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REVIEW

Ethnobotanical Use, Phytochemistry, Pharmacology, and Toxicity of *Canavalia gladiata*

Huiqin Qian, Di Meng, Lu Yue, Haibo Xu, Kun Feng, Jianan Wang

College of Pharmacy, Sanquan College of Xinxiang Medical University, Xinxiang, 453000, People's Republic of China

Correspondence: Huiqin Qian, College of Pharmacy, Sanquan College of Xinxiang Medical University, Xinxiang, 453000, People's Republic of China, Email 14522009@sqmc.edu.cn

Abstract: *Canavalia gladiata* (*C. gladiata*) is a significant traditional Chinese medicine that has been used to treat hiccups, vomiting, nausea, amenorrhea, chronic dysentery, larynx arthralgia, lumbago, and inflammatory diseases in Asia for a long history. Although the chemical composition of *C. gladiata* has been reported, no thorough review of *C. gladiata* has been published. Therefore, the present study aimed to comprehensively analyze the ethnobotanical use, phytochemistry, pharmacology, and toxicity of *C. gladiata*. All the available information on *C. gladiata* was actualized by systematically searching scientific databases including Web of Science, ScienceDirect, PubMed, Google Scholar, Springer, Wiley, CNKI, CSPD, and Baidu Scholar between 1967 and up-to-date. Based on the reported information, more than 231 components have been identified in *C. gladiata*, including flavonoids, terpenes, steroids, organic acids, nitrogenous compounds, amino acids, proteins, etc. Crude extracts, fractions, and constituents from *C. gladiata* show various pharmacological activities, including antioxidant, antitumor, antimicrobial, anti-inflammatory, antiallergic, immunomodulatory, antiobesity, hepatoprotective, antidiabetic, etc. Notably, the immature seeds are poisonous. Besides, modern research reveals that *C. gladiata* is rich in chemical constituents and pharmacological activities, which are of great research value. However, more in-depth studies including chemical composition, pharmacological mechanism, quality standardisation, toxicology, and clinical research trials are needed for *C. gladiata* as a new candidate for future drug development.

Keywords: ethnobotanical use, phytochemistry, pharmacology, toxicity, *Canavalia gladiata*

Introduction

Canavalia gladiata (Jacq). DC. (*C. gladiata*) belongs to the leguminous plants of the Fabaceae family, according to The Plant List (https://www.theplantlist.org/). It is widely grown in Asia and Africa, including China, India, Korea, and Japan. Because of their broad, flat fruit resembling a sword, *C. gladiata* is also called "sword beans". The immature fruits of *C. gladiata* are tender folder, crispy, and thick meat flavour, which often make fresh vegetables. Notably, ripe seeds contain antinutritional substances like canavanine, urease, concanavalin A and B, and canavalin. Therefore, ripe seeds are not considered a primary commercial product. The ripe seeds are poisonous, and overconsumption results in nausea and tiredness. It is possible but time-consuming to detoxify by altering the cooking water, soaking, rinsing, or fermenting.[1] When sprayed on the leaves of watermelon and cucumber crops, *C. gladiata* seed extract effectively repels cucumber beetles (*Diabrotica* spp.) and white flies (*Aleyrodidae* spp).[2] Besides, *C. gladiata* is occasionally grown as cover, green manure, and fodder crops. To summarize, science has paid attention to *C. gladiata* as a noteworthy plant with culinary and economic values.

C. gladiata has a long history of application in China. *C. gladiata* has been used medicinally since the 16th century when Li Shizhen's "Compendium of Materia Medica" (本草纲目) from the Ming Dynasty noted that the seeds could strengthen vital energy and yang, treat spleen and kidney deficiencies, and treat stagnant qi in the thoracic and epigastric regions. Currently, *C. gladiata* seeds are utilized in Chinese medicine clinics. In various Asian countries, *C. gladiata* has been employed as a folk remedy for conditions such as hiccups, inflammatory diseases, schizophrenia, intercostal neuralgia, coughs, nausea, vomiting, and abdominal dropsy, among others.[3–5] Overall, *C. gladiata* holds significant clinical importance in Asia.

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Globally, *C. gladiata* has been the subject of numerous studies in recent years. Modern research reveals that *C. gladiata* is rich in chemical constituents and pharmacological activities, which are of great research value. Many traditional uses of *C. gladiata* have now been substantiated by modern pharmacological studies. Bioactive components found in *C. gladiata* include flavanol glycosides, diterpene glycosides, and gallic acid derivatives.[6,7] These chemicals display numerous pharmacological properties, including antioxidative, antibacterial, anti-inflammatory, and antiangiogenic properties.[8] A review of the chemical composition of *C. gladiata* was published in 2000, which only reviewed the active ingredients found in the plant before 2000. In addition, it did not review its pharmacological activity and toxicity.[9] Therefore, the review provides a thorough insight into the ethnobotanical use, phytochemistry, pharmacology, and toxicity of *C. gladiata* to give a wealth of information for the in-depth exploitation of *C. gladiata* resources.

Botany

C. gladiata is an annual shrub that grows to a height of 1 to 2 meters (Figure 1). The roots are deep and grow up to 2 meters. Typically, the roots are rhizomatous. The stems are either glabrous or sparingly pubescent. The leaves have three oval leaflets and are pinnately complex. The petiole is shorter than the leaflets, has a groove above it, and typically expands at the base . The inflorescence is a raceme, borne in the axils of leaves, with long peduncles and several flowers above the rachis' center. The pedicles of the florets are very short, borne on the nodes of the elevated inflorescence axis. The bracteoles are often caducous and oval. The calyx is bilabiate, tubular, and typically has two lobes. The lower lip has three lobes and little teeth, while the top lip is about one-third of the calyx tube and has two broads and rounded cleft teeth. The papilionaceous corolla, which has a butterfly-like appearance, is either pink or white. The flag petals are broadly elliptic. The keeled and winged petals have downward auricles and are curled. The stamens are dimorphic. Nine filaments are bundled together in the dimorphic stamens, whereas one stamen is unattached. The ovary is hairy and linear. Fruits are legumes with a strap-like, somewhat curved form. The fruits have dorsal and ventral sutures on their surface. On either side of the ventral suture line are two longitudinal ribs measuring 4–6 mm. The fruits are green in color when young and light brown when ripe. The seeds are oval or oblong ellipsoid. The seeds are oval or oblong ellipsoid. The seed coat is typically red, reddish brown, or white.

Figure 1 Photograph of *C. gladiata* (**A**) The whole plant, (**B**) Leaf, (**C**) Flower, (**D**) Fruits, (**E**) Seeds.

Ethnobotanical Use

C. gladiata is an underutilized legume plant with various ethnomedicinal and therapeutic properties. According to the Ming Dynasty's "Compendium of Materia Medica" (本草纲目), the seeds in China are believed to warm the middle, lower the qi, promote bowel movement, stop eructation, tonify the kidneys, and replenish vital energy. They primarily boost vital energy and yang, treat splenic and renal deficits, and treat stagnant qi in the thoracic and epigastric areas. Currently, the seeds are included in the Chinese Pharmacopoeia. They are sweet in taste and warm in nature. Furthermore, the seeds can reduce qi, warm the middle, and stop diarrhea, which is used to cure cold and deficiency-related hiccups and vomiting. According to "Chongqing Herbal Medicine" (重庆草药), it is written that "the seeds can activate qi and blood circulation and can be used to treat lumbago due to kidney deficiency, hernia, and heart qi pain". Also, the seeds are believed to ease hiccups, direct qi downward, and warm the middle energizer.[10] Notably, the seeds are utilized to alleviate costalgia by the Yao people of Guangxi, China.[11] The seed husks are called concanavalin shells. They are sweet in taste and neutral in properties, which warm the spleen and stomach, lower the Qi, activate blood circulation, and relieve dysentery. They are frequently used to treat nausea, amenorrhea, chronic dysentery, larynx arthralgia, and lumbago.[12] According to the "Anthology of Chinese Herb of Whole Nation" (全国中草药汇编), the roots have the effect of dispersing blood stasis and relieving pain, which can be utilized for the treatment of bruises and lumbago. Besides, the roots, such as Hakka, are used in China to treat Genu arthralgia.[13] Hemorrhoids are treated using the leaves.[14] Besides, the plant is a sedative and hypnotic herb used in traditional medicine to treat stomachache and obesity.[12,15]

In India, *C. gladiata* is also extensively used in ayurvedic medicine. The fruits are employed as a tonic, appetizer, astringent, cooling, and pacifier.[16,17] They additionally function effectively against vitiated kapha and pitta, burning sensation, over precipitation, anorexia, wounds, ulcers, kidney stones, colic, anorexia, bronchitis, and jaundice.[17–20] Primitive Porja tribes in Koyyuru Mandalam, Visakhapatnam District, Andhra Pradesh, India, prepare a powder from the seeds to treat fever and make a powder from the entire plant to treat uterine cancer.[21] In Nallamalais, Andhra Pradesh, India, the Chenchu Tribes use a root paste (20 grams) and rice gravel for 2 to 3 days to treat liver enlargement.[22] Guinea worm swelling is treated with crushed roots in water, and animal wounds are treated with crushed leaves in the Saurashtra region of Gujarat, India.[23] In Andhra Pradesh and the Angul District of Odisha, India, the root and bark were used to heal stomach issues and earaches.[24,25] Fresh leaf extract is given externally on the scorpion-stung part to relieve pain. In Tamil Nadu's Tirunelveli District and Odisha's Angul District, it is also administered to the forehead to alleviate half-portion headaches and to the anus to ease pain from external piles.[25,26] Besides, the seeds are used in Korea and India to cure swellings, epilepsy, headaches, stomachaches, diarrhea, obesity, and asthma.[4,27]

C. gladiata has been used as folk medicine in other Asian. In Korea, for instance, fruits are traditionally used in soap to treat acne and athlete's foot.[4,28] The seeds cure lower soreness, injury pain, and constipation.[28] Moreover, the leaves have been utilized to treat hiccups, rhinitis, sinusitis, pertussis, and low back pain.[3] In addition, *C. gladiata* has been used traditionally in Korea to treat inflammatory illnesses, schizophrenia, intercostal neuralgia, coughs, nausea, vomiting, and abdominal dropsy.[4,5] The Japanese utilize fruits to cure inflammatory diseases, pyorrhea, otitis media, ozena, boils, malignancies, hemorrhoids, and atopic dermatitis.[4] Malays in Malaysia use the leaves to treat gonorrhea. In addition, the leaves are pressed into the eyes and combined with other extracts that work as an eye tonic.[4] In Bangladesh's Rangamati district, children with measles are treated with leaves and seeds.[29] In Sri Lanka's Western and Sabaragamuwa provinces, the entire plant is applied externally to treat cobra, viper, krait, and hump-nosed viper snakebite.[30]

In Asia, *C. gladiata* is consumed as a dietary food, and the seeds and immature fruits are consumed as green vegetables.[4,31–33] Seeds and fruits are often consumed in boiled, roasted, stir-fried, or cooked form.[34–36] Young fruits are referred to as "Fukujin-zuke", "Nukazuke", and "Miso-zuke" in Japan following being cut and pickled in soy sauce. In Cuba, Guatemala, and Indonesia, mature seeds are frequently roasted, ground, and drunk as a coffee-like beverage.[4,37] In Sri Lanka, southern India, and Indonesia, they are used as an alternative to mashed potatoes or curries.[37–39] The seeds are known as "Adua Nkrante" in Ghana, and when they are boiled, they can substitute or complement meat or fish in stews and soups.[40] In addition, Asians use the seeds and green parts to manufacture animal feed.[41,42]

Phytochemistry

So far, more than 231 components, including flavonoids, terpenes, steroids, organic acids, nitrogenous compounds, amino acids, proteins, and others, have been extracted and identified from different parts of *C. gladiata*. Table S1 describes the compounds from various parts of *C. gladiata*, and Figures 2–5 display the chemical structures.

