The Pharmacological Importance of Benincasa hispida. A review

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Abstract:

Benincasa hispida was probably native in Japan and Java, cultivated more or less throughout warm countries. It was a popular vegetable crop widely used for nutritional and medicinal purposes. Phytochemical analysis showed that the major constituents of *Benincasa hispida* fruits are volatile oils , flavonoids, glycosides, sacchrides, proteins, carotenes, vitamins, minerals, ß-sitosterin and uronic acid. The pharmacological studies revealed that the plant exerted many pharmacological activities , including central nervous effects (anxiolytic , muscle relaxant , antidepressant , in the treatment of Alzheimer's disease and to minimize opiates withdrawal signs), antioxidant, anti-inflammatory, analgesic, antiasthmatic, diuretic , nephroprotective , antidiabetic , hypolipidemic and antimicrobial effects . This review was designed to highlight the chemical constituents and pharmacological effects of *Benincasa hispida*.

Keywords: *Benincasa hispid* , chemical constituents, pharmacology

Introduction:

Benincasa hispida (Synonym: *Benincasa cerifera*) [(1)], which commonly called (winter melon, ash gourd, ash guard, winter gourd, white pumpkin and wax gourd. white gourd, tallow gourd, gourd melon and Chinese watermelon) belongs to the cucurbitaceae family , it was probably native in Japan and Java, cultivated more or less throughout India and in warm countries. It is a popular vegetable crop, especially among Asian communities both for nutritional and medicinal purposes [(2-3)]. It was preferred as a cooked vegetable, boiled alone, boiled with meat, or included in a variety of dishes. Also, it was used raw like sliced cucumbers [(4)]. However, the plant was used medicinally in various complains such as gastrointestinal problems, respiratory disease, heart diseases, diabetes mellitus and urinary diseases [(5)]. Fruits were traditionally used as a laxative, diuretic, tonic, aphrodisiac, cardiotonic, urinary calculi, blood disease, insanity, epilepsy, schizophrenia and other psychologic disorders, jaundice, dyspepsia, fever, and menstrual disorders [(6-8)]**.** The major constituents of *Benincasa hispida* fruits are volatile oils , flavonoids, glycosides, sacchrides, proteins, carotenes, vitamins, minerals, ß-sitosterin and uronic acid [(2,9-13)]. The pharmacological studies revealed that the plant exerted many pharmacological activities , including central nervous effects (anxiolytic , muscle relaxant , antidepressant , in the treatment of Alzheimer's disease and to minimize opiates withdrawal signs), antioxidant, anti-inflammatory, analgesic, antiasthmatic, diuretic , nephroprotective , antidiabetic , hypolipidemic and antimicrobial effects . The present review aimed to highlight the chemical constituents and pharmacological effects of *Benincasa hispida*.

Chemical constituents:

The major constituents of *Benincasa hispida* fruits were volatile oils , flavonoids, glycosides, sacchrides, proteins, carotenes, vitamins, minerals, ß-sitosterin and uronic acid[(2,9-11)].

Chemical analysis showed that the main sugars in the *Benincasa hispida* peels were galactose, glucose, xylose and sorbose [(12)]. The antioxidant activity and total phenolic content (TPC) of *Benincasa hispida* seeds extract was investigated using conventional Soxhlet extraction (CSE), and DPPH and ABTS scavenging activity tests. The ethanolic extract gave the highest total phenolic content 11.34±1.3 mg GAE/g and antioxidant activity followed by ethyl acetate and n-hexane extract [(13)]. *Benincasa hispida* seeds contained high amount of fatty acids 24.3% , saturated fatty acids represented 75.38% and unsaturated fatty acids (75.38%), it was apparent that linoleic and oleic are the principal fatty acid components in the seed's extracts [(13)].

The seeds revealed that the total dietary fiber was 58.43% of the seed. The seed crude fat and crude protein were found to be 20.70 and 11.63% respectively. It appeared that the extracted seed oil was mainly consisted of linoleic acid accounting for 67.37% of the total fatty acids. However, palmitic, oleic, and stearic acids represented 17.11, 10.21 and 4.83% respectively [(1)].

Central nervous effects:

The anxiolytic effects of alcoholic extract of *B. hispida* were evaluated in mice using elevated plus maze and light-dark transition test and spontaneous motor activity measured by actophotometer. The oral administration of the extract increased the percentage of time spent and the percentage of open arm entries in the elevated plus maze, as well as increase the time spent in the illuminated side of the light-dark test. The same extract was not able to modify the spontaneous motor activity measured in actophotometer [(2)].

The methanolic extract of *Benincasa hispida* exhibited significant anti-compulsive effect in marble-burying behavior test in mice, the effect which may be attributed to the enhancement of serotonergic function [(14)].

