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Chemical Compounds and Pharmacological Activities of Cucumis genus

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Abstract: Cucumis genus is one of the genera from the Cucurbitaceae family. Cucumis genus plants have many health benefits. They are known as traditional medicinal plants in several countries in Asia, including Indonesia. This literature review discusses the topic of traditional use, phytochemical compounds, nutritional content, pharmacological activity, genotoxicology, and toxicity tests of the Cucumis genus plants based on data obtained from scientific databases and search engines such as PubMed, Scopus, Science Direct, and Google Scholar. Cucumis genus plants contain many chemical compounds, such as cucurbitacin, phenolic compounds, vitamins, minerals, essential oils, and fatty acids. Several studies have shown that Cucumis genus plants exhibited some pharmacological activities such as antimicrobial, analgesic, antioxidant, anti-inflammatory, antidiabetic, antiwrinkle, and anticancer activity. Cucumis genus plants also have useful therapeutic effects for osteoarthritis, ulcerative colitis, and wound healing. Each part of Cucumis genus plants contains phytochemical compounds that are different from one another. Their pharmacological activities are also different, depending on the phytochemical compounds and Cucumis genus plants' plant parts. However, more recent studies are needed regarding the genotoxicology and toxicity of the Cucumis genus plants.

Keywords: Cucumis genus; chemical compounds; pharmacological activities.

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1. Introduction

The Cucurbitaceae family consists of 130 genera and 800 species [1]. Cucurbitaceae has long been known as a traditional medicine in several countries in Asia, including Indonesia because Cucurbitaceae contained protein and antioxidants. Cucurbitaceae fruits were known to be low in fat and calories, so people often consumed them as food [2]. Many researchers had developed Cucurbitaceae plants to be used as cosmetics and skincare for skin problems such as wrinkles and aging [3]. One of the popular genera from the Cucurbitaceae family is Cucumis. There are 25 species of Cucumis in Asia. Cucumis plants that people mostly consume are cucumber (*Cucumis sativus*) and melon (*Cucumis melo*). *C. sativus* and *C. melo* have many wild relatives in Asia and Australia [4]. Their tap and fibrous roots characterize Cucumis plants. The stems of Cucumis plants are green, wet, and watery, but they are strong. The stems are segmented, and they have fine hair. Cucumis plants are creepers. They have broad leaves that grow alternately. Chemical compounds contained in several Cucumis plants and their pharmacological activities will be explained in this review.

2. Materials and Methods

Data in this review were based on data obtained from scientific databases and search engines such as PubMed, Scopus, Science Direct, and Google Scholar. The search was performed using the keywords Cucumis, pharmacological activities, and chemical compound. Source articles were published for a maximum of 10 years, with a minimum of 20 articles in the last 2 years. Each source article has a DOI number. This literature review was done by reviewing 57 articles. Each source article was checked for quality by checking each journal index. Scopus indexed the articles used in this review. They were checked on the scopus.com website.

3. Results and Discussion

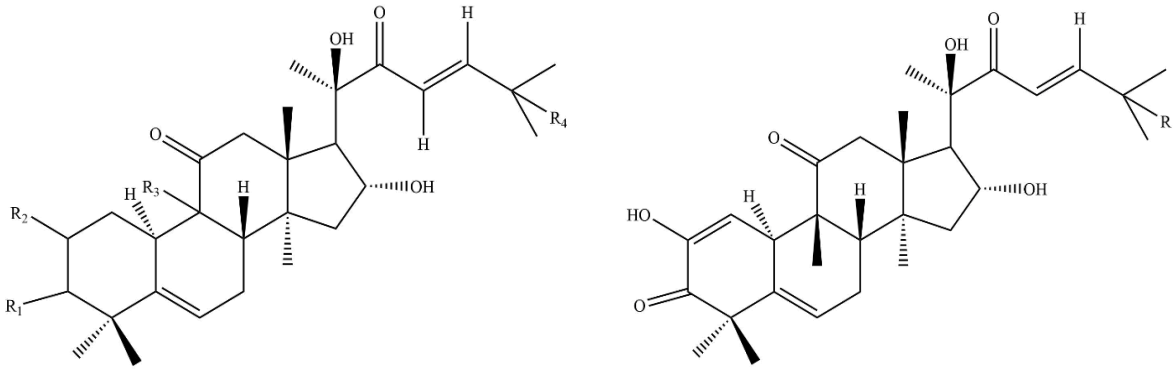
3.1. Chemical compounds.