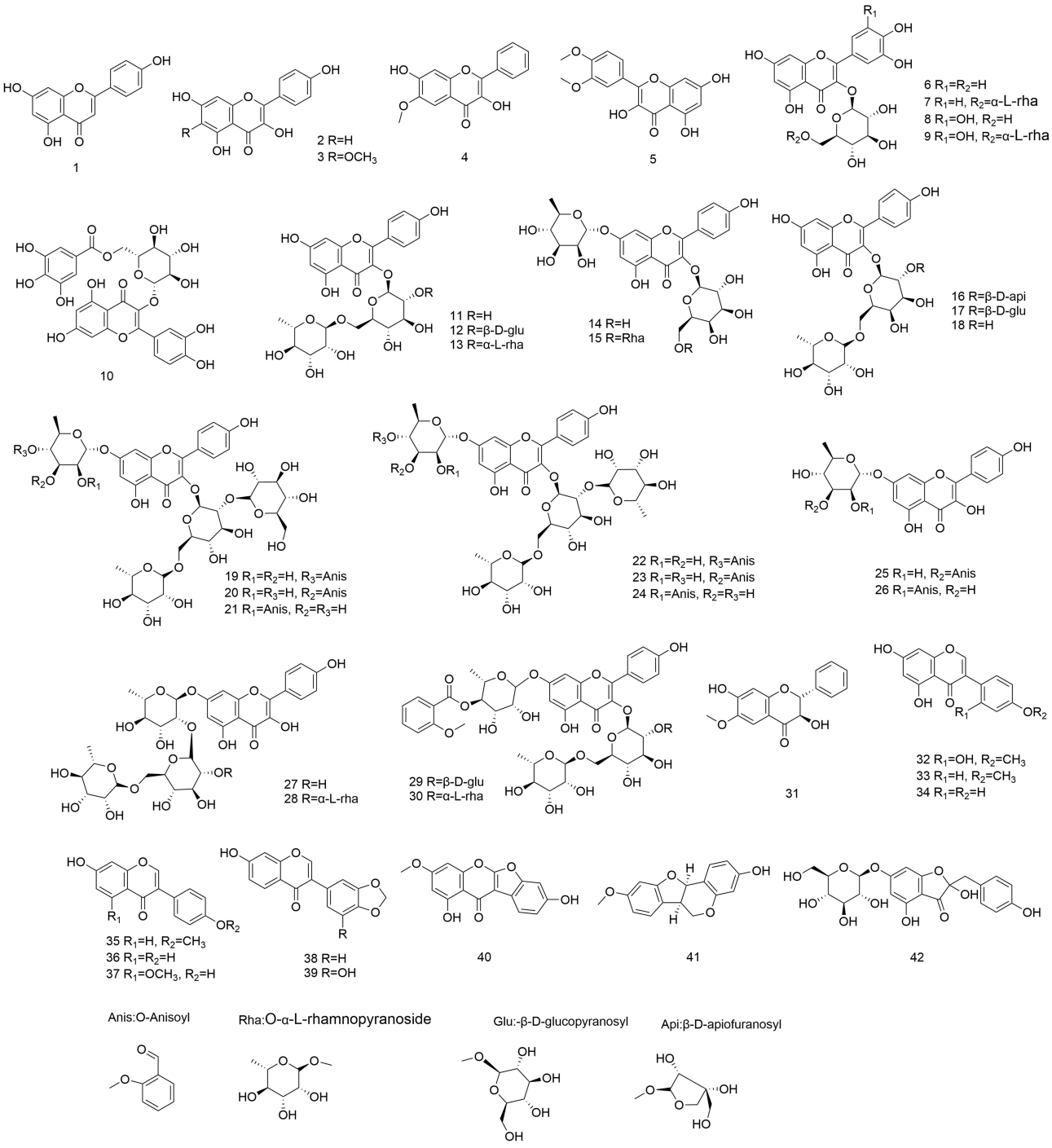

Figure 2 The chemical structures of the flavonoids **(1–42)**.

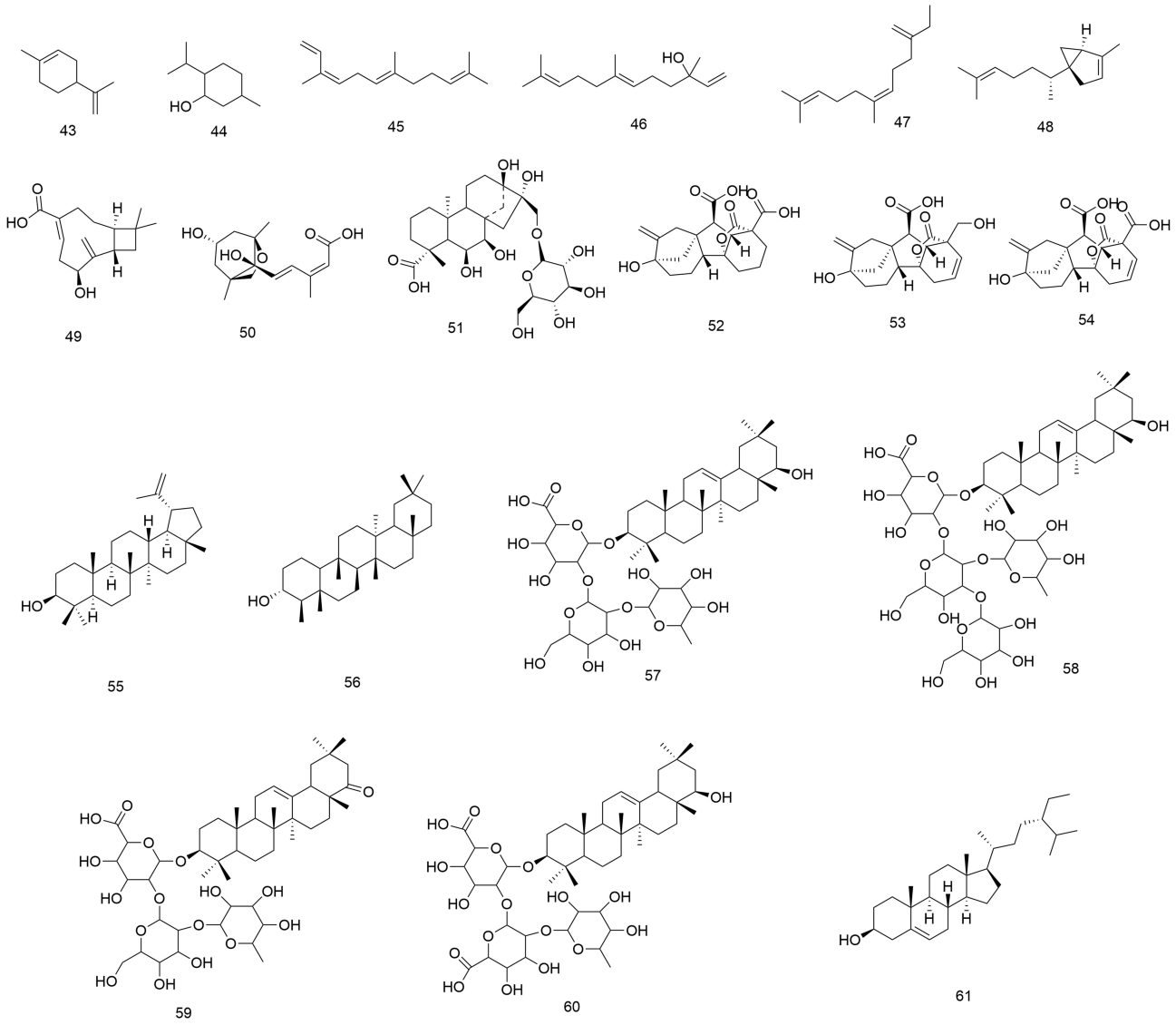

Figure 3 The chemical structures of the terpenes and steroids **(43–61)**.

Flavonoids

To date, a total of 42 flavonoids have been discovered from *C. gladiata*, including flavones (**1**), flavonols (**2–30**), dihydro flavonoids (**31**), isoflavones (**32–41**), chalcones (**42**). The majority of flavonols exist as glycosides. Of these, three compounds (**6–7, 10**) have quercetin as their mother nucleus, two compounds (**8–9**) have myricetin as their mother nucleus, and twenty compounds (**11–30**) have kaempferol as their mother nucleus. In terms of structure, glucopyranoside, rhamnopyranoside, galactopyranoside, and apiofuranoside are used to replace the C-3 and C-7 positions of quercetin, myricetin, and kaempferol. Numerous structurally unique flavonols have been reliably extracted from *C. gladiata* since 2000. For instance, the methanol extract of *C. gladiata* fruits has yielded a novel 5-deoxyflavonol called gladiatin (**4**).[43] Moreover, eight new acylated flavonol glycosides, known as gladiatosides A1, A2, A3, B1, B2, B3, C1, and C2 (**19–26**), were identified from the methanol extract of *C. gladiate* seeds.[44] Besides, kaempferol-7-*O*-*α*-L-dirhamnopyranosyl (1→2;1→6)-*O*-*β*-D-glucopyranosyl(1→2)-*O*-*α*-L-rhamnopyranoside (**28**), a novel flavonol tetraglycoside, was discovered from the methanol extracts of seeds.[45] Silica gel, semi-preparative high-performance liquid chromatography (HPLC), and repeated column chromatography (CC) were used to isolate the isoflavones, formononetin (**36**), and myricetin 3-*O*-rutinoside (**9**) from the fruit methanol extract for the first time.[46] For the chalcones, maesopsin-6-*O*-*β*-