The methanolic extract of fruit of *Benincasa hispida* caused reduction in spontaneous motor activity with no muscle relaxant activity. It also significantly potentiated the barbiturate induced hypnosis, and showed significant antihistaminic activity [(15)].

The anticonvulsant properties of alcoholic extract of *Benincasa hispida* was studied on maximal electroshock test (MEST), pentylenetetrazole and strychnine-induced seizures model in mice. The alcoholic extract of *Benincasa hispida* protected animals against maximal electroshock-induced convulsion and reduced the mean recovery time from convulsion. It also showed anticonvulsant activity against pentylenetetrazole-induced convulsion and protected mice against strychnine-induced convulsions [(16)].

The antidepressant activity of the methanolic extract (50, 100, and 200 mg/kg, administered orally for 14 successive days) was tested in Swiss male albino mice incomparison with classical antidepressant drugs (imipramine 15 mg/kg, fluoxetine 20 mg/kg, and phenelzine 20 mg/kg). The methanolic extract of *B. hispida* showed significant antidepressant-like activity in mice probably by inhibiting MAO-A, and through interaction with dopaminergic, α1- adrenergic, serotoninergic, and GABAergic systems [(17)].

The juice of *Benincasa hispida* showed significant activity against symptoms of morphine withdrawal. The results showed that *Benincasa hispida* was active in preventing the development of morphine addiction and suppression of opioid withdrawal in animals [(18)].

The chronic treatment with the aqueous extract of *Benincasa hispida* pulp (400mg/kg bw) appeared beneficial in the management of colchicines-induced rat model of Alzheimer's disease. It was also increased antioxidants in different brain areas and increased the number of correct choices out of 10 daily trials and decreased latency time dose dependently [(18-19)].

Effects on gastrointestinal system:

The free radical scavenging and antiulcer potential of the methanol extract of *Benincasa hispida* seeds was evaluated by DPPH method for antioxidant effect and by using pyloric ligation, water immersion stress and indomethacin induced gastric ulcer model for antiulcer effects in rats. The methanolic extract showed concentration dependent DPPH radical scavenging activity. It was also inhibited gastric ulceration by decreasing the gastric volume and free and total acidity. The high dose (300 mg/kg bw) showed significant reduction in the above parameters which was comparable to the standard drug ranitidine ($p<0.05$). The methanol extract of *Benincasa hispida* seeds caused 52.7, 67.4 and 61.2% inhibition of ulcers in pyloric ligation, water immersion stress and indomethacin induced ulcer models, respectively at a dose of 300 mg/kg [(20)].

Antiulcer activity of petroleum ether and methanol extracts of *Benincasa hispida* were also investigated in rats. Petroleum ether and methanol extracts were administrated orally at a dose of 300 mg/kg bw, and omeprazole (reference standard) at the dose of 20 mg/kg bw. Both extracts produced significant reduction in ulcer index ($P < 0.05$) in all the models (ethanol-induced gastric mucosal damage, pylorus ligated ulcer model, cold and restraint stress-induced gastric ulcer model), and the results were comparable with that of omeprazole-treated group. Furthermore, a significant reduction in vascular permeability ($P < 0.05$) was also observed. However, in cold and restraint stress-induced gastric ulcer model, MDA content was significantly reduced along with increase in CAT levels as compared to control group [(21)].

The fruit peel ethanolic extracts of the *Benincasa hispida* displayed a significant anthelmintic activity ($p<0.05$) in dose dependent manner. The assay was performed in *vitro* using adult earthworm (*Pheretima posthuma)* owing to its anatomical and physiological resemblance with the intestinal roundworm parasites of human beings [(22)].

The methanolic extract of fruit of *Benincasa hispida* (BHFE) was evaluated for its antidiarrheal potential against several experimental models of diarrhea in rats. BHFE treated animals showed significant inhibitory activity against castor oil induced diarrhea and inhibited PGE_2 induced enter pooling in rats. It also showed significant reduction in gastrointestinal motility following charcoal meal in rats [(23)]. Various doses of the methanol extract of *Benincasa hispida* (MEBH) (0.2-1 g/kg, ip) were administered to Swiss albino mice to investigate the anorectic effect. (MEBH) significantly reduced the cumulative food intake over a 7 hours period in a dose-dependent manner. The percentage reduction of cumulative food intake at 7^{th} hour for MEBH treated

mice with 0.2, 0.6 and 1 g/kg was 27%, 38% and 54% respectively. The 4 hours gastric emptying was not significantly influenced by MEBH when compared to control. It was postulated that the anorectic activity of *Benincasa hispida* was mediated through the central nervous system without affecting the gastric emptying [24]

Antioxidant effects:

The antioxidant activity and total phenolic content (TPC) of *Benincasa hispida* seeds extract were investigated using conventional Soxhlet extraction (CSE), and DPPH and ABTS scavenging activity tests. The ethanolic extract gave the highest total phenolic content 11.34±1.3 mg GAE/g and antioxidant activity followed by ethyl acetate and n-hexane extract [13].