Plants produce many secondary metabolites. They can be used for medicine [5]. *C. sativus* fruit contained phytochemical compounds such as carbohydrates, flavonoids, glycosides, and steroids [6]. *C. sativus* fruit was made up of 95% water and contained lots of vitamin A and C. Phytochemical screening of the ethanol extract of the leaf and stem of *C. sativus* showed the presence of alkaloids, glycosides, steroids, saponins, and tannins. The chloroform extract of the leaf and stem of *C. sativus* contained alkaloids, glycosides, steroids, flavonoids, saponins, and tannins. In *C. sativus* leaves, there were also flavone glycosides such as isovitexin, saponarin, and acylated C-glycosides [7]. Ethanol extract of *C. sativus* leaves contained alkaloids, glycosides, steroids, flavonoids, saponins, and tannins. The acetone extract of *C. sativus* leaves also contained flavonoids [8]. *C. melo* contained polyphenols such as flavonoids and tannins [9]. Besides that, *C. melo* also contained sterols, saponins, and amino acids [10]. *C. melo* seeds had phenolic glycosides [7]. Alkaloids, flavonoids, tannins, steroids, saponins, glycosides, and phenols were distributed in the peel of *Cucumis metuliferus* [11].

3.1.1. Cucurbitacin.

Cucurbitacins are triterpenoid compounds with various structures. Cucurbitacin is an oxygenated tetracyclic triterpene that can be found in many Cucurbitaceae plants, including in Cucumis genus [12]. Researchers have widely studied cucurbitacin because of its pharmacological potentials [5]. Cucumis fruits and roots have a high cucurbitacin content, while Cucumis seeds have a low cucurbitacin content [13]. Based on the structure, Cucurbitacin compounds are divided into 17, Cucurbitacin A, B, C, D, E, F, G, H, I, J, K, L, O, P, Q, R, and S [13]. The structures of a few cucurbitacins (A, B, C, D, E, and I) were given in Figure 1. *C. sativus* contained Cucurbitacin A, B, C, D, E, and I. Cucurbitacin C in *C. sativus* caused a bitter taste [14,15]. Cucurbitacin E had high toxicity properties because its hydrophobicity was the highest compared to other cucurbitacins [5]. Cucurbitacin E could inhibit cell adhesion [16].

Cucurbitacin B, D, E, I, and L were also accumulated in *C. melo* [17,18]. *C. melo* had a high amount of Cucurbitacin B, D, E, and 2-O-β-D-glucopyranosyl cucurbitacin B [10]. Cucurbitacin B from *C. melo* was commonly used as liver protection medicine in curing hepatic lesions and liver cancer [18]. Cucurbitacin extract from *C. melo* fruit has the ability to reduce systolic blood pressure (SBP) by improving blood vessel tension [10].



(1) R_1 = =O R_2 = -OH R_3 = -CH_2OH (5) R = -OC OC H_3
(2) R_1 = =O R_2 = -OH R_3 = -H (6) R = -OH
(3) R_1 = -OH R_2 = -H R_3 = -CH_2OH
(4) R_1 = =O R_2 = -OH R_3 = -H

Figure 1. Structure of Cucurbitacin A (1), Cucurbitacin B (2), Cucurbitacin C (3), Cucurbitacin D (4), Cucurbitacin E (5), and Cucurbitacin I (6).

Cucurbitacin B, D, E, I, IIa, L glucoside, Q, dan R were the most active cucurbitacin components against cancer through inhibition of migration and invasion, proapoptosis, and cell cycle arrest promotion [19].

3.1.2. Phenolic compounds.

Phenolic compounds are secondary metabolites that are widely found in plants. Most of the phenolic compounds are flavonoids and phenolic acid. Phenolic compounds had antioxidant activity potential, so they are commonly used for disease prevention [20]. Based on research, there were 73 phenolic compounds identified in *C. sativus*. The identification was made by the mass spectrometry (MS) method. Phenolic compounds that were identified in *C. sativus* using this method such as quercetin 3-L-rhamnoside, naringenin 7-O-β-D-glucoside, kaempferol-3,7-O-α-L-dirhamnoside, apigenin 7-rutinoside, kaempferol 3-O-sambubioside, vicenin 2, diosmetin-apiosylglucoside, theaflavanosidel, luteolin-6-C-(6-malonyl)hexoside-8-C-pentoside, laricresinol 9-O-β-D-glucopyranoside, luteolin 7-O-glucuronide, and isorhamnetol 3-O-rutinoside. Through this research, it can be stated that *C. sativus* is a good source of phenolic compounds [21].

