19.6 ± 11.6, 20.1 ± 1.55 & 15.3 ± 1.28 respectively	
				450 mg/kg	After 8 hours, it ↓glucose levels in the blood to 16.2 ± 1.08, 9.4 ± 0.46, 14.3 ± 1.31 & 10.4 ± 1.56 respectively	
	Aqueous leaf extract	*In vivo*	Swiss-type albino rats	3 mL/kg body weight	It ↓glucose level & has exhibit antidiabetic effect	[81]
	Ethanol, methanol & chloroform extract	*In vivo*	Wistar-type albino rats	100 mg/kg	It possesses potential ability to ↓plasma lipids	[82]
	Aqueous & ethanolic extract	*In vitro*	Alpha amylase and alpha glucosidase	62.5, 125, 250, 500 & 1000 µg/mL	It ↓postprandial hyperglycemia & help with diabetic complications	[83]
	Methanolic extract	*In vivo*	Rats	125, 250 & 500 mg/kg	It has potential antidiabetic & antihyperlipidemic properties	[84]
	Fruit extract	*In vivo*	Rats with diabetes	250 mg/kg	It possesses considerable antihyperglycemic activity	[85]
	Aqueous extract	*In vivo*	Wistar rat model	0.75 g/kg	It possesses potential antidiabetic effect	[86]
	Chloroform, ethyl acetate, methanolic & n-hexane extract	*In vitro*	α-glucosidase inhibition assay	0.5–7 mg/mL	It possesses effective α-glucosidase inhibitor	[9]
Antioxidant	Petroleum ether, Chloroform, hydroalcoholic extract of stem	*In vivo*	Wistar-type albino rats	250 & 500 mg/kg	It has antioxidant property, ↓glucose level in blood, ↓lipid peroxidation (LPO) & ↓oxidative stress	[87]
	Ethanolic	*In vitro*	2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging assay	20–800 µg/mL	It possesses significant antioxidant activity	[88]
	Ethanolic extract	*In vitro*	DPPH free radical scavenging assay	2 mL	It possesses significant antioxidant effect	[69]
	Petroleum ether, chloroform & ethyl acetate	*In vivo*	Rats	200 mg/kg	It possesses potential antioxidant effect	[9]
	Aqueous extract	*In vitro*	DPPH free radical scavenging assay	40%, 50%, and 70%	Free radical inhibition	[71]
	Aqueous extract of leaves	*In vitro*	DPPH free radical scavenging assay	100–500 µg/mL	It possesses significant antioxidant potential	[89]

Table 4. Continued.

Activity	Type of preparation	Study type	Study models/methods	Administered dosage	Biological effects	Ref.
	Methanolic extract	*In vitro*	DPPH free radical scavenging assay	200, 100, and 50 µg/mL	Protects the cell from oxidative damage during extended periods of inflammation	[67]
	Methanolic extract	*In vitro*	DPPH free radical scavenging assay	1 mg/mL	It has DPPH radical scavenging activity, ↓oxygen radical formation	[80]
	Methanolic & ethanolic extract	*In vitro*	DPPH scavenging assay	20, 40, 60, 80, 100 µg/mL	It prevents oxidative damages	[90]
	Aqueous extract of leaves	*In vivo*	Swiss-type Albino rats	3 mL/kg body weight	It ↓free radical & exhibit antioxidant activity	[81]
	Ethanolic extract	*In vitro*	DPPH Radical Scavenging Activity	10–100 µg/mL	It possesses potential antioxidant activity	[86]
	Aqueous extract with encapsulated alginate nanoparticles	*In vitro*	DPPH, ABTS (2,2′-azinobis (3-ethylbenzothiazoline-6-sulfonic acid)) radical scavenging assays, and FRAP (ferric reducing antioxidant power) assays	1–5 mg/mL	Encapsulation ↑antioxidant efficacy, as assessed by the ABTS assay, in comparison to AqCG	[69]
	Methanolic extract	*In vitro*	DPPH free radical scavenging assay	10 µL	It has potential antioxidant activity	[93]
	Hydroalcoholic extract	*In vitro*	DPPH & H_2O_2 assay	20, 40, 60, 80 µg/mL	It has strong antioxidant activity	[69]
Antiulcer	Aqueous extract of leaves	*In vivo*	Rats	250 & 500 mg/kg	It ↓gastric volume & ↓free acidity	[92]
	Ethanol, aqueous extract	*In vivo*	Wistar-type albino rats	400 mg/kg	It ↓total acidity, ↓gastric volume, ↓ulcer index & It ↓free acidity, indicating its effectiveness in preventing ulcers through an anti-secretory mechanism	[93]
Anti-inflammatory	Methanolic extract	*In vitro*	Human Fibroblast (hFB)-Cell and human epidermal keratinocytes (HaCaT)	200 µg/mL	It ↑migratory capacity of cells, which ↑wound healing process	[67]
	Aqueous extract of the leaves	*In vivo*	Swiss mice & Wistar rat models	50 mg/kg	It has potent anti-inflammatory activity	[94]
	Aqueous extract	*In vivo*	Swiss-type albino mice & Sprague Dawley rat models	0.2 mL	It has potent anti-inflammatory activity	[95]
	Aqueous extracts	*In vivo*	Rats	50, 100 & 200 mg/kg	It has potential anti-inflammatory effect	[95]
Antibacterial	Aqueous, ethanol, methanol & petroleum ether extract	*In vitro*	Bacteria species such as *Pseudomonas aeruginosa, Bacillus subtilis*, *Vibrio anguillarum*. *Escherichia coli* & *Staphylococcus aureus*	100, 250 & 500 µL	It shows strong antibacterial effects against *Vibrio anguillarum*, with a zone of inhibition measuring 31 ± 1.00 mm at a concentration of 500 µL	[96]
	Aqueous & methanolic extract	*In vitro*	Bacteria species namely *Escherichia coli* & *Staphylococcus aureus*	0.1 mL	It exhibits potent antibacterial activities	[97]
Antifungal	Aqueous, ethanolic, methanolic & petroleum ether extract	*In vitro*	Bacteria species namely *Candida albicans*, *Aspergillus niger*, *Aspergillus flavus* & *Aspergillus fumigatus*	100, 250 and 500 µL	It displays substantial antifungal effects against *Aspergillus niger*, with a distinct zone of inhibition (30.33 ± 1.53 mm) at a concentration of 500 µL	[96]

Table 4. Continued.

