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Review

Ethnopharmacology, phytochemistry and pharmacology of *Benincasae Exocarpium*: A review

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ABSTRACT

Benincasae Exocarpium (BE, Dongguapi in Chinese), as the dried outer pericarp of *Benincasa hispida* (wax gourd) in Cucurbitaceae family, is one of traditional Chinese medicines with the same origin as medicine and food. Up to now, 43 compounds were isolated from BE, including flavonoids, alkaloids, tannins, phenolic acids, soluble fiber and carbohydrates. Modern pharmacological studies and clinical practice showed that BE has diuretic, hypolipidemic effects, hypoglycemic, antioxidant, antibacterial, and other effects. The folk uses, functional factors, pharmacological activities, patents and clinical applications of BE were reviewed in this paper. In addition, the paper also discussed the current problems for the further studies. The information summarized in this paper provides valuable clues for the comprehensive utilization of medicine and food resources and gives a scientific basis for the development of medicinal plants of BE.

Contents

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1. Introduction

Benincasa hispida (Thunb.) Cogn. (Wax gourd) is a plant of the Cucurbitaceae family, whose fruits have been used as food for thousands of years. *B. hispida* was originated in China and East India and later widely distributed in tropical, subtropical and temperate regions of Asia for now (Palamthodi, Kadam, & Lele, 2019). In addition to being used as vegetables, the fruits of *B. hispida* can also be dipped into various candies. The dried outer peels can be used as a medicinal, called *Benincasae Exocarpium* (BE, Dongguapi in Chinese), as traditional Chinese medicine (TCM) in China with a long history of use (Fig. 1). As a TCM, BE was first recorded in *Materia Medica of the Kaibao Reign* for removing lower abdomen water distension, diuresis and quenching thirst with taste sweet and slightly cold, authored by Han Liu and Zhi Ma in Song Dynasty. Now, BE, a kind of homology of medicine and food with some curative effects (Guo et al., 2022; Lee, Choi, & Kim, 2005), is documented in the first part of the 2020 edition of the *Chinese Pharmacopoeia* and its main functions are to dilute water to remove edema, relieve dysuria and heat (Commission, 2020). Phytochemistry analysis displayed that the main components of BE are flavonoids, alkaloids, tannins, trace elements and vitamins, which have pharmacological effects such as anti-oxidation, lipid-lowering, anti-cancer and bacteriostasis (Lee, Choi, & Kim, 2005; Shetty et al., 2008; Soliman et al., 2020). This review summarized the ethnopharmacology, functional constituents, modern pharmacology and applications of BE by searching the literatures over the years, with view to providing a trustworthy basis for the follow-up research on the homology of medicine and food of BE.

2. Ethnopharmacology of *Benincasa Exocarpium*

BE had been used in various countries for thousands of years as medicine and food. It not only appeared on the dining-table, but also often was made into medicinal food (Lan, Chen, & Yanagida, 2009; Yao et al., 2019). As food, it is a vegetable that is loved by people, especially in Asian regions such as China, India, Korea, and Japan. BE can be cooked on its own or eaten with meat or other vegetables, and it is mostly used as kimchi in Korea (Al-Snafi, 2013). As medicine, BE can be used as a single drug or in combination with other natural medicines to prevent or treat diseases such as poor urination, obesity and high blood sugar. In India, BE, known as *Kushmanda*, had been used to treat diabetes, diuretic diseases, urinary tract infections, and chronic inflammatory diseases under the guidance of traditional Ayurvedic medicine (Deeksha et al., 2021). A review, published in 2021, sorted out antiviral drugs or local plants commonly used in Thailand since ancient times, showing that BE has antiviral pharmacological activity (Julsrigival et al., 2021). Compared with the above countries, BE is more widely used in China. According to the guidance of traditional Chinese medicine theory, the nature of BE is slightly cool, and the taste is sweet (Li, 2020), mainly attributed to the spleen and small intestine meridians (Shih et al., 2001). BE has a long history of folk medicine to treat symptoms such as heat syndrome, dysuria, low back pain and urticaria. The ancient medical books about BE were arranged in Fig. 2. BE was recorded in various medical books, including *Materia Medica of the Kaibao Reign* published in A.D. 974, and recorded in books such as *Illustrated Classic of Materia Medica* and *Compendium of Materia Medica* latterly. In the *Compendium of Materia Medica*, BE is sweet, flat, non-toxic and mainly used to treat fall damage and low back pain. In 2020, BE was included in *Chinese Pharmacopoeia* as a traditional Chinese medicine.

Fig. 1. Photograph of *Benincasae Exocarpium.*

3. Functional constituents

In recent years, there had been many studies on the chemical constituents of the whole fruit of *B. hispida*, which mainly contain phenolic compounds, flavonoids, alkaloids, volatile compounds, and polysaccharides. However, there were few studies on the chemical constituents of BE, and only 43 compounds have been reported at present. The analysis of functional factors has demonstrated that BE contains flavonoids, alkaloids, tannins, trace elements and vitamins. Flavonoids and alkaloids are the main chemical components related to the biological activity and pharmacological properties of BE. The main compounds obtained from BE were exhibited in Table 1.

Flavonoids, a class of substances with a wide range of pharmacological activities, are one of the main chemical components in BE (Hakiki, Fauziyyah, & Wijanarti, 2021; Ryu, Lee, & Whang, 2021). A total of 14 flavonoids were isolated and identified from BE (**1**–**14**). These flavonoids were classified according to the structure, including six flavones (**1**–**6**), one flavonol (**7**), four isoflavones (**8**–**11**), one flavanone (**12**) and two flavanonols (**13**–**14**). The chemical structures of flavonoids in BE were shown in Fig. 3. There was a total of nine flavonoid glycosides in BE, among which there were five C8-glycosides and one C6-glycoside. Vitexin and orientin are both flavone C8-glycosides, while isovitexin belongs to flavone C6-glycoside. Flavonoids gained from medicinal and food homologous plants had special significance for the treatment of chronic diseases, due to the advantages of low cost, high safety, and high patient compliance (Hajiaghaalipour et al., 2015).

There were 11 alkaloids isolated and identified from BE (**15**–**25**), and their structures were exhibited in Fig. 4. These alkaloids were classified as heterocyclic alkaloids and non-heterocyclic alkaloids based on the position of nitrogen atoms. In 11 alkaloids of BE, nine compounds (**15**–**24**) were heterocyclic alkaloids and one (**25**) was non-heterocyclic alkaloid (Bhambhani, Kondhare, & Giri, 2021). According to the chemical structures, there were two piperidine alkaloids (**15**,**16**), four terpenoids alkaloids (**17, 21**–**23**), one steroid alkaloid (**18**), one macrocyclic spermine alkaloid (**19**), one tetrahydroisoquinoline alkaloid (**20**), one carboline alkaloid (**24**), and one spermidine alkaloid (**25**). Through combing and analyzing the pharmacological effects of alkaloids, it was exposed that they have preventive effects on obesity, diabetes, and oxidation and might be the functional constituents of BE (Dinda et al., 2020).