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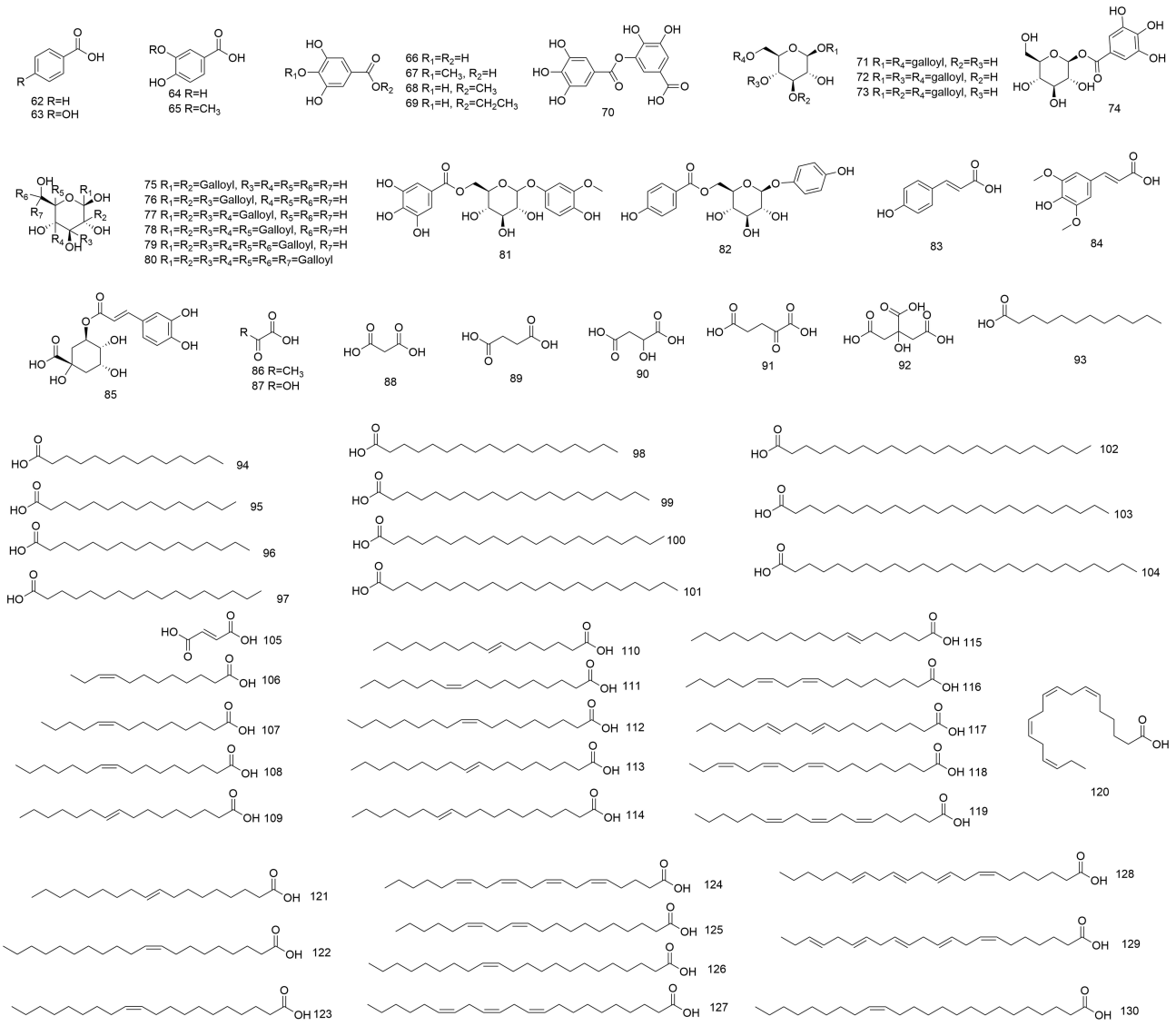

Figure 4 The chemical structures of organic acids **(62–130)**.

D-glucopyranoside (**42**) was identified in the 75% ethanol extract of seeds for the first time and showed estrogen-like activity.[47] Remarkably, 2′-hydroxy biochanin A (**32**), rutin (**7**), and myricetin 3-*O*-rutinoside (**9**) demonstrated substantial IL-33 inhibitory efficacy.[46] The chemical structures of the flavonoids are listed in Figure 2.

Terpenes and Steroids

One steroid and eighteen terpenes have been discovered in *C. gladiata* thus far. These compounds can structurally separate into monoterpenes (**43–44**), sesquiterpenes (**45–50**), diterpenes (**51–54**), triterpenes (**55–60**), and steroids (**61**). Among them, one novel sesquiterpene of the caryophyllene type (Z,1R,7S,9S)-7-hydroxy-11,11-dimethyl-8-methylenebicyclo[7.2.0]undec-4-ene-4-carboxylic acid (**49**), and dihydrophaseic acid (**50**), a known apo-carotenoid-type sesquiterpene, have been found from the methanol extracts of seeds.[45] Moreover, using high-resolution mass, infrared, and NMR spectra, three novel gibbane-type diterpenes—Canavalia gibberellin-I (**52**), Canavalia gibberellin-II (**53**), and Gibberellin A59 (**54**)—were extracted from immature seeds of *C. gladiata*.[48–50] Furthermore, the seed of *C. gladiata* was used to identify canavalioside (**51**), a novel ent-kaurane-type diterpene glycoside.[44] Interestingly, all the isolated triterpenes are derived from pentacyclic triterpenoids of the lupane, friedelane, and oleanane types. Phaseosides IV and V (**59, 60**), two novel triterpene saponins, abrisaponin So_I (**58**) and

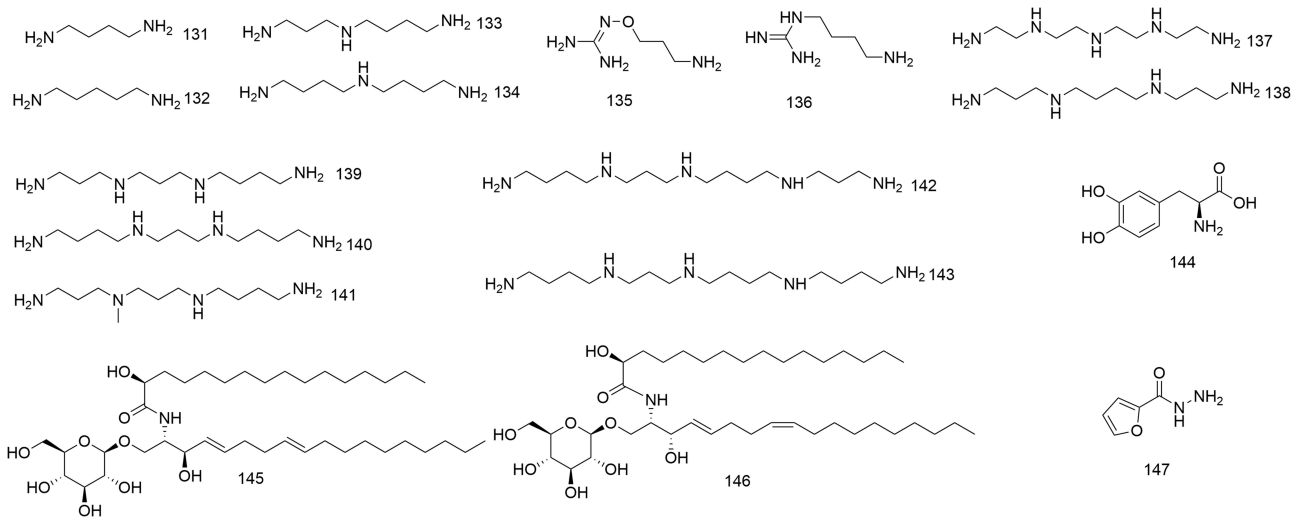

Figure 5 The chemical structures of polyamines **(131–143)** and amide **(144–147)**.

kaikasaponin III (57), were also extracted from the roots.[51] Besides, from the fruits, only one steroid—*β*-sitosterol—has been identified.[46,52] Figure 3 lists the chemical structures of steroids and terpenes.

Organic Acids

Preliminary identification of 49 organic acids (**62–130**) in *C. gladiata* seeds revealed that they could be divided into two major groups: aromatic acid (**62–85**) and fatty acids (**86–130**). Gallic acid and its derivatives were the primary bioactive components of aromatic acids in seeds. Gan et al found that the red and black seeds exhibited antioxidant activities compared to the white seeds, which was attributed to the high phenolic content of their red and black seed coats. The primary phenolic chemicals found in the red and black seed coats were gallic acid and their derivatives, including methyl gallate (**68**), digalloyl hexoside (**75**), and digallic acid (**70**).[8] Later, Gan et al also found that monogalloyl to hexagalloyl hexosides comprised most of the gallic acid and its derivatives found in red seed coats. Interestingly, tetragalloyl, pentagalloyl, and hexagalloyl hexosides were identified as the possible candidates responsible for the red seed coatings. Moreover, fractions rich in gallic acid derivatives showed various antioxidant and antibacterial properties. The gallic acid derivatives containing tetragalloyl hexoside had the most vigorous antimicrobial and free radical scavenging activities among them.[7] Notably, gallic acid (**66**), methyl gallate (**68**), 1,6-di-*O*-galloyl *β*-D-glucopyranoside (**71**), 1,4,6-tri-*O*-galloyl *β*-D-glucopyranoside (**72**), 1,3,6-tri-*O*-galloyl-*β*-D-glucopyranoside (**73**), 4-hydroxy-3-methoxyphenol-1-*O*-*β*-D-(6′-*O*-galloyl)glucoside (**81**), and breynioside A (**82**) have been successively identified from the methanol extracts of seeds for the first time.[47,52–54] The DPPH radical-scavenging effects were demonstrated by gallic acid (**66**), methyl gallate (**68**), 1,6-di-*O*-galloyl *β*-D-glucopyranoside (**71**), and 1,4,6-tri-*O*-galloyl *β*-D-glucopyranoside (**72**).[53] 1,3,6-Tri-*O*-galloyl-*β*-D-glucopyranoside (**73**) had estrogen-like properties.[47] Besides, 4-*O*-methylgallic acid (**67**) was extracted from the methanol extract of seeds, which suppressed endothelial cell invasion and tube formation stimulated with essential fibroblast growth factor at low micromolar concentrations.[55]

The composition and quantity of seed oil from different locations vary regarding fatty acids. *C. gladiata* seeds from South India have an oil content of 0.4% to 2.3%. Unsaturated fatty acids (69.1–81.8%) were more abundant in *C. gladiata* seed oil than saturated fatty acids (18.2–30.9%). It was discovered that the primary ingredient in the seed oils was *cis*-oleic acid (**112**).[56] The Chinese seed oils had a fatty acid content of 1.54%, with linoleic acid (58.33%), palmitoleic acid (16.2%), and linolenic acid (12.98%) having the highest concentrations.[57] In addition, Han X.C. also used the GC-MS method to examine the fatty acids in Chinese seed oils. The findings indicated that the primary fatty acids, which made up approximately 85.29% of the total fatty acids, were palmitic acid (**96**), *cis*/*trans*-oleic acid (**112, 113**), and linoleic acid (**116**).[58] Notably, fatty acids are also differentially distributed in the organs of *C. gladiata*. Relatively higher contents of oxalic acid (**87**) and citric acid (**92**) were found in leaves and fruits, respectively. Of the fatty acids found in the hull and

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fruits, linoleic acid (**116**) had a higher percentage of polyunsaturated fatty acids, and palmitic acid (**96**) had a higher percentage of saturated fatty acids.[59] The chemical structures of organic acids are listed in Figure 4.

Nitrogenous Compounds

Polyamines (**131–143**), amide (**144–147**), nitrogenous heterocycles (**148–170**), and other nitrogenous compounds (**171–174**) are present in *C. gladiata* seeds, seedlings, and fruits. As for polyamines, a new tetraamine, canavalmine, together with a tertiary methylated tetraamine, N4-Methylthermospermine, have been detected from *C. gladiata* seeds using HPLC and GC-MS technology.[60,61] Furthermore, two new pentaamines in *C. gladiata* seeds have been identified as aminopropyl and aminobutyl derivatives of canavalmine, namely aminopropylcanavalmine and aminobutylcanavalmine.[62] Hamana and Matsuzaki have reported the isolation and characterization of a new guanidinooxyamine, Gamma-Guanidinooxypropylamine, from *C. gladiata* seeds and seedlings.[63] Besides, headspace solid-phase microextraction gas chromatography-mass spectrometry (HS-SPME-GC-MS) detected nitrogenous heterocycles (**149–170**) in the roasting seeds.[64] The chemical structures of polyamines and amides are listed in Figure 5.