Activity	Type of preparation	Study type	Study models/methods	Administered dosage	Biological effects	Ref.
Antimicrobial	Aqueous extract of the leaves	*In vitro*	Disc-diffusion assay using bacteria species-*Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Serratia marcescens*, *Vibrio cholerae*, *Shigella sannei*, *Klebsiella pneumonia*, *Proteus vulgaris*, *Salmonella typhi* & *Proteus mirabilis*	15 mm, 13 mm	Exhibits potential antibacterial efficacy against *Vibrio cholerae*, *Serratia marcescens* & *Proteus vulgaris* with a zone of inhibition measuring 14 mm	[71]
	Ethanolic extract	*In vitro*	Chequerboard Assay using bacteria species such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pyogenes*, *Acinetobacter baumanni*, *Escherichia coli* & *Candida albicans*	0.0625 to 32 mg/mL	Effectively inhibits the growth of all tested microorganisms	[98]
	Ethanolic extract	*In vitro*	Disc-diffusion assay using both gram (+) bacteria (*Staphylococcus aureus*, *Sarcina lutea*, *Bacillus cereus)* & gram (–) bacteria (*Pseudomonas aeruginosa*, *Salmonella typhi*, *Escherichia coli*)	300 µg/disc	Showed significant antimicrobial activity	[99]
	Aqueous extract of the leaves	*In vitro*	Disc-diffusion assay using both gram (+) bacteria (*Micrococcus luteus*, *Staphylococcus aureus*, *Methicillin resistant*) & gram (–) bacteria *Escherichia coli*	25 µL/disc	Maximum zone of inhibition (33 mm) *Micrococcus luteus*	[89]
	Aqueous, & hexane extracts of leaves	*In vitro*	Well-diffusion assay using both gram (+) bacteria (*Staphylococcus aureus*, *Bacillus cereus*, *Streptococcus pyogene*, *Corynebacterium diptheriae*) & gram (–) bacteria (*Shigella boydii*, *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Salmonella typhi*, *Pseudomonas aeruginosa*)		The aqueous extract produced moderate effectiveness against *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* & *Salmonella typhi* while the hexane extract demonstrated a moderate level of activity against all bacteria types except *Proteus mirabilis*, which showed no response	[100]
	Aqueous, hexane & ethyl acetate extract of stem	*In vitro*	Well-diffusion assay using both gram (+) (*Bacillus cereus*, *Corynebacterium diptheriae*, *Staphylococcus aureus*, Streptococcus pyogene) & gram (–) bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Salmonella typhi* & *Shigella boydii*)		Effectiveness was observed with the aqueous extract exclusively against *Shigella boydii*, while the hexane extract demonstrated activity against *Shigella boydii* along with *Klebsiella pneumoniae*, *Streptococcus pyogenes*, *Escherichia coli*, *Pseudomonas aeruginosa* & *Salmonella typhi*. Similarly, the fraction of ethyl acetate was effective against all the tested bacteria apart from *Staphylococcus aureus* & *Proteus mirabilis*	[100]
	Aqueous, acetone & ethanolic extracts	*In vitro*	Uropathogenic *Escherichia coli* (UPEC)/agar well diffusion method	200 µg to 1000 µg	It has antimicrobial effects on biofilm formation & uropathogenic *Escherichia coli*, capable of producing the enzyme Extended Spectrum Beta-Lactamase (ESBL)	[101]

Table 4. Continued.

Activity	Type of preparation	Study type	Study models/methods	Administered dosage	Biological effects	Ref.
	Petroleum ether, chloroform, ethyl acetate, acetone, methanol & aqueous extract	*In vitro*	Agar well diffusion assay with *Acinetobacter* species, *Klebsiella* species, *Pseudomonas aeruginosa*, *Staphylococcus aureus* & *Proteus mirabilis*	25 mg/mL	It has bactericidal activity	[102]
	Aqueous extract	*In vitro*	Agar well diffusion assay using both gram (+) bacteria (*Staphylococcus aureus*) & gram (–) bacteria (*Escherichia coli*)	100 µL	It has potential antibacterial activity	[51]
Hepatoprotective	Aqueous, petroleum ether, n-hexane, chloroform & methanolic extract	*In vivo*	Albino rat models	0.6 mg/g body weight/day	It ↓inflammation-related oxidative stress & ↓apoptosis (by ↓pro-apoptotic mediators & ↓pro-inflammatory factors) thereby protecting the heart & liver	[65]
	Aqueous extract of leaves	*In vivo*	Wistar-type Albino rats	250 mg/kg body wt	It ↓alkaline phosphatase (ALP), ↓aspartate aminotransaminase (AST) & ↓alanine amino transaminase (ALT)	[103]
	Methanolic extract	*In vivo*	Albino rat models (Female)	200 mg/kg	It ↓AST, ↓ALT & ↓ALP enzymes present in the serum	[104]
	Methanolic extract	*In vivo*	Wistar-type Albino rat models	100, 200 mg/bw	It ↑antioxidant levels, ↓oxidative stress & reverses liver parameters	[105]
	Aqueous & methanolic extract	*In vivo*	Swiss-type albino mice	200 mg/kg	It has potent hepatoprotective activity	[72]
Cardioprotective	Aqueous, petroleum ether, n-hexane, chloroform & methanolic extract	*In vivo*	Albino rat models	0.6 mg/g body weight/day	It maintains typical lipid profile, ↓cellular toxicity markers level, ↓inflammatory responses & ↓programmed cell death	[65]
Larvicidal	Essential oil extracted from leaves	*In vitro*	*Anopheles stephensi*, *Aedes aegypti* & *Culex quinquefasciatus*	3.125, 6.25, 12.50, 25, 50 and 100 ppm	It exhibits promising larvicidal activity against three mosquito species	[106]
	Ethanol, ethyl acetate, chloroform & aqueous extract	*In vitro*	*Anopheles stephensi*, & *Aedes aegypti*	1 mL	It exhibits promising larvicidal activity	[107]
	Ethanol, ethyl acetate, chloroform & aqueous extract	*In vitro*	Larvae and pupae of *C. quinquefasiatus*	20, 40, 60, 80, 100%	It has larvicidal & pupicidal activity	[108]
	Aqueous leaves extract, synthesized silver nanoparticles of *C. grandis*	*In vitro*	*Aedes aegypti* & *Culex quinquefasciatus*	50–250 ppm	It is effective in controlling *Culex quinquefasciatus* & *Aedes aegypti* larvae	[75]
Anti-cancer	Ethanolic extracts	*In vitro*	Ehrlich Ascites Carcinoma (EAC) cell	200 & 400 mg/kg body weight	It ↓viable cell & ↑ no. of non-viable cell count showing anticancer property against EAC cells	[81]
Antitussive	Methanolic extract	*In vitro*	Guinea pigs & Swiss-type albino mice	100, 200 & 400 mg/kg	It has significant antitussive effect	[109]
Anti-Alzheimer	Ethanolic extract	*In vivo*	Wistar-type albino rats	500 & 1000 mg/kg	It ↑learning & ↑memory activity	[74]

Table 4. Continued.

Activity	Type of preparation	Study type	Study models/methods	Administered dosage	Biological effects	Ref.
Anticataract	Methanolic & aqueous extract	*In vivo*	Wistar-type albino rat models	200 mg/kg	It has potential anticataract activity	[73]
Antileishmanial	Leaf extract (crude extract)	*In vivo*	BALB/c mice models (female, adult)	12, 24, 48 mg/kg	Possible immunomodulator for treating visceral leishmaniasis	[110]
Anti-anaphylactic	Ethanolic extract	*In vivo*	Swiss-type albino mice models	100, 125 & 150 mg/kg	It shows potential anti-anaphylactic activity by ↓histamine release in anaphylactic reaction & ↓clonidine induced catalepsy	[111]
Antihistaminic	Ethanolic extract	*In vivo*	Swiss-type albino mice models	100, 125 & 150 mg/kg	It has potential antihistaminic activity	[111]
Anthelmintic	Methanolic extract	*In vivo*	Earth worm, tape worm & round worm	5, 10 mg/mL	It has significant anthelmintic activity	[68]
Wound healing	Aqueous extract	*In vivo*	Wistar-type albino rat models	0.5 mg/cm	It ↑collagen synthesis & ↑granulation tissue formation	[51]
	Methanolic extract	*In vivo*	Albino rat models (male)	1.5 mg/g	It has wound healing capacity	[55]

Upward (↑) and downward (↓) arrows represent increases and decreases in activity or levels, respectively.

cations. This condition stems from inadequate insulin, essential for glucose transport from blood to tissues [112]. Integrative approaches combining herbal and ayurvedic medicine with conventional treatments offer a comprehensive strategy for managing diabetes, with proven safety and effectiveness, particularly when coupled with dietary control and exercise [113–115]. Traditional medicinal plants have gained traction as alternative treatments and novel drug sources for diabetes, aligning with the WHO's guidelines on diabetes care.

