Review Article

A Literature-Based Update on *Benincasa hispida* (Thunb.) Cogn.: Traditional Uses, Nutraceutical, and Phytopharmacological Profiles

Muhammad Torequl Islam, Cristina Quispe, Dina M. El-Kersh, Manik Chandra Shill, Kanchan Bhardwaj, Prerna Bhardwaj, Javad Sharifi-Rad, Rajib Hossain, Ahmed Al-Harrasi, Ahmed Al-Rawahi, Monica Butnariu, Lia Sanda Rotariu, Hafiz Ansar Rasul Suleria, Yasaman Taheri, Anca Oana Docea, Daniela Calina, and William C. Cho

1Department of Pharmacy, Life Science Faculty, Bangabandhu Sheikh Mujibur Rahman Science and Technology University, Gopalganj (Dhaka) 8100, Bangladesh
2Facultad de Ciencias de la Salud, Universidad Arturo Prat, Avda. Arturo Prat 2120, Iquique 1110939, Chile
3Pharmacognosy Department, Faculty of Pharmacy, The British University in Egypt (BUE), El Sherouk, Cairo Governorate, Egypt
4Department of Pharmaceutical Sciences, North South University, Bashundhara, Dhaka 1229, Bangladesh
5Department of Botany, Shoolini University of Biotechnology and Management Sciences, Solan-173229, H. P., India
6Facultad de Medicina, Universidad del Azuay, Cuenca, Ecuador
7Department of Nutrition and Dietetics, Faculty of Pharmacy, and Centre for Healthy Living, University of Concepción, 4070386 Concepción, Chile
8Natural and Medical Sciences Research Centre, University of Nizwa, Birkat Almouz, 616, Oman
9Babat's University of Agricultural Sciences and Veterinary Medicine "King Michael I of Romania" from Timisoara, 300645, Calea Aradului 119, Timis, Romania
10Department of Agriculture and Food Systems, The University of Melbourne, Australia
11Phytochemistry Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
12Department of Toxicology, University of Medicine and Pharmacy of Craiova, 200349 Craiova, Romania
13Department of Clinical Pharmacy, University of Medicine and Pharmacy of Craiova, 200349 42 Craiova, Romania
14Department of Clinical Oncology, Queen Elizabeth Hospital, Kowloon, Hong Kong

Correspondence should be addressed to Javad Sharifi-Rad; javad.sharifirad@gmail.com, Monica Butnariu; monicabutnariu@yahoo.com, Daniela Calina; calinadaniela@gmail.com, and William C. Cho; chocs@ha.org.hk

Received 5 May 2021; Revised 29 June 2021; Accepted 20 September 2021; Published 10 December 2021

Academic Editor: Anderson J. Teodoro

Copyright © 2021 Muhammad Torequl Islam et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*Benincasa hispida* (Thunb.) Cogn. (Cucurbitaceae) is an annual climbing plant, native to Asia with multiple therapeutic uses in traditional medicine. This updated review is aimed at discussing the ethnopharmacological, phytochemical, pharmacological properties, and molecular mechanisms highlighted in preclinical experimental studies and toxicological safety to evaluate the therapeutic potential of this genus. The literature from PubMed, Google Scholar, Elsevier, Springer, Science Direct, and database was analyzed using the basic keyword "Benincasa hispida.” Other searching strategies, including online resources, books, and journals, were used. The taxonomy of the plant has been made by consulting "The Plant List". The results showed that *B. hispida* has been used in traditional medicine to treat neurological diseases, kidney disease, fever, and cough accompanied by thick mucus and to fight intestinal worms. The main bioactive compounds contained in *Benincasa hispida* have cytotoxic, anti-inflammatory, and anticancer properties. Further safety and efficacy investigations are needed to confirm these beneficial therapeutic effects and also future human clinical studies.
1. Introduction

Food and food products are being used as medicines over centuries worldwide. Many species from the family Cucurbitaceae have been used as medicaments in various diseases in Ayurveda and ancient Chinese medicine. This family is also known as the gourd family. It provides approximately 5 to 6% of the total vegetables in the world. To date, 825 species from under 118 genera have been reported growing in temperate regions of the world [1]. It should be mentioned that the Cucurbit species can grow in diverse climatic conditions, including arid deserts, tropical, subtropical, and temperate regions. These various types of species are included in food systems and Indian traditional medicines. Generally, the gourd family vegetables provide vitamins, essential minerals, antioxidants, and soluble fibres [2].

The word “herb” derived from the Latin word “herba” and an old French word “herbe” refers to any part of the plant like fruit, seed, stem, bark, flower, leaf, stigma, or a root, as well as a non-woody plant. Many herbs are currently under-using as a source of foods, flavonoids, medicines, or perfumes as well as in certain spiritual activities. Ancient era literature including Unani manuscripts, Chinese writings, and Egyptian papyrus also depicted the use of herbs in various diseases. The Indian Vaids, Unani Hakims, and European and Mediterranean cultures are using herbs for more than 4000 years as medicines. Native people of Iran, Rome, Egypt, Africa, and America used medicinal herbs in healing habits. The Unani, Ayurveda, and Chinese Medicine are using herbal remedies systematically. These all are the potential sources of medicinal plant-based modern medicines. According to World Health Organization (WHO), about 80% of people in the world depend on herbal medicines to fulfil their basic health care needs, and around 21,000 species of plants have been identified as potential medicinal plants. In developed countries, around 25% of the total drugs come from plant origin, while in fast-developing countries as much as 80% [3].

*Benincasa hispida* (Thunb.) Cogn. (synonym: *Benincasa cerifera* Savi) (Cucurbitaceae) especially in Asian countries is considered as one of the famous crops under the Cucurbitaceae family that grows mainly for its fruits and well renowned for its nutritional and medicinal properties [4, 5]. Scientific reports suggest that *B. hispida* possesses many important nutritious substances, including vitamins, natural sugars, amino acids, organic acids, and mineral elements [4, 6, 7]. This review is aimed at sketching an up-to-date scenario on the indigenous uses, nutraceutical, and phytochemical composition along with the pharmacological activities of *B. hispida* based on database reports.

2. Review Methodology

Using the PubMed database and the search engines Google scholar, Elsevier, Springer, Science Direct, research articles, and reviews related to *B. hispida* were analyzed. Abstracts and papers peer reviewed were selected according to the objectives of the research: the molecular pharmacological mechanisms of action proven by preclinical experimental studies [8] and which scientifically justify the traditional uses of *B. hispida*.

Other sources of “grey literature” information such as Web pages, book chapters, and specialized monographs were also analyzed to obtain maximum updated information on the biological properties of this plant. The keywords used were “*Benincasa hispida*” or “traditional uses” or “phytochemistry” of “pharmacological properties” or “biological activities” or “toxicology” or “safety” or “side effects.” The scientific names of the plants were verified according to PlantList, and the chemical formulas were revised by consulting the PubChem database (https://scholar.google.com).

Inclusion criteria: the most relevant articles written in English on taxonomy, ethnopharmacology, phytochemistry, pharmacology, various biological activities, and toxicity of this plant were included and analyzed.

Exclusion criteria: the papers containing homoeopathic preparations, papers written in languages other than English, publications without pharmacological mechanisms of action.

3. Botany and Traditional Uses

3.1. Botany (Plant Profile). *B. hispida* (Figure 1), also known as *kundur fruit*, *chalkumra*, *wax gourd*, *winter gourd*, *ash pumpkin*, and *(alu) puhul*, a creeper grown for its very big size fruit, is eaten as a green mature vegetable or greens [9–11].

There is a fine hairs fuzzy coating outer side of the young fruit and has solid thick white flesh of sweet in tastes. The mature fruit sheds its hairs and forms a waxy white coating, giving the name of “wax gourd.” The gourd wax coating increases the storage facilities of it. It can grow of a length up to 80 cm and also have broad leaves and yellow flowers. The taste is rather bland. *B. hispida* is a native of South and Southeast Asia. However, it is commonly grown all over Asia, including Japan, Burma, Ceylon, Sri Lanka, Java, and Australia [10].

| Taxonomy | Kingdom: Plantae |
|----------|-----------------|
| Phylum:  | Tracheophyta    |
| Class:   | Magnoliopsida   |
| Order:   | Cucurbitales    |
| Family:  | Cucurbitaceae   |
| Genus:   | Benincasa       |
| Species: | *Benincasa hispida* (Thunb.) Cogn. |

3.2. Traditional Uses and Ethnopharmacology. In India, *B. hispida* is used as a winter season vegetable for a wide variety of diseases. Its medicinal properties have been also recognized in the Ayurvedic system of medicine, spiritual traditions of India and Yoga. In Vietnam, its soup (cooked with pork short ribs) is traditionally used by breastfeeding mothers. In north India and almost all regions in Bangladesh, it is added with pulses like as moong which usually crushed, along with wax gourd, makes a dish locally called *bori*, which after sun drying is used in curry dishes and eaten with rice or chapati [12]. To make wax gourd soup in China, it is used in stir-fries or added into pork or pork/beef bones, which often served in the scooped-out gourd, carved by
scraping off the waxy coating. It is also cut into pieces, candied and normally eaten during the time of New Year festivities, or used as filling in Sweetheart cake. For the Moon Festival, the Chinese and Taiwanese also used it in mooncakes as a base filling. It is candied by the people of the Philippines and is used as a pastry filling for bakpia. In some savoury soups and stir-fries, it also acts as an ingredient. In Nepal, India, and Bangladesh, the tendrils, shoots, and leaves of the plant are consumed as green vegetables [6].

