

Phytochemicals of Cucurbitaceae Family – A Review

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Available Online: 22nd December, 2015

ABSTRACT

The family cucurbitaceae includes a large group of crops like cucumbers, and melon which are medicinally essential. The plants of the family are collectively known as cucurbits. It is a distinct family without any close relatives. Plants of this family have many medicinal and nutritional benefits. So it is important to find out the active agents possessing pharmacological activity in plants coming under the family. The major elements present are the phytochemicals like Glycosides, Terpenoids, Saponins, Tannins, Steroids, Carotenoids, and Resins etc. and most commonly the terpenoid substance called Cucurbitacins

Keywords: Cucurbita, Momordica, Cucumis, Citrullus, Trichosanthes, Cucurbitacins

INTRODUCTION

Plants were used to cure diseases and infections during ancient time. Medicinal plants are cheap, easily available and affordable. The medicinal importance of plants lies in some chemical substances that produce a specific physiological action on the human body. The most essential of these bioactive constituents of plants are alkaloids, saponins, tannins, flavonoids and phenolic compounds¹. Cucurbits form an important and a big group of vegetable crops cultivated extensively in the subtropical and tropical countries. All of the cultivated species are found in subfamily Cucurbitoideae. Fruit of *Cucurbita maxima* is the largest known fruit of all flowering plants, and are often used in contests for the largest pumpkin category. Based on world production, the most popular cucurbit is watermelon, followed by cucumber and the leading producers of cucurbits are China and Turkey². The family consists of about 130 genera and 800 species. A lot of work has been done by the researchers throughout the world on various plants of the family Cucurbitaceae. The important genera belonging to the family are Trichosanthes, Lagenaria, Luffa, Benincasa, Momordica, Cucumis, Citrullus, Cucurbita, Bryonopsis and Corallocarpus. Some of the important plants that have been extensively studied are *Momordicacharantia*, *Cucurbitapepo*, *Cucumissativus*, *Cucumismelo*, *Citrulluscolocynthis*, *Luffaechinata*, *Trichosantheskirilowii*, *Lagenariasiceraria*, *Benincasahispidaetc*³. Cucurbit plants were used actively as traditional herbal remedies for various diseases. They have demonstrated anti-inflammatory, antitumor, hepatoprotective, cardiovascular and immunoregulatory activities^{3, 4}. In general, members of this family have always been considered as a subject of research due to the

fact that they are rich source of proteins, with many biological activities like anti-fungal, anti-bacterial, antiviral, anti-diabetic, anti-tumor and anti-AIDS. It is also known to contain several bioactive compounds such as cucurbitacins, triterpenes, sterols and alkaloids⁵. The present study is to review the pharmacologically important plants and phytochemicals present in cucurbits and to understand their pharmacological activity.

PHYTOCHEMICALS PRESENT IN CUCURBITS

Phytochemicals are non nutritive chemical constituents of plants which occur naturally in it, or the chemicals which is derived from plants are called Phytochemicals¹. Phytochemical analysis of the plants belongs to cucurbitaceae family confirms the presence of various phytochemicals like tannins, cardiac glycosides, terpenoides, carbohydrates, resins, saponins, Carotenoids and phytosterols⁶. Glycosides play various important roles in living organisms. The first glycoside identified was Amygdalin in 1830. Cardiac glycosides are the type of drugs which is mainly used in the treatment of heart disease or cardiac disease. Their function is to increase the cardiac output by increasing the force of contraction. By increasing the intracellular calcium, the cardiac glycosides help to increase calcium-induced calcium release and thus contraction¹. Cardiac glycosides have anti-inflammatory activity, offer protection against lethal endotoxemia and are used in cardiac treatment of congestive heart failure⁶. The leaves, seeds and bark of the plant *Momordicabalsamina* of cucurbitaceae family contain cardiac glycosides¹. The terpenoides, is sometimes called as isoprenoids. These have large and different class of naturally occurring organic chemicals which is similar to terpenes¹. Terpenoides have membrane disruption and inhibitory effect against fungi

and bacteria. It also has antineoplastic activity. These are widely found in *Citrulluscolocynthis*⁶. Saponins have haemolytic property, induced cytotoxic effect, expectorant action, antitumor and anti-mutagenic activities and can lower the risk of human cancers, by preventing cancer cells from growing⁶. Saponins have the property of precipitating and coagulating red blood and are used to stop bleeding and in treating wound. *Hensleyagracilaria*, a Chinese medicinal plant of this family contains saponins¹. Tannins, sometimes called as tannoid, is a type of biomolecule, present in plant and is assigned by Phytochemical process¹. Tannins have been found in the extracts of *Cucumis sativa* (Cucumber) and *Praecitrullusfistulosus* (Tinda). Tannins have astringent properties; hasten the healing of wounds and inflamed mucous membrane. Tannins are potential metal ion chelator, proton precipitating agent and biological antioxidant. Ellagitannins have free radical scavenging activity⁶. Steroids have a special type of component called Sterol, Phytosterols have been found in the extracts of *Momordicacharantia* (Karela), *Cucumis sativa* (Cucumber), *Lagenariasiceraria* (Loki). Phytosterols have a significant hypocholesterolemic effect⁶. Carotenoids are more than 600 in nature and are found in two classes, xanthophylls (contain oxygen) and carotenes (which having purely hydrocarbons, and no oxygen). Carotenoids can be found in watermelon (*Citrulluslanatus*)¹. Resins were found in all seed extracts except *Cucumis sativa* (Cucumber) and found in *Momordicabalsamina*¹.