For instance, the methanolic extract of *C. grandis* leaves has demonstrated significant antidiabetic effects in streptozotocin (STZ)-induced diabetic rats at doses of 125, 250, and 500 mg/kg, showing an ability to reduce hyperlipidemia associated with diabetes [84]. Studies using *C. grandis* fruit extracts have revealed strong antioxidant and radical-scavenging activities, evaluated through nitric oxide and radical-scavenging assays, and inhibitory effects on key enzymes α-glucosidase and α-amylase, with IC_{50} values of 81.6 and 117.64 µg/mL, respectively [64]. These properties, combined with its ability to lower blood glucose levels in oral glucose tolerance tests (OGTT), suggest *C. grandis* has a notable antihyperglycemic impact comparable to Glibenclamide, a common diabetes medication [116]. When diabetes was induced in rats using alloxan, an ethanol-based *C. grandis* leaf extract at 750 mg/kg showed hypoglycemic effects akin to metformin, without statistically significant differences ($p > 0.05$). This extract also improved pathological markers like serum glutamic oxaloacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), and creatinine levels, indicating potential benefits for diabetic patients while demonstrating safety in non-diabetic models [66]. Furthermore, *C. grandis* hydroalcoholic stem extract-derived silver nanoparticles (AgNPs) exhibit promising antidiabetic effects *in vitro*, with effective glucose-lowering properties. The AgNPs were validated using multiple analytical techniques and offered potential applications in targeted drug delivery systems [117].

7.2 Antioxidants

The biological degenerative processes associated with excessive free radicals can result in damaging oxidative reactions within the body [118]. Antioxidant activity, defined as a bioactive compound's ability to neutralize these harmful radicals, plays a crucial role in protecting cellular integrity by inhibiting lipid peroxidation (LPO) and preventing oxidative damage. Antioxidants not only contribute to cellular defense but are essential for various biological functions, including anticancer, anti-inflammatory, and anti-aging effects. Research suggests a link between antioxidant activity and the prevention of chronic diseases like cancer, diabetes, and cardiovascular diseases [119]. Many plants contain potent antioxidants such as carotenoids, phenolics, flavonoids, anthocyanins, unsaturated fatty acids, vitamins, enzymes, and cofactors—providing therapeutic potential for preventive healthcare. Recent research has further reinforced the antioxidant potential of *C. grandis*. A study evaluating the genetic variability of *C. grandis* germplasm under rainfed semi-arid conditions found significant variations in antioxidant activity among different accessions. High heritability and genetic advance were observed for key antioxidant markers such as total phenols, total flavonoids, and 2,2-diphenyl-1-picrylhydrazyl (DPPH) assays, suggesting strong genetic control over these traits and highlighting the potential of *C. grandis* for breeding programs aimed at enhancing its antioxidant properties [120].

Studies have highlighted the value of plant-derived antioxidants for disease prevention, showing that diets rich in secondary plant compounds can reduce the risk of degenerative conditions, including cancer and arteriosclerosis [121,122]. Medicinal plants like *C. grandis* have shown promising antioxidant effects, which are particularly evident in ethanol extracts. For instance, the DPPH free radical scavenging assay demonstrated that *C. grandis* ethanol extract exhibited significant antioxidant activity (IC_{50} 1.15 µg/mL), outperforming the standard, ascorbic acid (IC_{50} 5.80 µg/mL), which displays the highest inhibition of free radical activity [123]. *In vitro* studies further support the efficacy of *C. grandis* fractions, revealing their robust hydrogen-donating ability. Chloroform (IC_{50} 0.135 µg/mL), ethyl acetate (IC_{50} 0.154 µg/mL), pet-ether (IC_{50} 0.39 µg/mL), and methanolic fractions (IC_{50} 0.8 µg/mL) all exhibited significant antioxidant activity. The methanolic fraction had the highest reducing power (0.426 µg/mL), followed by ethyl acetate, pet-ether, and chloroform fractions. These findings were benchmarked against standards like butylated hydroxytoluene (BHT), ascorbic acid, α-tocopherol, and curcumin, underscoring the comparable efficacy of *C. grandis* [124]. In animal models, *C. grandis* extracts restored antioxidant enzyme activity in rats on a high-fat diet, reducing oxidative stress through increased levels of enzymes such as superoxide dismutase (SOD), glutathione (GSH), and catalase. In these studies, *C. grandis* was nearly as effective as metformin, reducing oxidative markers at doses of 100 mg/kg and 200 mg/kg [125]. The DPPH assay, used to measure antioxidant activity, confirmed that the methanolic extract of *C. grandis* callus powder showed 46.66% efficacy, surpassing the 30% activity observed in fruit powder and showing effectiveness close to that of ascorbic acid. Rat peritoneal macrophages treated with these extracts showed decreased oxygen radical production, attributed to the DPPH scavenging action [80]. The detailed mechanisms by which *C. grandis* exerts its antioxidant effects are illustrated in Fig. 4.

7.3 Anti-Microbial Activity

Bacterial infections remain a major global health threat, with rising antimicrobial resistance and biofilm-

associated infections heightening the need for novel antibacterial solutions [126]. The misuse and overuse of antibiotics have accelerated this resistance, rendering many existing drugs ineffective. This issue, deemed by the WHO as one of the most urgent challenges in medicine, highlights the necessity for new antimicrobial agents [127]. Since the late 20th century, resistance has surged among pathogens, complicating treatment options [128]. Reducing dependence on traditional antibiotics by exploring alternative sources, especially medicinal plants, is now critical [129]. Roughly half of existing drugs and nutraceuticals are derived from natural sources, driving researchers to investigate bioactive compounds from plants to combat microbial resistance.

Medicinal plants like *Coccinia grandis* (ivy gourd) have demonstrated significant antimicrobial effects. The methanol extract of *C. grandis* showed a 14.10 mm zone of inhibition against *Pseudomonas aeruginosa in vitro*, close to that of the standard antibiotic ciprofloxacin, which showed a 16.07 mm inhibition zone. *C. grandis* demonstrated strong activity against various gram-positive and gram-negative bacteria, such as *Staphylococcus aureus* and *Escherichia coli*, with minimum inhibitory concentrations (MICs) ranging from 10 to 25 µg/mL and minimum bactericidal concentrations (MBCs) from 25 to 50 µg/mL [130]. Further analysis of *C. grandis* extracts confirmed antimicrobial activity against a range of pathogens, including gram-positive bacteria like *Staphylococcus aureus* and gram-negative strains like *Klebsiella pneumoniae* and *Proteus vulgaris*. The purified protease inhibitor of *C. grandis* showed inhibition zones in antimicrobial tests, with *K. pneumoniae* and *Aspergillus flavus* being the most sensitive (MIC-0.01 mg/mL and MBC/minimal fungicide concentration (MFC)-0.5 mg/mL). Meanwhile, *Staphylococcus aureus* and *Bacillus subtilis* showed relatively higher resistance [131]. In another study, *C. grandis* ethanol leaf extracts demonstrated antibacterial activity against both gram-positive and gram-negative strains, including *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, and *Klebsiella pneumoniae*, with MIC values less than 31.5 µg/mL against certain bacteria [132]. The extract also exhibited antifungal effects against *Candida albicans* and *Aspergillus niger*, particularly effective against oral and vaginal infection strains. Ethanol extracts showed higher activity against *Aspergillus niger*, responsible for aspergillosis, compared to aqueous extracts [133].