Phenolic acids are polyphenols with a carboxylic acid (–COOH) functional group. Phenolic acids are commonly classified as hydroxybenzoic acid and hydroxycinnamic acid based on the carbon framework (Tatipamula & Kukavica, 2021). Five phenolic acids, *p*-hydroxybenzoic acid (**26**), protocatechuic acid (**27**), gallic acid (**28**), methyl chlorogenate (**29**), and caffeic acid (**30**) were also discovered in BE and their structures were listed were listed in Fig. 5. Three phenolic acids (**26**–**28**) belong to hydroxybenzoic acid struc-

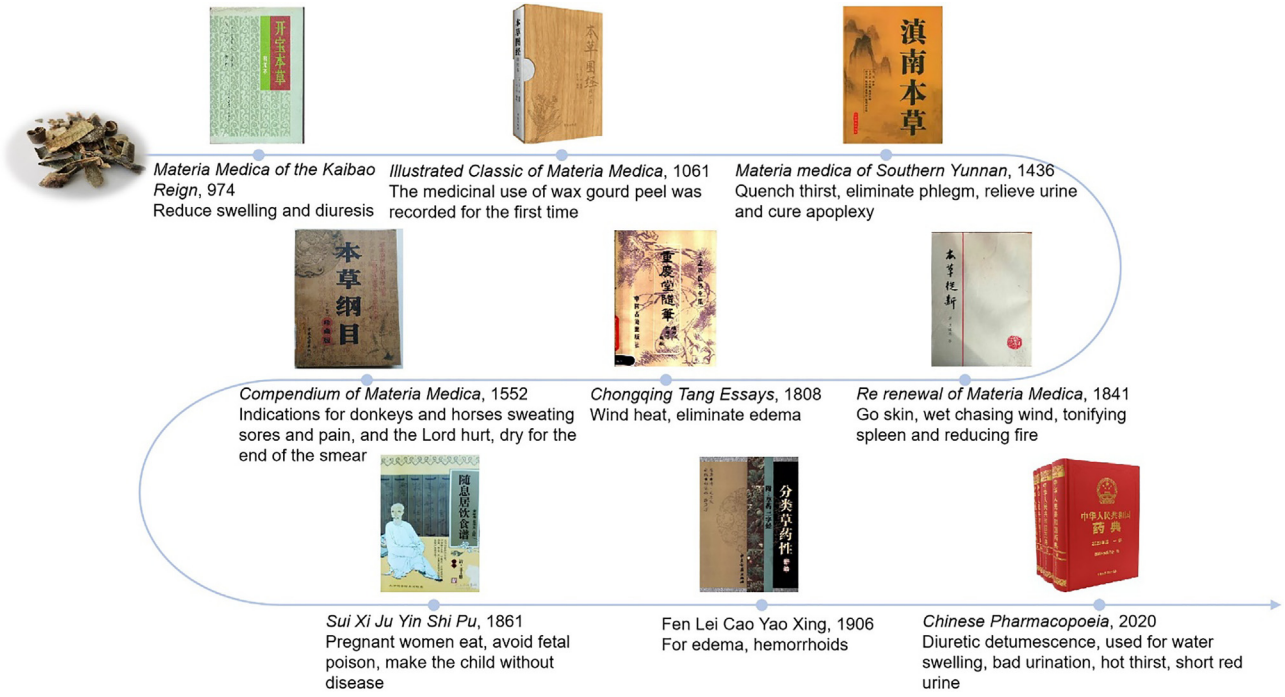

Fig. 2. Ancient medical books of *Benincasae Exocarpium*.

ture, and the other two (**29**–**30**) belong to hydroxycinnamic acid structure.

In addition, other types of components in BE, such as triterpenes, heptane, adenosine, soluble fibers, vitamins, trace elements and carbohydrates, were also identified. Some of these ingredients were listed in Table 1, and the structures were displayed in Fig. 6. Trace elements such as potassium and calcium may be diuretic components in BE (Kumar, Mythily, & Mythily, 2012). In addition, the study found that galactose, glucose, xylose and sorbose were identified in BE by thin-layer analysis (Kumar, Mythily, & Chandraju, 2012).

4. Modern pharmacology of *Benincasa Exocarpium*

BE contains a variety of functional ingredients that are beneficial to the human body, and has high edible and medicinal value. Modern pharmacological studies have verified that BE showed many biological functions, such as lipid-lowering, hypoglycemic, anti-oxidation, antibacterial, diuretic and so on (Fig. 7).

4.1. Diuretic function

The number of patients with hypertension, chronic kidney disease, and edema is increasing, and medicinal and food homologous substances with diuretic properties have been found to help urinate, reduce fluid retention, and assist in the treatment of cardiovascular disease (de Souza, Mariano, Cechinel-Zanchett, & Cechinel-Filho, 2021). The diuretic effect of BE had been reported since it was recorded for the first time in *Materia Medica of the Kaibao Reign*. There has been extensive clinical experience using BE to treat patients with systemic edema and dysuria, dating back to ancient times. A Chinese herbal tea containing BE has been shown to increase the urine production of rats (Chen et al., 2000). After drinking Chinese tea for two weeks, the urine volume of the control group was (20.7 ± 5.6) mL/d, and the urine volume of the administration group was (28.4 ± 8.9) mL/d, which indicated that there was a significant difference between the two groups of data ($P < 0.001$). At the same time, a decrease in blood pressure afterward was also observed, possibly due to the diuretic effect of the Chinese tea.

Although the diuretic effect of BE had a long history, there was little research on the active ingredient and mechanism of action with diuretic function. Therefore, the diuretic effect of BE still has great potential in modern pharmacological research.

4.2. Lipid-lowering function

Occasionally, medicinal and food homologous substances are referred to as “functional foods”. BE is one of the functional foods, which has a certain relieving effect on obesity and a controlling effect on weight (Choudhary & Grover, 2012). In the study on the prevention of obesity with BE, the weight gain of mice fed in the extract of BE (EBE), which was derived from 75% ethanol, was significantly inhibited ($P < 0.05$), by comparing with the normal high-fat diet group. Meanwhile, there was no significant difference in food consumption among each group, but the contents of low-density cholesterol, total protein, and triglycerides in serum and liver were reduced in C57BL/6 mice in EBE group. In the study of BE in treating obesity, mice were divided into normal HF group and HF with 1% EBE group, accompanied by two weeks of feeding. However, the weight of the administration group did not decrease significantly. These results suggested that the ethanolic extract of BE had the function of preventing obesity, but the treatment was not observed. It was indicated that the lipid-lowering effect of BE could originate from the inhibition of peroxisome proliferators-activated receptor (PPAR) and HMG-CoA reductase (HMGCR) signaling through studies at the cellular level and gene expression level (Gu et al., 2013).

At present, lipid-lowering effects of drugs were mainly through the following four pathways: affecting total cholesterol (TC) pathway, triglyceride (TG) pathway, TC and TG pathway, and genomics intervention. Genistin is an isoflavone component of BE, which could inhibit lipid accumulation by adipocytes by affecting TC and TG pathways. The inhibition rate was 21.7% with the concentration of genistin 50 μmol/L and 69.2% with the concentration of

Table 1
Functional factors isolated from *Benincasae Exocarpium*.