Amino Acids

The seeds possessed essential and non-essential amino acids, such as lysine (Lys), phenylalanine (Phe), threonine (Thr), alanine (Ala), arginine (Arg), aspartic acid (Asp), glutamic acid (Glu), etc. Several studies have highlighted the predominance of leucine as the essential amino acid and aspartic acid and glutamic acid as the non-essential amino acids in seeds.[41,65–67] Besides, a non-protein amino acid, canavanine, was present in the mature seeds, which was considered the predominant amino acid and showed specific toxic and antitumor activity.[68–70]

Proteins

Lectins are proteins or glycoproteins that bind reversibly to specific monosaccharides or oligosaccharides and are widely distributed in nature, with a relatively high content, especially in the seeds of legumes. Interestingly, the seeds of the genus Canavalia, such as *C. bicarinata, C. bonariensis, C. ensiformis, C. gladiata*, etc, showed the presence of lectins, and their contents and extractability at different pH showed some differences. It indicated that lectins could be used as chemotaxonomic markers within the genus Canavalia.[71] A lectin, Concanavalin A (Con A), has been isolated from *C. gladiata* seeds. A crystallization of Con A comprises four identical subunits, each with a molecular weight of 25,000. Each complete Con A subunit contains 237 amino acids but lacks cystine. Con A has been reported to show the properties of precipitating glycogen, agglutinating red blood cells of animals, and promoting the transformation of lymphocytes.[72] The content of lectins is variable at different developmental stages. Con A was present in relatively large quantities in the tissues of cotyledon and embryo. The quantity gradually declined in cotyledon as the growth of seedlings advanced.[73] Moreover, the synthesis and accumulation of Canavalin were most active at 30–50 days after flowering (DAF). In contrast, the content of Con A continued to increase gradually until the seed maturation was nearly completed (80DAF).[74] Kojima et al isolated and purified *C. gladiata* agglutinin (CGA) from *C. gladiata* by affinity chromatography on a maltamyl Sepharose column. Notably, a glucose/mannose/rhamnose-specific lectin has been isolated from the legumes of *C. gladiata* by the combination of affinity chromatography on Affi-gel blue gel, ion exchange chromatography on Mono S, and gel filtration by FPLC on Superdex 200. The two lectins all possess a protein subunit with a molecular weight of 30 kDa and its sugar specificity like that of Con A. Notably, the glucose/mannose/rhamnose-specific lectin was shown to be homodimeric with a molecular mass of 60 kDa and it demonstrated specificity toward rhamnose. Furthermore, the N-terminal sequences of the two lectins were remarkably alike as found, but the molecular masses were different.[75,76] The crystal structure of a lectin isolated from *C. gladiata* seeds has been demonstrated to have a new binding pocket. A non-protein amino acid, α-aminobutyric acid (Abu), is bound on this site. It indicated the ability of lectins to carry secondary metabolites.[77] The lectins of *C. gladiata* differ from Con A since they form more van der Waals and hydrogen bonds, creating a larger contact surface and promoting a higher affinity for dimanosides.[78] Besides, *C. gladiata* lectins have been reported to stimulate mitosis in cultured human lymphocytes and show no reactivity to lymphocytic leukemia cells. In contrast, their expression in acute myeloid leukemia is significant. Therefore, lectins can differentiate myeloid leukemia from lymphocytic leukemia.[79,80]

Others

In addition to the aforementioned compounds, hydrocarbons (**175–197**), alcohols (**198–205**), ketones (**206–207**), esters (**208–211**), phenols (**212–217**), ethers (**218–221**), aldehydes (**222–226**), saccharides, oligosaccharides, lipids, and others (**227–231**) also exist in *C. gladiata*. Both macro and micro minerals were found in *C. gladiata* seeds. As for macro minerals, numerous studies have reported that the seeds have the highest concentrations of potassium (K), phosphorus (P), calcium (Ca), and magnesium (Mg).[41,65,81–84] As for micro-mineral, the seeds contained iron (Fe), zinc (Zn), copper (Cu), manganese (Mn), nickel (Ni), and selenium (Se).[41,66,81,84–86] Notably, *C. gladiata* seeds contained antinutritional components such as tannins, total free phenols, L-DOPA (3,4-dihydroxyphenylalanine), hydrogen cyanide, phytic acid, trypsin inhibitor activity, etc.[67,85,87–89]

Pharmacological Activities

To date, numerous studies have disclosed that the effective crude extracts from *C. gladiata*, mainly its fruits or seeds, possess a variety of pharmacological activities, including antioxidant, antitumor, antimicrobial, anti-inflammatory, antiallergic, immunomodulatory, anti-obesity, hepatoprotective, antidiabetic, and other biological properties. The relevant pharmacological properties of *C. gladiata* are displayed in Table 1.

Antioxidant Activity

The development of many degenerative diseases, including cancer, heart disease, and immunological dysfunction, is linked to an overabundance of free radicals, which are unstable molecules. Free radicals are neutralized and scavenged from the body by antioxidants. Several studies have shown that the various solvent extracts of seeds and fruits exhibited radical scavenging (DPPH·, ABTS·, O^{2-}·, OH·), as well as ferric/cupric-reducing antioxidant activities.[106,113,128,138–140] The ovariectomized rats' plasma triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), total liver lipids, and cholesterol levels were all markedly decreased by feeding them seed flours, according to an in vivo study. Additionally, the activities of catalase (CAT) and superoxide dismutase (SOD) were markedly elevated when seed flours were fed. The findings indicated that by enhancing antioxidant activity and lipid profiles, seed flour prevents oxidative stress in ovariectomized rats.[90]

The seed coats of *C. gladiata* are often red, white, and black. Due to their incredibly high phenolic content, Gan et al discovered that the red and black seeds exhibited antioxidant potential compared to the white seeds. The researchers then found that 80% methanol extract from red seed coatings exhibited greater ferric-reducing antioxidant potency and ABTS radical scavenging activity than black seed coatings. Component analysis indicated that gallic acid and its derivatives were the main phenolic compounds in the red and black seed coatings, contributing to their antioxidant properties.[8,141] In an additional investigation, Gan et al extracted the gallotannin-rich fractions from the 70% ethanol extract of red seed coatings. Based on the findings, gallotannin-rich fractions demonstrated various antioxidant properties, and the gallotannins found in red seed coatings were primarily composed of monogalloyl to hexagalloyl hexosides. The maximum ABTS radical scavenging activity was exhibited by tetragalloyl hexoside.[7] The findings suggested that red seeds might be utilized as a potent antioxidant to lower the incidence of cancer and other associated illnesses.

The various processing techniques impact the antioxidant activity of *C. gladiata* seeds. Vadivel et al, for instance, showed that seeds processed by sprouting + oil-frying had noticeably higher antioxidant activities than those of open-pan roasting or soaking + cooking.[126] Similarly, Sasipriya and Siddhuraju discovered that, in addition to dry heating, autoclaving and soaking in various solutions (plain water, ash, sugar, and sodium bicarbonate) significantly decreased the radical scavenging and reducing activities, β-carotene bleaching inhibition activity in seeds—furthermore, 80% methanol extracts from raw and dry heated seeds protected against DNA damage.[91] Besides, coffee was outperformed by roasted and cryogenically ground (cryo-ground) seeds in terms of DPPH and ABTS radical scavenging capabilities.[64] The results indicated that light roasting, dry heating, sprouting with oil-frying, and cryogenic grinding are suitable for home and commercial processing.

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Table 1 Summary of Pharmacological Activities and Mechanism of C. Gladiata

Pharmacological Property	Research Object/Model	Pharmacological Activity	Reference
Antioxidant activity	Ovariectomized rats	Consumption of seed flour inhibited oxidative stress in ovariectomized rats by increasing antioxidant activity and improving lipid profiles.	[90]
	DPPH, ABTS, O_2^- and OH, FRAP, metal chelating, β-carotene bleaching, and DNA protection assays	Seed extract significantly showed radical scavenging and reducing activities, β-carotene bleaching inhibition activity and protected DNA damage.	[91–94]
	DPPH assay	Compounds **68** and **71** showed remarkable DPPH radical-scavenging activities with inhibition of 85.6% and 90.6%, superior to ferulic acid (71.3%).	[45]
Antitumor activity	B16 melanoma cells	Red seed lectins exerted a significantly stronger antiproliferative effect than Con A.	[95]
	Colon carcinoma HT-29 cells	Seed lectins possessed cytotoxic activity via inducing apoptosis, especially causing cell cycle arrest at the G0/G1 phase in HT-29.	[96,97]
	Colon adenocarcinoma Caco-2 cells	Methanol and water extracts from leaves showed cytotoxic activity with an IC_{50} at 82 μg/mL and 95 μg/mL, respectively.	[98]
	DLA cells, DLA induced ascites tumor in mice	Methanol extract from seeds induced apoptosis in cancer cells in vitro and inhibited ascites and solid tumor development in vivo.	[99]
	Colon carcinoma MC38 injected tumor-bearing mice	70% Ethanol mixture extract from *C. gladiata* seeds and *A. lappa* roots suppressed tumor growth.	[100]
Antimicrobial activity	*G+* and *G-* bacteria	Seed extract showed antimicrobial activity against *G+* and *G-* bacteria.	[7,54,101–103]
Anti-inflammatory activity	LPS-induced inflammation in RAW264.7 cells	70% Ethanol mixture extract from *C. gladiata* seeds and *A. lappa* roots decreased the LPS-induced ROS and NO production without cell toxicity in RAW264.7 cells.	[100]
	Non-sensitized Rats	*C. gladiata* lectins of seeds exhibited anti-inflammatory activity by decreasing PGE2, nitric oxide and TNF-α in non-sensitized rats.	[104]
	Alcohol-induced gastric inflammation in Sprague-Dawley (SD) rats	Ethanol and water extracts from seeds possessed inhibitory and protective effects on alcohol-induced gastric inflammation in SD rats.	[105]
	HAase inhibitory assay	The HAase inhibitory activity of non-fermented/fermented white seeds was higher than that of non-fermented/fermented red seeds	[92]
	Red blood cells, egg albumin denaturation	Leaf extract and seed extract could protect the RBC membrane from heat-induced lysis and hypotonicity-induced hemolysis. Seed extract exhibited protein denaturation inhibitory activity.	[106,107]
	LPS-induced inflammation in RAW264.7 cells, DSS-induced colitis in mouse	Ethanol extract from mature fruits showed anti-inflammatory activity in vitro and in vivo.	[108–110]
	LPS-induced inflammation in bone marrow-derived macrophages	80% Ethanol extract from seeds inhibited the activation of NF-κB and MAPKs and the production of LPS-triggered pro-inflammatory cytokines in BMDMs.	[111]

