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Review Article

Phytochemical and Pharmacological Activities of *Cucumis sativus*: An Updated Review

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ABSTRACT

Due to the rising demand for cost-effective herbal medicines as alternatives to expensive synthetic drugs, investigations into the pharmacological properties of medicinal plants have witnessed a remarkable surge. *Cucumis sativus*, a member of the *Cucurbitaceae* family, is a popular vegetable crop that possesses a wealth of phytoconstituents linked to various therapeutic applications. Accordingly, this review explores the recent phytochemical and pharmacological information on *Cucumis sativus* aimed at providing an updated template for its possible development as a therapeutic agent for various disorders. In this study, several databases were searched to ascertain the active compounds in *Cucumis sativus* and to identify the reported pharmacological activities in *In-vitro* and *In-vivo* studies. Findings from this review highlight the diverse pharmacological actions of *Cucumis sativus*, including anti-microbial, anti-cancer, cytotoxic, wound healing, anti-ulcer, anti-inflammatory, anti-diabetic, anti-oxidant, analgesic, and hepatoprotective effects. Also, this study noted a paucity of literature information on the neuroprotective and reproductive activities of *Cucumis sativus* in experimental models. Altogether, this review provides updated information and highlights the potential of *Cucumis sativus* for future pharmaceutical investigations and the possible development of drugs that can be useful in the management of various disorders.

Keywords: *Cucumis sativus*, Phytochemicals, Pharmacological activity, Drug development

Introduction

Cucumis sativus, a major vegetable crop with significant economic and ecological importance, is a member of the gourd family (*Cucurbitaceae*) and is native to the southern Himalayas in Asia.[1] It is a common ingredient in salads and is primarily consumed in its raw form or cooked in various dishes across different cultures.[2, 3] Originally from South Asia, *Cucumis sativus* is now grown on most continents.[4] Due to the labile nature of the *Cucumis* genome throughout evolution, there are several distinct genetic variants of *Cucumis sativus* around the world. There are two different subgenuses in the *Cucumis* genus; one which evolved in Africa and the other in Asia.[5] Cytological reports indicate that *Cucumis sativus* is the only species with $n = 7$ chromosomes, having developed from its ancestral form of *Cucumis* with karyotype [$n = 12$].[6] *Cucumis sativus* is one of the oldest cultivated thermophilic vegetable crops and can be found in nearly all countries in temperate zones; growing best at temperatures above 20 °C.[7] It is referred to as Cucumber in English, *Kheera* in Hindi, *Huang Gua* in China, *Tavsini* in Marathi, *Vellari* in Malayalam, *Khira* in Panjabi, *Sakusa* in Sanskrit, *Kheyar* in Arabic, and *Kheera* in Urdu.[3] Locally, it is called *Okokon* in Ibibio, *Gbomgbom* in Plateau, *Ogiebo* in Benin, *Alo-ose* in Port Harcourt, and *Guruji* in Hausa.[8]*Cucumis sativus* fruits exhibit a range of sizes and shapes, often appearing compressed, elongated, and ellipsoid, with a convex dorsal-ventral shape and ridges along the sides.

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The fruits can vary from small, stubby types measuring around 10 to 12 cm in length to longer varieties reaching up to 50 cm.[9] The seeds are white or cream-coloured and have a firm, smooth outer covering.[10] *Cucumis sativus* fruits are frequently consumed due to their high nutritional contents.[11] *Cucumis sativus* is botanically considered a fruit since it develops from flowers and contains dicotyledonous seeds.[10] The traditional and medicinal properties of *Cucumis sativus* have been reported since ancient times, and various parts of the plant have been investigated for their pharmacological and therapeutic benefits. Fresh fruits from the *Cucumis sativus* are used topically to cure skin rashes, acne, and other exterior conditions. The entire fruit is applied topically as a poultice for burns, cold sores, and wounds. It is also used in cosmetics to soften and lighten skin.[12] Traditional cultures have long recognized the skincare benefits of *Cucumis sativus* as its high water content and soothing properties make it a natural remedy for skin care. *Cucumis sativus* slices have been used for centuries to alleviate puffiness and dark circles around the eyes.[13] The leaf, stem, and root are employed in Chinese traditional medicine as anti-diarrheal and anti-gonorrheal medicines. In addition, it possesses detoxifying properties and is used to quench thirst, reduce swelling, and promote urination.[14, 15] Also, reports indicate that it is used to alleviate dyspepsia and throat infections in children.[16] In Ayurveda, *Cucumis sativus* is often recommended to soothe digestive discomfort and manage urinary tract issues. Its hydrating properties have been harnessed to combat dehydration and heat-related illnesses [15]. *Cucumis sativus* has also been used as a traditional medicine to lower blood pressure.[17] The significance of *Cucumis sativus* extends beyond its practical uses and holds cultural and symbolic meanings. For instance, in Korea, it is associated with good fortune and is often included in rituals and celebrations. In some parts of Eastern Europe, *Cucumis sativus* is used in folk traditions and rituals to predict the future.[17] Also, it is believed that close observation of the shape of *Cucumis sativus* seeds can reveal insights into weather conditions. Despite the widespread use of *Cucumis sativus*, there is a paucity of updated scientific literature evidence on its pharmacological activity. Accordingly, this review explores the recent phytochemical and

pharmacological information on *Cucumis sativus* with the aim of providing an updated template for its possible development as a therapeutic agent for various disorders.

Research Methodology

An extensive literature search was conducted to find and assemble updated information on the phytochemical and pharmacological activities of *Cucumis sativus*. The databases and search engines used include Google Scholar, BioMed Central, PubMed, EMBASE/Excerpta Medica, ScienceDirect, Scopus, SciFinder, and Springer Link, from January 1960 till March 2024, as previously reported.[18] Emphasis was placed on the phytochemical constituents, isolated compounds, and pharmacological activity of *Cucumis sativus*. Published article titles, abstracts and data were assessed for duplication and inclusion criteria. All research articles published in the English language were included, and non-English articles were excluded. The EndNote X9 (2018) reference management software was utilized for in-text citations and reference lists.