C. melo seeds, leaves, flesh, peels, and stems were also contained phenolic compounds. Flavonoids were the main phenolic compounds in *C. melo*. *C. melo* was also a good source of phenolic compounds [22]. *C. melo* leaf extract showed the highest total phenolic content compared to other plant parts (26.4 ± 0.3 mg GAE/g extract) and total flavonoid content (69.7 ± 3.37 µg RE/g extract). This research also revealed that *C. melo* leaf and stem extract figured the best antioxidant activity compared to other plant parts [23].

C. melo peels were identified using the High-Pressure Liquid Chromatography (HPLC) method. The result showed that 3-hydroxybenzoic acid and flavones were their main phenolic compounds. The total 3-hydroxybenzoic acid content in *C. melo* peels was 33.45 mg/100 g. Besides that, apigenin-7-glycosides were also found 29.34 mg/100 g [24].

These were other phenolic compounds that were also identified in *C. melo*: gallic acid, hydroxytyrosol, protocatechuic acid, tyrosol, chlorogenic acid, 4-hydroxybenzoic acid, isovanillic acid, luteolin-7-glycoside, naringenin, oleuropein, m-cumaric acid, phenylacetic

acid, luteolin, pinoresinol, and amentoflavone [24-26]. The structures of few phenolic compounds identified in *C. melo* peels were displayed in Figure 2.

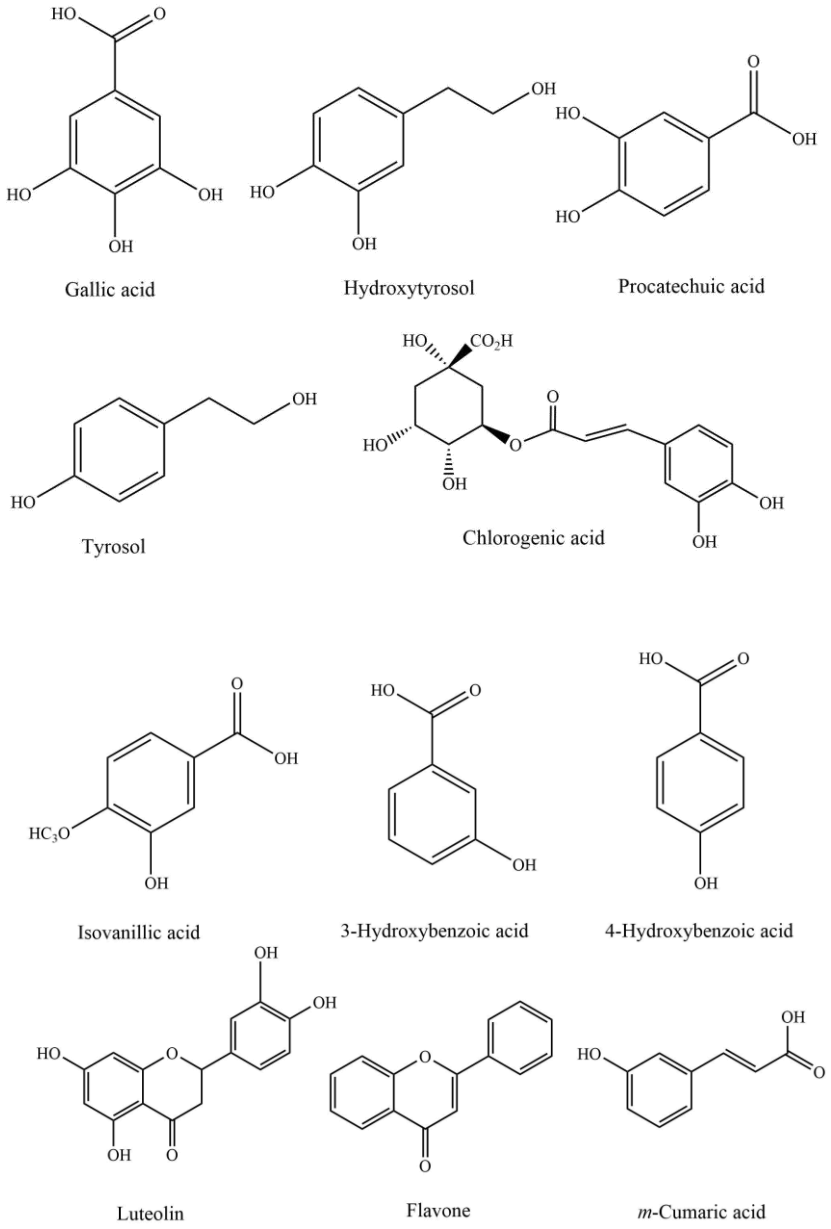


Figure 2. Structure of phenolic compounds identified in *C. melo* peels.