Antiallergic activity	Compound 48/80-induced mast cells, anti-DNP IgE in rat	Water extract from Dodutang could prevent most cell-mediated acute and chronic allergic diseases.	[112]
	Anti-DNP IgE-induced RBL-2H3 cells, OVA/Alum, or ovalbumin-treated mice	Ethanol extract from fruits exhibited antiallergic effects in vitro and in vivo.	[109,113]
	Cholera toxin and peanut extract-induced allergy in mice	Ethanol extract from seeds suppressed cholera toxin and peanut extract-induced allergy by inhibiting Ara h1 secretion.	[114]
	NC/Nga mice	Ethanol extract from seeds fermented with *Aspergillus oryzae* could improve atopic dermatitis by improving the balance of Th1/Th2 cytokines and producing anti-inflammatory effects.	[115]
	Egg albumin-induced allergic rhinitis in mice	Fermented mixture extract from *A. paniculate, S. plebeia, C. gladiata, E. senticosus, U. davidiana* var. *japonica*, and *C. trichotomum* exhibited anti-allergic efficacy.	[116]
Immunomodulatory activity	Male or female subjects	Ethanol mixture extract from *C. gladiata* seeds and *A. lappa* roots could enhance immune function by stimulating the activation of NK cells and increasing IL-10 expression	[117]
	DSS-induced IBD in mice	Ethanol mixture extract from *C. gladiata* seeds and *A. lappa* roots could ameliorate the progression of DSS-induced IBD by enhancing immune responses and recovering functional immune cell defects.	[118]
	Chronic immobilization-stress mice	Ethanol mixture extract from *C. gladiata* seeds and *A. lappa* roots exhibited immune enhancement by stress-mediated immunocyte.	[119]
	LPS-induced inflammation in bone marrow-derived macrophages	Water extract from seeds could modulate the immune response of macrophages.	[111]
Anti-obesity activity	Preadipocyte 3T3-L1 cells, C3H10T1/2 cells, HFD-induced obesity in mice	Ethanol extract from seeds and immature fruits could prevent obesity through fat catabolism by increasing the expression of thermogenic factors and inhibiting fat synthesis.	[120,121]
	3T3-L1 adipocytes	*Bacillus subtilis*-fermented white seed extract promoted lipolysis in mature 3T3-L1 adipocytes by increasing the transcription levels of PPARA, Acox, and Lcad and the protein levels of pHSL and ATGL.	[122]
Hepatoprotective activity	D-GalN or AZP induced hepatotoxicity in rats	Ethanol extract from roots and methanol extract from fruits could protect the liver from severe damage caused by D-GalN or AZP.	[6,123]
	Primary cultured rat hepatocytes	Kaikasaponin III showed a significant inhibition of liver injury.	[51]
Antidiabetic activity	HFD and STZ-induced diabetic rats	Ethanol extract from seeds, and total triterpenoids and total flavonoid fractions showed significant hypoglycemic, hypolipidemic and antioxidant potential	[124,125]
	α-Amylase and α-glucosidase inhibition assays	Methanol extracts from raw and processed seeds showed α-amylase inhibition (17.11%, 14.78%, 22.35%, 12.85%) and α-glucosidase inhibition (41.46%, 38.54%, 47.58%, 36.26%).	[126]
	Maltase and sucrase inhibitor assays	Red seed extract showed inhibitory activity against maltase and sucrase.	[127]

(*Continued*)

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Table 1 (Continued).

Pharmacological Property	Research Object/Model	Pharmacological Activity	Reference
Other biological properties	Tyrosinase and collagenase inhibitory assays	Red seed extract exhibited obvious tyrosinase and collagenase inhibitory activity.	[92,128]
	Xanthine oxidase inhibitory assay	Ethanol extracts from ripe and unripe seeds inhibited xanthine oxidase activity with the IC_{50} value of 8.3 mg/mL and 5.7 mg/mL	[102]
	Acetic acid-induced abdominal writhing and formalin murine-induced pain in mice	Seed lectins showed antinociceptive activity in the first phases of the formalin murine model of pain and reduced acetic acid-induced abdominal writhing.	[129]
	Aspirin-induced gastric ulcer in Wistar albino rats	Ethanol extract from fruits showed a significant decrease in the number of ulcers, ulcer score index, and an increase in the percentage protection, and possessed substantial antiulcer properties.	[130]
	IL-33 inhibitory assay	Methanol extract from fruits and compounds **7, 9, 32** displayed significant IL-33 inhibitory activity.	[46]
	Mastocytoma, Ogun, HR-1, Janosky and monocytic leukemia cells	Concanavalin A could rapidly adhere to the glass surface and gradually spread their cytoplasm-like monolayer cells.	[131]
	Bovine aortic endothelial cells (BAECs) and fibrosarcoma HT1080 cells	4-*O*-Methylgallic acid showed antiangiogenic activity via suppressing endothelial cell invasion and tube formation stimulated with bFGF, inhibiting VEGF production under hypoxic conditions and the production of ROS in the endothelial cells stimulated with VEGF.	[55]
	Mouse, sheep, rabbit, chicken and human erythrocytes	Seed lectins showed agglutinating activity against the erythrocytes	[95,132]
	Male Wistar rats, isolated aorta	Seed lectins induced paw edema, increased vascular permeability in rats, and induced relaxation in endothelial aorta pre-contracted with phenylephrine.	[133]
	Hematopoietic stem cells	Water extract from seeds had hematopoietic enhancement via hematopoietic cytokine-mediated JAK2/GATA-1/STAT-5a/b pathway.	[134]
	Male ICR mice	Ethanol extract from seeds significantly prolonged the swimming time to exhaustion, decreased blood lactate and increased non-esterified fatty acid and muscle glycogen levels.	[135]
	MPTP-induced Parkinson in mice	Ethanol extract from seeds significantly dose-dependently increased spontaneous motor activity, grip strength, and alertness, increased the brain's dopamine and other amines, such as norepinephrine, epinephrine, and serotonin, and decreased glutathione and MDA levels.	[136]
	Osteoblast MC3T3-E1 cells	Ethanol extract from seeds and immature fruits induced differentiation in MC3T3-E1 osteoblast cells by activating the BMP2/SMAD/RUNX2 pathway.	[137]
	Breast cancer MCF-7-Luc cells	Compounds **6, 10, 16–18, 42, 73, 205** showed estrogen-like activity.	[47]

Antitumor Activity

Recently, lectins that were extracted from *C. gladiata* seeds exhibit anticancer activity. With a dose-dependent IC_{50} value of 10.45 μg/mL, seed lectins could considerably limit the proliferation of human colon cancer HT-29 cells without damaging human normal kidney HEK293T cells. It was further demonstrated that seed lectins induced HT-29 cells to exhibit apoptotic morphology, including chromatin condensation, deoxyribonucleic acid fragmentation, and apoptotic bodies. Similarly, seed lectins dose-dependently raised the sub-G0/G1 proportions, confirming that they induced apoptosis in HT-29 cells. Mechanically, apoptosis was caused by the down-regulation of serine/threonine kinase 1 (AKT1), extracellular signal-regulated kinase 1/2 (ERK1/2), and tumor suppressor protein p53. The findings demonstrated that seed lectins have a cytotoxic effect by triggering apoptosis, particularly cell cycle arrest in HT-29 cells at the G0/G1 phase.[96,97] Abeesh et al found that methanol extract from seeds disrupted cell shape and cell membrane integrity in a concentration-dependent manner, prompting Dalton's lymphoma Ascites (DLA) cells apoptosis. Methanol extract at a dose of 10 mg/kg significantly reduced the volume of ascite fluid and tumor and body weight of the tumor-bearing animals in DLA-induced solid and ascitic tumor models compared to untreated tumor control animals. Methanol extract treatment dramatically decreased the increased glutathione (GSH) and serum alkaline phosphate (ALP) levels in DLA tumors. The findings implied that the administration of methanol extract might considerably prevent the growth of tumors and induce tumor cell apoptosis.[99] Besides, in tumor-bearing mice, 70% ethanol extract of *C. gladiata* seeds, 70% ethanol mixed extract from *C. gladiata* seeds and *Arctium lappa* roots, and its primary active constituent mixture (lupeol +chicoric acid) reduced tumor weight and volume as well as the percentages of cell cycle S phase. In mice's several immunological organs, this mixture also boosted the immune cell numbers of macrophages, CD4+T, CD8+T, and NK cells, as well as NK cell activity. The findings showed that a 70% ethanol mixed extract of *A. lappa* roots and *C. gladiata* seeds, along with their constituents, may enhance immune responses and suppress tumor growth.[100] *C. gladiata* seed extract can inhibit tumor development as a natural antitumor drug. However, more research is required to determine its precise antitumor active ingredients and targets. The potential antitumor activity of *C. gladiata* is shown in Figure 6.

Antimicrobial Activity

Numerous pharmacological investigations have been conducted utilizing disk diffusion, agar well diffusion, and paper disc methodologies regarding the antibacterial properties of *C. gladiata*. The antibacterial properties of many solvent

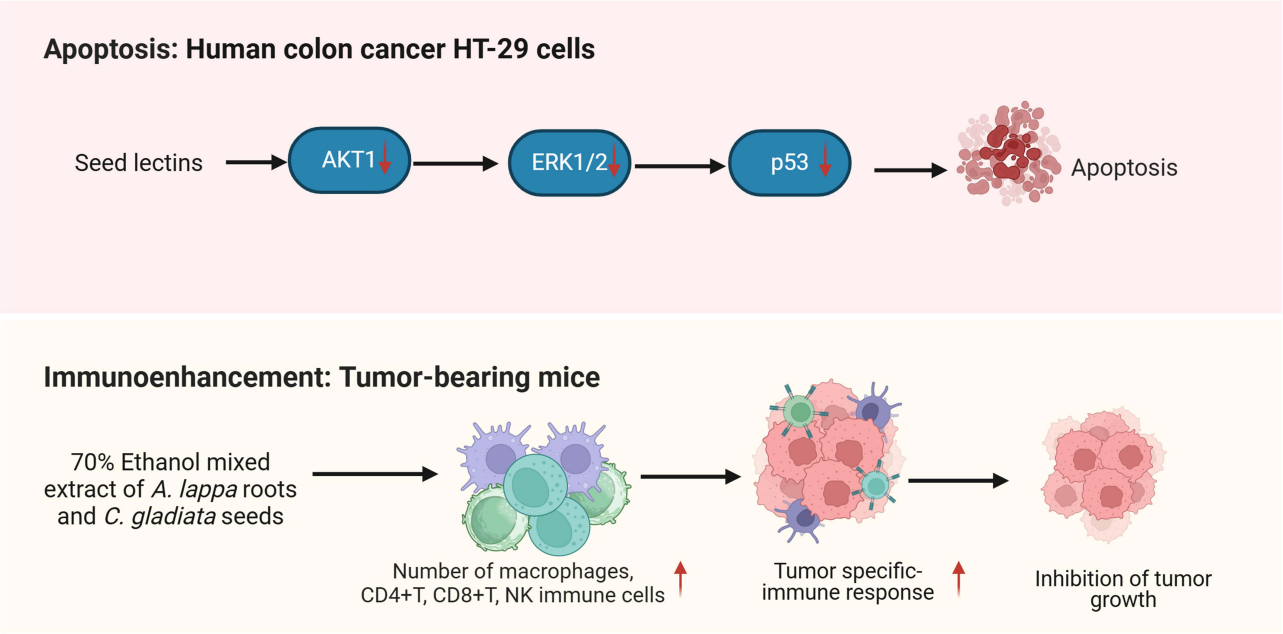

Figure 6 The potential antitumor activity of *C. gladiata*.