7.4 Hepatoprotective Activity

The liver, a crucial organ responsible for metabolism, secretion, storage, and detoxification, plays a fundamental role in maintaining overall health [134]. Its vital functions make it susceptible to damage, especially due to continuous exposure to toxins via direct blood flow from the intestines [135,136]. Liver diseases are among the leading causes of global morbidity and mortality, often triggered by unhealthy habits, excessive alcohol and drug use, sugary diets, and infections from microbes like bacteria, viruses, and parasites, along with autoimmune diseases like hepatitis and cirrhosis [137]. These diseases can be acute or chronic, classified into hepatitis (inflammatory), hepatosis (non-inflammatory), and cirrhosis (degenerative fibrosis) [138,139]. Current treatments for liver disorders are controversial, as synthetic medications often produce significant side effects. For centuries, herbal remedies have offered alternative therapies due to their lower toxicity and fewer adverse effects, leading to modern medicines inspired by medicinal plants [138]. Among these plants, *C. grandis* demonstrates hepatoprotective properties.

Studies indicate that alcoholic extracts from *C. grandis* fruit can reduce liver damage in rats exposed to carbon tetrachloride (CCl_4), significantly lowering serum enzyme and bilirubin levels, comparable to the effects of the standard drug silymarin [140]. Similarly, an ethanolic extract of *C. grandis* leaves administered in varying doses has shown hepatoprotective effects against CCl_4 and paracetamol-induced liver damage. Rats treated with the extract exhibited statistically significant reductions in liver enzymes and other biochemical markers of liver damage [141] (Fig. 4). Furthermore, a mechanistic study demonstrated that *C. grandis* protects against monosodium glutamate and high-lipid diet-induced systemic damage in rats by ameliorating oxidative stress, metabolic disturbances, and inflammatory responses, suggesting its potential as a hepatoprotective agent [142].

7.5 Antileishmanial Activity

Leishmaniasis, a major global health challenge, is a vector-borne disease caused by protozoan parasites of the genus Leishmania and ranks among the top six neglected tropical diseases according to the World Health Organization (WHO). Affecting 98 countries across five continents, it presents two primary clinical forms: visceral leishmaniasis (VL) and cutaneous leishmaniasis, with annual incidences of approximately 0.2–0.4 million VL cases and 0.7–1.2 million cutaneous cases [143]. Due to the high toxicity and emerging resistance of conventional treatments, there is a pressing need for novel therapeutic agents. Natural products, particularly plant derivatives, have shown promise as alternative antileishmanial agents, demonstrating efficacy against *Leishmania major* (causing cutaneous leishmaniasis) and *Leishmania infantum* (responsible for VL) [144].

Research into *C. grandis* has revealed significant antileishmanial potential. The leaf extract of *C. grandis* (Cg-Ex), tested *in vitro* against *Leishmania donovani*, achieved a 50% inhibitory concentration (IC_{50}) of 193 $\pm$ 0.78 µg/mL, significantly reducing intracellular parasite load without harming murine RAW 264.7 macrophages. Additionally, Cg-Ex stimulated nitric oxide (NO) and reactive oxygen species (ROS) production, both potent antimicrobial agents, within infected macrophages. Treatment with Cg-

Ex also induced a shift in cytokine profiles, enhancing Th1 cytokines (IL-12, TNF-α) while reducing Th2 cytokines (IL-10, TGF-β), suggesting that serine protease inhibitors in Cg-Ex contribute to its antileishmanial action through immunomodulation [145]. Another study demonstrated the leishmanicidal effects of an ethanolic extract of *C. grandis* leaves (Cg-LE) on *L. donovani* strains, including those resistant to standard treatments like Sodium Stibogluconate (SSG) and Miltefosine (MIL) (Fig. 4).

7.6 Anti-Inflammatory Activity

Inflammation is a complex immune response triggered by microbial infections, tissue damage, or sterile causes [146]. Globally, chronic pain associated with inflammation affects millions, including over 100 million adults in the U.S. and 27% of adults in Europe, with rates in Asia ranging from 7.1% to 61% [146,147]. If untreated, acute pain can lead to delayed wound healing, immune dysfunction, cardiovascular stress, and respiratory issues, while chronic pain disrupts the quality of life, daily activities, sleep, and work productivity, resulting in substantial economic costs [147]. Key immune cells such as leukocytes, macrophages, and mast cells release signaling molecules and activate complement factors, creating a cascade that recruits leukocytes, along with fluid and protein, to inflammation sites. While non-steroidal anti-inflammatory drugs (NSAIDs) and steroidal anti-inflammatory drugs (SAIDs) are widely used to manage inflammation, they pose risks of gastrointestinal (GI) and cardiovascular complications. As a result, plant-derived compounds are increasingly favored as natural anti-inflammatory alternatives with fewer side effects [148,149].

Studies on *C. grandis* have highlighted its anti-inflammatory potential. Using the human red blood cell (HRBC) membrane stabilization method, hydroethanolic leaf extract of *C. grandis* demonstrated dose-dependent HRBC protection rates of 30.7%, 47.11%, 58%, and 62% approaching the efficacy of diclofenac sodium, which showed protection rates of 68.85%, 78.41%, 89.8%, and 92.92% at similar concentrations [150].

In vivo studies showed that a 100 mg/kg dose of *C. grandis* methanolic leaf extract effectively reduced carrageenan-induced paw edema in rats, achieving similar results to diclofenac sodium, albeit with a 4-hour onset compared to diclofenac's 3-hour effect. The compound *C. grandis* leaf (CGL) reached 35.84% efficacy, close to diclofenac's 45.28%, and presents a safer, natural option for anti-inflammatory use [53]. Fig. 4 illustrates the mechanisms of *C. grandis* in modulating anti-inflammatory responses.

7.7 Anti-Ulcer Activity

Ulcers are open sores found on the skin or mucous membranes, characterized by shallow tissue damage. They can develop on the skin of the lower extremities and within the gastrointestinal (GI) tract, with peptic ulcers being among the most common types [151]. Peptic ulcers involve the erosion of the stomach or duodenal lining and penetrate deep layers, often leading to tissue necrosis, immune cell infiltration, reduced blood flow, oxidative stress, and inflammation [152,153]. These ulcers arise from an imbalance between harmful agents (such as acid, pepsin, and *Helicobacter pylori*) and protective factors like mucin, prostaglandins, bicarbonate, nitric oxide, and growth factors. Factors such as poor digestion, stress, and metabolic issues can exacerbate ulcer formation [154]. Current treatments include sucralfate, histamine, prostaglandin, muscarinic receptor antagonists, proton pump inhibitors (PPIs), and antacids, though many have adverse side effects like hypersensitivity, fatigue, blood disorders, and arrhythmias. This underscores the need for safer, natural remedies to treat peptic ulcers effectively.