Phytochemical Constituents

Cucumis sativus is rich in various phytochemical constituents (Table 1), which contribute to its nutritional and potential health benefits. Some of the key phytochemicals reported in different varieties of *Cucumis sativus* include Cucurbitacins A - E and I (Figure 1).[19] This group of phytochemicals is often reported to be responsible for the bitter taste of the plant.[20]

The leaves of *Cucumis sativus* have been reported as major sources of phytochemical constituents. For instance, flavonoids (Figure 2) previously identified in *Cucumis sativus* leaves include Quercetin (A), Apigenin (B), 4-hydroxycinnamic acid (C), Apigenin 8-C-*β*-D-Glucopyranoside (vitexin, D), Kaempferol (E), luteolin-8-C-*β*D-glucopyranoside (orientin; F), Apigenin 6-C-*β*-D-glucopyranoside (isovitexin; G) and luteolin-6-C-*β*-D-gluco pyranoside (isoorientin; H).[21] Two other C-glycosyl flavonoids products include vitexin-6-(4-hydroxy-1-ethylbenzene) [cucumerin A] and isovitexin-8-(4-hydroxy-1-ethylbenzene) [cucumerin B].[5]

For the fruits, already identified constituents include protein, fat, carbohydrate, mineral, calcium, manganese, phosphorus, potassium, iron, vitamins B, C, and K, oxidase, succinic, malic dehydrogenase, cucurbitacins, quercetin, apigenin, and kaempferol. Triterpenes (Figure 3) such as lupeol (A) and *β*-sitosterol (B), lignans (Figure 4) such as pinoresinol (A), lariciresinol (B), and secoisolariciresinol (C); and carotenoids (Figure 5) such as beta-carotene (A), lutein (B), and zeaxanthin (C).[5, 11]

The flowers contain kaempferol 3-O-rhamnoside and 3-O-glycosides, quercetin, and isoramnetin [22]. The peel contains lactic acid, Z-6-nonenol, E-2-nonenol, E, Z-2,6-nonadienal, E-2- nonenal, Z-3-nonenol, 3-nonenal, pentadecanal, 9,12,15 octadecatrienal, and 9,17-octadecadienal.[2, 5] The seeds contain crude proteins, and fatty acids such as palmitic, stearic, linoleic, and oleic acids; as well as sterols such as codisterol, dehydroporifersterol, cholesterol, isofucosterol, stigmasterol, campesterol, 22-dihydrobrassicasterol, and sitosterol.[5, 23, 24]

Pharmacological Activities

Several pharmacological activities of *Cucumis sativus* have been reported and are summarized in Table 2. They include the following:

Antimicrobial activity

Cucumis sativus has been reported to possess antifungal and antibacterial activities. For instance, the antifungal properties of ethanol and chloroform extracts of *Cucumis sativus* stem and leaves were investigated by Das and colleagues using the agar disc diffusion technique at a dose of 80 µg disc^{-1} against Griseofulvin (standard drug) at 30 µg disc^{-1}.[1] [25] The extracts demonstrated moderate antifungal activities against all tested organisms (*Aspergillus niger, Blastomyces dermatitides, Candida albicans, Pityrosporum ovale, Trichophyton,* and *Microsporum* species) with the zones of inhibition ranging from 4.40 ± 0.18 to 1.67 ± 0.08 mm for the ethanol extract and 3.45 ± 0.04 to 1.50 ± 0.12 mm for the chloroform extract. The antifungal properties of *Cucumis sativus* were attributed to the presence of certain phytoconstituents such as tannin, flavonoid, saponin, steroid, glycoside, and alkaloids.[25] In a similar study, the ethanol extract of *Cucumis sativus* peels displayed strong antifungal activities against *Aspergillus niger, Candida albicans, Microsporum spp., Trichophyton spp., Pityrosporum ovale,* and *Blastomyces dermatitides*.[26] Likewise, Sanghamitra and colleagues reported that the acetone extract of *Cucumis sativus* stem and fruits significantly exhibited effective antifungal activity against *Curvularia lunata, Drechslera avenaceum, Fusarium oxysporum, Aspergillus niger* and *Trichoderma viridi*.[27] The antimicrobial potential of *Cucumis sativus* seeds against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, and Proteus vulgaris* was investigated by Al Akeel and co-authors.[28] The results showed that *E. coli* was the most sensitive to the *Cucumis sativus* seed extract and underscored its significant potential as a novel antimicrobial agent.

In a different study, the antibacterial activities of the aqueous and ethanol fruit extracts of *Cucumis sativus* against *Escherichia coli, Salmonella typhi, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pyogenes, Bacillus subtilis* and *Corynebacterium* species was investigated using the disc diffusion method.[29] The results suggest that the ethanol extract was bactericidal at low concentrations while the aqueous extract was bacteriostatic at low concentrations and bactericidal at high concentrations against *Corynebacterium spp*, thus highlighting its potential use as a natural antibacterial agent. Similarly, the leaf extract of *Cucumis sativus* was investigated to estimate their antibacterial activity against two strains of Gram +ve and −ve bacteria like *Klebsiella pneumoniae, Streptococcus pneumoniae, Staphylococcus aureus,* and *Escherichia coli* using the well diffusion method.[30] The results revealed that *Cucumis sativus* was powerful in inhibiting the microbial growth of pathogenic bacteria. A study by Begum and coauthors investigated the antimicrobial activity of *Cucumis sativus* seed extract against selected bacteria and fungi by the agar well diffusion method. [31] In the antibacterial activity, the crude ethanolic extract was most active against *Staphylococcus aureus*, the n-hexane fraction was highly active against *Salmonella typhi*, the dichloromethane fraction against *E. coli* and *Salmonella typhi* showed 16.0 mm inhibition with ethyl acetate.[31] Also, the crude extract of ethanol was tested against *Acremonium, Verticellium, Pythium,* and *Tricoderma* species and showed high zones of inhibition of 15 mm, 14 mm, 17 mm, and 15 mm, respectively. The *Pythium* species were highly susceptible to the n-hexane fraction (20.00 mm), *Acremonium* to dichloromethane fraction (20.00 mm), and ethyl acetate (16.00 mm).[31] Consequently, the findings showed significant antibacterial and antifungal activity, which was attributed to the presence of flavonoids, terpenoids, tannins and phenols. The antimicrobial activity of *Cucumis sativus* peel extracts was determined against *Shigella flexneri, E coli, Staphylococcus aureus* and *Klebsiella pneumonia* using the agar well diffusion method.[32] Findings showed that *Cucumis sativus* inhibited the growth of all the tested pathogens by forming inhibition zones ranging from 11-21 mm, thus highlighting antimicrobial activity.[32] In a different study, the antibacterial activity of the phosphate-buffered saline (PBS) pulp and peel extract of *Cucumis sativus* was determined against *Bacillus cereus, Staphylococcus aureus, Staphylococcus epidermidis, gram-negative Escherichia coli, Pseudomonas aeruginosa,* and *Klebsiella pneumoniae,* following the disc diffusion method.[33] Findings showed that *Cucumis sativus* was active against *Staphylococcus aureus* (inhibition zone of 7.0±0 mm) and *Klebsiella pneumoniae* (7.0 ±0 mm).This effect was attributed to the presence of saponins and flavonoids.[33]