GENUS CUCURBITA

The genus *Cucurbita*, indigenous to the western hemisphere, is comprised of five domesticated species. Of the 50 common varieties of *Cucurbita* throughout the world, there are 2 general categories: the pumpkin and the squash. *Cucurbitapepo*, *Cucurbita maxima*, *Cucurbitamoschata*, *Cucurbitaandreaana*, and *Cucurbitaficifolia*, represent economically important species cultivated worldwide.

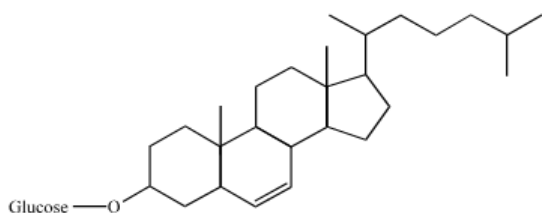
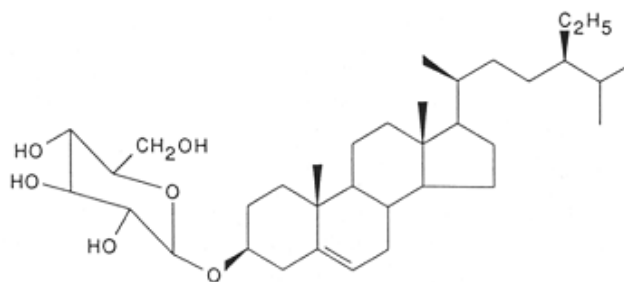
Cucurbitapepo (Gourd)

Also known as pumpkin, gourd, acorn squash, marrow, and summer squash and locally known as kaddu, konda, and kumra. It is grown for its fruit and edible seeds. It has white seeds enclosed in a husk. These seeds are chewable and sweet with a little nutty flavour^{3,4}. The pumpkin seeds yield approximately 50% oil, (mostly linoleic and oleic acid) but the main active constituents are Δ^7 sterols (avenasterol, spinasterol) and Δ^5 sterol (sitosterol, stigmasterol). It also contains Triterpenoids, Sesquiterpenoids, Squalene, Tocopherols (tocopherol is predominant), Carotenoids, Minerals (Particularly phosphorus, potassium, magnesium, calcium, iron, zinc and trace elements), Proteins and amino acids, Carbohydrates (6-10%), Vitamins (thiamine, riboflavin, niacin, pyridoxine, and pantothenic acid), Phenolic glycosides, and Lignans. *Cucurbitapepo* has been traditionally used as diuretic and anthelmintic. The seeds and oil from pumpkin seeds have been used for many years for the relief of difficulties associated with an

enlarged prostate gland and micturition problems related to irritable bladder. The advantage of pumpkin seed treatment arises from its tonic influence on the bladder and sphincter relaxation. The relaxations of the bladder and decrease in-bladder pressure are related to the increased productions of NO via the arginine or NO Pathway. *Cucurbitapepo* treatment alleviates micturition symptoms but does not decrease the augmented volume of prostate gland. It possess Antioxidant activity (inhibitory activity against lipid peroxidation and freeradical scavenging activity), Antiandrogenic activity, Immunological activity, Antiviral activity, Antifungal activity, Cardiovascular activity, Anti-inflammatory activity and Hepatoprotective activity⁷. Its seeds have shown immunosuppressive activity in peripheral mononuclear blood cells, the seed extracts modulate immunobiochemical pathways induced by interferons. It has antibacterial properties. Anti-ulcer and antioxidant activities are exhibited by tetracyclitriterpenoids (cucurbitacins) extracted from *C. pepo* seeds. Also cause inhibition to the testosterone induced hyperplasia of the prostate. The fruit is cooling and astringent to the bowels, increases appetite, cures leprosy and purifies the blood. Seeds cure sore chests, haemoptysis, bronchitis and fever^{3,4}.

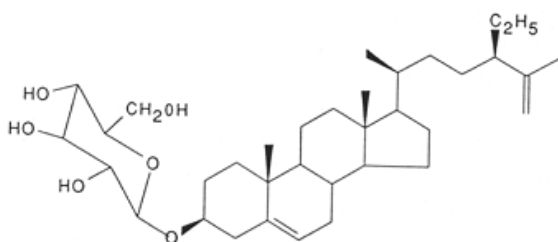
Cucurbita maxima (pumpkin)