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(hexane, ethanol, methanol, ethyl acetate, chloroform, and hot water) extracts from seeds were investigated by Chung et al. The findings demonstrated that whereas ethanol and methanol extracts exhibited antibacterial properties, chloroform, hexane, ethyl acetate, and hot water extracts did not. Interestingly, methanol extract showed significant antibacterial activity against *V. parahemolyticus* (22 mm), *S. sonnei* (21 mm), and *L. monocytogenes* (20 mm).[101] Lee and Jeong examined the antibacterial properties of various fractions from 75% methanol extract of seed coatings, including n-hexane, chloroform, ethyl acetate, and water. The ethyl acetate fraction exhibited the most remarkable growth inhibition against *B. subtilis, B. cereus, M. luteus, L. monocytogenes, S. aureus, S. typhimurium, E. coli*, and *P. aeruginosa*. Methyl gallate (**68**) was identified as the primary antibacterial active component by additional research.[54] Furthermore, the growth of gram-positive (*B. cereus* and *S. aureus*) and gram-negative (*E. coli* and *S. typhimurium*) bacteria was inhibited by the 80% methanol extract from red seed coats, with minimal inhibitory concentration (MIC) values of 2.500, 1.250, 1.250, and 1.250 mg/mL, respectively. However, *B. cereus* and *S. aureus* were inhibited by the 80% methanol extract from black seed coats, with MIC values of 2.500 and 0.625 mg/mL, respectively.[141] Gallotannins that were separated from the 70% ethanol extract of red seed coats were mainly comprised of monogalloyl to hexagalloyl hexosides. Tetrapropylhexose had the most vigorous antibacterial activity among the gallotannin-rich fractions, which showed varied levels of antimicrobial activity against *G+* and *G-* bacteria.[7] Besides, Nakatsuka et al found that 50% ethanol extract and canavanine effectively reduced *P. gingivalis*-induced alveolar bone resorption and prevented the growth of *P. gingivalis* and *Fusobacterium nucleatum*.[142] The potential for antimicrobial activity in vivo still requires investigation despite the seed crude extracts demonstrating antimicrobial efficacy in vitro tests.

Anti-Inflammatory Activity

Numerous chronic diseases, including diabetes, Alzheimer's, cancer, and cardiovascular disease, are closely linked to inflammation. *C. gladiata* has been demonstrated to have anti-inflammatory properties using several in vitro assays, including egg albumin denaturation, heat-induced and hypotonicity-induced red blood cells (RBC) membrane stabilization, as well as hyaluronidase (HAase) inhibitory activity methods, etc.[92,106,107] In lipopolysaccharide (LPS), immunoglobulin E (IgE) and dextran sulfate sodium salt (DSS)-stimulated inflammatory conditions, the fruit extract exerted anti-inflammatory effects by inhibiting NF-κB signaling pathway. Specifically, the fruit extract suppressed the activation of the NF-κB subunits p65 and p50, and it also inhibited the degradation and phosphorylation of inhibitor kappa B (IκB). This inhibition prevented the translocation of NF-κB transcription factor subunits to the nucleus. Ultimately, this led to an increase in the production of anti-inflammatory cytokines (IL-4/IL-13) and a decrease in pro-inflammatory cytokines (IFN-γ, TNF-α, PGE2, IL-1β/IL-6/IL-12), as well as a reduction in nitric oxide production, iNOS, and COX-2 protein expression.[108–110] Similarly, the anti-inflammatory mechanism of 80% ethanol extract from seeds was in accordance with the above results. Besides, 80% ethanol extract from seeds reduced the phosphorylated forms of p38, JNK, and ERK in LPS-triggered inflammation in bone marrow-derived macrophages (BMDMs). Taken together, through inhibiting NF-κB and MAPK activation, 80% ethanol extract from seeds demonstrated anti-inflammatory activity.[111]

Researchers utilize various experimental inflammation models to demonstrate *C. gladiata*'s anti-inflammatory properties. Pinto et al reported that *C. gladiata* lectins of seeds (CGL) prevent paw edema brought on by carrageenan, dextran, and L-arginine. CGL suppressed the rise in PGE2 and TNF-*α* triggered by L-arginine and decreased the neutrophil migration triggered by carrageenan by 55%.[104] In an ethanol-induced gastric inflammatory rat model, Kim et al discovered that water and ethanol extracts from seeds significantly reduced stomach acid secretion and gastric mucosal damage in a dose-dependent manner. The water and ethanol extracts decreased the expression of NF-κB and COX-2. Moreover, oral administration of water extract drastically boosted SOD activity and significantly reduced melanoldehyde (MDA) level expression. The findings indicated that water and ethanol extracts inhibited ethanol-induced stomach inflammation in rats.[105] To summarize, *C. gladiata* might alleviate inflammation by regulating inflammation-related substances and possess healthy functional food and natural anti-inflammatory drug properties. The anti-inflammatory mechanism of crud extracts from *C. gladiata* is displayed in Figure 7.

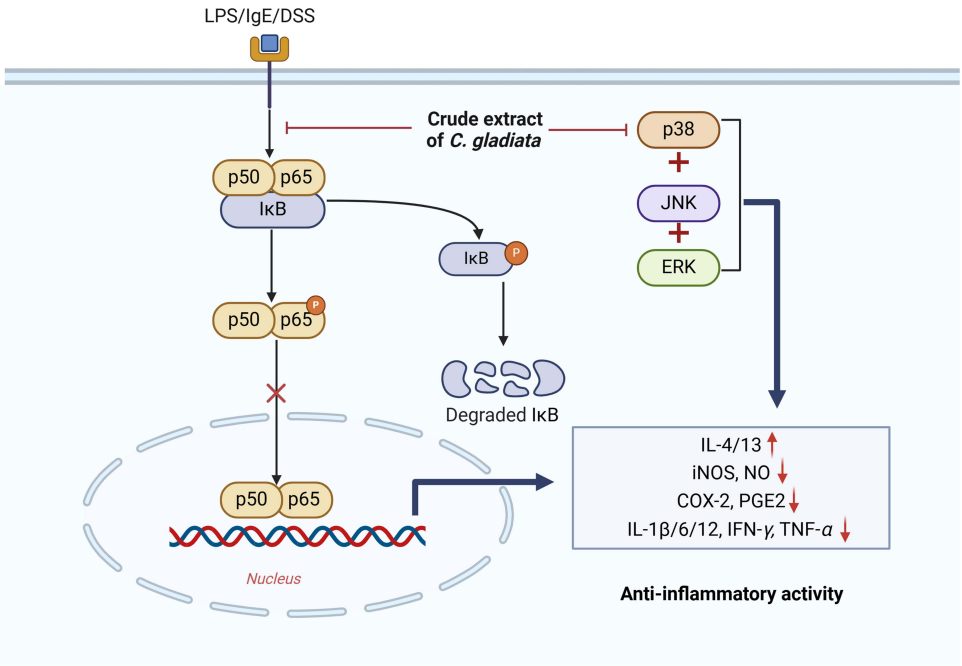

Figure 7 The anti-inflammatory mechanism of crud extracts from *C. gladiata*..

Antiallergic Activity

The prevalence of immune-mediated allergic disorders, including food allergies, atopic dermatitis, allergic asthma, and allergic rhinitis, is rising globally. In various allergic animal models, crude extracts from *C. gladiata* have been shown to exhibit antiallergic activity. Huang et al discovered that 30% ethanol extract from fruits down-regulated PI3K, AKT, and mTOR mRNA expression, as well as reduced the release of *β*-hexosaminidase (Hexb) and histamine degranulation in rat RBL-2H3 mast cells triggered by anti-dinitrophenyl (anti-DNP) IgE. The 30% ethanol extract increased the expression of Th1 cell differentiation transcription factors (p-STAT1, T-bet, and IRF1) while suppressing the expression of Th2 cell differentiation transcription factors (p-STAT6, GATA3, and c-maf). The findings demonstrated that 30% ethanol extract treatment further inhibited degranulation and the production of allergy mediators by inhibiting PI3K/mTOR signaling activity, which in turn controlled the balance of Th1/Th2 cells, resulting in antiallergic activity.[109] Researchers also discovered that in male mice with ovalbumin (OVA) plus aluminium hydroxide (Alum)-induced asthma, 30% ethanol extract from fruits administered at doses of 100 and 300 mg/kg for three weeks dramatically decreased the infiltration of inflammatory cells as well as the release of histamine, IgE, and leukotriene in serum and bronchoalveolar lavage fluid (BALF). Furthermore, 30% ethanol extract has been discovered to significantly inhibit the activation of the MAPK signalling pathway and the expression of Th2-type cytokines (IL-5 and IL-13) and inflammatory proteins (TNF-*α*). Therefore, it was hypothesized that by reducing pulmonary inflammation, 30% ethanol extract might effectively reduce allergic inflammation in OVA/Alum-induced asthma.[113] In a food allergy mouse model vaccinated to cholera toxin and peanut extract, Yang et al discovered that ethanol extract from seeds could dramatically reduce the increase in mast cells triggered by these substances and alleviate the symptoms of inflammation in the ear tissue. Moreover, ethanol extract from seeds treatment significantly decreased the secretion of IL-10, IL-4, IFN-*γ*, and Ara h1 in serum and splenocytes.[114] Besides, when compared to the atopic dermatitis (AD) control group, Kim et al showed that the ethanol extract from *Aspergillus oryzae* fermented seeds significantly reduced the frequency of scratching episodes and attenuated macroscopic and histopathological changes in the dorsal skin of NC/Nga mice. Furthermore, by reducing the production of proinflammatory cytokines and chemokines and the imbalance of Th1/Th2 cytokines, ethanol extract from seeds fermented with *Aspergillus oryzae* could enhance immunological responses.[115] The ethanol extract from fruits could exert antiallergic activity by stimulating the immune system, inhibiting histamine release, and decreasing the production of proinflammatory cytokines. The antiallergic mechanism of ethanol extracts from fruits is displayed in Figure 8.

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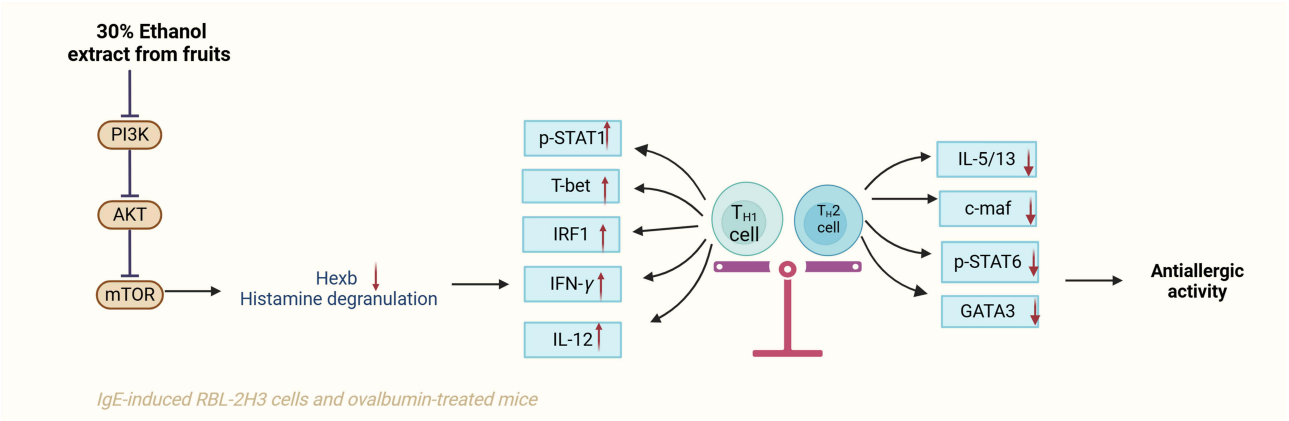

Figure 8 The antiallergic mechanism of ethanol extracts from fruits.