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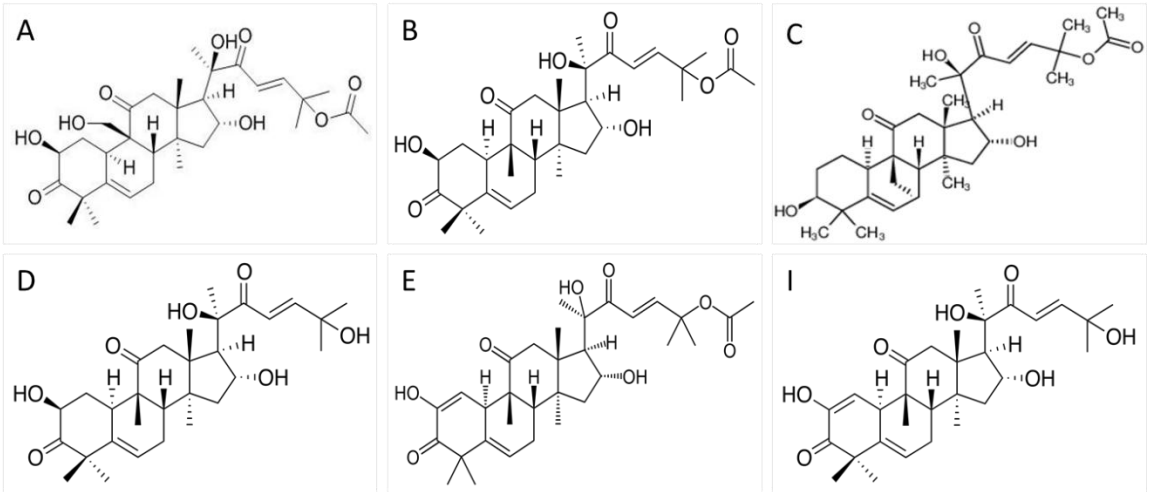

