IJPSR (2020), Volume 11, Issue 4 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 06 July 2019; received in revised form, 13 September 2019; accepted, 06 February 2020; published 01 April 2020

ETHNOMEDICINAL USES AND PHARMACOLOGICAL ACTIVITIES OF DIFFERENT PARTS OF *CUCUMIS SATIVUS* LINN: AN UPDATE

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Keywords:

Anti-carcinogens, Anti-diabetic, Anti-inflammatory, *Cucumis sativus* L, Diuretic, Maghze tukhme khayarain

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ABSTRACT: Increasing demand of herbal medicines in the treatment of diseases has once again gained the immense importance due to its viable efficacy and compliance to the patients. *Cucumis sativus* L. is commonly known as cucumber and Khayarain in Unani medicine. It is found wildly in the Himalayan regions and also cultivated throughout India. Maghze tukhme khayarain (seeds of Cucumis) is in use in traditional Unani medicine for various ailments such as Waram al-mathana (Cystitis), ziabetes (Diabetes), waram al-shoab (bronchitis), zaheer (diarrhoea), and renal diseases as it possesses musakkin-i-safra (yellow bile), muskkain-i-hiddat–i-dam(blood), Muhallil (anti-inflammatory) and Mudi-i-bawl (diuretic) properties. Not only seeds but other parts of the Cucumis such as root, leaves, flower, and fruits are also useful in various diseases. Further, the various part of the plant contains phytochemical constituents such as potassium, cucurbitacin A, B, C and D, flavanoid-fisetin, ascorbic acid, lactic acid, lariciresinol, pinoresinol and secoisolariciresinol, saponin and hypo-xanthine. Furthermore, it is pharmacologically proven for analgesic, anti-carcinogenic, anti-inflammatory, anti-microbial, anti-oxidant, diuretic, hypoglycemic, hepatoprotective and wound healing activities. As the world is turning back towards the herbal drug, it is need of the hour to re-evaluate the knowledge of traditional medicine through reverse pharmacology and review it.

INTRODUCTION: For centuries traditional medical systems (TMS) were the primary medical system in the countries of origin, and now nevertheless the present dominance of the scientific medical model, due to its viable efficacy and compliance to the patients the demand of herbal medicinal products for medicinal purpose increasing vigorously over last three decades for the treatment of diseases.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(4).1549-56

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(4).1549-56

Since ancient, plants have been used as a radix to provide humans with medicines carrying the high therapeutic potential to cure health disorders and to combat numerous pathogenic infections [1]. *Cucumis sativus* Linn. (cucumber) is a widely cultivated plant in the gourd family, Cucurbitaceae like melon, squash and pumpkins. It is commercially cultivated globally as seasonal vegetables [2].

Amongst 30 species of Cucumis, *C. sativus* L. has the most economical value. The curative properties of the cucumber have been identified since antiquity [3, 4]. Cucumber is the 4th important vegetable worldwide [5]. They can mainly be found wild in the Himalayas from Kumaon to Sikkim, but also cultivated throughout the India [6]. All parts of the plant such as root, leave, fruit and seeds are

useful in treating diseases [7]. In India, numerous varieties of Cucumis are widely cultivated up to an altitude of 1200 m [8]. It is an annual trailing and climbing plant that grows up to 2 m in length/height and flowers from July to September and seed ripen from August to October. With benefits, cucumbers can be consumed or eaten as dessert flavors with lemon juice, pepper and salt to get the maximum amount of vegetable juices and vitamins. They can also be cooked as a vegetable. The large variety of it, when ripe is called tavas in Marathi is much used in curries, in pickles and eaten raw [6]. In this review, the phytochemical constituents and pharmacological research knowledge about this well-known plant species *C. sativus* L. are explored and updated.