Classes	No.	Formula	Compounds	References
Flavonoids	**1**	$C_{28}H_{32}O_{15}$	Diosmin	Hakiki, Fauziyyah, & Wijanarti, 2021
	2	$C_{21}H_{20}O_{10}$	Isovitexin	Ryu, Lee, & Whang, 2021
	3	$C_{21}H_{20}O_{10}$	Vitexin	Ryu, Lee, & Whang, 2021
	4	$C_{21}H_{20}O_{11}$	Orientin	Ryu, Lee, & Whang, 2021
	5	$C_{27}H_{30}O_{14}$	Vitexin-2″-*O*-rhamnoside	Hussain et al., (2022)
	6	$C_{27}H_{30}O_{15}$	Vitexin-4″-*O*-glucoside	Hussain et al., (2022)
	7	$C_{15}H_{10}O_7$	Quercetin	Deeksha et al., (2021)
	8	$C_{20}H_{18}O_4$	Neobavaisoflavone	Hakiki, Fauziyyah, & Wijanarti, 2021
	9	$C_{22}H_{22}O_{11}$	Tectoridin	Hakiki, Fauziyyah, & Wijanarti, 2021
	10	$C_{21}H_{20}O_{10}$	Genistin	Hakiki, Fauziyyah, & Wijanarti, 2021
	11	$C_{27}H_{30}O_{14}$	Puerarin-4′-*O*-glucoside	Hakiki, Fauziyyah, & Wijanarti, 2021
	12	$C_{20}H_{20}O_5$	Kushenol S	Hakiki, Fauziyyah, & Wijanarti, 2021
	13	$C_{30}H_{36}O_7$	Kushenol M	Hakiki, Fauziyyah, & Wijanarti, 2021
	14	$C_{30}H_{38}O_8$	Kosamol A	Hakiki, Fauziyyah, & Wijanarti, 2021
Alkaloids	**15**	$C_{34}H_{57}NO_7$	Ningpeisinoside	Hakiki, Fauziyyah, & Wijanarti, 2021
	16	$C_{22}H_{25}NO_2$	Lobelanine	Hakiki, Fauziyyah, & Wijanarti, 2021
	17	$C_{24}H_{39}NO_6$	Neoline	Hakiki, Fauziyyah, & Wijanarti, 2021
	18	$C_{30}H_{37}N_5O_5$	Ergosine	Hakiki, Fauziyyah, & Wijanarti, 2021
	19	$C_{27}H_{43}NO_6$	Pingpeimine C	Hakiki, Fauziyyah, & Wijanarti, 2021
	20	$C_{30}H_{40}N_4O_5$	Ephedradine C	Hakiki, Fauziyyah, & Wijanarti, 2021
	21	$C_{24}H_{39}NO_7$	Fuziline	Hakiki, Fauziyyah, & Wijanarti, 2021
	22	$C_{26}H_{41}NO_7$	Delbruline	Hakiki, Fauziyyah, & Wijanarti, 2021
	23	$C_{37}H_{42}N_2O_6$	Daurinoline	Hakiki, Fauziyyah, & Wijanarti, 2021
	24	$C_{18}H_{23}N_3O_2$	Picrasidine K	Hakiki, Fauziyyah, & Wijanarti, 2021
	25	$C_{28}H_{42}N_4O_6$	Kukoamine A	Hakiki, Fauziyyah, & Wijanarti, 2021
Phenolic acids	**26**	$C_7H_6O_3$	p-hydroxybenzoic acid	Ryu, Lee, & Whang, 2021
	27	$C_7H_6O_4$	Protocatechuic acid	Ryu, Lee, & Whang, 2021
	28	$C_7H_6O_5$	Gallic acid	Ryu, Lee, & Whang, 2021
	29	$C_{17}H_{20}O_9$	Methyl chlorogenate	Hakiki, Fauziyyah, & Wijanarti, 2021
	30	$C_9H_8O_4$	Caffeic acid	Ryu, Lee, & Whang, 2021
Others	**31**	$C_{13}H_{18}O_8$	Tachioside	Hakiki, Fauziyyah, & Wijanarti, 2021
	32	$C_{14}H_{20}O_8$	Cimidahurinine	Hakiki, Fauziyyah, & Wijanarti, 2021
	33	$C_{14}H_6O_8$	Ellagic acid	Deeksha et al., (2021)
	34	$C_{30}H_{46}O_6$	Elculentic acid	Hakiki, Fauziyyah, & Wijanarti, 2021
	35	$C_9H_{20}N_2O_2$	Laminine	Hakiki, Fauziyyah, & Wijanarti, 2021
	36	$C_{10}H_{13}N_5O_4$	Adenosine	Hakiki, Fauziyyah, & Wijanarti, 2021
	37	$C_8H_8O_3$	Isovanillin	Ryu, Lee, & Whang, 2021
	38	$C_{20}H_{20}O_4$	Tsaokoarylone	Hakiki, Fauziyyah, & Wijanarti, 2021
	39	$C_{25}H_{28}O_4$	Mulberrofuran N	Hakiki, Fauziyyah, & Wijanarti, 2021
	40	$C_6H_6O_3$	5-Hydroxymethylfurfural	Hakiki, Fauziyyah, & Wijanarti, 2021
	41	$C_{19}H_{22}O_5$	Thannilignan	Hakiki, Fauziyyah, & Wijanarti, 2021
	42	$C_{17}H_{24}O_3$	Shogaol	Hakiki, Fauziyyah, & Wijanarti, 2021; Yao et al., 2016
	43	$C_{19}H_{18}O_4$	Moracin C	Ryu, Lee, & Whang, 2021

100 μmol/L. Further studies discovered that genistin can inhibit the production of specific proteins in adipocytes and the expression of genes responsible for these proteins, including adipocyte binding protein 2 (aP2)/fatty acid-binding protein 4 (FABP4), CCAAT-enhancer-binding protein α (C/EBPα), and peroxisome proliferator-activated receptor γ (PPARγ). At the same time, the production of lipase was also inhibited, such as fatty acid synthase (FAS), ATP citrate lyase (ACL), and acetyl-CoA carboxylase 1 (ACC1) (Choi, Shim, & Kim, 2020).

Delbruline is an alkaloid found in BE that exhibits bioactivity against lipid aggregation *in vitro*. The levels of TG, TC, alanine transaminase (ALT) and Aspartate transaminase (AST) in free fatty acid (FFA)-induced BRL cells were evaluated. Results indicated that Delbruline (1, 5, and 10 μmol/L) inhibited the levels of TG, ALT, and AST in a dose-dependent manner (Ma et al., 2022).

p-Hydroxybenzoic acid obtainedfrom BE also had the effect on lipid-lowering by affecting the TC pathway. After administration of *p*-hydroxybenzoic acid, the mRNA expression of stearoyl-CoA desaturase-1, ACC1, sterol regulatory element-binding protein 1c, peroxisome proliferator- activated receptor were decreased, compared with the comparison model group (Lin, Yang, Chen, & Yin, 2021). Through network pharmacology and molecular docking technology analysis, the total docking score of *p*-hydroxybenzoic acid in low density lipoprotein receptor (LDLR) was 5.75, indicating a good affinity with LDLR. LDLR is the receptor that encodes low density lipoprotein. Lan et al. speculated that *p*-hydroxybenzoic acid increased the expression of LDLR, enhanced low density lipoprotein (LDL) absorption and metabolism in the liver, and decreased the level of LDL in the serum. Therefore, *p*-hydroxybenzoic acid showed the activity of lipid-lowering (Lan et al., 2020). The lipid-lowering mechanisms of these components were shown in Fig. 8. The lipid-lowering effect of BE is widely used in the folk, and the mechanism of action could be the TC and TG pathway, which regulates lipid-metabolizing enzymes and other proteins such as PPAR.