The free radical scavenging potential of aqueous and methanolic extract of dried ripe peels of *Benincasa hispida* was evaluated by DPPH (1.1,-diphenyl-2-picryl-hydrazyl). The extracts showed significant potential in a dose dependant manner when compared with the ascorbic acid. The highest scavenging activity of methanol extract was found to be 87.87% at a concentration of 100µg mL^{-1} and that of aqueous 86.5% at concentration of 100 µg /ml [11]. *Benincasa hispida* fruit extract caused significant increase in SOD in RBC and antral homogenate levels and vitamin C in plasma in rats. There was an apparent decrease in ulcer index in animals treated with *Benincasa hispida* fruit extract. The authors postulated that Benincasa hispida fruit extract probably inhibit gastric mucosal injury by scavenging the free radicals [25].

The antioxidant capacity of skin, pulp and seed of wax gourd extracts were measured by three different assays such as scavenging activity, ferric reducing activity and -arotene bleaching assays. For total phenolic content, Folin-Ciocalteau assay was used in the study. The seed extract of wax gourd showed the highest antioxidant capacity for scavenging activity, ferric reducing activity and –carotene bleaching assays and also exhibited highest total phenolic content as compared to skin and pulp extract of wax gourd. A positive correlations were obtained for parts (pulp, skin and seed) of wax gourd extracts between total phenolic content with ferric reducing activity (R = 0.874) and also with 2 % antioxidant activity (R2 = 0.989). However, negative correlation was found between total phenolic content with scavenging activity (R2 = - 0.077) for various parts of wax gourd extracts studied [26].

Benincasa hispida in a dose of 250 and 500 mg/kg in mice induced dose dependent decrease in glucose, triglyceride and insulin levels in plasma. It was also increased MDA level as well as decrease GSH, SOD [27].

Anti-inflammatory and analgesic effects:

The preliminary investigations of aqueous extract of *Benincasa hispida* showed that it exhibited anti-inflammatory properties. Petroleum ether and methanolic extract of *Benincasa hispida* fruit, at the dose of 300 mg/kg bw, produced dose dependent and significant inhibition of carrageenan- induced paw edema, histamine induced paw edema and cotton pellet induced granuloma in rat model. In carrageenan- induced paw edema model, petroleum ether and methanolic extracts showed maximum inhibition in inflammation (0.270 ± 0.063 and 0.307 ± 0.043 respectively) as compared to control group (1.27 ± 0.059) and standard valdecoxib (0.247 ± 0.033). In histamine-induced paw edema, both extracts showed (62.86% and 54.84% respectively) inhibition as compared to control. The effects were comparable with that of standard drug cetrizine (95.24%). Petroleum ether and methanolic extracts showed slight insignificant reduction in granuloma tissue formation in cotton pellet implanted rats [28].

The mechanism of anti-vascular inflammatory activity of an aqueous extract of *B. hispida* (ABH) in human umbilical vein endothelial cells (HUVECs) was investigated. ABH inhibited high glucose-induced cell adhesion molecules (CAMs) surface and protein expression, resulting in reduced adhesion of U937 monocytes. ABH also inhibited the mRNA expression level of monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8). High glucose-induced ROS production was also inhibited by ABH. Pretreatment of HUVECs with ABH blocks NF-κB activation via blocking phosphorylation and degradation of its inhibitory protein, IκB-α. ABH also reduced NF-kB promoter activity [29].

The methanolic extract of *Benincasa hispida* at doses of 250 and 500 mg/kg bw, significantly ($P<0.05$) increased the antinociceptive effective (as determined by analgesiometer which exerts force at a constantly-increasing rate on the rat paw) in a dose dependent manner in rats. Similarly, at doses of 250 and 500 mg/kg bw, the extract significantly ($P<0.05$) decreased the Brewer'syeast induced pyrexia in rats [30].

Anti asthmatic effects:

Two triterpenes, namely alonusenol and multiflorenol extracted from the methanolic extract of *B.hispida* fruit exhibited mast cell stabilizing effect and found to have potential inhibitory effect on the histamine release induced by antigen antibody reaction [31].