2. Vernacular Names:

Unani Tibbi	:	Khiyaar, Khira
English	:	Cucumber
Ayurvedic	:	Trapusha, Traapusha, Trapushi, Tiktakarkatikaa
Siddha/Tamil	:	Vellarikkai [9], Kakrikai [6]
Folk	:	Khira
Sanskrit	:	Ervaru, Karhati [6]
Bengali	:	Phuti (ripe), Karcha (unripe) [6]
Hindi	:	Tuti
Telgu	:	Pedda dosari [6], Dosakaya [7]
Kannada	:	Mullu savte, Santekayi [10]
Bombay	:	Kakri, Kankari
Burma	:	Thagwa, Thakhwathee
Dutch	:	Konkommer
French	:	Concomber, Concombre communi
German	:	Gurke, Kunkummer
Greek	:	Sikys
Indo-china	:	Bi bai, Dua chuot, Dua gang, Hoang qua, Ho qua
Portugese	:	Pepineiro, Pepino
Russian	:	Oguretz
Swedish	:	Gurca
Italian	:	Cedriuolo, Cetriolo, Cetriuolo [11]

3. Botany and Etymology:

3.1. Botany: *Cucumis sativus* L. is a member of the Cucurbitaceae, which comprises 90 genera and 750 species. It is one of the oldest cultivated vegetable crops and is cultivated in nearly all countries of temperature zones. It is a thermophilic and frost-susceptible plant species, growing best at temperatures above 20 °C. It is an herbaceous vine with pubescent stems and unbranched tendrils up to 30 cm long; its leaves are simple and alternate with 3-7 palmate lobes and serrated margins, the flowers pentamerous with radical symmetry. The flower of its female plant is solitary thick covered with very bulbous hairs, whereas male flowers are clustered, bearing anthers with cohering, connective crushed or elevated above cells. The fruits are cucumiform (roughly cylindrical but elongated with tapered ends) and can be 50 cm long with 10 cm of diameter [12].

The seeds of this plant are fishy shaped, compressed, elongated, ellipsoid, dorsoventrally convex and lateral rigid. The size of the seeds can be up to 1 cm or more in length and 0.5 cm in width, micropyle pointed, distinctly visible. The outer surface is glossy, peelable, brittle, and color yellowish-white. The kernel is oily, creamish white, odorless and tastes mildly sweet. Each cotyledon shows five distinct patches of small, thin-walled, polygonal cells and the outer most layer of testa is absent [8]. *Cucumis sativus* L. grows on moist region, slightly alkaline and well- drained soil rich in organic matter. It grows well under full sun exposure in warm and humid climate [13].

3.2. Etymology: Cucumis in Latin word means cucumber, the word was derived from Greek for cucumber, ‘kykyon’. The epithet sativus is also Latin word means that is sown referring to the common agricultural use of the species [14].

4. Traditional Unani and Other Ethno Medicinal Use: This plant exists since bygone and mainly consumed as raw fruit world-wide. In between rich medicinal plants identified so far, *C. sativus* has been proven to carry remarkable therapeutic potential and extensively used in traditional Unani system and other traditional systems of medicine [15]. Parts like seeds, leaves, fruit and root of *C. sativus* plant have been used. **Table 1** summarizes the details of the ethnopharmacological information of *C. sativus*.

4.1. Fruits: The fruits are mildly sweet, refrigerant, hemostatic and tonic. Traditionally it is used for the wide range of cure in rural and urban regions to remove general debility and also used as a cooling agent.

Cucumber fruits most likely are used to treat skin problems through decade/ centuries [12]. Moreover, it is also used as depurative, demulcent, emollient, and purgative, in indo-china traditionally its raw fruit is also used for the treatment of dysentery in children [15]. These fruits are also useful in burning sensation, hyperdipsia, insomnia, bronchitis, jaundice [10] and also be useful for the treatment of menstrual disorder in Khagrachari [16].