Figure 1: Chemical structure of Cucurbitacins A, B, C, D, E, I

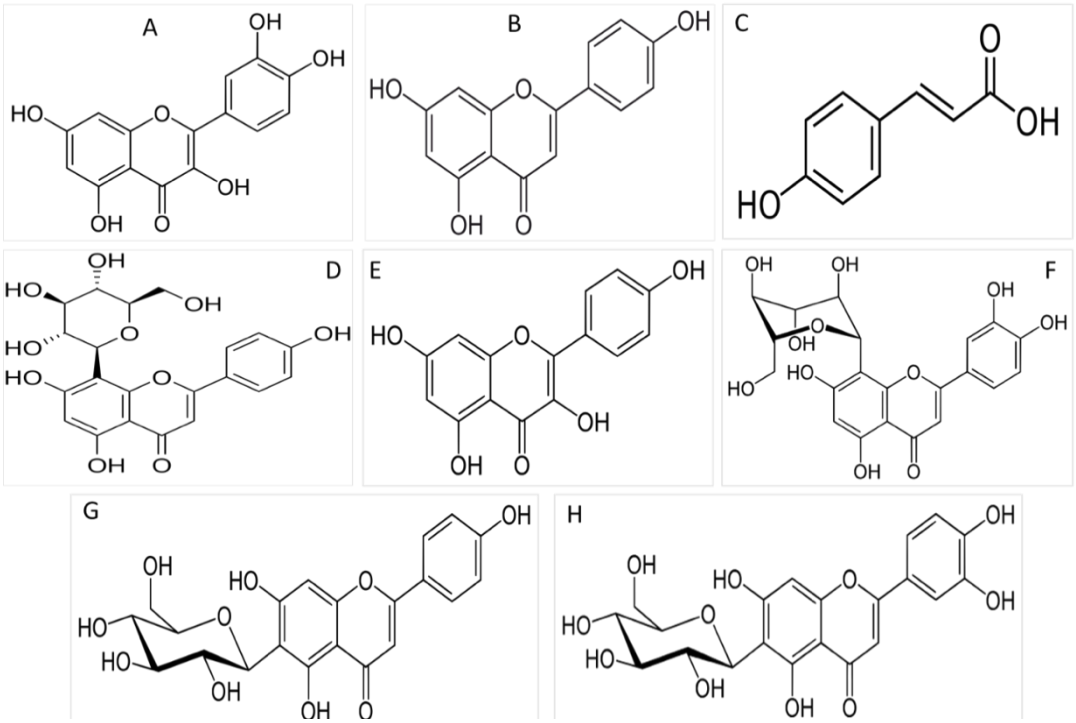

Figure 2: Chemical structure of Flavonoids identified in *Cucumis sativus*

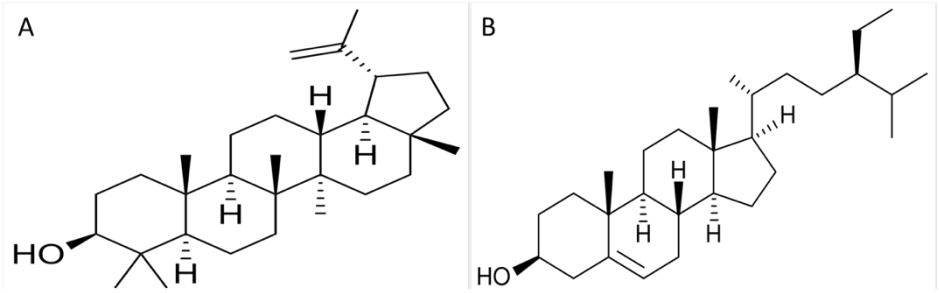

Figure 3: Chemical structure of Triterpenes identified in *Cucumis sativus*

Anti-cancer and cytotoxic activity

In a screening of the methanol and acetone leaf extracts of *Cucumis sativus*, the anti-cancer activity against the human prostate cancer cell line HeLa and the breast cancer cell line MCF-7 was investigated.[30] The results showed that the methanol extract of *Cucumis sativus* had significantly higher anti-cancer activity in MCF-7 and HeLa cells with IC_{50} values of 15.6 ± 1.3 and 28.2 ± 1.0, respectively. Similarly, the anti-cancer activity of ethanolic leaf extract of *Cucumis sativus* was tested on cell lines HeLa and HepG2 through the MTT assay method.[34] At doses of 62.5 µg, 125 µg, 250 µg, and 500 µg, there was significant anti-cancer activity against HeLa and HepG2 cell lines with cell inhibition of 43.93% and 52.46%, respectively. The authors suggested that the presence of triterpenoids in the extract could be responsible for the anti-cancer activities.

In a different study, the ethanolic extract of *Cucumis sativus* flowers was evaluated for anti-cancer activity against liver cancer HepG2 cells.[35] Findings revealed that *Cucumis sativus* extract, at concentrations of 1000 µg/mL, 500 µg/mL, 250µg/mL, 125µg/mL, and 62.5µg/mL, induced cell death in the HepG2 cells with LD_{50} values of 82.15 µg/mL, 73.06 µg/mL, 69.74 µg/mL, 56.21 µg/mL and 49.83 µg/mL, respectively.[35] The phosphate-buffered saline extract of *Cucumis sativus* pulp and peel was reported to be active against the human non-small cell lung carcinoma cell line [H1299] and human breast adenocarcinoma cell line [MCF-7].[33] The PBS pulp extract was active against H1299 (IC_{50} = 42.0 mg/mL) and against MCF-7 (IC_{50} = 125.0 mg/mL) when compared to the Phosphate buffered saline peel extract against H1299 (IC_{50} = 52.0 mg/mL) and MCF-7 (IC_{50} = 290.0 mg/mL). This pattern of activity of both extracts suggested that the content of alkaloids and saponins played an important role in its chemotherapeutic activity.[33]

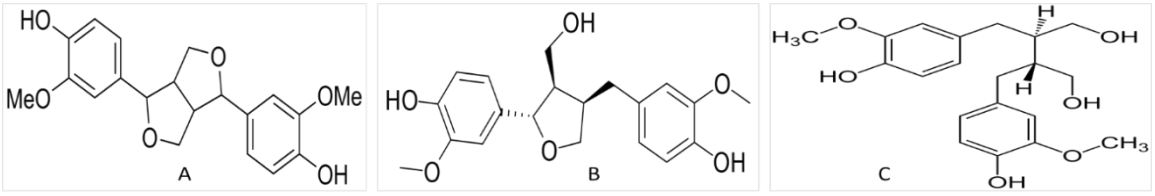

Figure 4: Chemical structure of Lignans identified in *Cucumis sativus*

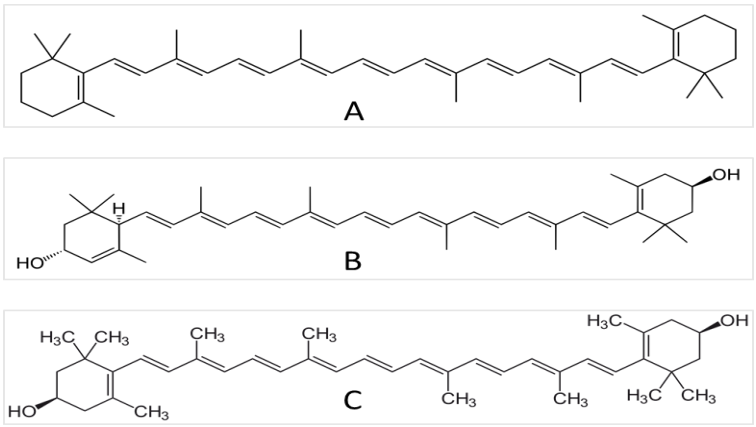

Figure 5: Chemical structure of Carotenoids identified in *Cucumis sativus*

Table 1: Identified constituents of *Cucumis sativus*

S/N	Part used	Identified constituent	References
1	Leaves	Quercetin, Apigenin, Apigenin 8-C-*β*-D-Glucopyranoside (vitexin), Kaempferol, 4-hydroxycinnamic acid, luteolin-8-C-*β*D-glucopyranoside (orientin), apigenin 6-C-*β*-D-glucopyranoside (isovitexin), luteolin-6-C-*β*-D-gluco pyranoside (isoorientin), Vitexin-6-(4-hydroxy-1-ethylbenzene) (cucumerin A) and isovitexin-8-(4-hydroxy-1-ethylbenzene) (cucumerin B).	[5, 21]
2	Fruits	Protein, fat, carbohydrate, mineral, calcium, manganese, phosphorus, potassium, iron, vitamins B, C, and K, oxidase, succinic, and malic dehydrogenase, cucurbitacins, quercetin, apigenin and kaempferol. Triterpenes (lupeol and *β*-sitosterol), lignans (pinoresinol, lariciresinol, and secoisolariciresinol), carotenoids (beta-carotene, lutein, and zeaxanthin), amino acids, phytosterols, and fatty acids.	[5, 11]
3	Flowers	Kaempferol 3-*O*-rhamnoside and 3-*O*-glycosides of kaempferol, quercetin, and isoramnetin	[22]
4	Peel	Lactic acid, Z-6-nonenol, E-2-nonenol, *E,* Z-2,6-nonadienal, E-2- nonenal, Z-3-nonenol, 3-nonenal, pentadecanal, 9,12,15 octadecatrienal, and 9,17-octadecadienal	[2, 5]
5	Seeds	Crude proteins, fatty acids (palmitic, stearic, linoleic, oleic acids), and sterols (codisterol, dehydroporifersterol, cholesterol, isofucosterol, stigmasterol, campesterol, 22-dihydrobrassicasterol, and sitosterol).	[5, 23, 24]