4.3. Hypoglycemic function

BE, as food with hypoglycemic function, could not only play an important role in lowering blood sugar, slowing down the occurrence of complications caused, but also reduce the frequency of use of conventional drugs (Jia, Gao, & Tang, 2003; Sharma, Chatterjee, Kumar, Variyar, & Sharma, 2010). In order to explore the hypoglycemic effect of BE, the experiment was conducted with the produced advanced glycation end products (AGE), α-glucosidase (α-G) and α-amylase (α-A) as indicators. The inhibitory effects of various extracts of BE (water, BuoH, ethyl acetate, *n*-hexane) on hypoglycemic indexes were determined. Among them, the comprehensive inhibitory effect of *n*-BuOH extract and ethyl acetate (EtOAc) extract of BE was better than others, showing sig-

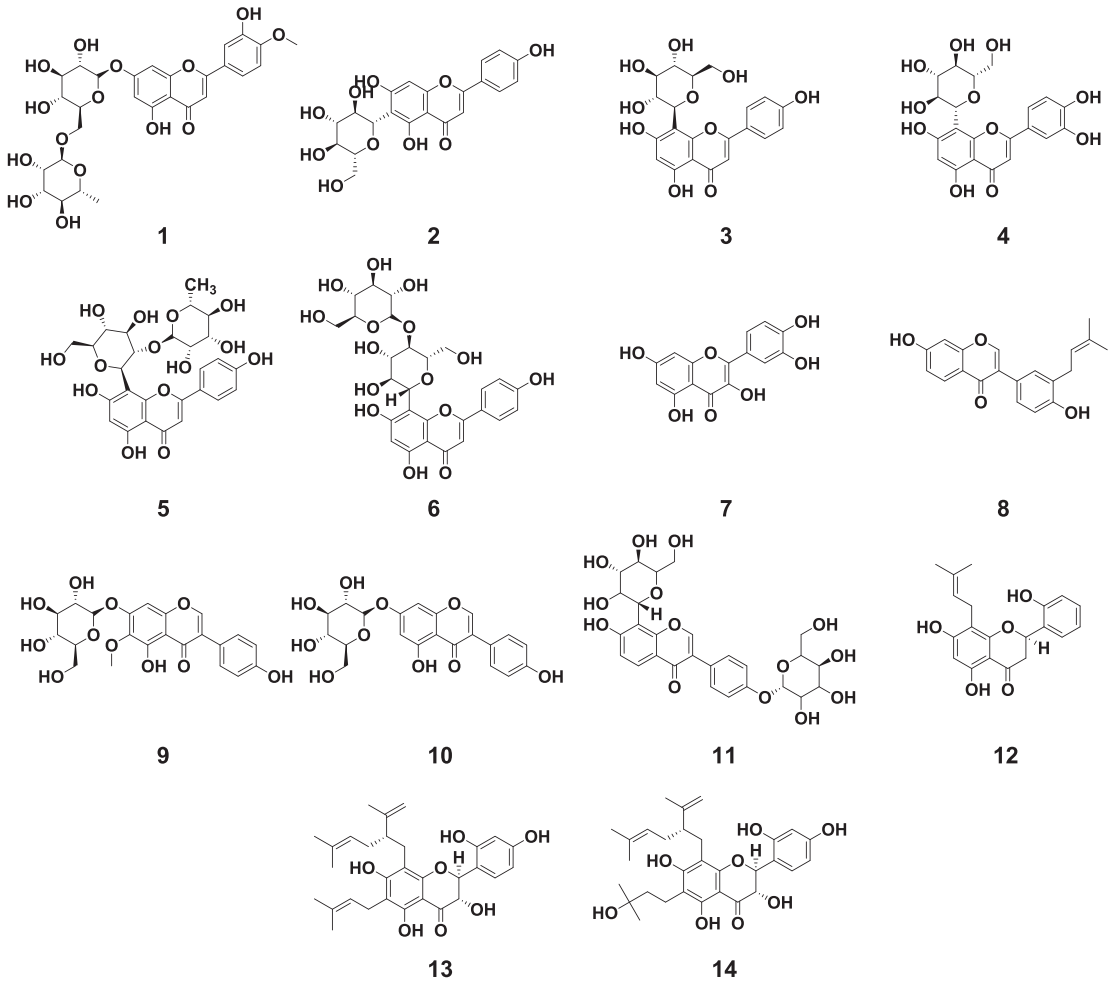

Fig. 3. Flavonoids compounds isolated from *Benincasae Exocarpium*.

nificant differences with acarbose group (Ryu, Lee, & Whang, 2021). In another study, the water extract of BE had about three times the inhibitory effect on α-A than the methanol extract. The reason could be that the water extract of BE had the highest content of polyphenols (335.39 mg/g), the methanol extract had the highest content of flavonoids (0.58 mg/g), therefore, polyphenols may be the active ingredients in BE (Bellur Nagarajaiah & Prakash, 2014).

At present, the anti-diabetic mechanisms of natural products include the following: inhibition of α-glucosidase and α-amylase in the digestive tract; mediating glucose uptake and glucose transporter through the insulin pathway; promotion of insulin secretion and pancreatic *β*-cell proliferation; inhibition of protein tyrosine phosphatase 1B activity (Rios, Francini, & Schinella, 2015).

Caffeic acid, a small phenolic acid in BE, has insulin-mediated hypoglycemic effects. C57BL/ KsJ-db/db mice were given a 0.02% caffeic acid diet for five weeks. The caffeic acid group significantly reduced blood glucose levels compared to the control group. In the treated group, plasma insulin, c-peptide, and leptin levels were significantly higher than those in the control group, while plasma glucagon levels were significantly lower. Glucokinase activity and glycogen content were increased, while the activities of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase were decreased in the administration group. At the same time, glucose transporter 2 (GLUT2) expression was decreased in the liver, and glucose transporter 4 (GLUT4) expression was significantly increased in adipose cells. Caffeic acid works (Fig. 9A) by increasing insulin secretion and reducing glucose output from the liver in animals with type 2 diabetes while increasing glucose processing levels in fat cells (Espinoza-Hernandez et al., 2021).