Research has explored various plant-based agents for ulcer treatment, including *C. grandis*, which has traditional applications in treating gastric and peptic ulcers. Studies using an aspirin-induced ulcer model demonstrated that both *C. grandis* leaf powder (CGL) and its methanol extract (CGM) significantly reduced ulcer indices in a dose-dependent manner ($p < 0.05$) and lowered lipid peroxidation (LPO) and superoxide dismutase (SOD) levels ($p < 0.01$), while increasing mucus secretion. These extracts inhibited ulcers by 26.76% and 34.84% at 2 g/kg, respectively, approaching the standard drug famotidine's 35.30% inhibition rate. Unlike famotidine, a synthetic drug, CGL, and CGM are natural, suggesting that *C. grandis* may offer a safer anti-ulcer option with antioxidant properties [155]. Additionally, the ethanol extract of *C. grandis* leaves was effective in treating indomethacin-induced ulcers in rats, reducing ulcer scores significantly ($p < 0.001$) and enhancing mucus secretion protection by 69.71%, close to omeprazole's 74.85% [156] (Fig. 4).

Further studies on *C. grandis* ethanol and aqueous extracts in a pylorus-ligated rat model revealed that both extracts reduced total acidity and ulcer index while increasing gastric juice pH in a dose-dependent manner. The ethanol extract showed a substantial ulcer-curative effect (78.57%), with the aqueous extract achieving a 64.28% effect, both comparable to omeprazole's 85.70% effectiveness. Notably, *C. grandis* extracts are natural, unlike omeprazole, a synthetic drug, highlighting the therapeutic value of these extracts, particularly the ethanol variant, in ulcer treatment [157,158]. Mechanisms underlying *C. grandis* anti-ulcer activity are illustrated in Fig. 4.

7.8 Anticancer and Hepatocellular Carcinoma

Cancer remains one of the most common causes of death worldwide [159]. It encompasses a group of diseases characterized by uncontrolled cell proliferation, influenced by multiple factors such as genetic mutations and epigenetic changes in cell cycle-regulating oncogenes [160]. Cancer

cells typically exhibit abnormal apoptosis and altered microtubule dynamics during mitosis. The World Health Organization (WHO) identifies primary cancer-inducing factors, including somatic mutations, ionizing radiation, reactive oxygen species (ROS), and exposure to various chemical and biological agents [161]. While chemotherapy remains a standard treatment, it can damage healthy cells, causing side effects like bone marrow suppression, nausea, vomiting, and hair loss [162]. Consequently, there is an urgent need for novel, safer treatments.

Medicinal plants offer promising alternatives, as their natural compounds may provide effective anticancer therapies [163]. Throughout history, natural products have served as key sources of medicine, offering bioactive compounds for direct therapeutic use [164]. Among these, *C. grandis* has shown notable anticancer properties. In one *in vivo* study, the ethanolic extract of *C. grandis* leaves was administered to mice with benzidine-induced hepatocellular carcinoma (HCC), where it reversed abnormalities in liver enzyme levels and serum proteins at a dose of 250 mg/kg. The tumor marker alpha-fetoprotein (AFP) significantly decreased in the extract-treated group, demonstrating a protective effect against HCC [165]. Fig. 4 illustrates the anticancer activity of *C. grandis*.

Further research using various extraction methods on *C. grandis* fruit showed that cold extracts more effectively reduced breast cancer cell proliferation in MDA-MB-231 cells compared to hot extracts, while acetone extracts exhibited greater activity than ethanol extracts [166]. Studies with Ehrlich Ascites Carcinoma (EAC) cell-induced tumors in rats also highlighted *C. grandis* anticancer efficacy, with ethanol extract injections increasing survival rates by up to 97% and reducing viable cell counts, paralleling the effects of vinblastine, a standard cancer treatment [167]. Additionally, the application of *C. grandis* seed extracts in zinc oxide nanocomposites demonstrated notable anticancer effects on hypertension -29 cells (IC_{50} = 45.4 µg/mL), offering a sustainable and cost-effective approach to cancer therapy [168].

7.9 Anti-Alzheimer's Disease

Alzheimer's disease (AD), a leading cause of dementia, represents one of the most pressing medical challenges of the modern era [169–171]. Dementia encompasses various neurodegenerative disorders marked by cognitive decline that disrupts daily functioning, with AD being the most prevalent accounting for 60% to 80% of dementia cases [172]. This neurodegenerative disease is defined by β-amyloid plaques outside cells and tau neurofibrillary tangles inside cells. While AD typically presents as memory loss, it also affects speech, executive functions, and visuospatial skills. Genetic factors in AD are complex, with most cases not inherited in a straightforward pattern [173]. Given public health concerns and the side effects associated with conventional synthetic drugs, medicinal plants have emerged as promising alternatives for AD treatment. Bioactive compounds and crude extracts from various plants show considerable potential in managing and preventing AD (Fig. 4) [174].

An *in vivo* study assessed the effects of *C. grandis* fruits on learning and memory using the Morris Water Maze, Elevated Plus Maze, and Hebb-William Maze tests. Researchers measured the brain concentrations of GSH, SOD, catalase, LPO, and acetylcholine esterase activity. Doses of *C. grandis* (500 mg/kg, 1000 mg/kg), in addition to diazepam (1 mg/kg), showed reduced transfer latency (TL) and swim latency (SL) compared to diazepam alone. This was accompanied by lower acetylcholine esterase and LPO activity and increased levels of catalase, SOD, and GSH, suggesting *C. grandis* enhances learning and memory through its antioxidant and neuroprotective effects [74]. Additionally, *in silico* studies identified β-Sitosterol (–8.70 Kcal/mol), Pectin (–7.82 Kcal/mol), Retinol (–7.24 Kcal/mol), and Taraxerone (–6.40 Kcal/mol) as superior to the synthetic drug rivastigmine (–5.6 Kcal/mol). Thus, *C. grandis* fruit consumption may help mitigate AD progression (Fig. 4) [175].

7.10 Larvicidal Activity

The rising environmental toxicity of insecticides can be mitigated by using plant-based alternatives for mosquito control. *Coccinia grandis* extracts show effective larvicidal properties against *Anopheles stephensi* and *Aedes aegypti*. At 100% ethanol concentration, mortality rates reached 73.3 $\pm$ 7.7% for *Anopheles stephensi* and 71.4 $\pm$ 4.4% for *Aedes aegypti*, with LC_{50} values of 64.10% and 62.3%, respectively. Ethyl acetate extracts showed the highest activity, achieving 71.1 $\pm$ 5.8% mortality for *Anopheles stephensi* and 74.4 $\pm$ 4.0% for *Aedes aegypti*, with an LC_{50} of 74.53%. Aqueous extracts had similar effects, with 72.2 $\pm$ 3.2% mortality for both species and an LC_{50} of 62.37% for *Aedes aegypti*. Chloroform extracts at high doses caused 71.1 $\pm$ 5.9% mortality for *Anopheles stephensi* and 68.3 $\pm$ 2.3% for *Aedes aegypti*, with LC_{50} values of 74.53% and 62.37%, respectively. These findings demonstrate the significant larvicidal potential of *C. grandis* fruit extracts against malaria and dengue vectors [107] (Fig. 4).