The plant *Cucurbitamaxima* Duchesne (commonly known as pumpkin) is widely cultivated throughout the world for use as vegetable as well as medicine. Both fruits and the aerial parts are commonly consumed as vegetable⁸. The flowers of *Cucurbita maxima* Duchesne afforded a 4:1 mixture of spinasterol and 24-ethyl-5 α -cholesta-7, 22, 25-trien-3 β -ol^{9,10}. Phytochemicals such as flavonoids, polyphenolics, saponins, proteins and carbohydrates are also present⁸. It is also a good source of vitamin A, iron, phosphorus, and calcium. Cucurbitaxanthin, gibberellin and α -tocopherol are also isolated from the plant⁹. Pumpkins have antioxidant β -carotene, which help to improve the immune function and can reduce the risk of diseases like heart disease and cancer. Traditionally it is used in most countries as antidiabetic, antitumor, antihypertensive, anti-inflammatory and immunomodulatory agents. It contains proteins and polysaccharides, which have shown anticancer activity against melanoma. Proteins from pumpkin seeds were reported to inhibit melanoma proliferation. Methanol extract of *Cucurbita maxima* Duchesne aerial parts shows activity against EAC (Ehrlich Ascites Carcinoma). It is a very rapidly growing carcinoma with very aggressive behavior. The ascitic fluid is essential for tumor growth, since it constitutes a direct nutritional source for tumor cells. MECM treatment significantly reduced tumor volume probably by lowering the ascitic nutritional fluid volume. Packed cell volume and viable cell count were also significantly lowered. The potent anticancer activity of MECM probably because of its direct cytotoxic effect which is further potentiated by its antioxidant properties. It provide protection against the tumor cell induced hepatotoxicity^{8,10}. The seeds were used in the treatment of liver and digestive disorders.

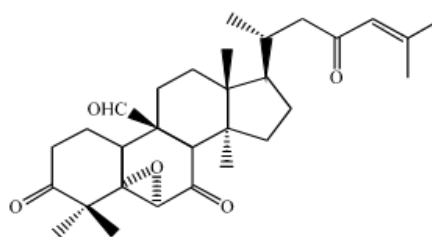
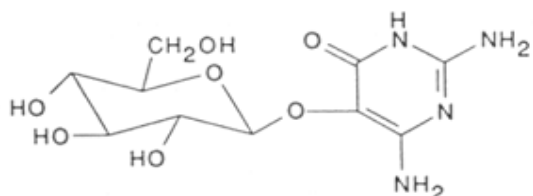
Structure of Charantin⁴

Sitosterol-D-glucoside

Sterol glucoside components of Charantin isolated from *Momordica charantia* fruit¹⁶



5,25-Stigmastadienol glucoside

Structure of kuguacin F⁴

Vicine

Vicine, a putative hypoglycaemic compound from *Momordica charantia* seeds.¹⁶

While the oil from the seeds exhibited anthelmintic property in a dose and time dependent manner¹¹. Spinasterol from the flowers of *C. maxima* showed potential anticarcinogenic, antigenotoxic, and antimutagenic activity. It shows antibacterial activity against the fungi (*Aspergillus niger* and *Candida albicans*) and the bacteria (*Bacillus subtilis* and *Pseudomonas aeruginosa*). It was inactive against *Escherichia coli*, *Staphylococcus aureus*, and *Trichophyton mentagrophytes*⁹. The extract shows diuretic action. Diuretic action of the extract happened by the suppression of renal tubular reabsorption of electrolytes, water and low molecular weight organic compounds into the blood stream and as a consequence promotes the formation of urine. The activity of the extract could be dose dependent one¹². *Cucurbita maxima* have a potential CNS stimulant effect that can be explored for therapeutic advantage as an alternative treatment in medical conditions associated with dizziness and sedation¹³. The alcoholic extract of *Cucurbita maxima* significantly reduced the elevated fasting blood glucose by potentiating the insulin effect of plasma by

increasing either the pancreatic secretion of insulin from β -cells of islets of Langerhans or its release from bound insulin or increased peripheral utilization of glucose. In addition it also possesses potent antihyperlipidemic effect, lowers both total cholesterol and triglycerides and at the same time increases HDL-cholesterol level¹⁴.

Cucurbita andreana

Cucurbita andreana exhibited potent anticancer and cyclooxygenase-2 (COX-2) inhibitory activities. Bioassay guided purification of the fruit extract yielded cucurbitacins B, D, E and I. These cucurbitacins were evaluated for their anti-inflammatory and inhibitory effects on the growth of human colon, breast, lung and central nervous system cancer cell lines. Also evaluated the action on cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes and on lipid peroxidation. Inhibitory activities of cucurbitacins B, D, E and I respectively, were for colon, breast, lung and CNS¹⁵.

Cucurbita ficifolia (Fig leaf gourd)

The plant cures wounds and used to treat hemorrhoids and fever and is used for the treatment of diabetes type 2.

It has shown acute hypoglycaemic activity in temporally hyperglycemic rabbits, in alloxan-diabetic rabbits and recently, in type 2 diabetic patients^{3,4}.

GENUS MOMORDICA

Momordicacharantia (Bitter gourd)

Commonly known as bitter melon or bitter gourd. It is an economically important, successful medicinal and vegetable plant for human health and belonging to the family Cucurbitaceae. Bitter gourd commonly called "Karela" in India^{3,4}. It consists of triterpenes, proteins and steroids. Several phytochemicals that isolated from *Momordicacharantia* are steroidal glycosides, Insulinomimeticlectins and alkaloids¹⁶.

Steroidal glycosides

The earliest reported active constituent of Karela fruit was "Charantin" a mixture of 13-sitosterol-D-glucoside and 5, 25- stigmastadien-3-I3-ol-D-glucoside^{16, 17}. It is now known that *Momordicacharantia* fruit, seeds and vines contain other steroidal glycosides (momordicosides and momordicines)¹⁶.