The therapeutic effect of flavonoids with multiple phenolic hydroxyl groups on diabetes could be due to its inhibitory effect on α-A and α-G, and the strength of this effect may be related to the structure of the compound. Isovitexin and vitexin have hypoglycemic effects, and the mechanism of action could be the certain inhibitory effect on α-G and α-A. Isovitexin (IC_{50} value of 23.26 μmol/L) had a stronger inhibitory effect on α-G than vitexin (IC_{50} value of 25.11 μmol/L) (Li et al., 2009), which may be due to different sugar binding sites in their structures. Isovitexin is a C6 glycoside and vitexin is a C8 glycoside (Zhu et al., 2020). Vitexin-2″-*O*-rhamnoside, a C8 glycoside compound with multiple phenolic hydroxyl groups, was reported from *n*-BuOH and ethyl acetate extracts of BE (Hussain et al., 2022). It had inhibitory effects on both α-A and AGE of bovine serum albumin (BSA) -glucose and BSA-methylglyoxal (MGO) systems with IC_{50} values of (12.82 ± 1.18), (29.58 ± 1.02) and (12.49 ± 0.81) μmol/L, respectively (Ryu, Lee, & Whang, 2021).

Orientin had been shown to improve substrate utilization during insulin resistance. The basic mechanism of orientin could be through the regulation of insulin signaling and energy metabolism (Mazibuko-Mbeje et al., 2021). C3A liver cells were treated with palmitate at 0.75 mmol/L concentration for 16 h, and the model cells were treated with orientin at 10 μmol/L for 3 h to observe the effect of orientin. Enhancing palmitate and glucose uptake in

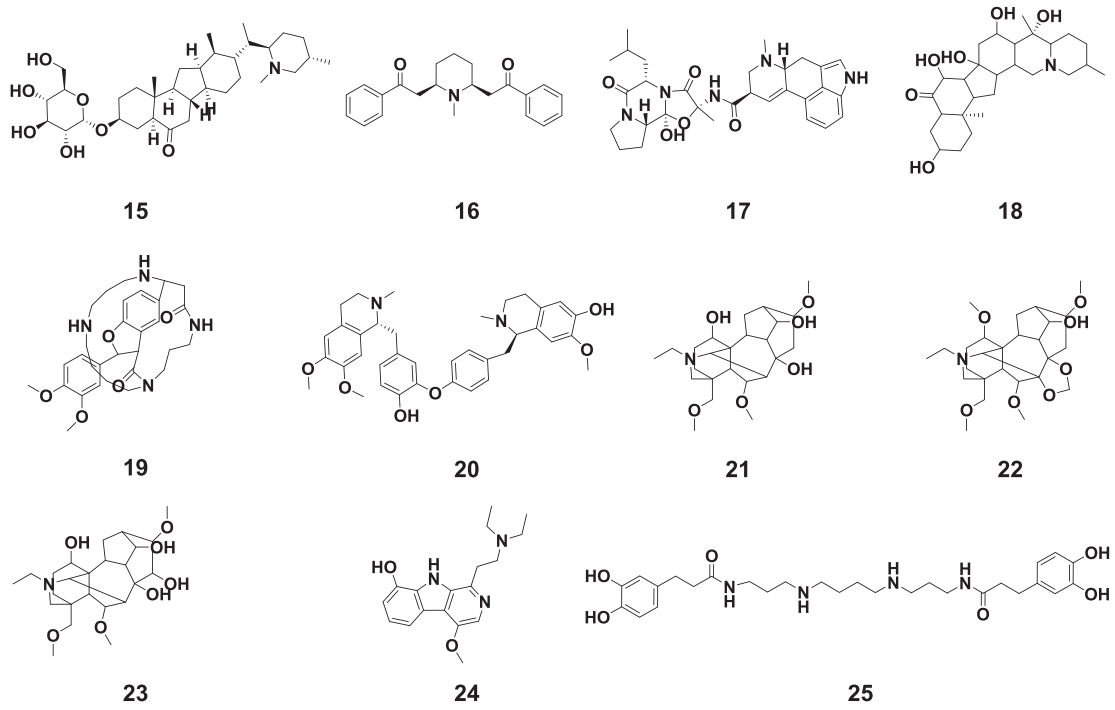

Fig. 4. Alkaloids compounds isolated from *Benincasae Exocarpium*.

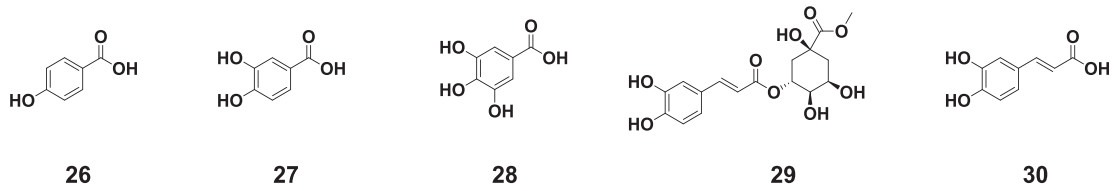

Fig. 5. Small-molecule phenolic acids compounds isolated from *Benincasae Exocarpium*.

cells by maintaining substrate utilization showed that orientin could effectively improve metabolic activity. Further studies had shown that the hypoglycemic effect of orientin may be associated with improved expression of genes related to insulin signal transduction (Irs1 and Pi3k), GLUT 2, and energy regulation (Ampk and Cpt1). The hypoglycemic mechanisms of orientin were shown in Fig. 9B.

4.4. Antioxidant function

Diseases caused by free radicals can be prevented by the use of antioxidants, which are used to eliminate over oxidizing free radicals (Abeyrathne, Nam, & Ahn, 2021; Munteanu & Apetrei, 2021). The DPPH free radical scavenging method was used to investigate the antioxidant effect of BE and its antioxidant components. The results showed that at the concentration range of 10–100 μg/mL, 80 μg/ mL water extract had the highest scavenging ability, reaching 86.36%, while methanol extract had the highest antioxidant activity, reaching 88.02% at the concentration of 100 μg/mL (Rana & Suttee, 2012). In addition, it was also reported that the antioxidant capacity of BE 50% methanol extract was 83.85%, and the antioxidant capacity of BE 75% methanol extract was 82.30% (Huang, Huang, Tso, Tsai, & Chang, 2004).

Flavonoids are the main antioxidant components of BE. Orientin is a flavonoid glycoside of BE with certain antioxidant capacity. The antioxidant capacity was investigated by scavenging DPPH experiment, and the result displayed that the IC_{50} value of orientin was 0.84 μmol/L (Ma et al., 2020). In addition, the antioxidant activity of orientin was stronger than vitexin, and investigators speculated that the reason could be that the orientin has more *O*-phenolic hydroxyl structure (An et al., 2012; Xie et al., 2022).

Dietary plants have extensive antioxidant pharmacological effects. As a very popular vegetable in Asia, BE has been proved by experiments.