Further studies on unripe fruit extracts showed strong larvicidal and pupicidal effects against *Culex quinquefasciatus*, with low LC_{50} values. Ethanol, chloroform, aqueous, and ethyl acetate extracts induced substantial mortality, with aqueous extracts showing the highest mortality (LC_{50} 61.97%). Statistical analysis revealed significant variations ($p < 0.05$) in larval mortality [108]. Essential oils from *C. grandis* leaves demonstrated strong larvicidal activity against *Culex quinquefasciatus* (LC_{50} 52.80 mg/L), *Anopheles stephensi* (LC_{50} 39.41 mg/L), and *Aedes aegypti* (LC_{50} 48.20 mg/L) after 24-hour exposure [106,167]. Aqueous leaf extracts showed higher mortality rates than controls, with LC_{50} and LC_{90} values of 135.35 and 117.62

ppm for *Aedes aegypti* and 93.73 and 108.26 ppm for *Culex quinquefasciatus*. Silver nanoparticles derived from *C. grandis* aqueous extract increased larvicidal effects, achieving an IC_{50} of 156.3 ppm for *Aedes aegypti* and 181 ppm for *Culex quinquefasciatus* [75].

7.11 Wound Healing Activity

Infectious diseases caused by microorganisms remain a major global health threat, with wound infections contributing significantly to morbidity and mortality [176]. Wound healing, a complex process of tissue repair, begins with inflammation, followed by collagen production and epithelial regeneration [177]. Disruptions in the inflammatory phase can lead to oxidative stress, delaying healing. Recent studies on *C. grandis* leaf extract, traditionally used for insect bites, revealed its antioxidant potential in wound healing. The extract demonstrated strong antioxidant activity, with an IC_{50} of 4.85 mg/mL for ROS scavenging and 21.39 mg/mL for iron chelation. It also enhanced cell survival and migration by up to 23%, suggesting its promise in skin care and wound healing applications [51].

Moreover, an investigation into the protein profile of *C. indica* revealed a significant similarity between the 17 kDa Protein Phosphatase 2 PP2 (CIA17) and phloem lectins within the PP2 superfamily. Mass spectrometry identified 16 probable allelic variants of CIA17, each with slightly varied structural characteristics. A key feature of CIA17, preserved across cucurbit species, is an intramolecular disulfide bond between cysteine residues at positions 34 and 51, essential for carbohydrate binding. Circular dichroism (CD) spectroscopy confirmed that CIA17 is rich in antiparallel β-sheets, akin to PP2 proteins found in *Arabidopsis thaliana* and *Cucurbita maxima*, both of which exhibit high thermostability up to 90 °C. Atomic force microscopy further revealed that CIA17 forms filamentous structures at higher concentrations, suggesting its potential role in pathogen defense and wound healing through chitin binding and filament formation [178].

7.12 Antibacterial Activity

The antibacterial properties of *C. grandis* were evaluated through *in vitro* studies using aqueous and organic solvent extracts, including chloroform, ethanol, and petroleum ether. These extracts were tested against *Bacillus subtilis*, *Enterobacter aerogenes*, *Salmonella typhimurium*, *Pseudomonas aeruginosa*, and *Staphylococcus epidermidis* using broth dilution and agar well diffusion techniques. The findings demonstrated notable antibacterial activity, with ethanol and aqueous extracts exhibiting the strongest inhibitory effects [179]. A subsequent study focused on the synthesis of silver nanoparticles (AgNP) using an ethanolic extract of *C. indica* leaves. The extract, prepared by maceration and used to reduce silver nitrate, led to the successful biosynthesis of AgNPs, as confirmed by surface plasmon resonance (SPR) at 425 nm, transmission electron microscopy (TEM), and scanning electron microscopy (SEM). The AgNPs ranged from 8 to 48 nm and showed a zeta potential of –55.46 mV, indicating moderate stability. Notably, AgNPs exhibited stronger antibacterial activity against gram-negative bacteria compared to gram-positive strains [180]. The antibacterial activity of *C. grandis* is further illustrated in Fig. 4.

Another study utilizing agar well diffusion reported that various solvent extracts, including acetone, ethanol, methanol, aqueous, and hexane, from *C. grandis* leaves exhibited substantial antibacterial activity, with ethanol extracts showing the most potent effects against *S. aureus*, *B. cereus*, *E. coli, K. pneumoniae*, and *S. pyogenes*. The minimal inhibitory concentration (MIC) for the ethanol extract ranged from 31.25 µg/mL to 1000 µg/mL, with concentrations below 31.5 µg/mL demonstrating strong inhibition, particularly against *K. pneumoniae*, *S. aureus*, and *E. coli* [132].

Moreover, a study found that hot ethanol and acetone extracts of *C. grandis* showed larger inhibition zones compared to cold extracts, especially against *S. aureus*, *E. coli*, and *Enterococcus faecalis*. In contrast, *P. aeruginosa* exhibited no significant inhibition at these concentrations. The antibacterial activity was comparable to that of the standard erythromycin, with varying MIC values, the highest for *P. aeruginosa* and the lowest for *S. aureus* [170]. Lastly, a screening of human pathogenic bacteria using the disc diffusion method revealed that the chloroform extract of *C. cordifolia* showed moderate antibacterial activity, while the n-hexane and ethyl acetate extracts demonstrated slightly less efficacy [181].

7.13 Antifungal Activity

In vitro assays on *C. indica* demonstrated antifungal activity against dermatophytes like *Candida albicans*, *Microsporum gypseum*, and *Microsporum canis* using Asthana and Hawker's and Sabouraud's dextrose agar. Methanol and petroleum ether extracts were most effective, particularly from the fruit, which showed larger inhibition zones (3–8 mm) than leaf (2–5 mm), root (1–4 mm), and stem (1–3 mm) extracts [182]. Moreover, ethanolic extracts of *C. grandis* effectively inhibited *C. albicans* and *A. niger*. While *A. niger* and *A. fumigatus* are known to cause aspergillosis, *C. albicans* is associated with conditions like oral and vaginal candidiasis. Fig. 4 illustrates the antifungal effects of *C. grandis* extracts [170].

A separate investigation explored the antifungal and antibacterial properties of *C. indica* leaves against various pathogens, including Methicillin-Resistant *Staphylococcus aureus* (MRSA), *Streptococcus pyogenes* (multidrug-resistant), *Candida auris*, *Trichophyton rubrum*, and *E. coli*. Using tube dilution and disc diffusion methods, the ethanolic extract showed strong inhibition against MRSA, *C. auris* (250 µg/mL), and *S. pyogenes* (200 µg/mL) compared to antibiotics. Higher concentrations were needed

to affect *E. coli*, while no significant impact was observed on *Trichophyton rubrum*. These findings highlight concentration-dependent antifungal and antibacterial effects, indicating potential for *C. indica* ethanolic extracts in addressing multidrug-resistant pathogens [183]. Additionally, methanol root extract (300 µg/disc) and kanamycin (30 µg/disc) were tested against various fungi. The plant extract showed strong antifungal activity, with the largest inhibition zone (19.0 mm) against *C. albicans* and *Colletotrichum falcatum*, followed by 17.0 mm against *Aspergillus niger*. Lesser effects (7.0 mm) were observed against *Aspergillus fumigatus*, and no inhibition was noted for *Aspergillus flavus* and *T. rubrum*. The petroleum ether extracts from leaves and calluses displayed potent antifungal effects at minimal concentrations of 0.3125 µg/100 µL against *C. albicans*, and 0.625 µg/100 µL against *Candida krusei* and *Candida tropicalis* [184].

8. Clinical Trial

The clinical trials conducted to date with *C. grandis* have primarily targeted its antidiabetic effects and potential to improve glucose metabolism in various health conditions (Table 5, Ref. [91,185–191]).