Similarly, it has been reported that specific preparations made from *C. gladiata* seeds have antiallergic properties. In an animal model of allergic rhinitis induced by egg albumin, Choi and Kim discovered that a mixed fermented extract of *Andrographis paniculate, Salvia plebeia, C. gladiata, Eleuthorococcus senticosus, Ulmus davidiana* var. *japonica*, and *Clerodendrum trichotomum* in a ratio of 0.5:1:1:1:1:1:1 decreased the amount of time spent rubbing the nose, the number of sneezes, and the production of serum histamine, IgE, 5-lipoxygenase (5-LO), and COX.[116] Dodutang containing *C. gladiata* seeds has been reported to significantly inhibit the histamine release from rat peritoneal mast cells (RPMCs) activated by compound 48/80. Dodutang dose-dependently inhibited a rat model's passive cutaneous anaphylaxis (PCA) reaction activated by anti-DNP IgE. In addition, Dodutang potently inhibited the secretion of TNF-α and IL-1β and enhanced IL-6 secretion. These findings showed that Dodutang may be beneficial in treating acute and chronic allergic diseases.[112]

Immunomodulatory Activity

The immune system, a host defense mechanism, comprises several cells and macromolecules with specific roles in disease prevention. Macrophages are complex cells that are crucial in innate and adaptive immune responses. Aqueous extract from seeds has been shown to modulate macrophage immune responses by triggering cytokine production via the NF-κB and MAPK pathways. In particular, aqueous extract enhanced the phosphorylated form of p65 in BMDMs in a time-dependent manner while decreasing the stability of IκB-α. Moreover, the phosphorylation of p38 and JNK was strongly activated, and the production of IL-6 and TNF-α in BMDMs was induced by aqueous extract treatment.[111] The findings showed that the aqueous extract from seeds can be exploited as a functional food for immune stimulation.

In the chronic immobilization-stress mice model, it was found that a 70% ethanol mixture extract from *C. gladiata* seeds and *Arctium lappa* roots at a 1:4 ratio improved immune cells like T/B cells, NK cells, and macrophages. Moreover, this mixture could considerably raise brain-derived neurotrophic factor (BDNF) expression in brain tissue.[119] In DSS-induced inflammatory bowel disease (IBD) of mice, this mixture has been reported to increase the population and activation of immune cells (T cells, B cells and NK cells), up-regulation of the cell cycle, and induction of IgA and IgG production. Furthermore, this mixture prevented clinical IBD symptoms and restored IgA production in IBD mice. Notably, chicoric acid and lupeol were the marker chemicals of the *C. gladiata* and *A. lappa* mixture. A mixture of chicoric acid and lupeol ameliorated IBD-associated clinical signs, improved the population and activation of immune cells and functional deficiencies in NK cells, and decreased the production of IgA in IBD mice.[118] More importantly, an 8-week, randomized, double-blind, placebo-controlled clinical trial revealed that this mixture was safe and enhanced immune function by stimulating the activation of NK cells and increasing IL-10 expression.[117] In conclusion, this mixture enhanced the immune system via stress-mediated immunocytes. The immunomodulatory mechanism of seed extract is depicted in Figure 9.

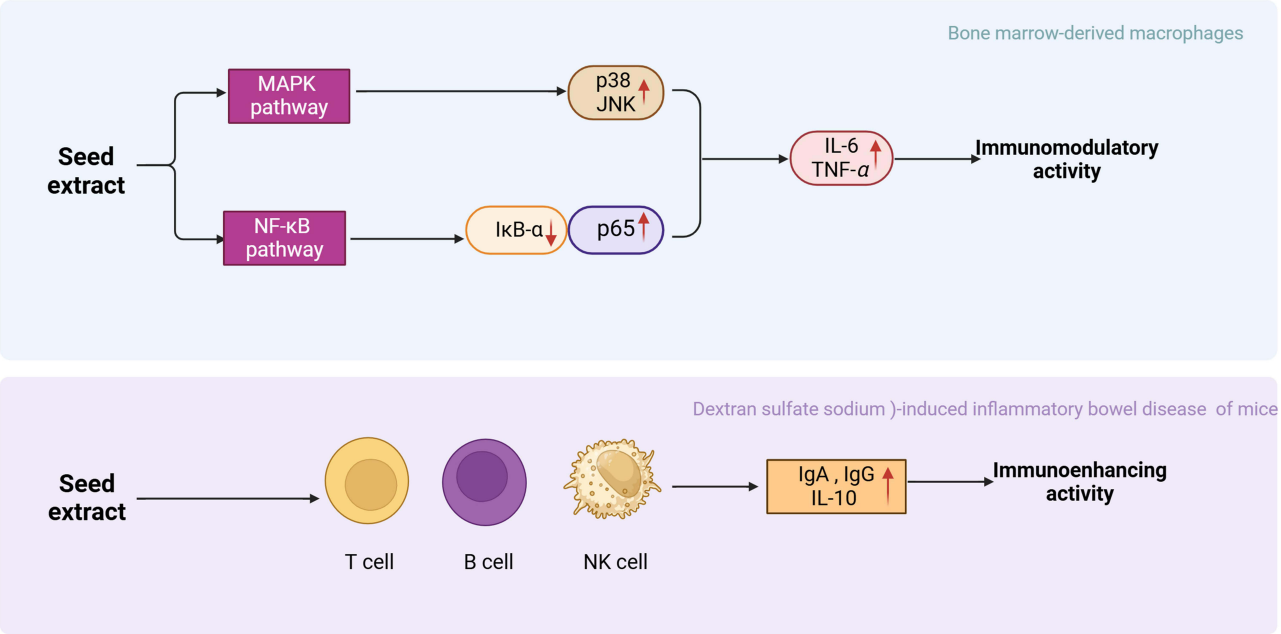

Figure 9 The immunomodulatory mechanism of seed extract.

Antiobesity Activity

Obesity is a complicated chronic inflammatory disease that leads to diabetes, dyslipidemia, metabolic syndrome, cardiovascular disease, and cancer. Researchers have used a high-fat diet (HFD)-induced obesity mouse model to confirm that *C. gladiata* seeds showed antiobesity activity by promoting lipolysis and thermogenesis while inhibiting adipogenesis and lipogenesis. In special, seed extract promoted lipolysis in mature 3T3-L1 adipocytes by increasing the transcription levels of peroxisome proliferator-activated receptor alpha (PPARα), acyl-CoA oxidase (ACOX), and long-chain acyl-CoA dehydrogenase (Lcad) and the protein levels of phosphorylated hormone-sensitive lipase (pHSL) and adipose triacylglyceride lipase (ATGL). Seed extract has been shown to modulate mitochondrial energy metabolism and promote adipocyte thermogenesis. This occurred through activating the AMPK/SIRT1/PGC-1α signalling pathway, which enhanced the expression of PPARα and UCP1. Additionally, seed extracts inhibited adipogenesis and lipogenesis by suppressing the C/EBP-PPARγ-Ap2 and SREBP-1c-PPARγ signalling pathways. Seed extracts activated AMPK and inhibited the cleavage of precursor SREBP-1c to mature SREBP-1c. This process promoted the down-regulation of ACC, FAS, and SCD1, which are genes transcribed by mature SREBP-1c. The inhibition of ACC increased the expression of the downstream target molecule CPT-1. These findings indicated that seed extracts ultimately encouraged a reduction in intracellular lipid accumulation.[120–122] The antiobesity properties of *C. gladiata* seeds make them a promising dietary supplement. The antiobesity mechanism of seed extract is displayed in Figure 10.

Hepatoprotective Activity

C. gladiata is traditionally used medicine for the treatment of hepatopathy. Researchers utilized D-galactosamine (D-GalN) or azathioprine (AZP) induced hepatic damage in the rat model to investigate the hepatoprotective properties of ethanol extract from roots and methanol extract from fruits. The findings demonstrated that the root and fruit extracts could reduce serum levels of TG, TC, total bilirubin (TB), ALP, serum glutamate pyruvate transaminase (SGPT), serum glutamate oxalate transaminase (SGOT), and decrease liver weight, total protein, and albumin in hepatotoxic rats treated with D-GalN or AZP. It indicated that ethanol extract from roots and methanol extract from fruits protected the liver from severe damage caused by D-GalN or AZP.[6,123] Interestingly, Kinjo et al extracted kaikasaponin III (**57**) from roots and discovered that, as compared to glycyrrhizin, kaikasaponin III (**57**) significantly inhibited liver injury on CCl_4-induced cytotoxicity in primary cultured rat hepatocytes.[51] Taken together, root and fruit extracts possess a therapeutic effect on

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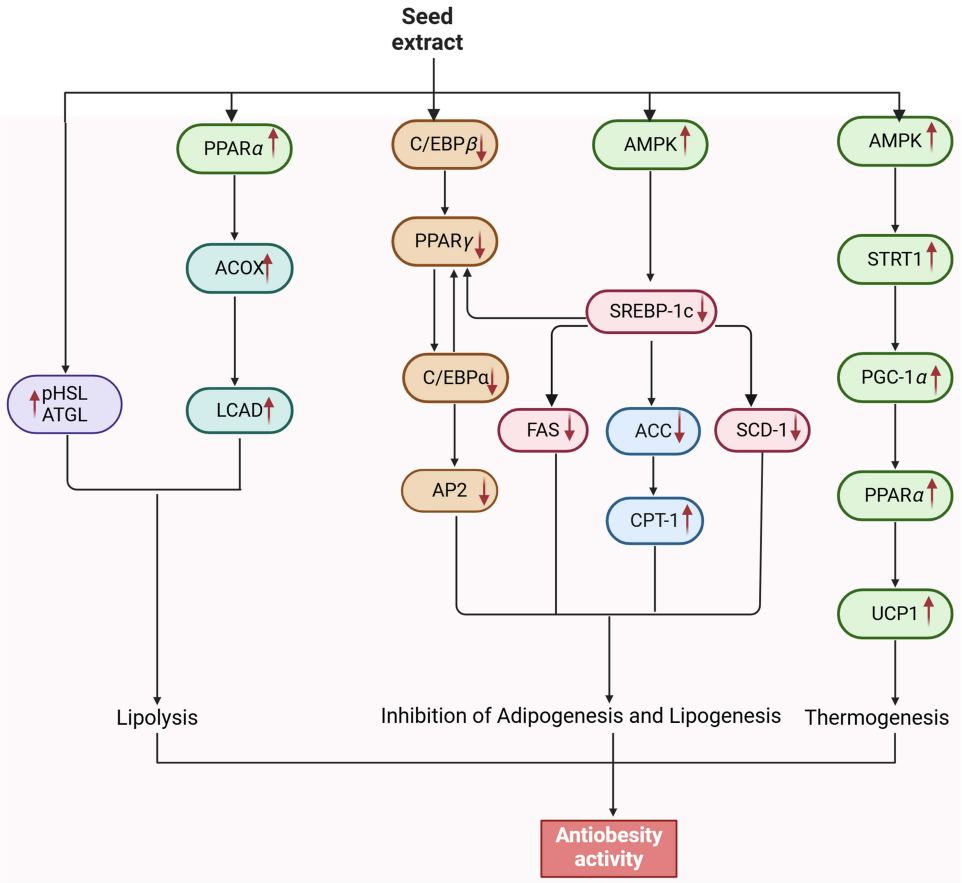

Figure 10 The antiobesity mechanism of seed extract.

liver diseases. The active ingredients still need to be further separated and refined to pinpoint their exact actions and provide a scientific basis for their application in the traditional medical system to treat liver diseases.