4.5. Antibacterial function

The bacteriostatic effect of BE has been concerned. The experimenters used the disc diffusion method to determine that the water extract of BE exhibited inhibitory effect on *Staphylococcus epidermidis* (the inhibition zone was 6.6 ± 0.07 mm) and *Proteus vulgaris* (the inhibition zone was 6.5 ± 0.08 mm) (Noriham Abdullah et al., 2012). In addition, the antibacterial effect of different extracts of BE was studied by pore diffusion method. The results showed that methanol extract and ethyl acetate extract had stronger antibacterial activity than chloroform extract. The MIC of methanol extract against *Bifidobacterium subtilis*, *Sarcina lutea*, *Xanthomonas campestris*, *Escherichia coli* and *Pseudomonas denitrificans* were 510, 260, 120, 510 and 120 μg/mL, respectively (Md et al., 2021). Gold nanoparticles (GNPs) was synthesized by the aqueous extract of BE. The effects of BE nanoparticles on the viability of *Klebsiella pneumonia*, *Salmonella abony*, Gram-positive *Staphylococ-*

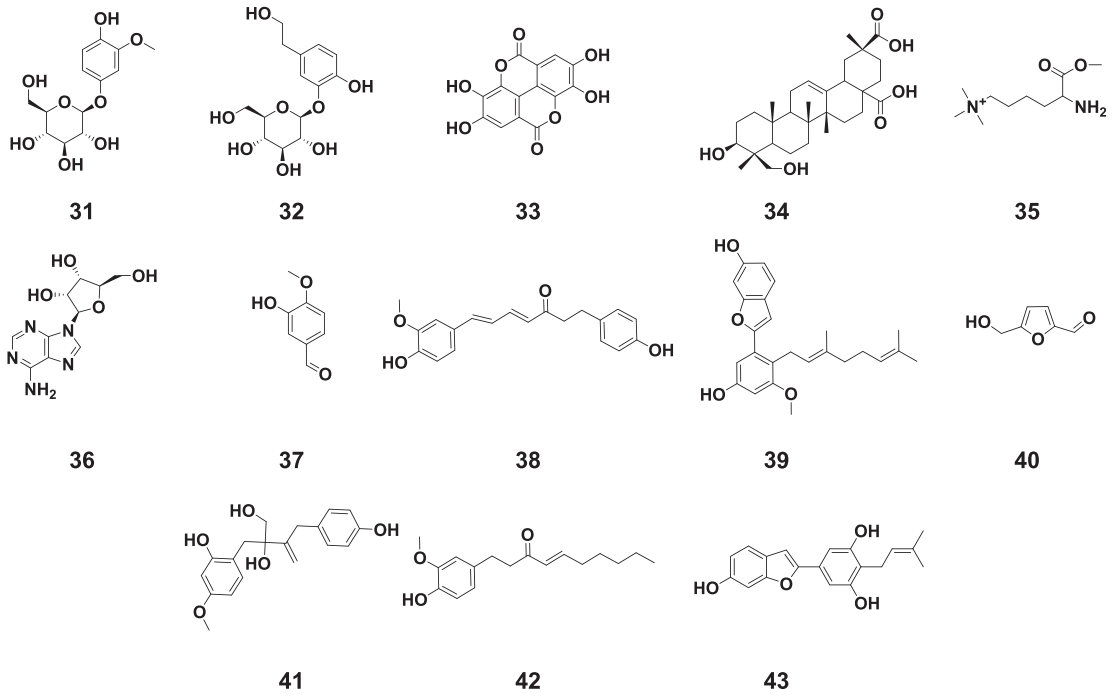

Fig. 6. Other compounds isolated from *Benincasae Exocarpium*.

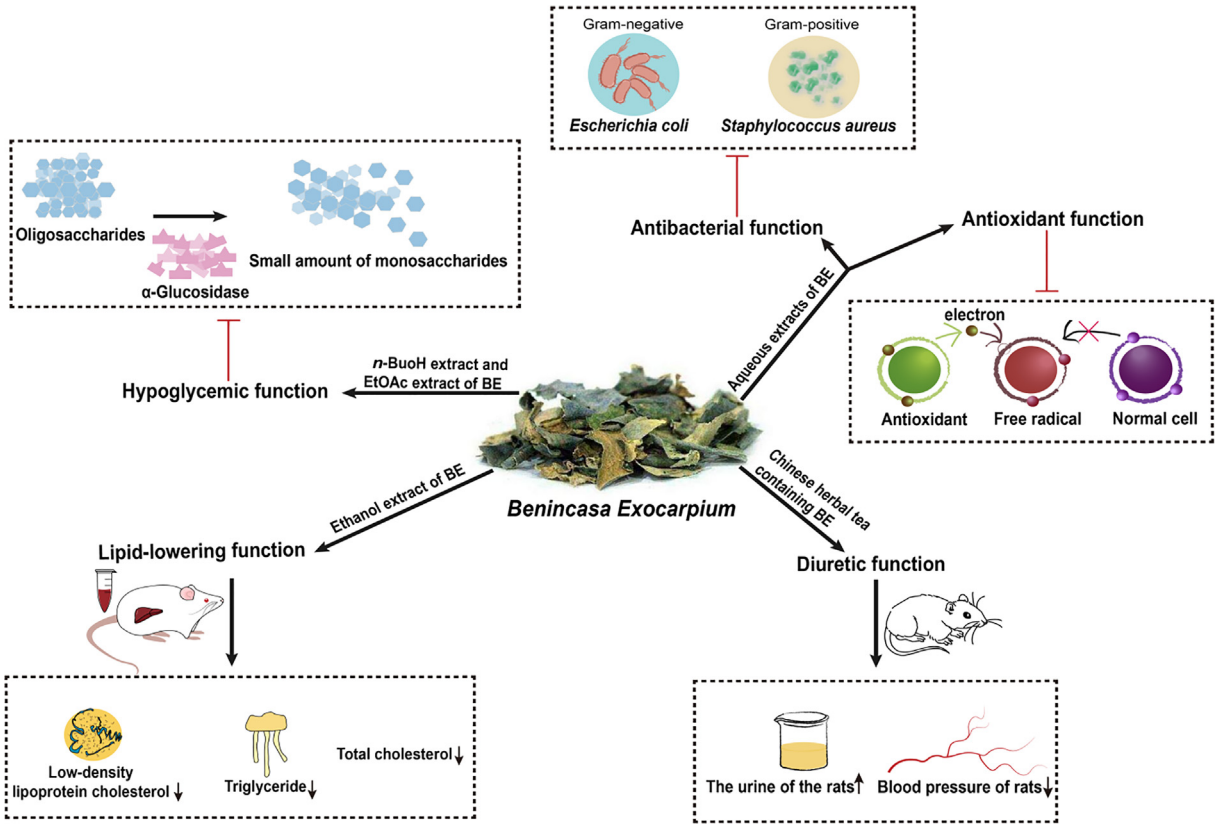

Fig. 7. Modern pharmacological functions of *Benincasae Exocarpium*.