*B. hispida* is widely used in Chinese medicine, in the treatment of fever, cough accompanied by thick mucus and urinary disorders, it is used especially in bark with a very good diuretic effect. The fruit is recommended for overweight people who want to follow diets. In Ayurvedic medicine, it is used in the treatment of epilepsy, cough, lung disease, hiccups, asthma, internal bleeding, and urinary retention. In India, a fruit compote called Petha Cubes is made from the pulp of the fruit, which is recommended for vegetarians [13].

The fruit is also used in peptic ulcer, and it is also used in diabetes mellitus, urinary infection, haemorrhages from internal organs, insanity, epilepsy, and other nervous disorders in Ayurveda [14]. The fruit is sweet and traditionally used as a cooling, styptic, antiperiodic, laxative, diuretic, tonic, aphrodisiac, and cardiotoxic, and also in jaundice, dyspepsia, urinary calculi, blood disease (e.g., haemorrhages from internal organs), insanity, epilepsy, asthma, diabetes, vitiatated conditions of pitta, fever, menstrual disorders, and balancing the body heat [15] (Figure 1).

### 3.3. Phytochemical Profile

#### 3.3.1. Nutritional Composition.

The edible portion of *B. hispida* contains moisture (93.80-96.80/100 g), proteins (0.30-0.70/100 g), carbohydrates (1.10-4.00/100 g), fat (0.02-0.20/100 g), fibre (0.50-2.10/100 g), and ash (0.27-0.70/100 g) [6, 16, 17]. The fruit contains water-soluble polysaccharides [18], such as arabinogalactans [19]. The fruit pulp contains homogalacturonan, β-(1→4)-D-galactan, acidic arabinan [20], and natural sugars (e.g., glucose and fructose) [21]. The mature fruit also contains organic acids such as malic and citric acid.

#### 3.3.2. Chemical Phytoconstituents.

The leaf contains alkaloids, flavonoids, steroids [22], and the fruit amino acids, pectic polysaccharides [20], hemicellulose polysaccharides [18], terpenes and terpenoids, flavonoid C-glycosides, steroids [23], proteins [24], phenols, alkaloids, glycosides, tannins, saponins [25], hydroxybenzoic acids, flavonols, hydroxynamic acids, and triterpenes [9] (Figure 2).

The seeds contain proteins [24], carbohydrates, phenolic compounds, amino acids, flavonoids, sterols [26], glycosides,
alkaloids, fixed oils and fats, phenolic compounds, steroids [27], and unsaturated fatty acids [28]. The peel contains alkaloids, saponins, steroids, carbohydrates, flavonoids [29], tannins, carotenoids, oxalates, and phytate [17].

The root contains proteins [24]. The fruit contains many volatile compounds, including (E,E)-2,4-nonadienial, (E)-2-hexenal, n-hexanal, n-hexyl formate, (E,E)-2,4-heptadienal, (Z)-3-hexenial, (E)-2-heptenal, 1-octen-3-ol [30], 2,5-dimethylpyrazine, 2-methyl pyrazine, 2-ethyl-5-methyl pyrazine, and 2,6-dimethylpyrazine, 2,3,5-trimethylpyrazine [30].

B. hispida is rich in phenolic compounds. Several other bioactive compounds present in it are isomultiflorenyl acetate, isovitexin, 1-sinapoylglucose, multiflorenol, 5-gluten-3-β-yacetate, alnusenol, and benzylalcolochol-O-α-l-arabignopyransyl-(1-6)-β-d-glucopyranoside [31]. The most representative phytochemicals present in B. hispida have been shown in Figures 2–5 and Table 1.

4. Pharmacological Activities

4.1. Antioxidant Effects. Oxidative stress is a term used for free radical diseases [51, 52]. It is defined as the imbalance between free radicals and antioxidants, given that oxidants (free radicals) are more and have a destructive potential on the human body [53, 54].

The methanolic seed extract showed a concentration-dependent (25–200 μg/mL) 2,2-diphenyl-1-picrylhydrazyl (DPPH) and hydrogen peroxide radical scavenging effects [55]. Another study revealed that the ethanolic seed extract shows better DPPH and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) radical scavenging along with total phenolic content (TPC) than its ethyl acetate and n-hexane extracts [43]. The seed oil (0.1 mg/mL) also showed significant DPPH and ABTS radical scavenging capacity [56]. This study also determined the TPC in seed oil. The aqueous extract of this plant reduced reactive oxygen species (ROS) in human umbilical vein endothelial cells (HUVECs) [57].

Polysaccharides of fruit extract showed DPPH free radicals scavenging activity with an EC_{50} value of 0.98 mg/mL [50]. The seed oil also showed DPPH and ABTS radical scavenging capacity. However, the antioxidant activity was lower than the catechin and BHT at the same concentration (0.1 mg/mL) [44]. Petroleum ether and methanol fruit extracts increased in catalase (CAT) levels in gastric ulcer rats [58]. Hispidalin isolated from this herb also showed DPPH radical scavenging and inhibition of lipid peroxidation capacity [59]. The aqueous fruit extract significantly increased the antioxidant status as well as levels of vitamin C concentration in gastric juice or rats [60].

Antioxidant effects of various parts of B. hispida on various test models have been also observed by several authors [17, 28, 29, 56, 61]. Table 2 shows the antioxidant effects of various parts of B. hispida.

4.2. Anti-Inflammatory Effect. The methanolic seed extract (100–300 mg/kg, p.o.) showed dose-dependent anti-inflammatory effects on carrageenan-induced paw oedema rat (n = 6) model [55]. The fruit peel methanic extract showed an anti-inflammatory effect on egg albumin-induced inflammation in rats [62]. The petroleum ether and methanolic fruit extract of B. hispida (300 mg/kg, p.o.) showed a dose-dependent anti-inflammatory effect on cotton pellet-induced granuloma models in rats, carrageenan-induced paw oedema, and histamine-induced paw oedema [58].

4.3. Antimicrobial, Antihelmintic, and Larvicidal Effects. Due to the excessive use of antibiotics that can lead to the development of antibiotic resistance of various strains of bacteria [63–65], attempts have been made to use natural antibiotic alternatives [66, 67]. Most of these options include plants with antiviral and antibacterial properties that can be
effective against gram-negative and gram-negative germs, which are often difficult to eradicate [68, 69]. The methanolic whole plant extract (500 μg/disc) was found to act against Pseudomonas aeruginosa and Vibrio parahaemolyticus [70]. In the latter case, the zone of inhibition was 6 mm only. Hispidalin, an isolated compound from this herb, was found to act against several bacteria (e.g., Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, and Salmonella...
**Figure 5**: The chemical formulas of some most important representative fatty acids, phenolic and flavonoid, oxygenated hydrocarbons, and hydrocarbons from *Benincasa hispida*.

4.4. Cytotoxic and Anticancer Effects. Cancer is a term used to define malignancies in which abnormal cells multiply in an uncontrolled and continuous manner and can invade the surrounding healthy tissues [73, 74]. Abnormal cells come from any tissue in the human body and can occur anywhere in the body [75-77]. Natural anticancer alternatives can have a direct effect on malignant cells, as well as by stimulating the body’s immune capacity in the fight against the aggression of carcinogenic factors, internal or external [78, 79]. The favourable effects of some medicinal plants are due to the main biochemical components: flavonoids—which inhibit the activity of carcinogens and prevent the metastasis of malignant cells; carotenoids—which protect the body against colon cancer; terpenes in essential oils—block the action of carcinogens, having a strong antioxidant action; β-carotene, a powerful antioxidant with anticancer protection and a recognized inhibitor of malignant cells; antioxidant vitamins C, E, and A, destroy free radicals, prevent cancer, and block the metastasis process [80-83].

The fruit, seed, and root proteins (10-1000 μg/mL) exerted a concentration-dependent cytotoxic effect on *Artemia salina*. The median lethal concentration (LC50) values of fruit, seed, and root extract were 44, 41, and 50 μg/mL, respectively [24]. In this study, the root proteins inhibited the proliferation of HeLa and K-562 cells by 28.50 and 36.60%, respectively. Another study reveals that the whole plant methanolic extract (5-50 μg/mL) exerted a cytotoxic effect on *A. salina* (LC50: 45.187 μg/mL) [70]. Moreover, the aqueous seed extract (20-800 μg/mL) did not exert cytotoxic effects on HUVECs and normal fibroblast (NIH/3T3) cells. On male C57BL/6 mice, the extract showed a potent inhibitory effect on basic fibroblast growth factor (bFGF) induced angiogenesis [84]. The aqueous extract (1-20 μg/mL) also reduced cell adhesion molecules activation by inhibiting monocyte adhesion, ROS, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) on high glucose (25 mM) induced HUVECs cells [57] (Figure 6).

Table 4 shows the cytotoxic and anti-cancer effects of various parts of *B. hispida*, and Figure 1 summarizes the most important anticancer mechanism.
4.5. Gastrointestinal Protective Effects

4.5.1. Gastroprotective Effect. Fresh juice (1-4 mL/animal, p.o.), ethanol (12, 24 and 48 mg/kg, p.o.), and pet ether extract (0.75, 1.5 and 3 mg/kg, p.o.) in swimming stress, aspirin plus restraint, serotonin-induced ulcers, and indomethacin plus histamine displayed a dose-dependent antiulcerogenic effect in rats and mice [13].