TABLE 1: TRADITIONAL USES OF DIFFERENT PARTS OF *CUCUMIS SATIVUS* L. AND FUNCTIONS OF CUCURBITACINS

Part used	Traditional uses	References
Seeds	Diuretic - useful in dysuria and urinary stones. Lipid lowering agent, anti-helminthic, cooloing, mubrid-i-badan, musakkin-i-safra, muskkain-i-hiddat -e -dam.	[9], [10], [20], [21], [22]
Fruits	Refrigerant, hemostatic, tonic and useful in hyperdipsia, thermoplegia *etc.* Anti-helminthic, skin conditioning agent and Anti-tumour effects. Applied externally to relieve pain.	[2], [11], [23], [24], [25]
Leaves	Anti-oxidant activity, leaf juice is emetic and is used to treat dyspepsia in children. Leaves boiled and mixed with cumin seeds, roasted and powdered, and administered in throat infections.	[6], [15]
Roots	Anti-inflammatory used as a cure for bronchitis, headache and boils.	[23]
Flowers	Anti-bacterial and anti-fungal activity	[26]
Function of cucurbitacins	Mechanism of action	
Anti-inflammatory activity	Cucurbitacin R has been reported to be mediated by inhibition of tumor necrosis factors (TNF)-alpha, nitric- oxide synthase-2 and cyclo-oxygenase-2. Cucurbitacins B, D, E, and I have been reported to inhibit cyclo-oxygenase enzymes	[25], [35], [36]
Anti-tumor activity	Inhibition of janus kinase/signal transducer activator of transcription 3 signaling pathway whose activation is required for the proliferation and sustainment of cells. In relation to cancer, targets of cucurbitacins action involve growth inhibition, the arrest of the cell cycle at G2/M phase and induction of apoptosis in a cancer cells.	[37], [38], [39]
Anti-atherosclerotic activity	Cucurbitacin B and E in glycosidic form to exhibit an inhibitory effect on lipid oxidation productions.	[40]
Anti-diabetic activity	Stimulates insulin release and regulation of hepatic glycogen metabolism.	[41]

4.2. Seeds: The seeds are widely used as refrigerant and Murattab (cooling agent). The seeds extract is useful in headache sanguine, meningitis and epistaxis [17]. Seeds are also beneficial in the case of dyspepsia, anuria, dysuria, and burning micturition as possess diuretic activity [18]. It also suppresses post-partum lactation and seminal debility [19]. It is also used in vitiated conditions of pitta, burning sensation, constipation, intermittent fevers, stran-guary, renal calculus, urodynia and general debility [10].

4.3. Leaves: The leaf juice is emetic and used to treat dyspepsia in children. A decoction of the root is used as diuretic [15].

5. Phytochemical Constituents: This review is to describe the main chemical constituents of different parts of *C. sativa* L. especially fruit, seeds, leaves, roots and flowers. The characteristic property of the family Cucurbitaceae is the presence of cucurbitacins (triterpenoid substances-well-known for their bitterness and toxicity) [2]. The contents of cucumber are rutin, seeds glucosides including cucurbitaside, leaves free cucurbitasides B & C ferredoxin, alpha-spinasterol.

Free and bound sterols are also present in seedling and in flowers of both genders. Proteolytic enzymes, ascorbic acid oxidase, succinic and malic dehydrogenase presence have also been reported [9, 19]. A tremendous resource for scientific and clinical research as well as new drug development is represented plant secondary metabolites [25].

5.1. Water: Cucumber fruit is rich in water; it contains about 95% of water [4]. Since ancient time it has been recognized that water is essential to life. Water is the principal or the element of things declared by Thales of miletus one of the sevens ages of ancient Greece, in the compendium of material medica (1578) Shizen-Li a Chinese physician of ming dynasty wrote that "Water is the best medicine". However, in renal disorders,

therapeutic effects of water have been particularly well studied [27]. Especially in dermatological (age preventing) terms and health water might be beneficial [28]. Cucumber is rich in water hence, it act as a diuretic, lipid-lowering agent, refrigerant and cosmetic agent.

5.2. Cucurbitacins: The structure of cucurbitacins is tetracyclic cucurbitane nucleus structure namely 9β-methyl-19-nor lanosta-5-enea, and the structure is divided into twelve categories [30]. Cucurbiricians A, B, C, D E and I (1-) were identified in cotyledons of different varieties of *C. sativus* seedlings [31]. Cucurbitacins are a class of highly oxidized tetracycline triterpenoids that confer a bitter taste to cucurbits such as cucumber, melon, pumpkin [32].

It has been reported that the cucurbitacins are the bitter principle in the Cucurbitaceae family. To date a large number of cus and cu- derived compounds have been isolated from the Cucurbitaceae family and from other species of the plant [33, 34]. A common feature among all compounds in the category of cucurbitacins is the presence of 5, 6 double bonds [25]. Various functions of cucurbitacins are mentioned in **Table 1**.

5.3. Tannins: From the use of tannins in tanning animal skins to make leather the term tannin was originally derived. This term is widely applied to any polyphenolic compound that forms strong complexes with proteins. It is an uncrystallizable colloidal substance that has pronounced astringent properties and ability to precipitate gelatin from solution, forming insoluble compounds with gelatin-yielding tissues, the property on which manufacture of leather is dependent [42].