In a double-blind, randomized, placebo-controlled trial on 48 pre-diabetic patients, daily administration of a 500 mg *C. grandis* tablet twice daily led to significant reductions in fasting glucose and triglyceride levels while enhancing glucose tolerance [185]. Another study with 122 healthy participants assessed the effects of *C. grandis* leaves, combined with grated coconut and salt, taken as a single 20 g dose with a meal, and reported a substantial drop in blood sugar levels [186]. Further investigations in T2DM patients demonstrated promising outcomes. For instance, a trial involving 158 T2DM patients who received a 500 mg *C. grandis* gelatin capsule daily observed regulated blood sugar levels alongside reduced activities of α-amylase, α-glucosidase, and dipeptidyl peptidase 4(DPP-4) enzymes, coupled with enhanced glucose absorption and antioxidant effects [187]. Similarly, a smaller study on 10 T2DM patients using 3 g of root powder twice daily showed notable reductions in fasting blood glucose [188]. Another double-blind, randomized, placebo-controlled trial with 90 participants, conducted with both diabetic and non-diabetic found that 500 mg capsules taken twice daily effectively lowered fasting blood sugar levels [189].

Additionally, research on herbal capsule formulation in 82 T2DM patients highlighted reductions in blood glucose levels and antioxidant benefits with a twice-daily 500 mg dose [190]. Another study tested a 500 mg herbal formulation in 158 T2DM patients, showing an improvement in glucose tolerance [191]. While these clinical trials indicate a consistent positive impact of *C. grandis* on blood sugar regulation and associated metabolic markers, the studies are preliminary, with varying methodologies and sample sizes. Further large-scale, rigorously controlled trials are necessary to confirm its efficacy and safety as an antidiabetic agent and fully understand its therapeutic potential in chronic disease management.

9. Safety Profile

C. grandis demonstrates a high safety profile, with no significant toxicity or side effects reported in various animal and human studies, supporting its use as a safe natural remedy. Multiple studies show that *C. grandis* extracts are safe for oral consumption. In acute toxicity tests, ethanolic and methanolic extracts of *C. grandis* leaves exhibited no toxicity or mortality at doses up to 2000 mg/kg in animal model [84,192,193]. Studies confirm that different plant parts, including leaves and stem, are non-toxic and safe for normal cells, showing no adverse effects on cell lines such as erythrocytes and Human Embryonic Kidney 293 (HEK293) cells [194,195]. Additionally, a 12-week randomized, double-blind clinical trial on prediabetic adults reported no significant adverse effects, suggesting tolerability in humans [155]. *In vivo* studies further substantiate the plant's safety: no toxicity was observed at doses up to 2.00 g/kg for anti-hyperglycemic effects, while hepatoprotective effects were noted up to 3.2 g/kg in laboratory rats [141,196]. Even at doses as high as 3500 mg/kg, *C. grandis* extracts were well-tolerated without lethality or toxicity in gastric ulcer models [155]. This extensive evidence suggests that *C. grandis* is a safe candidate for therapeutic applications, though future studies on drug interactions are recommended to confirm its safety for wider clinical use.

10. Functional Food

Chronic diseases such as heart disease, cancer, and diabetes are major public health concerns, often linked to poor dietary habits, including excessive intake of fats, refined sugars, salt, and cholesterol [197]. These conditions, exacerbated by unhealthy lifestyles, have contributed to a rise in non-communicable diseases [198]. Incorporating functional foods, which are rich in vitamins, minerals, fiber, antioxidants, and probiotics, can reduce the risk of these diseases and enhance both physical and mental health [199]. Functional foods, which resemble traditional foods but provide additional health benefits, help improve bodily functions and prevent diseases by adding beneficial ingredients or removing harmful ones. Such foods can boost immune function, reduce the risk of cardiovascular disease, osteoporosis, obesity, and cancer, and improve cognitive health [198,199]. These foods became widely recognized in Japan in the 1980s and have since spread globally [199,200]. Epidemiological studies indicate that consuming bioactive compounds in fruits and vegetables can lower the risk of metabolic disorders and cancer [199].

C. grandis is an underutilized functional food known for its numerous health benefits. Rich in bioactive compounds such as antioxidants, minerals, and phytochemicals, it offers significant nutritional value [17,201]. The tender

Table 5. Clinical studies conducted out using *C. grandis*.

Administered material	No. of subjects	Health state of the participants	Study model	Dosage regimen	Results	Ref.
Plant powder in tablet	48	Pre-diabetic patients	Double-blind, randomized, placebo-controlled trial	500 mg, one tablet taken twice daily	It ↓fasting glucose, ↑glucose tolerance & regulating TG levels	[185]
Leaves combined with a certain amount of grated coconut & table salt	122	Healthy participants	Double-blind, randomized, placebo-controlled trial	20 g of leaves once with a meal	Its ↓blood sugar level	[186]
Gelatine capsule as dietary supplement	158	Patients with T2DM	Double-blind, randomized, placebo-controlled trial	500 mg once a day	Control blood sugar levels, including ↓α-amylase, ↓α-glucosidase, ↓DPP-4 enzymes, ↑glucose absorption, & ↑antioxidant effects	[91,187]
Root powder	10	Patients with T2DM		3 g twice a day before food	It ↓fasting blood sugar	[188]
Capsule	90	Patients with & without diabetes	Double-blind, randomized, placebo-controlled trial	500 mg twice per day	It ↓fasting blood sugar level	[189]
Herbal capsule	82	Patients with T2DM	Double-blind randomized, placebo-controlled trial	500 mg 1 capsule to be taken twice a day	It ↓blood glucose & has an antioxidant effect	[190]
Herbal formulation	158	T2DM patients	Double-blind randomized, placebo-controlled trial	500 mg once daily	It ↑glucose tolerance	[191]

Upward (↑) and downward (↓) arrows represent increases and decreases in activity or levels, respectively.

leaves are commonly used in salads, while young fruits and shoots are incorporated into various dishes, providing a rich source of vitamins, protein, and minerals [202,203]. Unripe fruits are utilized in soups, and the bitter variants are particularly valued for their leaves and shoots [56]. *C. grandis* contains a wide range of phytochemicals, including alkaloids, phenolic acids, triterpenoids, carotenoids, flavonoids, saponins, beta-carotene, and polysaccharides. Among these, cucurbitacin, a triterpenoid, is noted for its broad therapeutic potential. Phenolic compounds, such as phenolic acids and flavonoids, exhibit strong antioxidant properties, offering protection against cancer, inflammation, atherosclerosis, and thrombosis [204,205]. Moreover, *C. grandis* demonstrates significant antioxidant potential and starch hydrolase inhibitory properties, further establishing its role as a functional food [206]. These findings underscore *C. grandis* as a promising candidate for functional food formulation, owing to its rich phytochemical composition and diverse health benefits.