The petroleum ether and methanol fruit extracts (300 mg/kg, p.o.) significantly ($P < 0.05$) reduced ulcer index, vascular permeability, and malondialdehyde (MDA) content, while an increase in CAT levels in comparison to

---

**Table 1: Chemical phytoconstituents of Benincasa hispida (Thunb.) Cogn.**

| Compounds | Plant parts | Locality/country | References |
|-----------|-------------|------------------|------------|
| E-2-hexenal, n-hexanal and n-hexyl formate; however, 2,5-dimethylpyrazine, 2,6-dimethylpyrazine, 2,3,5-trimethylpyrazine, 2-methylpyrazine, 2-ethyl-5-methylpyrazine | Fruit | Taipei, Taiwan/China | [30] |
| Cucumisin-like protease | Sarcocarp | Kagoshima/Japan | [32] |
| Triterpenes, sterols, flavonoid C-glucoside, benzyl glycoside, alnusenol, multioloreol | Fruit | Kyoto/Japan | [33] |
| Osmotin-like protein | Seeds | New York/USA | [34] |
| Chitinase | Seeds | New York/USA | [35] |
| Astilbin, catechin, naringenin | Fruit | Hainan/China | [31] |
| Di-2-ethylhexyl phthalate | Fruit | Hainan/China | [36] |
| W-sitosterol, V-amyrin, quercetin | Stem | Visakhapatnam/India | [37] |
| β-Carotene | Fruit | Faisalabad/Pakistan | [16] |
| Tryptophan | Fruit | Gwalior/India | [38] |
| Linoleic, palmitic, oleic, and stearic acids | — | — | — |
| Acetoin, octanil, nonanal | Fruit | Tenerlo, Pahang/Malaysia | [39] |
| α-Tocopherol, δ-tocopherol, linoleic acid, β-sitosterol, campesterol, stigmasterol, Δ5-avenasterol | Fruit | Serdang, Selangor/Malaysia | [41] |
| Galactose, glucose, xylose, sorbose | Peel | Karnataka/India | [42] |
| Linoleic acid, linolenic acid | Seeds | Serdang, Selangor/Malaysia | [43] |
| Myristic acid, palmitoleic acid, oleic acid, linoleic acid, stearic acid, α-linolenic acid, palmitic acid, other saturated and unsaturated fatty acids | Seed oil | Serdang, Selangor/Malaysia | [44] |
| 3α,29-O-di-trans-cinnamoyl-D-C-friedooleana-7,9(11)-diene, oleanolic acid 28-O-β-D-xylopyranosyl-[β-D-xylopyranosyl-(1 → 4)]-(1 → 3)-α-L-rhamnopyranosyl(1 → 2)-α-L-arabinopyranoside, oleanolic acid 28-O-β-D-glucopyranosyl-(1 → 3)-β-D-xylopyranosyl-[β-D-xylopyranosyl-(1 → 4)]-(1 → 3)-α-L-rhamnopyranosyl-(1 → 2)-α-L-arabinopyranoside, multifloroenol, isomultifloronyl acetate, stigmasterol, stigmasterol 3-O-β-D-glucopyranoside, α-spinasterol, α-spinasterol 3-O-β-D-glucopyranoside, β-sitosterol, daucosterol, arbutin, nicotinic acid, (+)-pinonesolin, ethyl β-D-glucopyranoside | Fruit | Jinghong/China | [45] |
| Phloem lectin-like protein | Exudate | Fukuoka/Japan | [46] |
| Linoleic acid, palmitic acid, oleic acid, stearic acid | Seeds | Rambagh, Allahabad/India | [47] |
| Gallic acid | Fruit | Kota Bharu/Malaysia | [15] |
| Lupeol | Seeds | Mumbai/India | [27] |
| Gallic acid, linoleic acid | Seeds | Serdang, Selangor/Malaysia | [28] |
| β-Sitosterol | Seeds | Serdang, Selangor/Malaysia | [28] |
| Ascorbic acid | Fruit | Kubang Kerian, Kelantan/Malaysia | [49] |
| β-Carotene, ascorbic acid | Peel | Mysore/India | [17] |
| Polysaccharides | Fruit | Guangzhou/China | [50] |
| Gallic acid, catechin, epicatechin, rutin, quercetin, quercetin-3-D-galactoside, trans-ferrulic acid, oleic acid, ursolic acid, methanol plus histamine | Fruit | Buzau/Romania | [9] |
the control group in pylorus ligated (PL) gastric ulcers, ethanol-induced gastric mucosal damage, and cold restraint stress- (CRS-) induced gastric ulcer rat models [58]. The fruit extract (1 mL/kg, p.o.) also decreased ulcer index as well as MDA, superoxide dismutase (SOD), and vitamin C levels in indomethacin-induced gastric ulcer in rats [23].

The hydromethanol, ethyl acetate, and aqueous ripe fruit extracts (20 mg/kg, p.o./alternative days) were treated for 14 days in ranitidine (5 mg/kg, p.o.) induced hypochlorhydria in rats. The aqueous extract showed better effects on the test animals. It increased the antioxidant status as well as levels of pepsin, vitamin C, and gastric juice chloride concentration than the other extracts [60]. On the other hand, the extract of fruits with the whole plant of *Fumaria vaillantii* Loisel (1:1) (20 mg/kg, p.o.) was administrated in ranitidine (5 mg/kg) induced hypochlorhydria in rats as pre-and cotreatment manners. The extract significantly ($P < 0.05$) enhanced the concentration of pepsin, iron levels in serum, chloride level in gastric juice, and liver along with blood haemoglobin level in experimental animals [85].

A prospective pilot study on dyspeptic patients ($n = 20$) (baseline between 30 days and 45 days) aged between 18 and 45 years with only single dose of 200 mL fruit juice every morning in empty stomach for thirty days suggests that a significant improvement of pain, nausea, belching, retrosternal burning, and bowel habits among the patients [86].

Table 5 shows the gastrointestinal-protective effects of various parts of *B. hispida*.

| Extract/isolated compounds | Test system | Results | References |
|---------------------------|-------------|---------|------------|
| Crude oil from seeds      | DPPH, ABTS, TPC | DPPH: $EC_{50} = 0.1$ mg/mL. ABTS: $EC_{50} = 0.1$ mg/mL. Significant antioxidant effect. | [56] |
| Seeds extract             | DPPH, ABTS, total phenolic content | Significant antioxidant effect. Standards: methyl ether, fatty acids $EC_{50} = 10 – 100 \mu$g/mL. | |
| Methanolic and aqueous peel extracts | DPPH | Concentration-dependent radical scavenging activity. The methanolic extract exhibited a better antioxidant effect. Standards: DPPH. TPC: $EC_{50} = 81.3 \pm 1.4 \mu$g gallic acid/g TFC: $EC_{50} = 486.8 \pm 4.1 \mu$g catechin/g dry mass DPPH: $EC_{50} = 0.6 – 3$ mg/mL. | [29] |
| Aqueous seeds extract     | DPPH, ABTS, H$_2$O$_2$, linoleic acid oxidation nitrite scavenging assay | Concentration-dependent antioxidant activity. Standards: catechin 0.05-0.5 mg/mL, BHT, ascorbic acid 10 mg/mL. DPPH: $EC_{50} = 0.1$ mg/mL. | [61] |
| Seed oil                 | ABTS radical scavenging assay | The antioxidant activity of the seed oil was lower than the catechin and BHT at the same concentration. Standard: FAME. DPPH: $EC_{50} = 2 – 40 \mu$g/mL $EC_{50} = 40 \mu$g/mL. | [44] |
| Hispidalin               | DPPH | Significant DPPH radical scavenging and inhibition of lipid peroxidation capacity. Standard: methyl ether. | [59] |
| Methanol, ethanol, aqueous peel extracts | Reducing power assay | Significant antioxidant effect. Standard: acarbose 20, 40, 60, 80, 100 $\mu$g.mL$^{-1}$ | [17] |
| Seed extract             | DPPH, ABTS | Significant antioxidant effect. Standard: FAME. $EC_{50} = 0.98$ mg/mL. | [28] |
| Polysaccharides of fruit extract | DPPH | Significant antioxidant effect. Standard: glucose | [50] |

**Table 2: Antioxidant properties of different parts or their extracts/fractions of isolated compounds.**

Abbreviations: TPC: total phenolic contents; TFC: total flavonoid contents (TFC); ABTS: 2, 2′-azinobis (3-ethylbenzothiazoline-6-sulfonic acid); DPPH: 2,2-diphenyl-1-picrylhydrazyl free radical-scavenging ability; BHT: antioxidant butylated hydroxytoluene; FAME: fatty acid methyl ester; EC 50: the half-maximal effective concentration.

4.5.2. Antidiarrheal Effect. Diarrhoea is a condition characterized by frequent watery stools, and usually, diarrhoea persists for a few days and is treated with diet [87]. But there are also more serious situations, in which diarrhoea requires drug/complementary treatment and is more difficult to cure [88, 89].
### Table 3: Antimicrobial, anthelmintic, and larvicidal effects of different parts or their extracts/fractions or isolated compounds.

| Extract/isolated compounds | Dose/concentration model (in vitro/in vivo) | Results/mechanisms | References |
|----------------------------|--------------------------------------------|--------------------|------------|
| **Antimicrobial effects**  |                                            |                    |            |
| Methanolic whole plant extract | *Pseudomonas aeruginosa*, *Vibrio parahaemolyticus* (<i>In vitro</i>) | IC<sub>50</sub> = 500 μg/disc Zone of inhibition = 6 mm | [70] |
|                            | Standard: DMSO                              |                    |            |
|                            | *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Salmonella enterica*; <i>In vitro</i> | Antibacterial: MIC = 30 – 120 μg/mL, Antifungal: MIC = 100 – 200 μg/mL | [59] |
|                            | Standard: acetoin (0.01–20 μg/μL)          |                    |            |
| Hispidalin                 | *Fungi*: *Penicillium chrysogenum*, *Fusarium solani*, *Aspergillus flavus*, *Colletotrichum gloeosporioides* (<i>In vitro</i>) | Antibacterial: MIC = 6.1 – 14.5 μg/mL | [11] |
|                            | *Staphylococcus aureus*, *Micrococcus luteus*, *Escherichia coli*, *Klebsiella pneumoniae* (<i>In vitro</i>) |                    |            |
|                            | Standard: DMSO 150 μL                       |                    |            |
| Aqueous peel extract       |                                            |                    |            |
| Ethanollic seed extract    | *Pheretima posthumani* (<i>in vitro</i>)   | IC<sub>50</sub> = 20, 40, and 60 mg Dose-dependent anthelmintic effect | [72] |
|                            | Standard: phenytoin sodium                  |                    |            |
| **Anthelmintic effect**    |                                            |                    |            |
| Phloem lectin-like protein from the exudate | *Samia ricini* larvae (<i>in vitro</i>) Standards: Precision Plus Protein™- serum albumin | ↑ inhibitory activity against the larvae Dose: 70 μg/g | [46] |

Abbreviations: IC<sub>50</sub>: value concentration that inhibits cell growth by 50%; MIC: minimum inhibitory concentration.