Insulinomimetic proteins

Insulin like polypeptides ("polypeptide-p," a 17-amino acid, 166-residue polypeptide which did not cross-react in an immunoassay for bovine insulin, this peptide was shown to be "Insulinomimetic")¹⁷, are responsible for hypoglycemic properties. P-insulin or V-insulin can cause hypoglycaemia in man and laboratory animals on parenteral administration^{16, 18}.

Alkaloids

Vicine (pyrimidine nucleoside) has been isolated from the seeds and it has been found that on intraperitoneal administration of vicine caused a hypoglycaemic response in normal fasting albino rats¹⁶ kuguacins F-S (cucurbitanetriterpenoids) have also been isolated from the plants⁴. This plant has a number of potential biological and pharmacological activities. Unripe fruits of the plant are mainly used for diabetes and extensive investigations have shown that an extract of the fruits has marked hypoglycemic properties both in animals and humans¹⁹. The seed extract normalize the impaired antioxidant status in streptozotocin induced diabetes by scavenging of free radicals there by reducing the risk of diabetic complications²⁰. Several constituents such as Charantin, vicine and insulin like polypeptides responsible for hypoglycemic properties are present²¹. In addition to its major use as an anti-diabetic agent, Karela has been used in India as a tonic, emetic and laxative. Ribosome inactivating protein from *M.charantia* can be used in antiviral therapy. The growth of herpes simplex virus I and human immunodeficiency virus I are inhibited by Karela extracts. The juice was administered rectally since the active anti-viral components of *Momordicacharantia* are believed to be the proteins α and β -momorcharin and MAP which would be expected to undergo hydrolysis by pancreatic enzymes if administered by the oral route. It exhibit antitumor activity towards human nasopharyngeal carcinoma cells. Anticancer properties are exhibited by Protein fractions obtained from the fruit and seed of *Momordicacharantia*

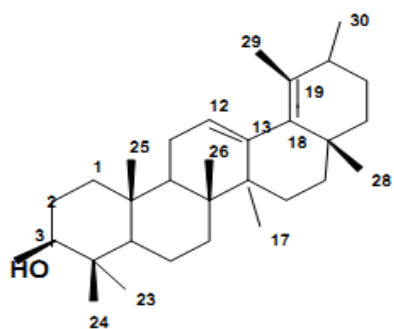
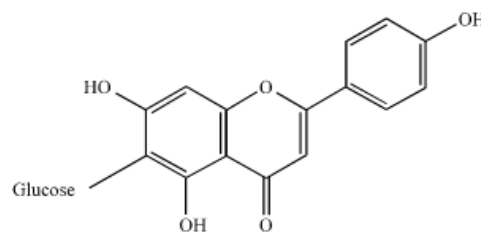
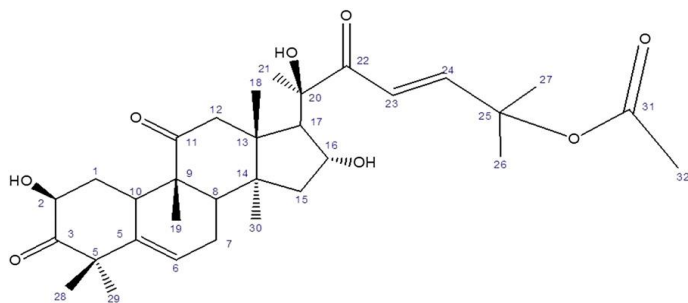
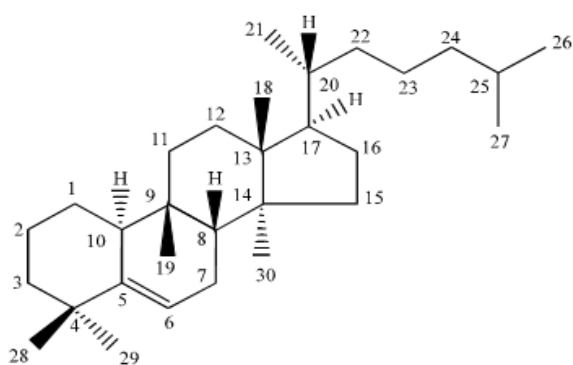
and have the ability to inhibit cell growth, guanylatecyclase activity and ribosomal activity. A leukaemia patient in whom regular intake of the extract led to a fall in white blood cell count, and an increase in blood haemoglobin¹⁶. It also possesses analgesic, antimicrobial, antioxidant, antiopacity, antifertility, anti-inflammatory and hypotensive activity. The fruits and leaves of *Momordicacharantia* Linn have been consumed to cure symptoms of liver diseases. The fruits are used traditionally as anthelmintic, antiemetic, carminative, purgative and for the treatment of anemia, jaundice, malaria, cholera, etc. The mature fruits are used externally for rapid healing of wounds and internally for the treatment of peptic ulcers^{3,4}. Extracts of various plant parts of *Momordicacharantia*, including leaf, fruit and seeds have been investigated and found to be pharmacologically active against microbes. *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* are inhibited²². The leaf, in addition to whole plant extracts have been shown to have anti-HIV activity.