Wound-healing and Anti-ulcer activity

In a study by Patil and colleagues, the ameliorative effect of aqueous extract of *Cucumis sativus* fruit cream formulation on experimentally induced wounds in rats was evaluated.[36] The cream was formulated using a soft white paraffin base containing 2.5%, 5%, and 10% w/w of aqueous extract of *Cucumis sativus* fruit, and excision wounds of size 300 mm^2 and 2 mm depth were utilized. Findings revealed that treatment with *Cucumis sativus* fruit cream formulation resulted in a significant decrease in the wound area, epithelization period, and scar width, while the rate of wound contraction increased significantly.[36] In a different study to assess the anti-ulcer properties of the ethanolic extract of *Cucumis sativus* in an aspirin-induced ulcer rat model, Pradhan and coauthors reported that 400 mg/kg of *Cucumis sativus* ethanolic extract significantly reduced ulcer index when compared to control.[37] Similarly, in indomethacin-exposed ulcerated rats, the anti-ulcer effects of ethanol leaf extract of *Cucumis sativus* at 150 mg/kg were investigated against a standard drug, Ranitidine.[38] The findings showed a maximum anti-ulcer activity comparable to Ranitidine. Satish and colleagues investigated the effects of hydroalcohol *Cucumis sativus* fruit extract on rats with gastric ulcers. Oral administration of *Cucumis sativus* at doses of 250, 500, and 1000 mg/kg significantly reduced ulcer index and free acidity following comparison to the control group.[39] In addition, Gill and coauthors investigated the anti-ulcer effect of methanol extract of *Cucumis sativus* seeds in Wistar rats. Findings showed that *Cucumis sativus* reduced gastric acid volume and free as well as total acidity at 300 mg/kg.[40]

Anti-inflammatory activity

The anti-inflammatory properties of *Cucumis sativus* fruit homogenate were examined by Agatemor and colleagues following subplantar injection of the right hind paw of rats with 0.1 ml of 2% agar-agar suspension to detect increases in paw volumes.[41] Findings revealed that paw volume progressively decreased within 5.5 hours in test groups after administration of 2 mL/kg and 4 mL/kg *Cucumis sativus*. In a different study, the methanol extract of *Cucumis sativus* leaves was investigated for anti-inflammatory activities in the Long Evans rat model at two different doses of 150 and 250 mg/kg body weight following comparison with the standard indomethacin.[42] Findings showed that the extract at both doses significantly inhibited the increase in the volume of paw oedema and reduced inflammation by 57.35 % for 150 mg/kg and 72.06% for 250 mg/kg, in comparison to the standard drug, indomethacin (79.41%) at the end of five hours.[42]

Using a carrageenan-induced rat paw oedema technique, Singh and coauthors assessed the *In-vivo* anti-inflammatory effectiveness of the methanol extract of *Cucumis sativus* seeds at concentrations of 100, 200, and 300 mg/kg.[43] Findings demonstrated significant anti-inflammatory effects of *Cucumis sativus* seeds in a dose-dependent manner following comparison to the standard drug, diclofenac sodium. Trejo-Moreno and colleagues evaluated the *In-vitro* effect of three subfractions (SF1, SF2, and SF3) from *Cucumis sativus* aqueous fraction and its ability to inhibit inflammatory factors induced by angiotensin II in HMEC-1 cells.[44] Findings revealed that both SF1 and SF3 subfractions decreased the induction of IL-6; also, SF1 and SF3 (10 µg/mL each) were the most effective combination to inhibit the production of IL-6 and inhibited the expression of adhesion molecules, in addition to increasing the bioavailability of nitric oxide; thus demonstrating that *Cucumis sativus* possesses anti-inflammatory effects.[44]

Anti-diabetic activity

Karthiyayini and coauthors investigated the anti-diabetic efficacy of powdered *Cucumis sativus* fruits in streptozotocin-induced diabetic rats.[45] Here, various ethanol extract concentrations (200 and 400 mg/kg) were examined for their effects on serum glucose levels.[45] Findings showed that both doses of *Cucumis sativus* showed substantial anti-diabetic benefits but with 400 mg/kg showing a more potent activity. In a study conducted by Antido and coauthors, the hypoglycemic activity of *Cucumis sativus* ethanolic extract was investigated using Sprague Dawley rats treated with 120 mg/kg alloxan.[46] The efficacy of *Cucumis sativus* at doses of 1 mL, 2.5 mL, and 5 mL was compared with an intraperitoneal injection of 0.1 mL insulin, a standard hypoglycemic drug. Findings showed that *Cucumis sativus* extract was able to significantly lower blood glucose levels, thus possessing anti-diabetic effects in alloxan-induced diabetic Sprague-Dawley rats.[46] Similarly, in a study by Saidu and colleagues, the hypoglycemic effect of methanol fruit pulp extract of *Cucumis sativus* on alloxan-induced diabetic rats was investigated.[47] Findings revealed that the methanol fruit pulp extract of *Cucumis sativus* at a dose of 500 mg/kg body weight significantly decreased the fasting blood glucose concentration (mg/dl) from 231.25 ± 1.11 to 82.25 ± 1.55, thus demonstrating its anti-diabetic effects.[47]

Minaiyan and coauthors investigated the effects of hydroalcohol and butanoic extracts of *Cucumis sativus* seeds in a model of streptozotocin-induced diabetic rats.[48] Here, diabetic male Wistar rats were treated daily with hydroalcohol (0.2, 0.4, 0.8 g/kg) and buthanol extract (0.2, 0.4, 0.8 g/kg) as well as glibenclamide (1 and 3 mg/kg) separately, for 9 days. Blood samples were taken at 0, 1, 2, 3, 4, and 8 hours on the first day and day 9 of treatments to measure the blood glucose levels. Findings indicated that both hydroalcohol (22.5-33.8 %) and buthanol (26.6- 45.0 %) extracts of *Cucumis sativus* were effective in reducing blood glucose levels and controlling the loss of body weight in diabetic rats after 9 days of continued daily therapy when compared to control.[48] The authors concluded that the anti-diabetic effects of *Cucumis sativus* seeds are possibly mediated through a mechanism similar to euglycemic agents. A study was carried out to evaluate the effect of *Cucumis sativus* methanol extracts on streptozotocin-induced diabetic rats by a single intraperitoneal injection at 40 mg/kg.[49] The diabetic rats were treated with *Cucumis sativus* methanol extract at 200 and 400 mg/kg for 21 days. Findings showed that *Cucumis sativus* normalized serum liver enzymes and oxidative stress markers, restored serum proteins and lipid profile, and significantly reduced blood sugar to values comparable to non-diabetic rats.[49] Also, there was an improvement in the immunohistochemical expression of insulin in *β*-cells of islets of Langerhans, thus confirming its potent hypoglycaemic activity.