---

**Figure 6:** A schematic diagram with anticancer mechanisms of natural compounds from <i>Benincasa hispida</i>. Legend: blue arrow: inhibition, reduction; red arrow: increase, stimulation, ROS reactive oxygen species, NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells).
The *B. hispida* fruit methanolic extract displayed potential anti-diarrheal activity on the castor oil-induced diarrheal rat model. It was also seen to inhibit induced PGE2, enter pooling, and reduce in the motility of gastro-intestine in rats [90]. The same extract also possessed a pooling, and reduce in the motility of gastro-intestine in rat model. It was also seen to inhibit induced PGE2, enter pooling and gastrointestinal signs of chronic diseases such as cardiovascular disease, fatty liver, endocrine disorders, and diabetes [94, 95]. Methanolic fruit extract (0.2-1 g/kg, i.p.) reduced food intake, suggesting anorectic activity in mice [96]. Hexane fraction from the aqueous fruit extract inhibited adipocyte differentiation by blocking leptin gene expression, peroxisome proliferator-activated receptor gamma (PPARγ), and CCAAT enhancer-binding protein alpha (C/EBPα), resulting in the reduction of lipid accumulation, increased releasing of glycerol and intracellular triglycerides in 3T3-L1 cells [97].

### 4.7. Neuroprotective Properties

#### 4.7.1. Anticonvulsant Effects

The fruit methanol extract (0.2-1 g/kg, p.o.) showed a dose-dependent anticonvulsant activity in pentylenetetrazole, strychnine and picrotoxin, and maximal electro seizures model [98]. On the other hand, the fruit peel methanolic extract exerted a dose-dependent (0.25-1.5 g/kg) anticonvulsant effect on pentylenetetrazol-induced convulsion in mouse models [62]. Ethanolic seed extract (250 and 500 mg/kg, p.o.) showed a dose-dependent anticonvulsant effect in anticonvulsant activity in Swiss albino mice [72].

#### 4.7.2. Effects on Alzheimer’s Disease

Neurodegenerative diseases such as Alzheimer’s disease are characterized by the presence of the central nervous system, protein aggregates, inflammation, and oxidative stress [99, 100]. Several factors are involved in triggering neurodegenerative diseases, including the lifestyle that leads to the gradual deterioration of the health of the nervous system, with serious consequences on the quality of life of the patient with such a disease [101]. Although there are still no treatment solutions to restore nerve function in neurodegenerative diseases, more and more studies insist on several natural formulas that have been shown to have the effect of reducing symptoms and improving the quality of life of patients with neurodegenerative diseases [102, 103].

### Table 4: Cytotoxic and anticancer effects of various parts of *B. hispida* extracts/fractions.

| Extract/isolated compounds | Model dose/concentration | Results/mechanisms | References |
|---------------------------|--------------------------|--------------------|------------|
| Aqueous seed extract      | HUVECs, NIH/3T3 cells/ *in vitro* Male C57BL/6 mice/ *in vivo* | No cytotoxicity on HUVECs, NIH/3T3 cells decrease bFGF-induced angiogenesis in mice | [84] |
| Fruit, seed, root proteins| IC₅₀ = 44, 40-50 μg/mL | Decrease cell proliferation by 28.50-36.80% | [24] |
| Aqueous extract           | IC₅₀ = 1-20 μg/mL on high glucose (25 mM) Standards: glucose 25 mM, glucose and ABH 5 μg/mL, 20 μg/mL | Decrease cell adhesion molecules activation, Decrease ROS, NF-κB Decrease inhibiting monocyte adhesion | [57] |
| Methanolic/whole plant extract | Artemia salina/ *in vitro* IC₅₀ = 45.186 μg/mL | Increase cytotoxic effect concentration-dependent | [70] |

Abbreviations: IC₅₀: value concentration that inhibits cell growth by 50%; bFGF: basic fibroblast growth factor; ROS: reactive oxygen species; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NNGH: N-isobutyl-N-(4-methoxyphenylsulfonyl)-glycylhydroxamic acid.
### Table 5: Gastrointestinal protective effects of different parts or their extracts/fractions of *B. hispida.*

| Gastroprotective Effect | Model/dose/concentration | Mechanisms | References |
|-------------------------|--------------------------|------------|------------|
| **Antulcer effect**     |                          |            |            |
| Fresh juice, petroleum ether, alcoholic/fruits extract | Aspirin plus restraint, serotonin-induced ulcers, indomethacin plus histamine | ↓ ulcer index formed by several ulcerogenic | [13] |
|                         |                          |            |            |
| Fresh juice, ethanol, petroleum ether extracts (5% v/v) | Aspirin plus restraint, swimming stress, indomethacin plus histamine, and serotonin-induced ulcers | Dose-dependent anti-ulcerogenic effect | The fresh juice treatment for 3 months did not change the indices (i.e., WBC, RBC counts HCT, HB, MCV, MCH urea, and sugar) No behavioural changes in experimental animals. | [13] |
| Petroleum ether, methanol/fruits extract | Pylorus ligated (PL) gastric ulcers, ethanol-induced gastric mucosal damage, cold restraint-stress- (CRS-) induced gastric ulcer | ↓ ulcer index | [58] |
| Fruit extract | Indomethacin-induced gastric ulcer | ↓ ulcer index, ↓ MDA, ↑ vitamin C | [23] |
| Hydromethanol, aqueous ripe fruit, ethyl acetate extracts | Ranitidine (5 mg/kg) induced hypochlorhydria | ↑ antioxidant status, ↑ pepsin, ↑ vitamin C, ↓ chloride in gastric juice | [60] |
| Fruit extract with the whole plant of *Fumaria vaillantii* Loisel (1:1) | Ranitidine (5 mg/kg) induced hypochlorhydria | ↓ iron levels in serum, ↑ pepsin, ↑ gastric juice chloride level and liver | [85] |
| Fruit juice | Prospective pilot study | ↓ blood haemoglobin level | |
| **Antidiarrheal effect** |                          |            |            |
| Methanolic fruit extract | Castor oil-induced diarrheal, PGE2-induced, enter pooling and charcoal meal models | ↓ activity against castor oil-induced diarrhoea; ↓ gastrointestinal motility | [90] |
| Methanolic fruit extract | Castor oil, charcoal meal, and anti-enter pooling models in rats | ↓ activity against castor oil-induced diarrhoea; ↓ gastrointestinal motility | [90] |

Abbreviations and symbols: ↓(increased); ↑(decreased); WBC: white blood cells; RBC: red blood cells; HCT: hematocrit; HB: haemoglobin; MCV: mean corpuscular volume; MCH: mean corpuscular haemoglobin concentration; MDA: malondialdehyde; CAT: catalase; SOD: superoxide dismutase; PGE2: prostaglandin E2.

The fruit extract at a dose of 400 mg/kg (p.o.) showed a protective effect on colchicine-induced Alzheimer’s disease rats, possibly through the presence of both vitamin E and β-carotene protecting rat neurons against oxidative stress. On the other hand, the aqueous fruit pulp extract (100-450 mg/kg, p.o.) dose-dependently increased SOD, CAT, and GSH, while reduced in LPO levels in the colchicine-induced Alzheimer’s rat model [16].

4.7.3. Effects on Memory and Cognitive Behaviour. Cognitive disorders are characterized by changes in brain structure and function that affect learning, orientation, judgment, memory, and intellectual abilities [104–106]. The methanolic fruit extract (200, 400, or 600 mg/kg, p.o.) showed a significant dose-dependent anticompulsive effect in marble-burying and motor coordination test models in mice [38]. The petroleum ether, methanolic, and aqueous fruit extracts (100, 200, and 400 mg/kg, p.o.) showed a dose-dependent nootropic activity in the cognitive behaviour mouse model [107]. Kumar and Nirmala [108] also studied the possible nootropic effects of the fruit on experimental animals.