Antidiabetic activity of *Momordica charantia*

Studies performed in vitro with *M. charantia* fruit extracts indicated a significant enhancement of glucose up-take in muscle tissue and of glycogen accumulation in muscle and hepatic tissue, but no effect on glucose uptake or triglyceride synthesis in adipose tissue¹⁷. That is it exhibit insulinomimetic effects, such as increased glucose uptake into muscle, stimulation of lipogenesis, and inhibition of lipolysis on tissue preparations in vitro. In vitro tests on tissues taken from animals treated with Karela have also shown a depression of hepatic gluconeogenic enzymes, and increased liver and muscle glycogen. It decreases the absorption of glucose from the gut. It is reported that glucose uptake by inverted gut was inhibited in the presence of extracts of Karela fruit¹⁸. Significant reduction of blood glucose level and increased concentration of plasma insulin have been observed in diabetic rats that were treated with fruit juice of *Momordicacharantia*. The observed effect was due to an increase in the number of β -cells in treated animals compared to untreated one^{17,18}. The phytochemicals momordicin, Charantin, and a few compounds such as galactose-binding lectin and insulin-like protein isolated from various parts of this plant have been shown to have insulinomimetic activity. Aqueous extract of unripe fruits of *Momordicacharantia* has also been shown to partially stimulate insulin release from isolated β -cell of obese-hyperglycemic mice suggesting that the insulin-releasing action is the result of perturbations of membrane functions. *Momordicacharantia* increases the renewal of partial cells in the pancreas or may permit the recovery of partially destroyed cells and stimulates pancreatic insulin secretion^{16, 18}.

Momordica dioica

It is also known as small bittergourd, spine gourd. It contains many phytoconstituents. Phytoconstituents of *Momordicadioica* are traces of alkaloids, steroids, triterpenoids, flavonoids, glycosides, saponins, triterpenes of urisolic acid, dark brown semidrying oil and saturated

Structure of *Momordicaursenol*²³Structure of *isovitexin*⁴Chemical structure of *cucurbitacin E*Structure of CucurbitacinA(1),Cucurbitacin B(2),Cucurbitacin C(3) and cucurbitacinD(4)^{3,4}

fatty acids, ascorbic acid, vitamin A, thiamine, riboflavins, niacin, protein carbohydrates, lectins, carotenes, bitter principles, oleanolic acid, stearic acid, gypsogenin, alpha-spirosterol hederagenin, momordicaursenol. The alkaloid present in seed is called momordicin and present in root is called momordicafoetida. Cucurbitacins and cucurbitaneglycosides: β -sitosterolsaponin glycosides and alkaloids. Three triterpenes and two steroidal compounds are isolated from dry roots of *Momordica dioica*. These compounds are alpha-spinasterol octadecanoate (I), alpha-spinasterol-3-O-beta-D-glucopyranoside (II), 3-O-beta-D-glucuronopyranosyl gypsogenin (III), 3-O-beta-D-glucopyranosyl gypsogenin (IV) and 3-O-beta-D-glucopyranosyl hederagenin (V). Constituent III is a new compound. The two new aliphatic constituents characterized as 6-methyl tritriacont-5-on-28-ol and 8-methyl hentriacont-3-ene from fruit rind of *Momordica dioica* along with the known sterol pleuchiol²³. It is traditionally used as astringent, febrifuge, antiseptic, anthelmintic, and spermicidal. Also used in bleeding piles, urinary infection and as a sedative. Alcoholic extracts of *Momordica dioica* show antimalarial activity against the NK 65 strain of *Plasmodium berghei* and anti-allergic activity. Aqueous and ethanolic extract of root of *Momordica dioica* are reported to have antifertility activity. The extracts showed moderate estrogenic activity and caused significant increase in uterine weight. Ethanolic extract shows 100% abortifacient activity. Fruit pulp has analgesic and anti-inflammatory activities. It also possesses antidiabetic activity, antioxidant activity and hepatoprotective activity

against carbon tetrachloride induced hepatic damage. The hepatoprotective activity of *Momordica dioica* may be due to presence of its phytoconstituents like steroids and triterpenoids²³.

GENUS CUCUMIS

Cucumis sativus (Cucumber)

It is a widely cultivated plant of gourd family which is eaten in the unripe, green form. Its local name is Khira or Sasha. Phytochemical screening of the ethanolic extract of leaves and stems of *Cucumis sativus* possessed phytoconstituents such as alkaloid, glycoside, steroid, saponin and tannin except gum, flavonoid and reducing sugars. While alkaloid, glycoside, steroid, flavonoid, saponin and tannin were found in the crude chloroform extract. The aqueous extract of *Cucumis sativus* fruits revealed the presence of glycosides, steroids, flavonoids, carbohydrates and tannins²⁴. The fruit has high water content, and they contain vitamin A and C. Flavone glycosides such as isovitexin, saponarin and various acylated flavone C-glycosides are present in the leaves of *Cucumis sativus*. Anti-ulcer 9-beta-methyl-19-norlanosta-5-ene type glycosides have been from *Cucumis sativus* Seeds^{25, 26}. Its fruit extract has shown free radical scavenging and analgesic activities in mice. It also has carminative and antacid property. Fruits help in removing constipation and aid indigestion. Seeds are cooling, tonic, diuretic and anthelmintic^{3,4}. Mature uncooked cucumbers bring relief for individuals suffering from celiac disease, and promote skin health. Immature cucumbers can be cooked and consumed to treat dysentery. A poultice made from fresh cucumbers can be applied to burns and open

sores. The seeds can be used to expel parasitic worms. The juice from the leaves induce vomiting and aid digestion²⁷.