Tannins are the complex polyphenolic substance found in plants and provide astringent and hemostatic properties [43]. Its molecular weight ranges from 500 to more than 3000. Tannins are the astringent obtained from various parts of the plant such as fruit, fruit pods, leaves, bark, wood and roots [44]. Tannins were identified in an aqueous extract of the cucumber fruit [45]. Cucumis acts as a hemostatic agent because of the presence of tannins. Thus; useful in epistaxis, dysentery *etc.* [17]

5.4. Others: Fruits contain a high concentration of ascorbic acid, which showed the anti-oxidant activity. Fatty acids primarily lauric, myristic, palmitic, stearic, oleic, linoleic, tricosanoic, tricosenoic, lignoceric, and nervonic acids present in cucumber. Fruits contain water (96.4%), protein (0.4%), fat (0.1%), carbohydrate (2.8%), mineral (0.3%), calcium (0.01%), phosphorus (0.03%), iron (1.5 mg/100 g) and vitamin B (30 IU/100 g). The fatty acid components are palmitic (0.63%), stearic (16.2%), linoleic (40.11) and oleic acid (38.70)4. Seeds are also rich by the number of constituents including crude proteins (42%) and fats (42.5%). The gibberellin hormone was also found in seeds [46]. Plant leaves are also sources for some major phytoconstituents. Vitexin-6-(4-hydroxy-1-ethyl-benzene) (cucumerin A) and isovitexin-8- (4-hydroxy-1-ethylbenzene) (cucumerin B) are the two new major C-glycosyl flavonoids products. It contains a number of sterols such as codisterol, 25 (27)-dehydro-porifersterol, clerosterol, isofuco-sterol, stigmasterol, campesterol, 22-dihydro-brassicasterol, sitosterol, 25 (27)-dehydrofungi-sterol, 25 (27)-hydrocondrillasterol, 24-β-ethyl-25 (27)-dehydrofungisterol, avenasterol, 22-dihydri-spinosterol and 24-methylenecolesterol. Other phytoconstituents such as 4′-X-O-diglucosides of isovitexin and swertiajaponin were found in the methanolic extract of the flowers [47].

6. Pharmacological Activity and Therapeutic Benefits:

6.1. Antiinflammatory Activity: Muruganantham *et al.,* (2016) show that ethyl acetate fractions of *C. sativus* L. flowers exhibited significant anti-inflammatory activity. Its fresh flowers extract was evaluated for antioxidant activities by 2,2-Diphenyl 1-picryl hydrazyl solution (DPPH), 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid (ABTS) assay and anti-inflammatory activity by human blood cell (HRBC) membrane stabilization method and inhibition of albumin denaturation method. The results obtained showed that the compound isolated from ethyl acetate fractions of *C. sativus* flowers can be considered as good sources of antioxidants and anti-inflammatory activity [25]. Agatemor and co-workers (2015) also studied the anti-inflammatory effect of *C. sativus* L using an animal models (four groups of Wistar rats). The control group received normal saline; the reference group received standard anti-inflammatory drug diclofenac, while 2 test groups received whole *C. sativus* L. fruit homogenate, respectively. They

found that paw volume progressive decreased within 5.5 h in the test groups after administration of *C. sativus* L. The authors concluded that the whole fruit homogenate of *Cucumis sativus* L. had anti-inflammatory activity.

6.2. Anti-oxidant Activity: *C. sativus* L. flower's ethyl acetate fractions when compared with the DPPH assay exhibited significant anti-oxidant activity. When compared with ABTS assay activity, the result showed 72.53%, 68.04%, 52.47% and 48.15% cytotoxicity for 1000 µg/ml, 500 µg/ml, 125 µg/ml and 31.25 µg/ml respectively. It was evident, that the sample possesses ABTS assay activity [26]. The presence of the bioactive compounds in the cucumber peel was shown by Sheila John *et al.,* (2018). They investigated the antioxidant activity of *C. sativus* L. using *in-vitro* assays namely DPPH assay and FRAP assay and phosphor molybdenum assay [49]. Kumar *et al.,* (2010) studied the aqueous fruit extract of *C. sativus* L. for free radical scavenging and analgesic activities.