In a comparative study, the ethanolic extracts of some fruits of the *Cucurbitaceae* family, such as *Cucumis sativus*, *Lagenaria siceraria*, *Luffa acutangula*, *Benincasa hispida*, *Citrullus lanatus*, and *Cucarbita maxima* were studied for their hypoglycemic effects on alloxan-induced diabetic rats.[50] Findings suggested that among the tested fruits, *Cucumis sativus* exhibited the highest hypoglycemic potency by reducing blood glucose level by 67% after 12 hours following a single intraperitoneal injection.[50] Ogbodo and colleagues investigated the effect of oral intake of *Cucumis sativus* on blood glucose in young healthy 14 male and 15 female students.[51] They were instructed to withdraw from *Cucumis sativus* for two weeks and received 400 g of whole cucumber for twenty-one days before their daily breakfast. Thereafter, samples were collected on day 0 and

day 22 after overnight fasting for glucose evaluation. Findings showed a significant decrease in the mean plasma glucose level in post-cucumber consumption when compared to pre-cucumber consumption, thus demonstrating the possible hypoglycaemic effects of *Cucumis sativus*.[51]

Anti-oxidant activity of Cucumis sativus

Nema and colleagues investigated the anti-oxidant activities of the lyophilized juice of *Cucumis sativus* fruit using the DPPH and superoxide radical scavenging assay in reference to butylated hydroxytoluene.[52] Findings showed that *Cucumis sativus* fruit juice exhibited potent DPPH-free radical and superoxide radical scavenging activity, with IC_{50} concentrations of 14.73 ± 1.42 and 35.29 ± 1.30 µg/mL, respectively, thus demonstrating its potent anti-oxidant and radical scavenging ability.[52] Similarly, using the DPPH-free radical scavenging activity, Kumar and coauthors evaluated the free radical scavenging activity of *Cucumis sativus* at doses of 250 and 500 µg/mL in comparison to ascorbic acid.[53] Findings showed that *Cucumis sativus* fruit extract displayed maximum anti-oxidant effects, which were attributed to the presence of flavonoids and tannins. A study by Begum and coauthors investigated the anti-oxidant activity of *Cucumis sativus* seed extract using the DPPH method.[31] Findings revealed that the crude ethanolic extract showed maximum DPPH scavenging activity of 46.05 ± 1.23 at 500µg/mL, which were attributed to the presence of flavonoids, terpenoids, tannins, and phenols.[31]

A study aimed to determine the anti-oxidant activity of *Cucumis sativus* pulp and leaves extracts using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) and cupric reducing anti-oxidant capacity methods, as well as the total phenolic, and total flavonoid contents was carried out.[54] The anti-oxidant activity index of *Cucumis sativus* pulp and leaves extracts was in the range of 0.22 - 2.18, while the anti-oxidant activity index of cupric reducing anti-oxidant capacity was 0.07 - 0.95.[54] Also, the ethyl acetate *Cucumis sativus* pulp extract had the highest anti-oxidant by DPPH assay, whereas n-hexane *Cucumis sativus* leaves extract had the highest anti-oxidant activity by cupric reducing anti-oxidant capacity assay.[54] Ethyl acetate *Cucumis sativus* leaves extract had the highest total flavonoid content value (21.47 g QE/100 g) and total phenolic content value (2.34 g GAE/100 g). Flavonoids in *Cucumis sativus* pulp extract contributed to the anti-oxidant activity of the cupric reducing anti-oxidant capacity method, and phenolic compounds in *Cucumis sativus* pulp extract contributed to the anti-oxidant activity of the DPPH method. Consequently, these findings demonstrated the potent anti-oxidant activity of *Cucumis sativus*.[54] In a study by Yunusa and coauthors, the anti-oxidant capacity of different parts of *Cucumis sativus* was evaluated using the DPPH and ferric reducing anti-oxidant power (FRAP), total flavonoid, and phenolic contents assay.[55] The findings showed that the ethanol peel extract demonstrated a significantly higher FRAP value, and a positive correlation between total flavonoid and phenolic contents was established, thus suggesting a potent anti-oxidant activity.[55]

The anti-oxidant potential of *Cucumis sativus* peel extracts was investigated using DPPH radical scavenging, FRAP, and Phosphomolybdenum assays.[32] For the findings, *Cucumis sativus* showed the highest radical scavenging activity of 71% at the concentration of 600 µg/mL. For FRAP and Phosphomolybdenum assays, *Cucumis sativus* showed the highest absorbance values of 0.80 and 0.94, respectively, at the concentration of 300 µg/mL, thus demonstrating potent anti-oxidant activity.[32] In a study designed to investigate the *In-vitro* anti-oxidant activity of *Cucumis sativus*, the aqueous, ethyl acetate, and n-butanol extracts of *Cucumis sativus* were screened using the DPPH radical scavenging assay.[56] Findings showed that the percentage anti-oxidant activity of ethyl acetate, n-butanol, and aqueous extract of *Cucumis sativus* at 300 µg/mL exhibited the maximum anti-oxidant potential of 47.13, 49.64, and 72.40 µg/mL, respectively.[56]

Analgesic activity

Akter and colleagues used the writhing method to assess the analgesic effect of the methanol extract of *Cucumis sativus* leaves in albino mice.[57] At dosages of 250 and 500 mg/kg of body weight, respectively, *Cucumis sativus* inhibited 54.72% and 55.66% writhing, thus highlighting the analgesic activity of *Cucumis sativus*.[57] The fruit extract of *Cucumis sativus* was investigated by Kumar and coauthors for analgesic efficacy at dosages of 250 and 500 mg/kg in mice using a hot plate test.[53] Findings revealed that the extract showed strong analgesic activity via the inhibition of acetic acid-induced writhing and by increasing the latency period.