4.7.4. Antidepressant and Anxiolytic Effects. Anxiety is defined as a diffuse fear, without a well-defined cause regarding various events of daily life [109]. Methanolic fruit extract (50, 100, and 200 mg/kg, p.o.) showed a dose-dependent
### Table 6: Other pharmacological activities of *Benincasa hispida* (Thunb.) Cogn.

| Extract/isolated compounds | Model dose/concentration | Results/potential mechanisms | References |
|----------------------------|---------------------------|-----------------------------|------------|
| **Lipid-lowering effect**  |                           |                             |            |
| Hexane, chloroform, ethyl acetate/aqueous fruit extract | 3T3-L1 cells/*in vitro* | Hexane extract: ↓ adipocyte differentiation, ↓ PPARγ, ↓ C/EBPα, ↓ leptin gene expression, ↓ lipids accumulation, ↑ releasing of glycerol, ↑ triglycerides | [97] |
| **Antidiabetic effect**    |                           |                             |            |
| Methanolic/stem extract    | Alloxan-induced diabetes Rats/*in vivo* | ↓ blood glucose level dose-dependent | [37] |
| Chloroform/fruits extract  | Alloxan-induced diabetes Rats/*in vivo* | Dose: 50, 100, 200 mg/kg p.o. | [91] |
| Ethanol, hexane, ethyl ethanoate/leaf extract | STZ-induced diabetes Mice/*in vivo* | Dose: 250, 500 mg/kg p.o. | [22] |
| **Antiobesity effect**     |                           |                             |            |
| Methanolic fruit extract   | Mice/*in vivo* | Anorexic activity | [96] |
| **Antiaging of skin**      | Petroleum ether, chloroform, ethyl acetate, methanol/dried fruit pulp extract | Stratum corneum of human skin and dansyl chloride fluorescence models *In vitro* | Cream prepared from the fruit extract showed the significant antiaging effect | [12] |
| **Effects on other diseases** |                           |                             |            |
| Fruit methanol extract     | Antigen-antibody induced reaction in rats exudate cells/*in vitro* | ↓ histamine release, anti-inflammatory effect | [33] |
| Methanolic fruits extract  | Histamine and acetylcholine-induced bronchospasm Guinea pigs/*in vivo* | Bronchodilator effect: dose-dependent protection against histamine and acetylcholine-induced bronchospasm | [115] |
| Petroleum ether, methanolic/fruits extract | Histamine stimulated paw oedema carrageenan- stimulated paw oedema cotton pellet stimulated granuloma Rats/*in vivo* | ↓ histamine release Anti-inflammatory effect | [58] |
| Juice                      | Isolated rat aortic ring/*in vitro* | Antihypertensive effect dose-dependent | [116] |
| Methanolic fruit extract   | Cultured porcine endothelial cells/*in vitro* | ↑ relaxation, ↓ contraction of isolated rat aortic ring | |
|                           | Rats/*in vivo* | ↑ NO in cultured porcine aortic endothelial cells | |
|                           | Dose: 0.4–1.6 mL/kg, i.v. |                             |            |
| Ethanolic seeds extract    | Renal ischemia/reperfusion injury model Rats/*in vivo* | Nephroprotective | [117] |
|                           | Dose: 500 mg/kg/day, p.o. for 5 days | ↓ MDA, ↑ SOD, CAT, ↑ GSH | |
| Neuroprotective effects    | Ethylene glycol induced chronic Hyperoxaluria model Rats/*in vivo* | Nephroprotective | [118] |
|                           | Dose: 250, 500 mg/kg, p.o. for 35 days | ↓ urinary oxalate, ↓ endogenous oxalate synthesis, ↓ urinary protein excretion, ↓ kidney oxalate and calcium; ↑ elevated serum levels of sodium, creatinine, calcium, phosphorus | |
| Fruit juice                | Morphine addiction model Mice/*in vivo* | The development of morphine addiction prevented along with the suppression of opioid withdrawal symptoms | [113] |
antidepressant-like effect in TST and FST models possibly through GABAergic involvement in mice in Swiss mice [110].

Petroleum ether, methanolic, and aqueous fruit extracts (100, 200, and 400 mg/kg, p.o.) confirmed a dose-dependent anxiolytic activity in mice [107]. Effects of various parts of B. hispida on the nervous system have been shown in Table 6.

4.8. Analgesic and Antipyretic Effects. The methanolic fruit extract (200, 400, and 600 mg/kg, p.o.) showed a dose-dependent analgesic effect in acetic acid-induced writhing and hot plate model in mice [111]. The ethanolic seed extract (250 and 500 mg/kg, p.o.) also showed a dose-dependent anticonvulsant effect on the rats (n = 6) model [72]. The methanolic leaf extract (50, 100, 200, 400 mg/kg, p.o.) exerted a dose-dependent analgesic effect in an acetic acid-induced writhing mouse model [112]. Petroleum ether, methanolic, and aqueous fruit extracts (100, 200 and 400 mg/kg, p.o.) showed a dose-

**Table 6: Continued.**

| Extract/isolated compounds | Model dose/concentration | Results/potential mechanisms | References |
|---------------------------|--------------------------|------------------------------|------------|
| Methanolic fruit extract  | Spontaneous motor, muscle relaxant, antihistaminic effect and barbiturate induced hypnosis models Mice, rats, and guinea pigs/in vivo Dose: 200-3000 mg/kg, p.o. Pentyleneetetrazole, strychnine, picrotoxin, and maximal electro seizures model Rats/in vivo Dose: 0.2-1 g/kg, p.o. Acetic acid-induced writhing and hot plate Model Mice/in vivo Dose: 200, 400, 600 mg/kg, p.o. Colchicine-induced Alzheimer's model | ↑ barbiturate induced hypnosis ↑ antihistaminic activity | [114] |
| Fruit methanol extract    |                          | Dose-dependent anticonvulsant activity | [98] |
| Methanolic fruit extract  |                          | Dose-dependent analgesic effect | [111] |
| Aqueous pulp extract      | Rats/in vivo Dose: 100-450 mg/kg, p.o. | ↑ SOD, ↑CAT, ↑GSH, ↓LPO dose-dependent | [16] |
| Ethanolic seed extract    | Rats/in vivo Dose: 250, 500 mg/kg, p.o. | Dose-dependent analgesic and antipyretic effects | [26] |
| Methanolic fruit extract  | Mice/in vivo Dose: 200, 400, 600 mg/kg, p.o. | Significant dose-dependent anticonvulsant activity | [38] |
| Methanolic leaf extract   | Mice/in vivo Dose: 50, 100, 200, 400 mg/kg, p.o. | Dose-dependent analgesic effect | [112] |
| Fruit peel methanolic extract | Egg albumin-induced inflammation in rats; acetic acid-induced writhing, formalin-induced pain, hot plate-induced, and pentyleneetetrazol-induced convulsions Mice/in vivo Dose: 50, 100, 200, 400 mg/kg, p.o. | Dose-dependently (0.25-1.5 g/kg) inhibited acetic acid-induced writhing, formalin-induced pain licking, and hot plate-induced pain in mice. Significantly inhibition of egg albumin-induced inflammation in rats and pentyleneetetrazol-induced convulsion in mice | [62] |
| Ethanolic seed extract    | Mice/in vivo Dose: 250, 500 mg/kg, p.o. | Dose-dependent anticonvulsant effects | [72] |
| Methanolic fruit extract  | Mice/in vivo Dose: 50, 100, 200 mg/kg, p.o. | Dose-dependent antidepressant effect possibly through GABAergic involvement. | [110] |
| Petroleum ether, methanolic, aqueous/fruit extracts | Mice/in vivo Dose: 100, 200, 400 mg/kg, p.o. | Dose-dependent anxiolytic, analgesic, and nootropic activity | [107] |
dependent analgesic effect in the mouse model [107]. The fruit juice (1 mL, p.o.) prevents morphine addiction development along with the suppression of opioid withdrawal symptoms [113]. In experimental animals such as rats, mice, and guinea pigs, the methanic fruit extract (200-3000 mg/kg, p.o.) significantly potentiated the barbiturate stimulated hypnosis [114].

Qadrie et al. [26] reported that the ethanolic seed extract (250 and 500 mg/kg, p.o.) displayed a dose-dependent antipyretic effect in rats.

4.9. Other Potential Biological Activities

4.9.1. Bronchodilator Effect. Fruit methanol extract inhibited histamine release. In this study, two triterpenes, the triterpenes and sterols, multiflorenol and alnusenol exerted better inhibitory effects [33]. The methanolic extract (50, 200, and 400 mg/kg, p.o.) of *B. hispida* exhibited significant protection in guinea pigs against the histamine and acetylcholine-induced bronchospasm [115]. The methanolic fruit extract (200-3000 mg/kg, p.o.) showed significant anti-histaminic activity on experimental animals (e.g., rats, mice, and guinea pigs) [114].

4.9.2. Antihypertensive Effect. The ACE inhibitory effect of the plant may show the pharmacological basis in the treatment of high blood pressure for its long time uses in traditional Chinese medicine. The fruit juice (0.4 – 1.6 mL/kg, i.v.) dose-dependently lowered blood pressure, concentration-dependently showed relaxation of isolated rat aortic rings and produced nitric oxide (NO) from the cultured porcine aortic endothelial cells [116]. Polysaccharides of fruit extract showed an antiglycation effect [50].

4.9.3. Nephroprotective Effects. Methanic fruit extract (500 mg/kg/day, p.o.) for five days reduced the MDA content, while the increase in SOD, CAT, and GSH levels in renal ischemia/reperfusion injury in female Wistar albino rats [117]. The seed ethanolic extract (250 and 500 mg/kg, p.o.) for 35 days significantly lowered the increased urinary oxalate, presenting a regulatory action on endogenous oxalate synthesis; decreased in the urinary excretion and kidney retention levels of protein, oxalate, and calcium; and reduced the increased serum levels of sodium, calcium, phosphorus, and creatinine levels in ethylene glycol induced chronic hyperoxaluria in Wistar albino rat [118].

Effects of various parts of *B. hispida* on the kidney have been shown in Table 6.

4.9.4. Antiageing of Skin. A cream prepared from the dried fruit pulp extract (petroleum ether, chloroform, ethyl acetate, and methanol) showed a significant antiageing effect on the stratum corneum of human skin and dansyl chloride fluorescence models [12].