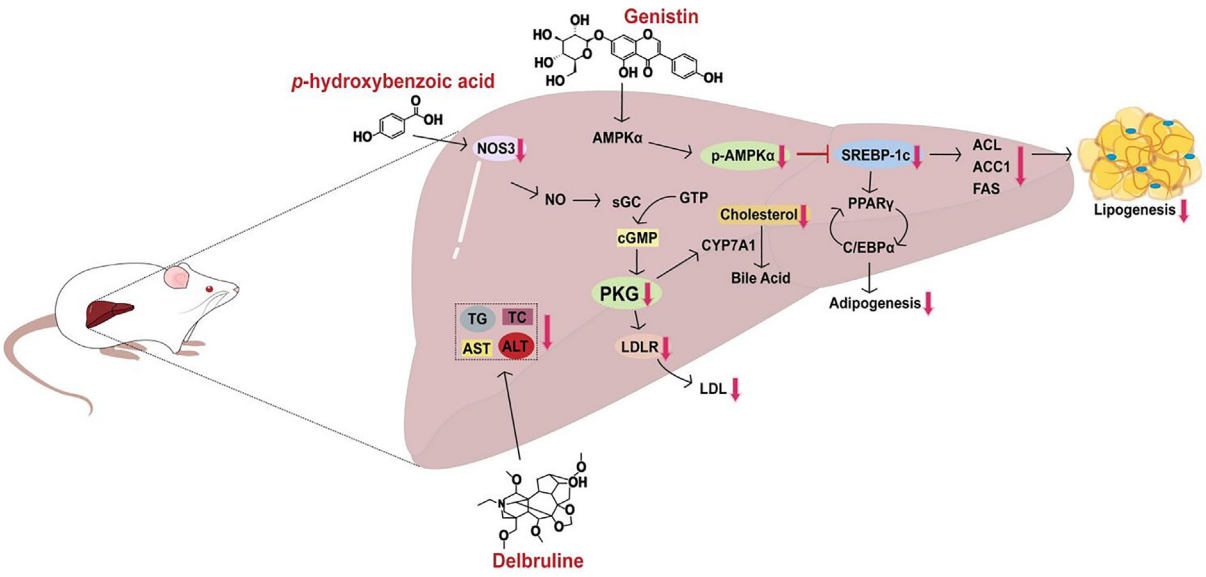

Fig. 8. Lipid-lowering function of some compositions of *Benincasae Exocarpium*.

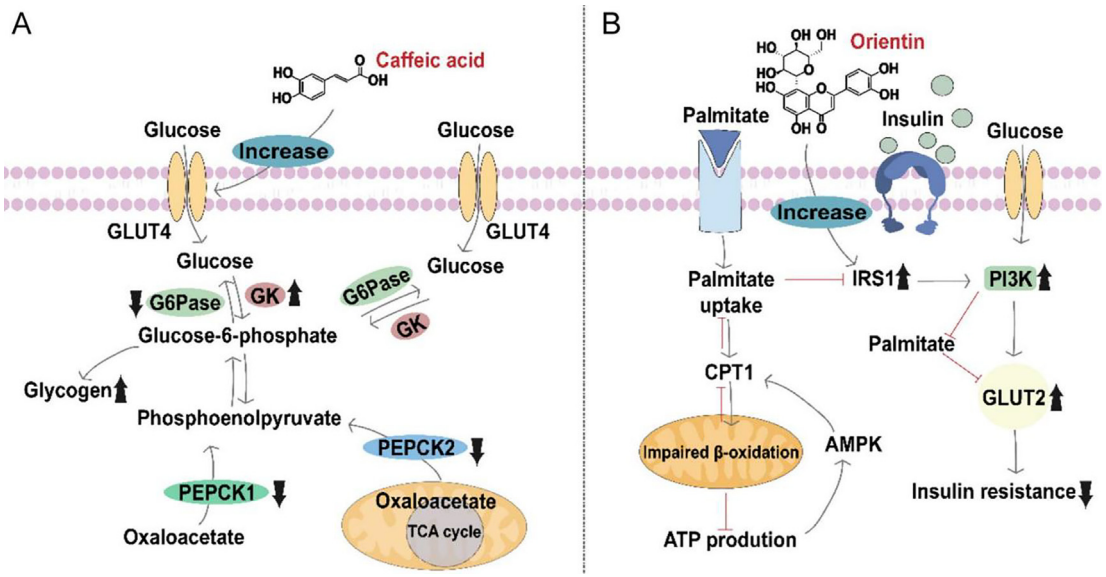

Fig. 9. Hypoglycemic function of caffeic acid and orientin from *Benincasae Exocarpium*.

cus aureus and Gram-negative *E. coli* were investigated. In addition, the minimum bactericidal concentration (MBC) values of the GNPs assayed against bacteria were 65.5, 84.5, 111.5 and 80.8 μg/mL, respectively. The above experimental results showed that BE had antibacterial effect, and the antibacterial effect was improved when BE was made into nanoparticles (Al Saqr et al., 2021; Devi & Ahmaruzzaman, 2016).

4.6. Other functions

In addition, BE had anti-inflammatory and analgesic effects. Methanol extract of BE inhibited hot plate pain in mice, acetic acid-induced writhing, and formalin-induced pain in a dose-dependent manner (0.25–1.5 g/kg). Moreover, the extract could inhibit the inflammatory response induced by fresh egg albumin in rats and the convulsion response induced by pentetetrazole in mice. These inhibitions were statistically significant (Parida, Sahu, Debata, & Panda, 2010).

Moreover, some scholars synthesized gold nanoparticles, namely GNPs, using water extract of BE as raw material. The MTT method was used to investigate the toxicity of BE Gold Nanoparticles on cancer cells (Hela) and normal cells (osteoblasts). The results presented that when the concentration of Nanoparticles was 0.62–20 μg/mL, cancer cells lost their viability quickly, and the IC_{50} value was 2.25 μg/mL. Interestingly, the nanoemulsion was less toxic to normal cells, and at a concentration of 20 μg/mL, the inhibition rate against normal cells was still<30% (Al Saqr et al., 2021). This means that GNPs have certain selectivity for tumor cells and have significance for targeted drug delivery of tumor cells.

5. Application

5.1. Patents of Benincasae Exocarpium

As "medicine and food homologous" food has received growing attention in the world, the research and product development of

medicine and food homologous food have been become the focus of studying (Wang et al., 2022). The Baiten website (https://www1.baiten.cn/) can be used to find patent information (Ji et al., 2020). As shown in Fig. 10, the patent application began in 1983. Till now, there are 2188 patents related to BE, of which 2057 published patents were applied for in China at most. And the number of applications reached a staged peak (413) and set a new record high in 2016. The number of patent applications in China was the top one, indicating that the region had a high degree of activity in technological innovation and fierce market competition. After technical classification analysis, it was found that most of these patents were developed around the necessities of human life, accounting for 91.91% of the total number of patents. Further data analysis revealed that most of the patents were related to drugs and food. The number of pharmaceutical and food patents accounted for a large proportion, accounting for 47.8% and 38.2% of the total number of patents respectively. Among them, food-related patents mainly include the production of tea, noodles, beverages, biscuits and other food products. In addition, there was also a patent for designing the waxy surface of BE as a fruit preservation layer, which is for the preservation of strawberries (Sreenivas, Chaudhari, & Lele, 2011).