In a study by Siddika and colleagues, the methanol extract of *Cucumis sativus* was administered at doses of 100 mg/kg, 200 mg/kg, and 300 mg/kg to mice.[58] The method of acetic acid-induced writhing was employed, and the number of writhes brought on by 0.6% acetic acid (10 ml/kg) was used to assess the analgesic efficacy of *Cucumis sativus*. The amount of writhing brought on by acetic acid was significantly decreased by *Cucumis sativus* and the highest percentage of writhing response inhibition was observed at 300 mg/kg. Consequently, the authors postulated that the significant analgesic qualities observed were possibly due to the suppression of prostaglandin production and central inhibitory mechanisms.[58]

Hepatoprotective activity

In a study by Heidari and colleagues, the cytotoxicity induced by cumene hydroperoxide and glyoxal was tested to ascertain the protective effects of the aqueous fruit extract of *Cucumis sativus* using freshly isolated rat hepatocytes.[59] Findings revealed that *Cucumis sativus* at 40 µg/mL prevented all cytotoxicity markers in both the oxidative and carbonyl stress models, including cell lysis, reactive oxygen species formation, membrane lipid peroxidation, depletion of glutathione, mitochondrial membrane potential decline, lysosomal labialization, and proteolysis.[59] The extract also protected hepatocytes from protein carbonylation induced by glyoxal, thus demonstrating that *Cucumis sativus* possessed potent hepatoprotective activity. In a different study by the same lead authors, Heidari and colleagues, the hepatoprotective effect of aqueous extract of *Cucumis sativus* fruit was evaluated against cumene hydroperoxide induced-cytotoxicity and ROS formation in isolated Sprague–Dawley rat hepatocytes.[60] Findings showed that *Cucumis sativus* inhibited reactive oxygen species formation following cumene hydroperoxide treatment in the isolated hepatocytes. The authors attributed the hepatoprotective effects to the anti-oxidant and radical scavenging components of *Cucumis sativus*.[60]

In a different study, the hepatoprotective activity of the ethanolic fruit extract of *Cucumis sativus* was investigated against paracetamol-induced toxicity in albino rats.[61] Findings revealed that *Cucumis sativus* had significant protection against hepatic damage by maintaining biochemical parameters such as glutamic oxalacetic transaminase, serum glutamic pyruvate transaminase, serum alkaline phosphatase, γ-glutamate transpeptidase, total bilirubin, conjugated bilirubin, unconjugated bilirubin, and lipid peroxidase as well as glutathione peroxidase, glutathione reductase, superoxide dismutase, catalase, and

reduced glutathione within normal range.[61] Also, liver histopathology showed that *Cucumis sativus* reduced space formation, loss of cell boundaries, and hepatic necrosis induced by paracetamol in the experimental rats.[61] The authors concluded that *Cucumis sativus* was significantly hepatoprotective at 500 mg/kg against paracetamol-induced toxicity. Similarly, Dhande and colleagues evaluated the hepatoprotective potential of *Cucumis sativus* against carbon tetrachloride-induced hepatotoxicity in rats.[62] Findings showed that *Cucumis sativus* significantly inhibited lipid peroxidation and restored the structural integrity of hepatocytes when compared to the carbon tetrachloride-treated rats, thus demonstrating the potent hepatoprotective activity of *Cucumis sativus*.[62]

Table 2: Pharmacological activities of *Cucumis sativus*

Pharmacology Activity	Plant Part	Extraction Type	Experimental Model/Method	Specie(s)	Concentration(s)	References
Anti-fungal	Stem and Leaf	Ethanol and Chloroform	*In-vitro* / Agar disc diffusion	*Spergillus niger, Blastomyces dermatitides, Candida albicans, Pityrosporum ovale, Trichophyton* and *Microsporum Species*	80 µg disc^{-1}	[25]
Anti-fungal	Peel	Ethanol	*In-vitro* / Agar disc diffusion	*Aspergillus niger, Candida albicans, Microsporum spp., Trichophyton spp., Pityrosporum ovale,* and *Blastomyces dermatitides*	30 µg/disc	[26]
Anti-fungal	Stem and Fruit	Acetone	*In-vitro* /Poison food technique	*Curvularia lunata, Drechslera avenaceum, Fusarium oxysporum, Aspergillus niger and Trichoderma viridi*	Not Specified	[27]
Anti-bacterial	Seed	Elute fraction	*In-vitro* / Agar disc diffusion	*Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, and Proteus vulgaris*	340 mg/mL and 370 mg/mL	[28]
Anti-bacterial	Fruit	Aqueous and Ethanol	*In-vitro* / Agar plate disc diffusion	*Escherichia coli, Salmonella typhi, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pyogenes, Bacillus subtilis* and *Corynebacterium*	200 mg, 400 mg and 600	[29]
Anti-bacterial	Leaf	Methanol and Acetone	*In-vitro* / Agar well diffusion	*Klebsiella pneumoniae, Streptococcus pneumoniae, Staphylococcus aureus* and *Escherichia coli*	25, 50, 75, and 100 µg/ml	[30]
Anti-bacterial	Seed	Ethanol; n-hexane, Dichloromethane, and Ethyl acetate	*In-vitro* / Agar well diffusion	*Pseudomonas aeruginosa, Shigella flexneri, Salmonella typhi, Escherichia coli and Staphylococcus aurous*	20 mg/ml	[31]