The free radical scavenging was compared with ascorbic acid, BHA and the extract was subjected to *in-vitro* anti-oxidant studies at 250 and 500 microgram/ml. The *C. sativus* L. fruit extract showed maximum antioxidant and analgesic effect at 500 micro gm/ml and 500 mg/kg respectively [50].

6.3. Anti-bacterial and Anti-fungal Activity: A significant anti-microbial and antifungal activity was exhibited from the compound isolated from ethyl acetate fraction of *C. sativus* L. flowers in comparison with standard drugs chloramphenicol and fluconazole [51]. Three anti-microbial sphingolipids were separated by bioassay-guided isolation from the chloroform fraction of the crude methanol extract of cucumber stems and identified as "(2S, 3S, 4R, 10E) -2- [(2'R)-2-hydroxytetra-cosan-oylamino]- 1, 3, 4-octadecanetriol-10-ene, 1-O-β-D-glucopyranosyl (2S, 3S, 4R, 10E)-2-[(2'R)-2-hydroxy-tetra-cosanoylamino]-1, 3, 4 octadeca-netriol-10-ene and soya-cerebroside I" by their physicochemical properties and spectroscopic analysis. They were evaluated to show antifungal and antibacterial activity on test microorganisms including four fungal and three bacterial species [52]. Sood *et al.,* (2012) conducted the anti-microbial activity of *C. sativus* L. against 4 human microbial pathogens. The antimicrobial assay was performed by the agar well diffusion method. The specific concentration of seed extract showed the highest zone of inhibition against *S. aureus*. These pathogens were highly sensitive to the methanol extract except *E. coli* (enteropathogen) and *P. aeruginosa*. Finally, they concluded that *C. sativus* L. seeds possess potential broad-spectrum antimicrobial activity. Sood *et al.,* also conducted the antifungal activity of *C. sativus* against two potent fungus. Finally, they concluded that *C. sativus* seeds possess potential antifungal activity [53]. Malik *et al.,* (2012) performed a study on the anti-fungal activity of the ethanolic extracts of *C. sativus* L and assessed the action against six funguses. The results (diameter of zone of inhibition) were compared with the activity of the standard drug, griseofulvin (30 µg/disc). At 80 µg/disc, the ethanol extracts of *C. sativus* L was active against fungus [54].

6.4. Diuretic Property: *C. sativus* L. (EECS) and fruits of *Corriandrum sativum* L. (EECRS) to make a polyherbal formulation (PHF). The extracts were administered to experimental rats orally at the dose level of 150 mg/kg and compared with standard drug furosemide (20 mg/kg). The diuretic effects of the extracts and PHF were evaluated by measuring the parameters like urine volume, sodium, potassium and chloride contents. The extract and PHF showed a marked level of increase in urine volume and electrolytes like Na+, K+ and Cl^- ion concentration. PHF showed a more diuretic effect than standard [55].

6.6. Cytotoxic Activity: Mallik *et al.,* (2012) studied the cytotoxic activity of the ethanolic extracts of *C. sativus* L. In brine shrimp lethality bioassay, the ethanol extract showed lethality against the brine shrimp. It showed a different mortality rates at different concentrations. From the plot of percent mortality versus log concentration on the graph paper, LC_{50} (µg/ml) and LC_{90} (µg/ml) of the ethanol extract of *C. sativus* L. were deduced respectively [54]. Another study also confirmed the cytotoxic effect of *C. sativus* L_{56}. Muruganantham and co-workers (2016) concluded the MTT assay of the compound isolated from ethyl acetate fractions of *Cucumis sativus* flowers shows that all concentrations are having anticancer activity [26].

6.7. Carminative and Antacid Activity: Sharma *et al.,* (2012) were investigate with the aqueous extract fruit pulp of *C. sativa* significantly neutralized acid and showed resistance against change in pH and also illustrate the good carminative potential. The extract of *C. sativa*, has shown to possess significant carminative and antacid property [57].

6.8. Effect on Ulcerative Colitis: Patil *et al.,* (2012) were described its activity against ulcerative colitis after an authentic investigation with the aqueous extract *C. sativus* L. fruit in ulcerative colitis in laboratory animals. In this investigation, the aqueous extract of *C. sativus* L. selected for screening against experimentally induced bowel disease. The extract of *C. sativa* L. has shown to possess significant property against ulcerative colitis [58].