3.1.3. Vitamin and minerals.

The result of vitamin analysis, exposed that methanol leaf extract of *C. sativus* contained a high amount of vitamin A (23.00 ± 0.01 mg/kg), vitamin B1 (0.03 ± 0.01 mg/kg), vitamin B2 (0.03 ± 0.02 mg/kg), vitamin B6 (0.44 ± 0.01 mg/kg), vitamin C (6.11 ± 0.02 mg/kg), vitamin E (0.09 ± 0.01 mg/kg), niacin (0.41 ± 0.01 mg/kg), and folate (15.00 ± 0.02 mg/kg) [27]. Rind and pulp of cucumber fruit contained high amount of vitamin C and vitamin B1 [28]. *C. sativus* rind and pulp contained mineral elements such as K, Ca, Mg, Zn, Fe, Mn, Na and Cu [29].

Another research showed that the rind of *Cucumis metuliferus* was rich in vitamins C, E, D, B9, and A with a high content of vitamins B2, K, B1, and β-carotene [11]. *C. melo* contained nutrients like vitamins and minerals [30]. *C. melo* was a good source of vitamin C and A [31]. *C. melo* contained minerals elements such as N, P, Ca, Mg, Fe, and Na [32].

3.1.4. Essential oils and fatty acids.

Essential oils are volatile liquids that can widely found in plants. *C. melo* seed oil was rich in essential oil. It contained α-spinasterol, stigmasta-7,22,25- trienol and stigmasta-7,25-dienol. They have phenol groups [33]. *C. melo* seed oil also contained some major fatty acids such as linoleic acid (4.6%), oleic acid (21.12%), palmitic acid (17.68%), and stearic acid (10.84%) [34].

C. sativus was a good source of essential oil. Chemical compounds of the essential oil of *C. sativus* fruits were 3-nonenal, nonanal, E,Z-2,6-nonadienal, Z-3-nonenol, E-2-nonenal, Z-6-nonenol, n-decanal, E,E-2,4-nonadienal, E,E-2,4 decadienal, E,Z-2,4-decadienal, E-β-damascenone, 1-tetradecene, tetradecane, α-humulene, β-ionone, tridecanal, caryophyllene oxide, tetradecanal, pentadecanal, 9,12,15-octadecatrienal, and 9,17,octadecadienal [35].

3.2. Pharmacological activities.

3.2.1. Antimicrobial activity.

C. sativus fruit extracts were analyzed for their antimicrobial activity against six Gram-negative and Gram-positive strains (*Staphylococcus aureus, Staphylococcus epidermidis, Pseudomonas aeruginosa, Enterobacter cloacae, Klebsiella pneumoniae,* and *Escherichia coli*). The tested extracts were dichloromethane peel extract, methanol peel extract, dichloromethane pulp extract, and methanol pulp extract. The result showed that *C. sativus* fruit extracts have a strong antibacterial activity, especially the dichloromethane and methanol pulp extract (MIC 2.43 -3.15 mg/ml) [35].

Sphingolipids were isolated and identified from *C. sativus* stems. These sphingolipids exposed vigorous antifungal activity on *Pythium aphanidermatum* and *Botrytis cinerea*. These sphingolipids also exhibited potent antibacterial activity on *Bacillus subtilis, Xanthomonas vesicatoria,* and *Pseudomonas lachrymans* [36]. *C. sativus* seed extract also had significant potential as an antimicrobial agent, especially on *E. coli* strains [37].

Cucumis anguria leaf extract was tested for its potential as an antibacterial agent. The result revealed that *C. anguria* leaf extract could be used to synthesize silver nanoparticles, making C. anguria leaf extract a good source of antibacterial agent, especially for *S. aureus* and *E. coli* [38].

C. melo had good antifungal activity. Vicilin-like proteins isolated from *C. melo* expressed potent antifungal activity against pathogenic fungal species such as *Fusarium oxysporum* [7]. *C. melo* methanolic and ethanolic leaf and seed extract gave antibacterial activity against *S. aureus* and other Gram-positive strains [39,40]. *C. melo* fruit had been traditionally used as an antiparasitic agent because of its anthelmintic and vermifuge activity [41].