Anti-fungal	Seed	Ethanol	*In-vitro* / Agar well diffusion	*Alternaria, Acremonium, Verticellium, Pythium and Tricoderma*	20 mg/ml	[31]
Anti-bacterial	Peel	Methanol and Acetone	*In-vitro* / Agar well diffusion	*Shigella flexneri, E coli, Staphylococcus aureus* and *Klebsiella pneumonia*	50, 75 and 100 µg/mL	[32]
Anti-bacterial	Pulp and Peel	Phosphate-buffered saline	*In-vitro* / Agar well diffusion	*Bacillus cereus, Staphylococcus aureus, Staphylococcus epidermidis, gram negative Escherichia coli, Pseudomonas aeruginosa and Klebsiella pneumoniae*	100 mg/disc	[33]
Anti-cancer	Leaf	Methanol and Acetone	*In-vitro* /MTT assay	HeLa and MCF-7 cells	(IC_{50} - MCF 715.6 ± 1.3) and (IC_{50} - HeLa 28.2 ± 1)	[30]
Anti-cancer	Leaf	Ethanol	*In-vitro* /MTT assay	HeLa and HepG2 cells	62.5 µg, 125 µg, 250 µg, and 500 µg	[34]
Anti-cancer	Flower	Ethanol	*In-vitro* /MTT assay	HepG2 cells	1000µg/ml, 500 µg/ml, 250µg/ml, 125µg/ml and 62.5µg/ml	[35]
Anti-cancer	Pulp and Peel	Phosphate-buffered saline	*In-vitro* /MTT assay	H1299 and MCF-7 cells	H1299 (IC_{50} = 52.0 mg/mL) and MCF-7 (IC_{50} = 290.0 mg/mL).	[33]
Wound healing	Fruit	Aqueous	*In-vivo*	Wistar rats	2.5%, 5%, and 10% w/w	[36]
Anti-ulcer	Not Specified	Ethanol	*In-vivo*	Wistar rats	400 mg/kg	[37]
Anti-ulcer	Leaf	Ethanol	*In-vivo*	Wistar rats	150 mg/kg	[38]
Anti-ulcer	Fruit	Hydroalcoholic	*In-vivo*	Wistar rats	250, 500 and 1000mg/kg	[39]
Anti-ulcer	Seed	Methanol	*In-vivo*	Wistar rats	300 mg/kg	[40]
Anti-inflammatory	Fruit	Homogenate	*In-vivo*/Rat paws oedema method	Wistar rats	2 mL/kg and 4 mL/kg	[41]
Anti-inflammatory	Leaf	Methanol	*In-vivo*/Carrageenan- and Formalin-induced paw oedema technique	Long Evans rats	150 and 250 mg/kg	[42]
Anti-inflammatory	Seed	Methanol	*In-vivo*/ Carrageenan-induced rat paw	Rat	100, 200, and 300 mg/kg	[43]

			oedema technique			
Anti-inflammatory	Fruit	Aqueous Subfractions	*In-vitro* / Angiotensin II	HMEC-1 cells	10 µg/mL	[44]
Anti-diabetic	Fruit	Ethanol	*In-vivo*/ Streptozotocin	Albino rats	200 and 400 mg/kg	[45]
Anti-diabetic	Fruit	Ethanol	*In-vivo*/Alloxan	Sprague Dawley rats	1 mL, 2.5 mL, and 5 mL	[46]
Anti-diabetic	Fruit	Methanol	*In-vivo*/Alloxan	Albino rats	500 mg/kg	[47]
Anti-diabetic	Seed	Hydroalcoholic and Buthanol	*In-vivo*/ Streptozotocin	Wistar rats	0.2, 0.4, 0.8 g/kg	[48]
Anti-diabetic	Fruit	Methanol	*In-vivo*/ Streptozotocin	Sprague Dawley rats	200 and 400 mg/kg	[49]
Anti-diabetic	Fruit	Ethanol	*In-vivo*/Alloxan	Long-Evans female rats	200 mg/kg	[50]
Anti-diabetic	Fruit	Whole	*In-vivo*	Human	400g	[51]
Anti-oxidant	Fruit	Crude Juice	*In-vitro* /DPPH and superoxide radical scavenging assay	None	DPPH (IC_{50} - 4.73 ± 1.42) and Superoxide radical scavenging (IC_{50} - 35.29 ± 1.30 µg/mL)	[52]
Anti-oxidant	Fruit	Aqueous	DPPH	None	250 and 500 µg/ml	[53]
Anti-oxidant	Seed	Ethanol	DPPH	None	500 µg/ml	[31]
Anti-oxidant	Pulp and Leaf	n-hexane, ethyl acetate, and ethanol.	DPPH	None	50 µg/mL	[54]
Anti-oxidant	Fruit and Seed	Ethanol	DPPH and ferric-reducing anti-oxidant power (FRAP)	None	0.1 mL (DPPH) and 15 µL (FRAP)	[55]
Anti-oxidant	Peel	Methanol and Chloroform	DPPH and FRAP	None	600 µg/mL (DPPH) and 300 µg/mL (FRAP)	[32]
Anti-oxidant	Fruit	Aqueous, Ethyl acetate, and n-butanol	DPPH	None	100, 200, and 300 µg/ml	[56]
Analgesic	Leaf	Methanol	*In-vivo*/Writhing	Mice	250 and 500 mg/kg	[57]
Analgesic	Fruit	Aqueous	*In-vivo*/Hot plate test/Acetic Acid-Induced Writhing Test	Mice	250 and 500 mg/kg	[53]
Analgesic	Not specified	Methanol	*In-vivo*/Acetic Acid-Induced	Mice	100, 200 and 300 mg/kg.	[58]

			Writhing Test			
Hepatoprotective	Fruit	Aqueous	*In-vivo*/cumene hydroperoxide	Isolated rat hepatocytes	40 µg/mL	[60]
Hepatoprotective	Fruit	Aqueous	*In-vivo*/cumene hydroperoxide (oxidative stress model) or glyoxal (carbonyl stress model)	Isolated Sprague–Dawley rat hepatocytes	40 µg/mL	[59]
Hepatoprotective	Fruit	Ethanol	*In-vivo*/Paracetamol	Albino rats	500 mg/kg	[61]
Hepatoprotective	Fruit	Homogenate	*In-vivo*/Carbon tetrachloride	Wistar rats	(2 mL/kg and 4 mL/kg)	[62]

Conclusion

Cucumis sativus, a plant with significant medicinal importance, boasts a rich history of traditional medicinal use. Numerous *In-vitro* and *In-vivo* studies have underscored its remarkable pharmacological benefits and provided substantial evidence to support many of its traditional uses. However, investigations into its neuroprotective and reproductive activities are still remarkably few. Consequently, this updated review will provide a template for further investigations in lesser-explored research areas such as the nervous and reproductive systems. Also, the updated information from this review will aid the possible development of drugs that can be useful against various disease conditions.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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