6.9. Hepatoprotective Activity: Heidari *et al.,* (2012) were studied the effect of *C. sativus* L. against cumene hydroperoxide induced-oxidative stress. The results showed that aqueous extract of *C. sativus* L. acts as a hepatoprotective and antioxidant agent against CHP-induced hepato-toxicity suggesting that antioxidants and radical scavenging components of *C. sativus* L. fruit extract can easily cross the cell membrane and cope with the intracellular ROS formation [59].

6.10. Hypoglycemic and Hypolipidemic Activity: Sharmin *et al.,* (2013) were studied hypoglycemic and hypolipidemic effects of cucumber in alloxan-induced diabetic rats. It was concluded that the ethanol extracts of Cucurbitaceae family fruits, cucumber, white pumpkin and ridge gourd have significant anti-hyperglycemic effects in AIDRs. They also have the capacity to reduce the elevated lipid profiles in AIDRs. Ridge gourd has also significant effects of restoring the depressed hepatic glycogen levels in AIDRs.

Therefore, we believe that these fruits extracts can be useful, at least as an adjunct, in the therapy of diabetes, a condition in which hyperglycemia and hyperlipidemia co-exist quite often. However, further study is necessary for the screening of chemical compounds and the structure elucidation of the respective anti-diabetic leads as well as their exact mechanism [60].

6.11. Wound Healing Activity: Patil *et al.,* (2011) were studied on the pharmacological evaluation of wound healing potential of *C. sativus* L. He stated that aqueous extracts of *C. sativus* L. have proper efficacy on wound healing. Herbal paste preparation showed significant ($P<0.05$) improvement in maturation, wound contraction and epithelialization [61].

6.12. Anti-wrinkle and Anti-aging Activity: The anti-oxidant, anti-hyaluronidase, and anti-elastase activity of the lyophilized juice of *Cucumis sativus* fruit were proven for their activities. The presence of ascorbic acid rationalizes the use of *C. sativus* as a potential anti-wrinkle agent in cosmetic product [62]. The fermentation of synthetic cucumber juice proved that there were some unknown compounds in cucumber extract that also contributed to fermentation and resulted in lactic acid production higher than that of total sugar content. The inclusion of soluble organic acid-bound magnesium in the fermented cucumber extract at high concentrations supported a novel application of this fluid as an ingredient of magnesium gels [63].

6.13. Skin Diseases: A case report of a 42-year-old man who used sulfur powder adhered to cucumber slices to successfully self-treat a vitiligo condition. The treatment has resulted in no recurrence of the disease for 21 years. The authors analyzed the mechanism of this folk prescription for vitiligo and concluded that the success of the self-treatment may be mainly associated with hydrogen sulfide (H_2S). The antibacterial activity of pentathionic acid ($H_2S_5O_6$) and the antioxidant activity of cucumber might also play a role in the treatment [64].

7. Toxicological Studies: The acute toxicity of *Cucumis sativus* L. fruit homogenate was evaluated on 20 albino mice grouped into five groups of four mice each. Animals in different groups were orally administered with different amounts of the whole fruit homogenate. The animals were monitored for dullness, nervousness, uncoordinated movement, and death within 24 h after administration. The administered *Cucumis sativus* L. did not induce adverse effects on the mice within the concentration range of 0.5 ml/kg body weight to 5 ml/kg body weight test animals.

They concluded there were no dose-dependent side effects [48]. Acute toxicity studies of aqueous extract of *C. sativus* fruit showed no sign and symptoms such as restlessness, respiratory distress, diarrhea, convulsions and coma and it was found safe up to 5000 mg/kg [61].

CONCLUSION: *C. sativa* is a medicinal plant of immense importance owing to its diverse ethnomedicinal uses, phytochemical constituents and pharmacological profile.

This review reveals that this plant is a strong source of new potential phytoconstituents having widespread pharmacological properties especially antioxidant, anti-bacterial, anti-mutagenic and cytotoxic activities. Identification of more by-products from *C. sativa* suggests a promising future for this plant.

ACKNOWLEDGEMENT: Nil

CONFLICTS OF INTEREST: Nil

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How to cite this article:
Saeedi R, Sultana A and Rahman K: Ethnomedicinal uses and pharmacological activities of different parts of *Cucumis sativus* Linn: an update. Int J Pharm Sci & Res 2020; 11(4): 1549-56. doi: 10.13040/IJPSR.0975-8232.11(4).1549-56.