Methanol extract of *Benincasa hispida* (MEBH) showed excellent protection in guinea pigs against the histamine-induced bronchospasm even at a very low dose, 50 mg/kg orally. However, even at a higher dose level 400 mg/kg, MEBH did not significant protect against acetylcholine- induced bronchospasm. The results

suggest that the protective effect against bronchospsam induced by histamine aerosol may be mediated by antihistaminic activity (H**1** receptor antagonism) [32]

Effects on renal system:

The diuretic activity of the *Benincasa hispida* fruit rind extract (outer thick pericarp) (25-200 mg/kg) was evaluated in adult male guinea-pigs. The extract produced a significant increase ($p<0.001$) in the urinary volume. There was a significant increase in the sodium and chloride excretion and a decrease ($p<0.001$) in the potassium excretion [8].

Benincasa hispida fruit rind extract (outer thick pericarp) was also significantly increased ($p<0.001$) urine volume, sodium and chloride levels, and significant decrease ($p<0.001$) potassium excretion in rats when used orally in a dose of 100mg/kg bw [33].

When 0.75% v/v ethylene glycol was given to the rats in drinking water to induce chronic hyperoxaluria, with simultaneous *Benincasa hispida* extract at the dose of 250 and 500 mg/kg bw, orally for 35 days. The supplementation with *Benincasa hispida* extract significantly lowered the urinary excretion and kidney retention levels of oxalate, protein and calcium. Moreover, elevated serum levels of sodium, creatinine, calcium and phosphorus were significantly reduced by the extracts [34]**.**

The nephroprotective activity of hydro-alcoholic extract of *Benincasa hispida* whole fruit extract was investigated in paracetamol induced nephrotoxicity in rats. Treatment with hydro-alcoholic extract of *Benincasa hispida* whole fruit extract at doses of 200 and 400 mg/kg bw prevented the paracetamol - induced nephrotoxicity and oxidative impairments of the kidney, as evidenced by a significantly reduced in kidney weight, blood urea, blood creatinine, urinary glucose, urinary potassium level and also increased body weight, urine volume, urinary creatinine and blood total protein level. Hydro-alcoholic extract of *Benincasa hispida* whole fruit extract significantly increased the tissue GSH levels and reduced lipid peroxidation levels. Furthermore, it was confirmed by the histopathological observation that the degenerative changes caused by paracetamol were also restored by treatment with hydro-alcoholic extract of *Benincasa hispida* whole fruit extract [35]. It was also produced nephroprotective activity against mercury poisoning in rats [36].

Hypoglycemic and hypolipidemic effects:

The stem chloroform extract of *Benincasa hispida* has significant hypoglycemic activity in normal male Wistar rats. The maximum reduction in blood glucose levels with stem extract of *Benincasa hispida* was recorded at a dose of 200 mg/kg bw [37]**.**

Salad was prepared by using 100gm of ash gourd (*Benincasa hispida*) and one gram of curry leaves (10 curry leaves) and five grams of skimmed milk powder (made into curd) and pepper and salt are added for taste. This salad was freshly prepared every day and given to hyperlipidemic diabetic patients in mid morning for a period of three months to find out the therapeutic effect of supplementation of ash gourd and curry leaves. Supplementation of ash gourd and curry leaves had significant hypoglycemic and hypolidemic effect and it reduced the blood glucose level (both fasting and post prandial), within the period of three months [38].

Benincasa hispida in a dose of 250 and 500 mg/kg in mice induced dose dependent decrease in glucose, triglyceride and insulin levels in plasma. It was also increased the glucose uptake from hemidiaphragm [27].

Antimicrobial effects:

The antibacterial activity of seed oil of *B. hispida* was tested against selected pathogens (gram positive, *M. luteus, S. aureus and B. subtilis*; and gram negative, *E. coli, P. multocida and P. aeruginosa*). Maximum mean zone of inhibition was observed against *B. subtilis* (16mm) and the minimum against *Micrococcus luteus* (11mm) [39]. However, the antibacterial activity of methanolic extract of *Benincasa hispida* was studied against three gram positive bacteria *Staphylococcus aureus, Staphylococcus epidermidis and Bacillus subtilis* and three gram negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia*, and the antifungal activity was studied against *Candida albicans* and *Aspergillus niger*. The methanolic extract of *Benincasa hispida* showed no antibacterial activity, but it caused significant zone of inhibition against *Candida albicans* at the concentration of 30 mg/ml, while, it caused no inhibition against *Aspergillus Niger* [40].

Contraindication and side effects:

In acute toxicity study in rats, the aqueous and ethanolic extract of *Benincasa hispida* (Thunb.) COGN. were found to be safe and no mortality was observed at a dose as high as 5 g/kg bw [30, 33].

The chloroform extract was tested for its acute toxicity in albino rats (0.25 g/kg, 0.5 g/kg, 0.75 g/kg and 1 g/kg**).** The parameters which were observed were hyperactivity, sedation, loss of righting reflex, respiratory rate and convulsions. No toxic effects and mortality were recorded [8].

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