Nanoparticles and Activated Carbon

The antidiabetic effects of *C. grandis* encapsulated in alginate nanoparticles were analyzed, revealing significant inhibition of α-amylase (60.8%), α-glucosidase (19.1%), and dipeptidyl peptidase IV (30.3%). Successful encapsulation was confirmed through encapsulation efficiency, loading capacity, and particle size analysis, with particles in the nanometer range. SEM and Fourier Transform Infrared (FTIR) analyses further confirmed the spherical morphology and effective encapsulation [207]. In another study, encapsulated *C. grandis* aqueous extract was synthesized into alginate nanoparticles and analyzed for antioxidant properties. The nanoparticles showed enhanced activity in DPPH, ABTS, and (FRAP) assays, surpassing the antioxidant effects of the unencapsulated extract. FTIR and SEM analyses confirmed successful encapsulation and particle formation at 71 nm, suggesting the potential for *C. grandis* encapsulated in alginate nanoparticles as an antioxidant enhancement agent and a foundation for future nano nutraceutical applications [208]. Eco-friendly calcium oxide (CaO) nanoparticles were synthesized using *C. grandis* fruit extract. These nanoparticles demonstrated effective photocatalytic degradation of dyes such as methyl red, methyl orange, and methylene blue. Additionally, the nanoparticles exhibited antimicrobial activity, inhibiting *Aspergillus niger*, *E. coli*, *Salmonella typhi*, *S. mutans*, and *S. aureus*, indicating potential applications in both antimicrobial and environmental fields [207]. Silver nanoparticles (Ag-NPs) synthesized from *C. grandis* leaf extract demonstrated significant antibacterial, anticandidal, and antibiofilm activities against pathogens associated with head and neck infections, including *S. aureus*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *C. albicans*, *C. tropicalis*, *C. orthopsilosis*, and *C. glabrata* [68]. Furthermore, gelatin-loaded zinc oxide nanocomposites (GN/ZnONCs) synthesized using *C. indica* seed extract exhibited strong antibacterial activity against both gram-positive and gram-negative bacteria. The nanoparticles also showed notable antioxidant properties and promising anticancer activity, along with enhanced wound healing [168].

Activated carbon (AC) synthesized from *C. grandis* leaves (CL-AC) was investigated for its electrochemical properties. The synthesis involved carbonization, impurity removal, and NaOH activation, resulting in a high surface area and nitrogen content. Compared to conventional bamboo-derived AC (B-AC), CL-AC demonstrated improved electrochemical performance, including reduced series and charge transfer resistance due to nitrogen incorporation. These findings suggest that nitrogen-rich *C. grandis* leaves serve as promising precursors for nitrogen-doped AC, offering a cost-effective alternative for electrochemical capacitor applications [209].

11. Conclusion and Future Prospects

Multiple *in vitro* and *in vivo* studies on *C. grandis* have demonstrated its remarkable medicinal potential, particularly in the management of diabetes and related metabolic disorders, providing strong support for its ethnobotanical uses. Various bioactive compounds in *C. grandis*, including flavonoids, alkaloids, and triterpenoids, have been reported to exhibit significant antidiabetic and antioxidant activities, which warrant further investigation for the development of novel therapies targeting diabetes. In addition, the anti-inflammatory properties of *C. grandis* may provide new avenues for the treatment of conditions such as arthritis and other inflammatory diseases, which should be explored in future research. The anticancer potential of *C. grandis* has also been studied, with promising results indicating its ability to inhibit the growth of various cancer cell lines. However, the specific molecular mechanisms involved in these effects have not yet been fully elucidated. Further studies are needed to investigate the underlying molecular pathways, which could lead to the identification of potential chemopreventive agents within *C. grandis*. Furthermore, the hepatoprotective effects of *C. grandis* have shown considerable promise, although additional studies are required to verify the compounds responsible for this activity and their safety profile. The use of *C. grandis* in the treatment of cardiovascular diseases has been supported by several studies, particularly regarding its effects on lipid metabolism and its antioxidant properties. However, conflicting results have been reported in terms of its efficacy in regulating blood pressure, suggesting the need for more comprehensive clinical trials. Bioassay-guided isolation of specific phytoconstituents in *C. grandis* could help identify the most potent compounds for treating hypertension and related cardiovascular issues. Likewise, the immunomodulatory activity of *C. grandis* extracts and its phytoconstituents deserves further exploration. Certain compounds in *C. grandis* have shown the ability to modulate

the immune system, both activating and suppressing immune responses. This dual action presents an interesting area for future research, particularly for conditions involving immune dysregulation, such as autoimmune diseases and chronic inflammation. While *C. grandis* has demonstrated substantial pharmacological effects, its toxicity profile remains a concern. Toxicological studies have shown that while *C. grandis* appears to be safe in recommended doses. Therefore, further in-depth investigations into the safety and toxicity of individual compounds, especially at higher doses, are crucial to ensure the plant's therapeutic viability. The promising outcomes from preclinical studies need to be translated into clinical settings to confirm their therapeutic potential. Exploration of various nanoparticles of extracts and constituents, along with their synergistic effects could help develop more potent therapeutic formulations. Additionally, pharmacokinetics and bioavailability studies of these formulations are crucial for attaining consistent therapeutic outcomes. Investigating the potentials of *C. grandis* in other therapeutic areas, such as neurodegenerative diseases, cardiovascular health, and immune modulation, could open new avenues for its application.

C. grandis shows significant promise as a multifunctional therapeutic agent for a range of diseases, including diabetes, cancer, cardiovascular diseases, and inflammatory disorders. However, to fully realize its potential, further pharmacological, toxicological, and clinical research is needed. Identifying the specific active compounds responsible for their therapeutic effects and assessing their safety profiles will be critical in developing *C. grandis* as a reliable and effective treatment option.

Abbreviations

ABTS, 2,2′-Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt; AD, Alzheimer's disease; AgNPs, Silver nanoparticles; BHT, Butylated hydroxyl toluene; *C. grandis*, *Coccinia grandis*; CCl_4 Carbon tetrachloride; CGL, *Coccinia grandis* leaf; CGM, *Coccinia grandis* methanolic extract; DM, Diabetes mellitus; DPP-4, Dipeptidyl peptidase 4; DPPH, 2,2-diphenyl-1-picrylhydrazyl; EECG, Ethanolic extract of *Coccinia grandis*; ER, Endoplasmic Reticulum; FRAP, Ferric reducing antioxidant power; Gly, Glycerol; GSH, Glutathione; H_2O_2, Hydrogen peroxide; HDL-C/TC ratio, High Density Lipoprotein-Cholesterol/Total cholesterol ratio; HF, High-fat; HRBC, Human red blood cell; HR-TEM, High-resolution transmission electron microscopy; HT, Hypertension; IC_{50}, Half-maximal inhibitory concentration; IL, Interleukin; LPO, Lipid peroxidation; MBC, Minimal bactericidal concentration; MFC, Minimal fungicide concentration; MIC, Minimum inhibitory concentration; MIL, Miltefosine; NIDDM, Non-insulin dependent diabetes mellitus; NO, Nitric oxide; NSAIDs, Non-steroidal anti-inflammatory drugs; OGTT, Oral Glucose Tolerance Test; PEF, Pet-ether fraction; PP2, Protein Phosphatase 2; ROS, Reactive Oxygen Species; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SGOT, Serum glutamic oxaloacetic transaminase; SGPT, Serum glutamate pyruvate transaminase; SOD, Superoxide dismutase; SSG, Sodium Stibo Gluconate; STZ, Streptozotocin; T1DM, Type-1 Diabetes Mellitus; T2DM, Type-2 Diabetes Mellitus; TC, Total cholesterol; TG, Triglyceride; TGF- β, Transforming growth factor-β; TNF-a, Tumor necrosis factor alpha; VL, Visceral leishmaniasis; VLDL-C, Very-low-density lipoprotein; WHO, World Health Organization.

Author Contributions

NHS, NNS, Supervision, Data acquisition, analysis, interpretation, Writing — review & editing, writing — original draft. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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