3.2.2. Antioxidant activity.

C. sativus fruit was tested by 2,2-diphenyl-1-picrylhydrazyl (DPPH) method and superoxide radical scavenging assay, which used butylated hydroxytoluene as standard for its antioxidant activity. *C. sativus* fruit extract exhibited significant DPPH free radical and superoxide radical scavenging activity with IC_{50} at 14.73 ± 1.42 and 35.29 ± 1.30 μg/ml, compared to butylated hydroxytoluene IC_{50} at 31.38 ± 1.43 and 51.79 ± 1.05 μg/ml [43].

Nonphenolic compounds such as uracil and 24-methylenecycloartenol in *C. sativus* fruit expressed a high antioxidant activity [35].

High content polyphenols and carotenoids in *C. melo* displayed a high antioxidant activity. *C. melo* leaf, peel, pulp, and seed extracts were examined by the DPPH method for their antioxidant activity. The results stated that they had antioxidant activity. The IC_{50} value of *C. melo* leaf methanolic extract was 780,1 µg/ml, *C. melo* lyophilized peel methanolic extract was 189.02 µg/ml, *C. melo* oven-dried peel methanolic extract was 370.93 µg/ml, *C. melo* pulp n-hexane extract was 335 µg/ml, and *C. melo* seed methanolic extract was 653.57 µg/ml [26, 43-45].

3.2.3. Anti-inflammatory activity.

The methanolic extract of *C. sativus* leaves was identified for its anti-inflammatory activity in the Long Evans rat model at two doses (150 and 250 mg/kg bw). The effects were compared to indomethacin (10 mg/kg bw) as standard. The result showed that *C. sativus* leaves extract could significantly reduce inflammation by 57.35% (150 mg/kg bw) and 72.06% (250 mg/kg bw) compared to the standard drug (79.41%) [46].

Other research also showed that *C. sativus* extract could attenuate lipopolysaccharide (LPS)-induced inflammatory response in endothelial cells [47]. *C. sativus* aqueous fraction also could reduce Angiotensin II-induced inflammatory factors [48]. Iminosugar idoBR1 (an iminosugar amino acid isolated from *C. sativus* fruit) could work as an anti-inflammatory agent by inhibiting sialidase in the production of functionally active HA adhesive CD44 [49].

C. melo was also known for its anti-inflammatory activity. *C. melo* fruit extract had a high Superoxide Dismutase Activity (SOD). SOD was responsible for anti-inflammatory activity in *C. melo* [50].

3.2.4. Anticancer activity.

C. sativus fruit methanol and acetone extracts were evaluated for their anticancer activity. The results reported that *C. sativus* fruit was rich in bioactive compounds which have anticancer activity with cell lines of IC_{50} (MCF 715.6 ± 1.3 and HeLa 28.2 ± 1) [8].

Cucurbitacins in *C. sativus* worked as an anticancer agent through some mechanisms of action by inhibiting cell proliferation, preventing migration and invasion, promoting apoptosis, and promoting cell cycle arrest. Cucurbitacins also inhibited some signaling pathways included JAK-STAT3 (Janus Kinase-Signal Transducer and Activator of Transcription Proteins 3), Wnt, PI3K/Akt (Phosphatidylinositol 3-Kinase/Protein Kinase B), and MAPK (Mitogen-Activated Protein Kinase) pathway. Those signaling pathways play important roles in cancer cells' apoptosis and survival. Synergistic anticancer effects using cucurbitacins together with chemotherapeutic drugs (such as methotrexate and docetaxel) had been discovered and used to treat cancer [19].

Cucumis prophetarum also demonstrated anticancer activities against six cancer cell lines, such as human breast cancer cell (MCF7, MDA-MB-231), colon cancer cell (HCT-116), ovarian cancer cell (A2780/A2780CP), and liver cancer cell (HepG2). Cucurbitacin compounds were responsible for their anticancer activity. Cucurbitacin E and Cucurbitacin B showed the best effect against cancer cells [51].

3.2.5. Antidiabetic activity.

Ethanolic extract of *C. sativus* peels was tested at 250 and 500 mg/kg dose for 15 days in the alterations in serum glucose and hepatic lipid peroxidation (LPO) in male mice. The result showed that ethanolic extract of *C. sativus* peels had the potential to regulate alloxan induces diabetes mellitus and associated changes in serum lipids and thyroid hormones. The better effects were tested at 500 mg/kg dose [52].