Antidiabetic Activity

C. gladiata seeds have been demonstrated to exhibit antidiabetic activity. In particular, ethanol extract from seeds may significantly reduce SGOT, SGPT, ALP, and lipid peroxidation (LPx) levels while raising GSH, SOD, and CAT levels in mice with diabetes caused by streptozotocin (STZ) and HFD. Furthermore, the ethanol extract treatment significantly restored the damaged pancreatic architecture. It indicated that the ethanol extract from seeds significantly reduced hyperglycemic conditions and possessed antioxidant properties.[124] Anitha et al purified total triterpenoid and total flavonoid fractions from the ethanol extract of seeds. In HFD + STZ-induced diabetic rats, they discovered that total triterpenoid and total flavonoid fractions at 400 mg/kg dramatically decreased the raised blood glucose and hemoglobin A1c (HbA1C) levels. Furthermore, total triterpenoid and total flavonoid fractions demonstrated considerable hypolipidemic potential in diabetic rats by lowering TC, TG, low-density lipoprotein (LDL), and very low-density lipoproteins (VLDL) while raising high-density lipoproteins (HDL) levels. Besides, the two fractions have been reported to increase the antioxidant indexes SOD and GSH levels, as well as decrease LPx and NO levels. The results showed that the two fractions had significant hypoglycemic, hypolipidemic, and antioxidant potential.[125] Generally, α-amylase, α-glucosidase, maltase, and sucrase are therapeutic targets for treating and maintaining elevated postprandial glucose. Numerous investigations have verified that the seed extract showed significant inhibitory activity against diabetic-related enzymes and exhibited potential antidiabetic activity.[126,127] Taken together, the seed extract exhibited apparent antidiabetic effects. Nevertheless, more characterization research will be conducted to identify the active principle compounds.

Other Biological Properties

In addition to the pharmacological activities mentioned above, several other pharmacological activities have also been reported, including antinociceptive,[129] antiulcer,[130] IL-33 inhibitory,[46] antiangiogenic,[55] hemagglutinating,[95] vasodilator,[133] estrogen-like,[47] hematopoietic enhancement,[134] enzyme (trypsin, tyrosinase, collagenase, and xanthine oxidase) inhibitory activities,[89,92,102,128] as well as adhesive property of suspension cell.[131] Kim et al discovered that 80% ethanol extract from seeds might increase their endurance swimming ability by increasing lipid catabolism and maintaining glycogen storage.[135] Banoth and Thaakur reported that ethanol extract from seeds administered at dosages of 100, 200, and 300 mg/kg for seven days markedly and dose-dependently enhanced spontaneous motor activity, grip strength, and alertness. Furthermore, the brain's dopamine and other amines, such as norepinephrine, epinephrine, and serotonin, were markedly enhanced. At the same time, GSH and MDA levels were lowered dose-dependently by ethanol and aqueous extracts from seeds. It indicated that seed extracts were potentially beneficial antiparkinsonian medication.[136] Besides, ethanol extracts from seeds and fruits could induce osteoblast differentiation by increasing the BMP2/SMAD/RUNX2 signalling pathway.[137]

Toxicity

The immature seeds of *C. gladiata* are a popular vegetable but contain hydrogen cyanide, canavanine, and lectins, which can lead to food poisoning if consumed raw or improperly processed.[69,89,143] In China, two poisoning incidents due to consumption of undercooked immature seeds occurred in 2019 and 2021, respectively. The predominant toxic symptoms were nausea, dizziness, vomiting, abdominal pain, headache, panic, weakness, diarrhea, acid reflux, and a burning sensation in the stomach.[144,145] Notably, Anitha et al conducted an acute toxicity test. They found that ethanol extract from mature seeds at doses ranging from 5 to 2000 mg/kg did not cause any lethal effects in rats and showed no signs of changes in the dermatopathy system, behavioural patterns, salivary secretions, and remaining parameters (eg, tremors, sleep).[125] Besides, acute toxicity tests found that the methanol extract from the aerial parts at 2000 mg/kg and the hydroalcoholic extract from roots at 4000 mg/kg had non-toxic effects on the rats.[6,123] In summary, the immature seeds of *C. gladiata* are toxic and must be cooked thoroughly to eliminate the toxins before consumption.

Discussion and Future Perspectives

The overview encompasses the ethnobotanical use, phytochemistry, pharmacology, and toxicity of *C. gladiata*. While current insights into *C. gladiata* offer promising prospects, but several questions remain for further research. First, the preliminary phytochemical studies revealed the presence of flavonoids, terpenes, steroids, organic acids, nitrogenous compounds, amino acids and proteins in *C. gladiata*. However, there are still many components of *C. gladiata* that remain uncharacterized, and there is the potential for discovering new substances and significantly expanding their applications. Therefore, it is necessary to continuously expand the research on the chemical composition of *C. gladiata*. Second, although the secondary metabolites of *C. gladiata* have been thoroughly explored, there are some questions about the stability and reproducibility of the chemistry. The species and content of secondary metabolites in *C. gladiata* are susceptible to seasonal, climatic and geographic influences, resulting in significant variations in the pharmacological activities of extracts from different batches. Therefore, it is necessary to establish a dynamic monitoring system based on the key components of *C. gladiata* and standardize the raw materials by combining the fingerprinting technique to ensure the consistency between batches. Third, crude extracts of *C. gladiata* exhibited a range of biological activities, including antioxidant, antitumor, antimicrobial, anti-inflammatory, antiallergic, immunomodulatory, antiobesity, hepatoprotective, antidiabetic, and other biological activities. However, some of these activities were revealed only by in vitro assays, and their bioactive components have not been identified. Additionally, the underlying mechanisms of these effects remain unclear. While many secondary metabolites have been isolated, their activity has not been thoroughly evaluated. Therefore, further studies should focus on revealing the bioactivities of crude extracts and the isolated components through both in vivo and in vitro experiments. The mechanisms of crude extracts and the isolated components needs to be analyzed through multi-omics (metabolomics-transcriptomics). To accurately characterize and quantify the composition and content of crude extracts, techniques such as LC-MS/MS or UPLC-Q-TOF-MS/MS can be employed. For example, the hydroalcoholic extracts of *C. gladiata* have significant hepatoprotective activity. These extracts

contain various bioactive components that may contribute to their protective effects on the liver through different mechanisms. Therefore, it is essential to isolate and purify the active components involved and to investigate their specific hepatoprotective mechanisms. Four, the available studies showed that 100 mg/kg and 300 mg/kg of fruits produced the identical anti-asthmatic effect. This might be attributed to the fact that the efficacy of the fruits reaches a plateau at 100 mg/kg, resulting in maximum effectiveness. Therefore, further in vivo experiments are needed to reveal the quantitative-effective relationship of the anti-asthmatic effect of the fruits. Five, the red seed is a good natural source of gallotannins with antioxidant and antimicrobial properties. However, the structure-function relationship of gallotannins, their biological activities, and their mechanisms need further investigation. Six, despite the fact that crude extracts and chemical constituents of *C. gladiata* exhibit excellent anti-inflammatory, anti-tumour and other activities. The complicated metabolic environment in the human body may lead to a significant reduction in its bioavailability. For instance, the active ingredients in crude extracts may be inactivated by intestinal flora metabolism or hepatic first-pass effects, thus resulting in the effects observed in vitro not being reproduced in clinical trials. In addition, in vitro models are difficult to predict the dynamics of multi-organ interactions and the immune microenvironment in the human body, which may overestimate the actual efficacy of the drug. Therefore, targeted clinical trials can be designed to validate the pharmacological effects while ensuring that the crude extracts and chemical constituents are safe and effective. Seven, the clinical case reports indicate that the immature seeds are toxic. However, the specific poisonous dose, the mechanism of toxicity, and the patterns of toxicity occurrence and development are not yet understood. Therefore, it is necessary to conduct acute and long-term toxicity tests and toxicokinetic studies on immature seed extract to reveal the toxicity dose, target organs of toxicity, and the relationship between the dose-toxicity response. Additionally, toxicological microarray technology can be utilized to uncover the genomic mechanisms behind the toxicity of immature seeds. *C. gladiata* is a herb with edible and medicinal properties, widely used in botany and exhibiting various pharmacological and biological activities.

Conclusion

This review provides comprehensive information on *C. gladiata*, covering its ethnobotanical uses, phytochemistry, pharmacology, and toxicity. It enhances our understanding of *C. gladiata* and offers a scientific basis and supporting data for future in-depth research on this plant. Additionally, the review serves as a valuable reference for the innovative development of new drugs. It also identifies gaps in the knowledge of *C. gladiata*'s chemical composition, pharmacological activities, and toxicity. Based on the existing research findings, suggestions are made for further exploration and development from the aspects of chemical composition, pharmacological mechanism, quality standardisation, toxicology, and clinical research trials.

Abbreviations

DPPH, 1,1-diphenyl-2-picrylhydrazyl; ABTS, 2, 2'-azino-bis(3-ethylbenz-othiazoline-6-sulfonic acid); TG, triglyceride; TC, total cholesterol; TB, total bilirubin; LDL-C, low-density lipoprotein cholesterol; LDL, low-density lipoprotein; VLDL, very low-density lipoproteins; HDL, high-density lipoproteins; SGPT, serum glutamate pyruvate transaminase; SGOT, serum glutamate oxalate transaminase; GSH, glutathione; ALP, alkaline phosphatase; LPx, lipid peroxidation; MDA, melanoldehyde; CAT, catalase; SOD, superoxide dismutase; iNOS, inducible nitric oxide synthase; COX, cyclooxygenase; HAase, hyaluronidase; 5-LO, 5-lipoxygenase; AKT, serine/threonine kinase; ERK, extracellular signal-regulated kinase; PI3K, phosphoinositide 3-kinase; mTOR, rapamycin; IgA/E/G, immunoglobulin A/E/G; NF-κB, nuclear factor kappa-B; IκB, inhibitor kappa B; IL, interleukin; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; ERK, extracellular regulated protein kinase; PGE2, prostaglandin E2; TNF-α, tumor necrosis factor alpha; Hexb, β-hexosaminidase; IFN-γ, interferon-gamma; STAT, signal transducer and activator of transcription; T-bet, T-box expressed in T cells; IRF1, interferon regulatory factor 1; GATA3, GATA binding protein 3; c-maf, cellular musculoaponeurotic fibrosarcoma; PPAR, peroxisome proliferator-activated receptor; ACOX, acyl-CoA oxidase; Lcad, long chain acyl-CoA dehydrogenase; HSL, hormone-sensitive lipase; ATGL, adipose triacylglyceride lipase; AMPK, adenosine monophosphate-activated protein kinase; SIRT1, sirtuin-1; PGC-1α, peroxisome proliferator activated receptor γ coactivator-1α; UCP1, uncoupling protein 1; C/EBP, CCAAT/enhancer-binding protein; Ap2, fatty acid binding protein 4; SREBP-1c, sterol regulatory element-binding protein-1c; ACC, 1-aminocyclopropane-1-carboxylic acid; FAS, fatty acid synthase; SCD1, stearoyl-CoA desaturase-1; CPT-1, carnitine palmitoyltransferase-1; BMP2, bone morphogenetic

protein 2; SMAD, suppressor of mother against decapentaplegic; RUNX2, runt-related transcription factor 2; BALF, bronchoalveolar lavage fluid; BDNF, brain-derived neurotrophic factor; RBC, red blood cells; RPMCs, rat peritoneal mast cells; BMDMs, bone marrow-derived macrophages; PCA, passive cutaneous anaphylaxis; D-GalN, D-galactosamine; AZP, azathioprine; STZ, streptozotocin; OVA, ovalbumin; Alum, aluminum hydroxide; AD, atopic dermatitis; HFD, high-fat diet; IBD, inflammatory bowel disease; DNP, dinitrophenyl; DSS, dextran sulfate sodium salt; DLA, Dalton's lymphoma Ascites; NK, natural killer; MIC, minimal inhibitory concentration; LC-MS/MS, liquid chromatography-tandem mass spectrometry; UPLC-Q-TOF-MS/MS, ultra-performance liquid chromatography coupled to quadrupole time-of-flight mass spectrometry.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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