Cucumismelo (Musk melon)

It is locally known as Kharbuja. Commonly known as Melon, muskmelon. The whole fruit is useful in chronic eczema and are used medicinally to promote skin hydration, to treat light burns and scrapes²⁸. Dose dependent cytotoxic activities were exhibited by aqueous fruit extract of *Cucumismelo* in human prostate carcinoma PC-3 cell line. As the dose of the extract increased, the number of viable cells decreased. This confirms the anti-cancer and cytotoxic potential of the fruit of *C.melo*²⁹. The fruit is tonic, laxative, diuretic diaphoretic and galactagogue. The flowers are expectorant and induce vomiting. The seeds are used as cough suppressant, fever reducer, and a digestive aid. A seed powder is mixed with water and used as a vermifuge²⁸. The fruit extract has a high Superoxide Dismutase Activity (SOD). The SOD activity is responsible for the in vitro and in vivo antioxidant and anti-inflammatory properties of the extract³⁰. The composition of fatty acids and amino acids present in seeds has been determined. A number of phenolic glycosides have been isolated from the seeds³¹.

GENUS CITRULLUS

Citrulluslanatus (water melon)

Water melon contains almost 95% water. It also contains small amounts of protein, fat, minerals and vitamins. The major nutritional components of the fruits are carbohydrates, vitamin A and lycopene. Lycopene content of the new dark red watermelon is higher than in tomato, pink grapefruit or guava. Orange flesh types do not contain lycopene, but have high carotene (vitamin A) content. Lycopene is a red pigment responsible for watermelon flesh colour, which is an anticancer agent. High amount of water content of watermelon makes it a powerful diuretic diet². The watermelon fruit is widely consumed and rich in water and pectin. Pectin is a substance used in jams for thickening and is believed to offer protection from radiation. It is also traditionally used to treat cardiovascular disease and kidney problems. When mature, they are used as fever reducer. Rind, root, Seed and leaf extract of water melon show painkilling and anti-inflammatory effects³².

Anti-inflammatory activities of cucurbitacin E isolated from Citrulluslanatus (Wild melon) belongs to Cucurbitaceae family

It is the wild ancestor of watermelon. This plant is often used for rheumatism, swellings, gout and as laxative⁵. CE was observed to inhibit both COX-1 and COX-2 with more selectivity towards COX-2. The inhibitory effects of CE on RNS and COX enzymes but not on ROS are suggested to be the mechanism of the anti-inflammatory activities of this natural compound⁵. Nitric oxide (NO) is a free radical gas with important immune, cardiovascular and neurological second messenger functions that are implicated in sepsis, cancer and inflammation. This molecule is synthesized from the amino acid L-arginine

by the enzymes nitric oxide synthases (NOS)^{33,34}. CE has dose-dependent anti-inflammatory activities related with its inhibition of NO production in macrophages without affecting the viability of these cells³⁵. Similarly, COX-2 is an inducible enzyme that catalyzes the production of prostaglandins, which contribute to the inflammatory process and tissue damage. It is reported that COX-2 can also be activated by high concentrations of nitric oxide, contributing toward more intense inflammatory responses as seen in many chronic inflammatory disorders³⁶. The acute inflammatory response is associated with the production of reactive oxygen species (ROS)³⁷. In a number of pathophysiological conditions associated with inflammation or oxidative stress, these ROS have been proposed to mediate cell damage. The anti-inflammatory effect exhibited by CE might not be related to its antioxidant properties. Fortunately, the compound did not affect normal human liver cells. Therefore, wild melon crude is a valuable source for potential anti-inflammatory compounds. Cucurbitacin E may have therapeutic potential and a possible effect treatment for a variety of inflammation-mediated diseases. Therapeutic potential of cucurbitacin E could be limited by the bitter taste of this compound but special pharmaceutical formulation is highly recommended to overcome this issue⁵.

Citrullus colocynthis (Bitter apple)

It is locally known as Makkal. The fruits are bitter, acrid, cooling, cathartic, carminative, antipyretic, and anthelmintic and are useful in hyperglycemia, tumors, ulcers, asthma, bronchitis and constipation. It was found to significantly increase insulin and decrease plasma glucose levels in alloxan induced diabetic rats. The plant contains cucurbitacins A, B, C and D, α -elaterin and various other constituents³⁸. The aqueous extracts of the roots, stems, fruits and seeds of the plant have been reported to possess analgesic and anti-inflammatory activities³⁹.