5.2. Food application

The fruits of *B. hispida* can be used as vegetables and fruits, and the peel is also used as food in daily life. The application about BE as food were arranged in Fig. 11. The nutritious compositions of peel and pulp are similar, but the content of each component is different (Deeksha et al., 2021). Interestingly, BE can also be used alone to make medicinal diet and tea. Wax gourd peel-black bean soup is the medicinal food using BE as the raw material with the effect of clearing heat and removing dampness, diuresis and detoxification. In addition, crucian carp-wax gourd peel soup is also a delicacy that was often eaten on the table. Soup can be used to relieve body edema and relieve bloating caused by irregular diet (Tan & Zhang, 2017).

Tea was the first Chinese herbal medicine used by the Chinese. Currently, tea has become an attractive complementary and alternative medicine (Pan et al., 2022). However, for people with weak spleen and stomach, long-term use of BE has certain sub-health risks, because the essence of BE is cool. Therefore, people tend to add warm ingredients to neutralize the cold of BE. As a material of tea, BE was often used with lotus leaf, cassia seed, adlay and tuckahoe. Wax gourd peels tea and wax gourd peel-lotus leaf tea had a great sales volume on Chinese shopping applications. These teas can be used daily, with a certain diuretic and detumescent effect, and they are benefit for edema and weight loss as one of the choices of daily drinks.

Furthermore, the dried and crushed BE was good food ingredient, which was added to the walnut cake to help reduce the content of oil and sucrose, and could decrease the risk of obesity and high blood sugar caused by long-term consumption (Li, Li, & Zhao, 2015). BE powder with an added amount of 4.6% was made into steamed bread together with strong flour. The final sensory evaluation was 95 points (Li, Li, & Zhang, 2015).

5.3. Clinical application

The diuresis and swelling effect of BE had been used by experts since ancient times. BE can be used as a single prescription or as a traditional Chinese medicine (TCM) compound with other TCM for the treatment of edema symptoms in all ages. A total of 100 patients with acute nephritis from Daye County People's Hospital in Hubei Province received the compound TCM containing BE, which reduced facial swelling and increased urination. The formula consists of 10 TCMs, among which the amount of BE was the largest. The 68% of patients were cured, and other patients supplied signs of improvement (Hu, 1991). Decoction of BE and red bean was recorded in *Modern Practical Chinese Medicine*, published in 1956, which can reduce swelling and diuresis. A total of 120 patients with primary nephrotic syndrome in the Department of Nephrology of the First Affiliated Hospital and the Second Affiliated Hospital of the Hunan University of Chinese Medicine from June 2016 to June 2017 were selected as clinical samples. A total of 60 patients were treated with conventional western medicine, and the other 60 patients were treated with BE decoction. The time of edema resolution was (13.6 ± 4.0) d in the BE group and (22.9 ± 5.0) d in the western medicine group. The time of edema resolution in BE group was significantly shorter than that in western medicine group ($P < 0.05$) (Cai et al., 2019). The experimental group used BE concentrate, and in the control group, the 11 patients were given the same amount of water (Antian Wang, 1964). The study found that patients in BE group urinated faster and had higher urine output in the first 2 h by compared with the two groups ($P < 0.01$). Professor Nie, a famous TCM expert, attributed kidney disease to edema of TCM. The frequency of BE

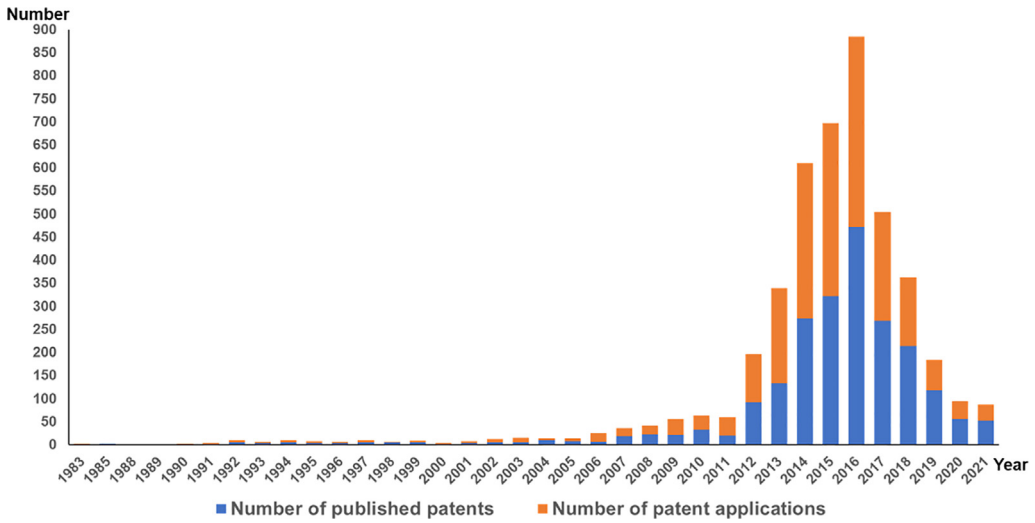

Fig. 10. Annual patent quantity of *Benincasae Exocarpium*.

Fig. 11. Application of *Benincasae Exocarpium.* in food and medicine.

used by Nie in the treatment of kidney diseases was 65.37% (Li, 2012).

In particular, BE can be used to treat urticaria, both acute and chronic. Dr. Chen had 495 prescriptions for urticaria, including 379 cases (76.57%) of BE (Xiao, 2021). BE treatment of acute urticaria in Guangdong folk has a long history. Later, under the guidance of folk experience, BE was designed as internal and external washing prescriptions, for the treatment of wind-heat and wind-cold acute urticaria (Huang, 1995).

Due to the reasons for pregnancy, the range of treatment options is greatly limited, but clinically, some doctors used BE and corn silk to prevent the occurrence of pregnancy poisoning. As wax gourd and corn are commonly used foods, they have less toxic and side effects, and are inexpensive and simple to prepare. Therefore, it is suitable for most pregnant women to prevent the occurrence of diseases at an early stage (Liu, 2017). Other doctors boiled BE and *Cyperi Rhizoma* (Xiangfu in Chinese), seasoned with honey, and relieved the swelling of the limbs and face of pregnant women (Guo, 2021). BE was widely used in clinical and was shown in Fig. 11.

6. Conclusion and prospect

BE has been used as a diuretic and dampness drug for thousands of years of clinical experience in the treatment of diseases. With practice and improvement, it gradually became a well-known medicine and food homologous substance. Current studies indicated that BE mainly contains flavonoids, alkaloids, tannins, trace elements, vitamins and other functional factors. Modern pharmacology of BE extract showed that BE had diuretic, hypoglycemic, lipid-lowering and antioxidant effects, but its specific active components were not clear. Guided by the theory of TCM, the effects of BE are detumescence, diuresis and antipyretic, which is a common drug in the treatment of nephrotic syndrome, diabetes and skin disease in TCM. At the same time, BE is also widely welcomed as a food. According to the history of medicine and food homology and modern pharmacological research of BE, it can be seen that it has very objective potential. Whereas studies on the efficacy of BE are mostly carried out on the extract, and its pharmacodynamic material basis and mechanism of action still need to be further studied. It is hoped that in future study, the quality evaluation, active fractionation and drug design of BE will be paid attention to by researchers.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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