5. Toxicological Profile: Safety and Adverse Effects

The fresh juice (5% v/v) treatment for 3 months did not change the total white blood cells (WBC), red blood cells (RBC), haemoglobin (HB), mean corpuscular haemoglobin (MCH), hematocrit (HCT), mean corpuscular volume (MCV), sugar, and urea levels in rats and mice. The treatment also caused no behavioural changes in experimental animals [13]. The methanolic extract of fruit was nontoxic and did not cause the death of mice, rats, and guinea pigs in doses up to 3.0 g/kg [114]. Other studies, performed in female and male rats, concluded that the standardized hydroalcoholic (70% ethanol) extract of the fruit pulp of *B. hispida* administered orally was relatively safe when to female and male rats [119]. Up to oral dose (1000 mg/kg body weight/day) level, no-observe-adverse-effect-level (NOAEL) was obtained for the extract in the 90-days toxicity study. The ethanolic seed extract up to 5000 mg/kg (p.o.) did not exert toxicity in rats [26]. Di-2-Ethylhexyl phthalate (18.3-75.5 mg/kg), isolated from the fruit of this herb, is a popularly used plasticizer and is harmful to human health [36].

6. Conclusions and Future Perspectives

*Benincasa hispida* (Cucurbitaceae) is an annual plant, originating in Indonesia. The Chinese have been cultivating it for over 2000 years; its medicinal uses first appeared in the medical field of the Tang Dynasty. In Chinese medicine, the crust is used to treat urinary dysfunction, and the fruits are used to treat fever. In Ayurveda, the fruits are also used to treat epilepsy, lung diseases, asthma, cough, and urinary retention. Starting from these traditional uses, the present paper evaluated the latest in vivo and in vitro pharmacological studies that demonstrated the molecular mechanisms which confirmed ethnopharmacological uses. However, a limiting aspect of this paper is the lack of clinical trials in human subjects. In the future, they are needed to complete the pharmacological properties and to pave the way for new pharmaceutical forms based on natural compounds with proven therapeutic effects. Improvements in control standards are also needed for future pharmacological studies that include *B. hispida*. In our work, they are relative, phytochemical compounds being identified only by high-performance liquid chromatography (HPLC). Another limiting aspect is represented by the antioxidant action of this plant which has been researched only in vitro, which does not guarantee the same effect on in vivo experimental models. Also, in future studies, the bioavailability, pharmacokinetics, mechanism of action, and study of the activity relationship of the identified and isolated pure phytochemicals should be analyzed, to better understand the reported biological actions.

Although experimental toxicological studies in animals have not shown any adverse effects, no human clinical trials have been performed to demonstrate pharmacological properties or to systematically assess toxicity and safety in humans. These studies are very important for the evaluation of short- and long-term toxicity as well as clinical therapeutic efficacy. However, the results of the present study support the clinical use of *B. hispida* in modern medicine and can serve as a basis for further studies based on this plant.
Abbreviations

ABTS: 2,2’-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid
ALP: Alkaline phosphatase
bFGF: Basic fibroblast growth factor
CAT: Catalase
C/EBP: CCAAT enhancer-binding protein alpha
DPPH: 2,2-diphenyl-1-picrylhydrazyl
HPLC: High-performance liquid chromatography
HUVECs: Human umbilical vein endothelial cells
GSH: Reduced glutathione
IL-6: Interleukin 6
ICAM-1: Intercellular adhesion molecule
MCL: Malondialdehyde
MCV: Mean corpuscular volume
MDA: Malondialdehyde
NIH/3T3: Normal fibroblast cells
NO: Nitric oxide
PGF2: Prostaglandin E2
PPARγ: Peroxisome proliferator-activated receptor-
ROS: Reactive oxygen species
SGOT: Serum glutamic oxaloacetic transaminase
SOD: Superoxide dismutase
STZ: Streptozotocin
TPC: Total phenolic content
TNF-α: Tumour necrosis factor-alpha.

Data Availability

The data supporting this review are from previously reported studies and datasets, which have been cited. The processed data are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

[1] A. G. Ghebretnisae, M. Thulin, and J. C. Barber, “Relationships of cucumbers and melons unraveled: molecular phylogenetics of Cucumis and related genera (Benincaseae, Cucurbitaceae),” American Journal of Botany, vol. 94, no. 7, pp. 1256–1266, 2007.
[2] S. Palamthodi and S. S. Lele, “Nutraceutical applications of gourd family vegetables: Benincasa hispida, Lagenaria siceraria and Momordica charantia,” Biomedicine & Preventive Nutrition, vol. 4, pp. 15–21, 2014.
[3] WHO, WHO monographs on selected medicinal plants, World Health Organization (WHO), 2014.
[4] P. Purohit, S. Palamthodi, and S. S. Lele, “Effect of karwanda (Carissa congesta Wight) and sugar addition on physicochemical characteristics of ash gourd (Benincasa hispida) and bottle gourd (Lagenaria siceraria) based beverages,” Journal of Food Science and Technology, vol. 56, pp. 1037–1045, 2019.
[5] S. Palamthodi, D. Kadam, and S. S. Lele, “Physicochemical and functional properties of ash gourd/bottle gourd beverages blended with jamun,” Journal of Food Science and Technology, vol. 56, pp. 473–482, 2019.
[6] N. A. M. Zaini, F. Anwar, A. A. Hamid, and N. Saari, “Kundur [Benincasa hispida (Thunb.) Cogn.]: a potential source for valuable nutrients and functional foods,” Food Research International, vol. 44, pp. 2368–2376, 2011.
[7] D. R. Andrias, U. Fahmida, and A. C. Adi, “Nutritional potential of underutilized food crops to improve diet quality of young children in food insecure prone areas of Madura Island, Indonesia,” Asia Pacific Journal of Clinical Nutrition, vol. 28, pp. 826–836, 2019.
[8] M. Heinrich, G. Appendino, T. Efferth et al., “Best practice in research - Overcoming common challenges in phytopharmaceutical research,” Journal of Ethnopharmacology, vol. 246, 2020.
[9] A. C. Busuio, A.-V. D. Botatuzatu, B. Furdue et al., “Comparative study of the chemical compositions and antioxidant activities of fresh juices from Romanian Cucurbitaceae varieties,” Molecules, vol. 25, 2020.
[10] J. K. Patil and M. R. Patel, “Pharmacognostic and phytochemical investigation of Benincasa hispida (Thunb.) Cogn. fruit,” Pharma Science Monitor, vol. 3, pp. 146–156, 2012.
[11] W. E. Soliman, S. Khan, S. M. D. Rizvi et al., “Therapeutic applications of biostable silver nanoparticles synthesized using peel extract of Benincasa hispida: antibacterial and anticancer activities,” Nanomaterials, vol. 10, no. 10, p. 1954, 2020.
[12] V. Sabale, H. Kunjwani, and P. Sabale, “Formulation and in vitro evaluation of the topical antiaging preparation of the fruit of Benincasa hispida,” Journal of Ayurveda and Integrative Medicine, vol. 2, no. 3, pp. 124–128, 2011.
[13] J. K. Grover, G. Adiga, V. Vats, and S. S. Rathi, “Extracts of Benincasa hispida prevent development of experimental ulcers,” Journal of Ethnopharmacology, vol. 78, pp. 159–164, 2001.
[14] M. Ramesh, V. Gayathri, A. V. N. A. Rao, M. C. Prabhakar, and C. S. Rao, “Pharmacological actions of fruit juice of Benincasa hispida,” Fitoterapia, vol. 60, pp. 241–247, 1989.
[15] Z. Fatariyah, T. Y. T. Zulkhairuaza, and W. I. Wan Rosli, “Quantitative HPLC analysis of gallic acid in Benincasa hispida prepared with different extraction techniques,” Sains Malaysia, vol. 43, pp. 1181–1187, 2014.
[16] C. Roy, T. K. Ghosh, and D. Guha, “Dose dependent activity of Benincasa hispida on cholchicine induced experimental rat model of Alzheimer’s disease,” International Journal of Pharmacology, vol. 4, no. 4, pp. 237–244, 2008.
[17] S. B. Nagarajaiah and J. Prakash, “Chemical composition and bioactive potential of dehydrated peels of Benincasa hispida, Luffa acutangula, and Sechium edule,” Journal of Herbs Spices & Medicinal Plants, vol. 21, pp. 193–202, 2015.
[18] S. Mazumder, P. Lerouge, C. Loutelier-Bourhis, A. Driouich, and B. Ray, “Structural characterisation of hemicellulosic polysaccharides from Benincasa hispida using specific enzyme hydrolysis, ion exchange chromatography and MALDI-TOF mass spectroscopy,” Carbohydrate Polymers, vol. 59, pp. 231–238, 2005.
[19] S. Mazumder, B. Ray, and P. K. Ghosal, "Chemical investigation on the polysaccharides present in the mesocarp of chakkumra (Benincasa hispida) fruit," *Asian Journal of Chemistry*, vol. 13, pp. 1389–1395, 2001.

[20] S. Mazumder, C. Morvan, S. Thakur, and B. Ray, "Cell wall polysaccharides from chakkumra (Benincasa hispida) fruit. Part I. Isolation and characterization of pectins," *Journal of Agricultural and Food Chemistry*, vol. 52, pp. 3556–3562, 2004.

[21] R. B. H. Wills, A. W. K. Wong, F. M. Scriven, and H. Greenfield, "Nutrient composition of Chinese vegetables," *Journal of Agricultural and Food Chemistry*, vol. 32, no. 2, pp. 413–416, 1984.