GENUS LAGENARIA

Lagenariasiceraria (Bottle gourd)

Locally known as Loki, belonging to the family Cucurbitaceae. It is a common fruit vegetable used throughout the India. The fruit has light green smooth skin and white flesh. Seeds are cream to brown, compressed, and embedded in a white spongy pulp⁴⁰. The fruit is reported to have good source of vitamin-B complex and Choline along with fair source of vitamin-C, ascorbic acid, and β -carotene. It is also reported to contain Cucurbitacins B, D, G and H, mainly cucurbitacin B. Proteins, fibres, saponins, flavone-C-glycoside and polyphenol are also present. Two sterols namely campesterol and sitosterol have been identified and is reported to possess antihepatotoxic activity⁴¹. A novel protein, Lagenin has also been isolated from its seeds and it possesses antitumor, immunoprotective and antiproliferative properties⁴². The fruits possess significant hepatoprotective activity^{43,44}. In the Central nervous it shows analgesic, sedative and CNS depressant activity⁴⁵. The fruit shows maximum antioxidant activity. The fresh juice of the fruit also shows antiradical activity^{43,46}. The

fruit is used as cardio-protective, cardio-tonic, diuretic, nutritive agent. It posses antihyperglycemic activity, antihyperlipidemic activity, anticancer activity and immunomodulatory activity⁴⁰. *Lagenariasiceraria* extract shows activity against *Pseudomonas aeruginosa* and *Streptococcus pyogenes*, but not against clinical isolates of *S. aureus* and *Escherichia coli*. Thus *Lagenariasiceraria* can be used to treat various skin disorders^{22,47}.

Antioxidant and Hepatoprotective Activity of methanol extract of Lagenariasiceraria (MELS)

Lagenariasiceraria is traditionally used in liver disorders and various free radical induced diseases. The methanol extract of *L.siceraria* aerial part was found to scavenge 1,1-Diphenyl-2-picrylhydrazyl (DPPH), nitric oxide, superoxide radical and hydrogen peroxide as well as inhibit lipid peroxidation in vitro in a concentration dependent manner⁴³. The hepatotoxicity induced by CCl₄ is due to its metabolite trichloromethyl free radical (CCl₃) that alkylates cellular proteins and other macromolecules and finally result in cell death. Administration of CCl₄ to animals, resulted in a marked elevation of serum transaminases (SGOT and SGPT), serum alkaline phosphatase (ALP) and total bilirubin (TB), when compared with those of normal control animals, which are released from the liver into the blood⁴⁸. However, serum total protein level was decreased indicating considerable hepatic injury. When treated with methanol extract of *L.siceraria* a significant decrease in all the elevated serum marker levels, SGOT, SGPT, ALP and TB, and significant increase in total protein occurs, which indicates the restoration of the level of liver function biochemistry to the near normal values. The body's innate defense mechanism consists of a set of endogenous antioxidant enzymes, including enzymatic system such as catalase (CAT), superoxide dismutase (SOD) and non-enzymatic system such as reduced glutathione (GSH). In CCl₄ induced hepatotoxicity, the balance between ROS production and this antioxidant system will be lost, hence oxidative stress results which in turn is associated with a number of pathological conditions. This was reflected by the reduced level of SOD and CAT and the exhausted GSH content in CCl₄ control group animals. The free radicals generated in the metabolism of CCl₄ react with the unsaturated lipid of the cell and initiates the chain reactions of lipid peroxidation, which may cause peroxidative tissue damage in inflammation, cancer, aging, ulcer, cirrhosis and atherosclerosis. Antioxidants can combat against this oxidative stress either by scavenging free radicals or by their potent reductive ability. There are restrictions on the use of synthetic antioxidants, such as Butylated Hydroxy Toluene (BHT), Butylated Hydroxy Anisole (BHA), as they are suspected to be carcinogenic. Natural antioxidants, therefore, have gained importance. DPPH is a relatively stable nitrogen centered free radical, which is widely used to evaluate free radical scavenging property of natural antioxidants. MELS was found to scavenge DPPH in a concentration dependent manner. Further, MELS effectively scavenged superoxide, nitric oxide, hydrogen peroxide and lipid peroxide in vitro. It can also decrease lipid peroxidation

in the treated groups, thus further potentiates its antioxidant activity in vivo. The significant antioxidant activity of the extract thus, suggests the possible therapeutic value of this plant, which may be due to its good amount of phenolic and flavonoid contents^{43,49}.

GENUS TRICHOSANTHES

Trichosanthescucumerina (Snake gourd)

Trichosanthescucumerina, the fruit of which is mainly consumed as a vegetable. It is commonly called as Snake gourd, Vipergourd, Snake tomato and long tomato²². It is rich in protein and vitamin C. It also contains water, fat, carbohydrate, fibre, Fe, P, Vitamin B₁, Vitamin B₂ and Niacin. The major active constituents of the drug are triterpenoids, saponins, cucurbitacins. The plant is richly constituted with a series of chemical constituents like flavonoids, carotenoids, phenolic acids which makes the plant pharmacologically and therapeutically active⁵⁰. Anti-inflammatory activity is exhibited by the root tubers and antidiabetic activity by the seeds. Both the root and fruit are considered to be cathartic. It is used in the treatment of bronchitis, headache, fever, abdominal tumors and skin allergy. Seeds have antibacterial, anti-spasmodic, insecticidal and gastroprotective properties⁵¹. Antimicrobial activities of petroleum ether, chloroform, ethyl acetate and methanol extract of the leaves gives activity against various pathogenic bacteria such as *Bacillus cereus*, *Enterobacter faecalis*, *Salmonella paratyphi*, *Staphylococcus aureus* and *Escherichia coli*. The antimicrobial potency of this plant extract is due to the presence of phenolic compounds flavonoids and carotenoids²².