Cucumis trigonus fruit aqueous extract was evaluated for its antidiabetic activity in streptozotocin-induced diabetic rats. The result figured statistical data that indicated a significant increase in serum insulin level and a decrease in the blood glucose, glycosylated hemoglobin levels, total cholesterol, and serum triglycerides. So it can be concluded that *C. trigonus* had a beneficial effect as an antidiabetic agent by reducing the elevated blood glucose level and lipid profile of STZ-induced-diabetic rats [53].

3.2.6. Antiwrinkle activity.

Lyophilized juice of *C. sativus* fruit was calculated its ascorbic acid content concerning the standard compound. The result presented that its ascorbic acid content was 3.5 ± 0.23% w/w. It can be concluded that *C. sativus* lyophilized juice was a good source of ascorbic acid, so it had the potential to be an antiwrinkle agent for cosmetic products [42].

3.2.7. Analgesic.

The aqueous extract of *C. sativus* fruit was examined at 250 and 500 mg/kg. The analgesic effect of aqueous extract of *C. sativus* fruit was compared with diclofenac sodium as the standard. Strong analgesic effects were shown. In mice, a dose of 500 mg/kg inhibited the acetic acid-induced writhing and increased the latency time in the hot-plate test. Flavonoids and tannins were discovered in an aqueous extract of *C. sativus* fruit. The presence of them was responsible for its analgesic effects [28].

Cucumis ficfolius crude methanolic root extract and solvent fractions have analgesic activity. *C. ficfolius* crude root extract and solvent fractions have been evaluated with acid-induced writhing, hot plate, and formalin-induced paw licking test. The result revealed that the crude extract had analgesic activity (72.5%) to acetylsalicylic acid in the acetic acid writhing test. Both crude extract and solvent fractions exhibited significant prolongation of nociception reaction time in the hot plate test. In the formalin-induced paw licking test, crude methanolic extract and solvent fractions showed a significant reduction of mean lick time with maximum protection, 64% in the early phase and 83% in the late phase. From those three tests, it can be concluded that *C. ficfolius* had good analgesic activity [54].

3.2.8. Ulcerative colitis.

C. sativus showed a potential therapeutic effect in the amelioration of experimental ulcerative colitis in Wistar rats that were administered with acetic acid via intrarectal. The acetic acid in Wistar rats enhanced ulcer area, ulcer index, spleen weight, colon weight to length ratio, colonic MPO (myeloperoxidase), and hematological parameter. Pretreatment with *C. sativus* for 7 days showed significant effects in lowering ulcer area and ulcer index at 250 and 500 mg/kg in acetic acid-induced colitis [55].

3.2.9. Osteoarthritis.

One hundred twenty-two patients (56 males and 66 females) aged between 40 and 75 years and diagnosed with moderate knee osteoarthritis were included in this test. Sixty-one patients received 1350 mg glucosamine-chondroitin drug twice daily, and the other patients received 10 mg *C. sativus* aqueous extract twice daily. The result showed that the Western Ontario Master Universities Osteoarthritis Index (WOMAC) score was decreased in *C. sativus* aqueous extract group by 22.44% on day 30 and 70.29% on day 180, compared to 14.8% and 32.81% decrease in the glucosamine chondroitin group. *C. sativus* aqueous extract had no adverse effect on patients. So, *C. sativus* aqueous extract could be an effective moderate knee osteoarthritis pain reducer and can be potentially used in the management of knee pain, stiffness, and other physical functions related to osteoarthritis [56].

3.2.10. Wound healing.

The purified Cucumis protease from *C. sativus* showed primary and secondary hemostatic activities as it cleaves both fibrinogens as well as fibrin. The purified Cucumis protease from *C. sativus* also reduced Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT), and recalcification time. Because of its hemostatic activity, purified Cucumis protease from *C. sativus* can be used as an active agent for wound healing [57].

4. Conclusions

After a thorough literature review, we found that Cucumis genus plants are rich in phytochemical compounds, cucurbitacins, phenolic compounds, vitamins, minerals, fatty acids, and essential oils. Cucumis genus plants have some pharmacological properties such as antimicrobial, antioxidant, anti-inflammatory, anticancer, antidiabetic, antiwrinkle, and analgesic agent. They also have some potential therapeutic effects for ulcerative colitis, osteoarthritis, and wound healing.

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Conflicts of Interest

The authors declare no conflict of interest.

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