[22] C. Arbotante and E. Arriola, "Investigation of the bioactive properties and hypoglycemic effects of ethanol, hexane and ethyl ethanoate extracts from kondo leaves (Benincasa hispida Cogniaux)," *American Journal of Clinical Pathology*, vol. 146, Supplement 1, pp. S33–S38, 2016.

[23] B. V. Shetty, A. Arjuman, A. Jorapur et al., "Effect of extract of Benincasa hispida on oxidative stress in rats with indomethacin-induced gastric ulcers," *Indian Journal of Physiology and Pharmacology*, vol. 52, pp. 178–182, 2008.

[24] Churiyah and L. K. Darusman, "Bioactive Proteins from Benincasa hispida (Thunb.) Cogn.," *Journal of Biosciences*, vol. 3, pp. 101–105, 2007.

[25] D. U. Hemant and G. M. Doshi, "Characterization of valuable compounds from winter melon (Benincasa hispida (Thunb.) Cogn.)," *Journal of Agricultural and Food Chemistry*, vol. 13, pp. 1389–1395, 2001.

[26] Z. L. Qadrie, N. T. Hawisa, M. W. Khan, M. Samuel, and B. V. Shetty, A. Arjuman, A. Jorapur et al., "Histamine release inhibitors from wax gourd, the fruits of Benincasa hispida (Thunb.) Cogn.," *Journal of Agricultural and Food Chemistry*, vol. 28, no. 1, pp. 137–144, 2005.

[27] J. Sharma, S. Chatterjee, V. Kumar, P. S. Vairiyar, and A. Girdhar, "Analysis of free and glycosidically bound compounds of ash gourd (Benincasa hispida): Identification of key odorants," *Food Chemistry*, vol. 122, no. 4, pp. 1327–1332, 2010.

[28] C. Sew, N. Zaini, F. Anwar, A. Hamid, and N. Saari, "Nutritional composition and oil fatty acids of kundur [Benincasa hispida (Thunb.) Cogn.] seed," *Pakistan Journal of Botany*, vol. 42, pp. 3247–3255, 2010.

[29] M. Bimakr, R. A. Rahman, F. S. Taip, N. M. Adzahan, M. Z. Sarker, and M. Noranianz, I. S. Zaidul, and G. Ali, "Antioxidant activity of winter melon (Benincasa hispida) seeds using conventional soxhlet extraction technique," *International Food Research Journal*, vol. 19, pp. 229–234, 2012.

[30] C. Kumar, R. Mythily, and S. Chandram, "Extraction and mass characterization of sugars from ash gourd peels (Benincasa hispida)," *Rasayan Journal of Chemistry*, vol. 5, pp. 280–285, 2012.

[31] M. Bimakr, R. A. Rahman, S. S. Sitt, and M. Z. Sarker, "Supercritical carbon dioxide extraction combined with pressure swing technique," *Food and Bioprocess Technology*, vol. 9, no. 3, pp. 396–406, 2016.

[32] S. Rana and D. A. Suttee, "Phytochemical investigation and evaluation of free radical scavenging potential of Benincasa hispida peel extracts," *International Journal of Current Pharmaceutical Review and Research*, vol. 3, pp. 43–46, 2012.

[33] C. C. Wu, S. E. Liou, Y.-H. Chang, and W. Chiang, "Volatile compounds of the wax gourd (Benincasa hispida, Cogn.) and a wax gourd beverage," *Journal of Food Science*, vol. 52, no. 1, pp. 132–134, 1987.

[34] Q. Du, Q. Zhang, and Y. Ito, "Isolation and identification of phenolic compounds in the fruit ofBenincasa hispida hieh HSCCC," *Journal of Liquid Chromatography and Related Technologies*, vol. 28, no. 1, pp. 137–144, 2005.

[35] T. Uchikoba, H. Yonezawa, and M. Kaneda, "Cucumisin like protease from the sarcocarp of Benincasa hispida var. ryukyu," *Phytochemistry*, vol. 49, no. 8, pp. 2215–2219, 1998.

[36] S. Yoshizumi, T. Murakami, M. Kadoya, H. Matsuda, J. Yamahara, and M. Yoshikawa, "Medicinal Foodstuffs. XI. Histamine release inhibitors from wax gourd, the fruits of Benincasa hispida Cogn.," *Yakugaku Zasshi*, vol. 118, no. 5, pp. 188–192, 1998.

[37] C. T. Shih, J. Wu, S. Jia, A. A. Khan, K. H. Ting, and D. S. Shih, "Purification of an osmotin-like protein from the seeds of Benincasa hispida and cloning of the gene encoding this protein," *Plant Science*, vol. 160, pp. 817–826, 2001.

[38] C.-Y. T. Shih, A. A. Khan, S. Jia, J. Wu, and D. S. Shih, "Purification, characterization, and molecular cloning of a Chitinase from the seeds of Benincasa hispida," *Bioscience, Biotechnology, and Biochemistry*, vol. 66, pp. 501–509, 2001.

[39] Q. Du, L. Shen, L. Xiu, G. Jerz, and P. Winterhalter, "Di-2-ethylhexyl phthalate in the fruits of Benincasa hispida," *Food Additives & Contaminants*, vol. 23, pp. 552–555, 2006.

[40] G. R. Battu, S. N. Mamidipalli, R. Parimi, R. K. Viriyal, R. P. Patchula, and L. R. Mood, "Hypoglycemic and anti-hyperglycemic effect of alcoholic extract of Benincasa hispida in normal and in alloxa-induced diabetic rats," *Pharmacognosy Magazine*, vol. 3, pp. 101–105, 2007.

[41] S. Girdhar, M. M. Wanjadi, S. K. Prayapati, and A. Girdhar, "Evaluation of anti-inflammatory effect of methanolic extract of Benincasa hispida Cogn. fruit in mice," *Acta Poloniae Pharmaceutica*, vol. 67, pp. 417–421, 2010.

[42] C. Sew, N. Zaini, F. Anwar, A. Hamid, and N. Saari, "Nutritional composition and oil fatty acids of kundur [Benincasa hispida (Thunb.) Cogn.] seed," *Pakistan Journal of Botany*, vol. 42, pp. 3247–3255, 2010.

[43] J. Sharma, S. Chatterjee, V. Kumar, P. S. Vairiyar, and A. Girdhar, "Analysis of free and glycosidically bound compounds of ash gourd (Benincasa hispida): Identification of key odorants," *Food Chemistry*, vol. 122, no. 4, pp. 1327–1332, 2010.

[44] F. Anwar, N. Mohammad, F. Othman, and N. Saari, "Inter-varietal variation in the composition of seeds and seed oils from winter melon [Benincasa hispida (Thunb.) Cogn.] fruit," *Pakistan Journal of Botany*, vol. 43, pp. 2029–2037, 2011.

[45] C. C. Kumar, R. Mythily, and S. Chandram, "Extraction and mass characterization of sugars from ash gourd peels (Benincasa hispida)," *Rasayan Journal of Chemistry*, vol. 5, pp. 280–285, 2012.

[46] B. Mandana, A. R. Rüss, S. T. Farah, M. A. Noranianz, I. S. Zaidul, and G. Ali, "Antioxidant activity of winter melon (Benincasa hispida) seeds using conventional soxhlet extraction technique," *International Food Research Journal*, vol. 19, pp. 229–234, 2012.

[47] M. Bimakr, R. A. Rahman, F. S. Taip, N. M. Azdahan, M. Z. Sarker, and A. Ganjloo, "Supercritical carbon dioxide extraction of seed oil from winter melon (Benincasa hispida) and its antioxidant activity and fatty acid composition," *Molecules*, vol. 18, no. 1, pp. 997–1014, 2013.

[48] X. N. Han, C. Y. Liu, Y. L. Liu, Q. M. Xu, X. R. Li, and S. L. Yang, "New triterpenoids and other constituents from the fruits of Benincasa hispida (Thunb.) Cogn.," *Journal of Agricultural and Food Chemistry*, vol. 61, no. 51, pp. 12692–12699, 2013.

[49] E. Ota, W. Tsuchiya, T. Yamazaki, M. Nakamura, C. Hirayama, and K. Konno, "Phytochemical investigation and recombinant protein expression of a phloem lectin-like anti-insect defense protein BPLP from the phloem exudate of the wax gourd, Benincasa hispida," *Phytochemistry*, vol. 89, pp. 15–25, 2013.
Oxidative Medicine and Cellular Longevity

[76] A. M. Buga, A. O. Docea, C. Albu et al., “Molecular and cellular stratagem of brain metastases associated with melanoma,” Oncology Letters, vol. 17, pp. 4170–4175, 2019.

[77] J. Sharifi-Rad, C. Quispe, M. Butnariu et al., “Chitosan nanoparticles as a promising tool in nanomedicine with particular emphasis on oncological treatment,” Cancer Cell International, vol. 21, no. 1, 2021.

[78] J. Sharifi-Rad, S. Kamiloglou, B. Yeskalievaya et al., “Pharmacological activities of psoraladin: a comprehensive review of the molecular mechanisms of action,” Frontiers in Pharmacology, vol. 11, 2020.

[79] B. Salehi, A. Prakash Mishra, M. Nigam et al., “Ficus plants: state of the art from a phytochemical, pharmacological, and toxicological perspective,” Phytotherapy Research, vol. 35, 2020.

[80] B. Salehi, A. Rescigno, T. Dettori et al., “Avocado-soybean unsaponifiables: a panoply of potentialities to be exploited,” Biomolecules, vol. 10, 2020.

[81] B. Salehi, J. Sharifi-Rad, E. Capanoglu et al., “Cucurbita plants: from farm to industry,” Applied Sciences, vol. 9, no. 16, p. 3387, 2019.

[82] B. Salehi, P. Lopez-Jornet, E. Pons-Fuster López et al., “Plant-derived bioactives in oral mucosal lesions: a key emphasis to curcumin, lycopene, chamomile, aloe vera, Green Tea and Coffee Properties,” Biomolecules, vol. 9, no. 3, p. 106, 2019.

[83] N. Akev, E. Candoken, and S. E. Kuruca, “Evaluation of aloe vera leaf extracts and aloe emollient on several cancer cell lines,” Farmácia, vol. 68, no. 6, pp. 1155–1165, 2020.

[84] K. H. Lee, H. R. Choi, and C. H. Kim, “Anti-angiogenic effect of the seed extract of Benincasa hispida Cogniaux,” Journal of Ethnopharmacology, vol. 97, no. 3, pp. 509–513, 2005.

[85] U. Mandal, K. M. Ali, K. Chatterjee, D. De, A. Biswas, and D. Ghosh, “Management of experimental hypochlorhydia with iron deficiency by the composite extract of Fumaria vaillantii L. and Benincasa hispida T. in rats,” Journal of Natural Science, Biology, and Medicine, vol. 5, pp. 397–403, 2014.

[86] T. M. Vinaya, B. S. Aravind, D. Sibbritt, T. Tapasbrata, and S. Shivakumar, “The use of Benincasa hispida for the treatment of uninvestigated dyspepsia: Preliminary results of a non-randomised open label pilot clinical trial,” Advances in Integrative Medicine, vol. 2, no. 3, pp. 130–134, 2015.

[87] C. Scheau, C. Caruntu, I. A. Badarau et al., “Cannabinoids and inflammations of the gut-lung-skin barrier,” Journal of Personalized Medicine, vol. 11, no. 6, p. 494, 2021.

[88] J. Sharifi-Rad, C. F. Rodrigues, Z. Stojanović-Radić et al., “Probiotics: versatile bioactive components in promoting human health,” Medicina, vol. 56, no. 9, 2020.

[89] P. Mitrut, A. O. Docea, A. M. Kamal et al., “Colorectal cancer and inflammatory bowel disease,” in Colorectal Cancer: From Pathogenesis to Treatment, pp. 185–199, Intech Europe, Rijeka, 2016.

[90] B. Vrushabendra Swamy, T. Rao, R. Dhanapal, V. Balamuralidhar, and V. Ashoka Babu, “Antidiarrheal evaluation of Benincasa hispida (Thunb.) Cogn. fruit extracts,” Iranian Journal of Pharmacology and Therapeutics (IJPT), vol. 4, pp. 24–27, 2005.

[91] R. N. Patil, R. Y. Patil, B. Ahirwar, and D. Ahirwar, “Evaluation of antidiabetic and related actions of some Indian medicinal plants in diabetic rats,” Asian Pacific Journal of Tropical Medicine, vol. 4, no. 1, pp. 20–23, 2011.

[92] A. Tsatsakis, A. O. Docea, D. Calina et al., “A mechanistic and pathophysiological approach for stroke associated with drugs of abuse,” Journal of Clinical Medicine, vol. 8, no. 9, p. 1295, 2019.

[93] S. Amir, S. T. A. Shah, C. Mamoulakis et al., “Endocrine disruptors acting on estrogen and androgen pathways cause reproductive disorders through multiple mechanisms: a review,” International Journal of Environmental Research and Public Health, vol. 18, no. 4, p. 1464, 2021.

[94] A. E. Gáman, A. M. Ungureanu, A. Turculeanu et al., “The impact of liver steatosis on early and sustained treatment response in chronic hepatitis C patients,” Romanian Journal of Morphology and Embryology, vol. 58, pp. 107–113, 2017.

[95] E. N. Tieranu, I. Donoiu, O. Istratǎoaei et al., “Rare case of single coronary artery in a patient with liver cirrhosis,” Romanian Journal of Morphology and Embryology, vol. 58, pp. 1505–1508, 2017.

[96] A. Kumar and R. Vimalavathini, “Possible anorectic effect of methanol extract of Benincasa hispida (Thunb.) Cogn. fruit,” Indian Journal of Pharmacology, vol. 36, pp. 348–350, 2004.

[97] Y. You and W. Jun, “Effects of fractions from Benincasa hispida on inhibition of adipogenesis in 3T3-L1 Preadipocytes,” Journal of the Korean Society of Food Science and Nutrition, vol. 41, no. 7, pp. 895–900, 2012.

[98] A. Kumar and P. Ramu, “Anti-convulsant activity of Benincasa hispida fruit, methanol extract,” Journal of Natural Remedies, vol. 4, no. 2, pp. 195–198, 2004.

[99] B. Salehi, D. Calina, A. Docea et al., “Curcumin’s nanomedicine formulations for therapeutic application in neurological diseases,” Journal of Clinical Medicine, vol. 9, no. 2, p. 430, 2020.

[100] D. Calina, A. M. Buga, M. Mitroi et al., “The treatment of cognitive, behavioural and motor impairments from brain injury and neurodegenerative diseases through cannabinoid system modulation-evidence from in vivo studies,” Journal of Clinical Medicine, vol. 9, no. 8, 2020.

[101] M. Sharifi-Rad, N. V. Anil Kumar, P. Zucca et al., “Lifestyle, oxidative stress, and antioxidants: back and forth in the pathophysiology of chronic diseases,” Frontiers in Physiology, vol. 11, 2020.

[102] B. Salehi, J. Sharifi-Rad, F. Cappellini et al., “The therapeutic potential of anthocyanins: current approaches based on their molecular mechanism of action,” Frontiers in Pharmacology, vol. 11, 2020.

[103] V. Siokas, A. M. Aloizou, Z. Tsouris et al., “ADORAl2A rs5760423 and CYP1A2 rs762551 polymorphisms as risk factors for Parkinson’s disease,” Journal of Clinical Medicine, vol. 10, no. 3, p. 381, 2021.

[104] M. Sharifi-Rad, C. Lankatillake, D. A. Dias et al., “Impact of natural compounds on neurodegenerative disorders: from preclinical to pharmacotherapeutics,” Journal of Clinical Medicine, vol. 9, no. 4, p. 1061, 2020.

[105] B. Salehi, S. Sestito, S. Rapposelli et al., “Epibatidine: a promising natural alkaloid in health,” Biomolecules, vol. 9, no. 1, p. 6, 2019.

[106] A. M. Aloizou, V. Siokas, G. Pateraki et al., “Thinking outside the ischemia box: advancements in the use of multiple sclerosis drugs in ischemic stroke,” Journal of Clinical Medicine, vol. 10, no. 4, 2021.

[107] D. Ambikar and G. Mohanta, “Effect of dried fruit extract of Benincasa hispida on brain behaviour in laboratory animals,”
A. Kumar and V. Nirmala, “Nootropic activity of methanol extract of Benincasa hispida fruit,” *Indian Journal of Pharmacology*, vol. 35, p. 130, 2003.

M. S. Islam, C. Quispe, R. Hossain et al., “Neuropharmacological effects of quercetin: a literature-based review,” *Frontiers in Pharmacology*, vol. 12, 2021.

D. Dhingra and P. Joshi, “Antidepressant-like activity of Benincasa hispida fruits in mice: possible involvement of monoaminergic and GABAergic systems,” *Journal of Pharmacology and Pharmacotherapeutics*, vol. 3, no. 1, pp. 60–62, 2012.

K. Hemamalini and M. V. M. Varma, “Antinociceptive effects of methanolic extract of Benincasa hispida (Thunb.) Cong. fruit,” *Pharmacologyonline*, vol. 3, pp. 327–332, 2007.

F. Jahan, M. Hossain, A. Mamun et al., “An evaluation of antinociceptive effect of methanol extracts of Desmodium gangeticum (L.) Dc. stems and Benincasa hispida (Thunb.) Cogn. leaves on acetic acid-induced gastric pain in mice,” *Advances in Natural and Applied Science*, vol. 4, pp. 365–369, 2010.

J. K. Grover, S. S. Rathi, and V. Vats, “Preliminary study of fresh juice of *Benincasa hispida* on morphine addiction in mice,” *Fitoterapia*, vol. 71, no. 6, pp. 707–709, 2000.

S. C. Babu, R. Ilavarasan, M. S. Refai, L. H. Thameemul-Ansari, and D. A. Kumar, “Preliminary pharmacological screening of Benincasa hispida Cogn,” *Journal of Natural Remedies*, vol. 3, 2003.

A. Kumar and P. Ramu, “Effect of methanolic extract of Benincasa hispida against histamine and acetylcholine induced bronchospasm in guinea pigs,” *Indian Journal of Pharmacology*, vol. 34, pp. 365-366, 2002.

M. Nakashima, Y. Shigekuni, T. Obi et al., “Nitric oxide-dependent hypotensive effects of wax gourd juice,” *Journal of Ethnopharmacology*, vol. 138, no. 2, pp. 404–407, 2011.

B. Yagnik, V. Jitendra, J. Nurudin, K. Nilesh, P. Rameshvar, and P. Natavarlal, “Antioxidant activity of Benincasa hispida on renal ischemia/reperfusion injury,” *Pharmacology*, vol. 1, pp. 44–49, 2009.

R. Patel, S. Patel, and J. Shah, “Anti-urolithiatic activity of ethanolic extract of seeds of *Benincasa hispida* (thumb),” *Pharmacology*, vol. 3, pp. 586–591, 2011.

A. Shakya, S. K. Chaudhary, H. R. Bhat, and S. K. Ghosh, “Acute and sub-chronic toxicity studies of *Benincasa hispida* (Thunb.) cogniaux fruit extract in rodents,” *Regulatory Toxicology and Pharmacology*, vol. 118, article 104785, 2020.