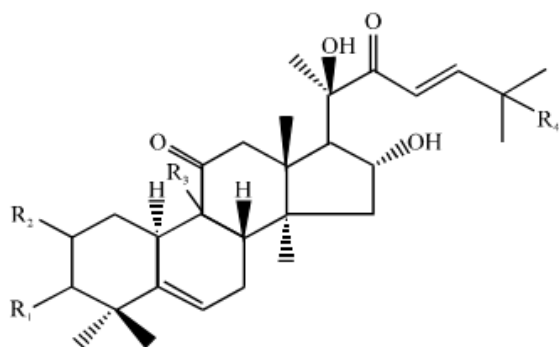
PROTEINS PRESENT IN CUCURBITS

Anti-fungal proteins

As we all know, fungi are disease causing agents for plants which are major threat in growing them successfully. The fungal strain *Fusarium oxysporum* causes a number of disastrous diseases in plants of different families. Fusarium wilt is one of the oldest diseases of water melons, musk melons and many other cucurbits. A number of anti-fungal plant proteins are known and researched; proteins from plants of Cucurbitaceae family are the most promising because of their specific pathogen related activities. Many species of this family produce very effective anti-fungal proteins which inhibit the growth of *Fusarium oxysporum*. During their course of evolution, these proteins are developed by the plants to defend themselves against various pathogens. On the basis of their nature and biological activity, we have classified anti-fungal proteins known from Cucurbitaceae family as pathogen related (PR) proteins, ribosomal inactivating proteins (RIP), vicilin like proteins and others⁵².

PR proteins

PR proteins are widely distributed in plant kingdom and many of them have been isolated from different parts of the plants such as leaves, stem, root and seeds. These are low-molecular weight proteins. PR proteins are further classified into different families (PR-1 to PR-5)



- | | | | |
|----------------------------------|---------------------|-------------------------------------|-------------------------------------|
| (1) R ₁ = =O | R ₂ = OH | R ₃ = CH ₂ OH | R ₄ = OCOCH ₃ |
| (2) R ₁ = =O | R ₂ = OH | R ₃ = H | R ₄ = OCOCH ₃ |
| (3) R ₁ = OH | R ₂ = H | R ₃ = CH ₂ OH | R ₄ = OCOCH ₃ |
| (4) R ₁ = =O | R ₂ = OH | R ₃ = H | R ₄ = OH |

Basic structure of Cucurbitacin^{3,4}

depending on their amino acid sequences and enzymatic or biological activity. PR-1 is the most abundant protein. PR proteins exhibit strong anti-fungal and anti-microbial activities which make them essential for the proper development and function of plant as a whole or in parts⁵³. Several PR proteins have been purified from plants of Cucurbitaceae family. PR-1 protein is known to inhibit the growth of several pathogenic fungi including *Botrytis cinerea*,

Fusarium oxysporum, *Fusarium solani*, *Rhizoctonia solani* and *Candida albicans*. It has membrane permeability activity by which it disrupts the integrity of the cell plasma membrane and results in the leakage of the cytoplasmic component and thus, inhibits the fungal growth⁵⁴.

RIPs

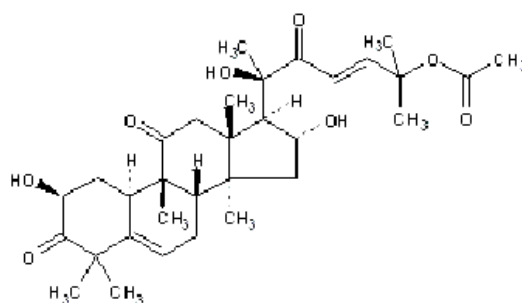
RIPs arrest the synthesis of foreign proteins by inactivating fungal ribosome by N-glycosidase activity. RIPs are further classified into three groups (Type1, Type2 and Type3) on the basis of their structure⁵². Hispin, an RIP purified from the hairy melon seeds shows potent anti-fungal activity against various pathogenic fungal species, such as *Coprinus comatus*, *Fusarium oxysporum*, *Physalospora piricola*, and *Mycosphaerella arachidicola*⁵⁵. α -momorcharin protein is also an anti-fungal RIP, extracted and purified from *Momordica charantia*. It not only inhibit the growth of fungi but is also known to possess many important biological activities⁵⁶.

Vicilin like proteins

There are many plant proteins known which perform dual functions like storage and defence. Vicilin like proteins purified from *Cucumis melo* and *Citrullus lanatus* has shown anti-fungal activity against *Fusarium oxysporum*⁵².

Cucurbitacins

Plants containing cucurbitacins were early recognized in folk medicine to have biological values. The cucurbitacins are a group of bitter tasting, highly oxygenated, mainly tetracyclic, triterpenic plant substances derived from the cucurbitane skeleton [19-(10 \rightarrow 9 β)-abeo-10 α -lanost-5-ene] also known as 9 β -



Molecular structure of cucurbitacin B⁵⁸

methyl-19-nor lanosta-5-ene. The cucurbitacins are arbitrarily divided into twelve categories, incorporating cucurbitacins A-T. The various cucurbitacins differ with respect to oxygen functionalities at various positions. These cucurbitacins are also present in their glycosidic forms such as cucurbitacin B glucoside containing glucose as the glycone moiety. They are predominantly found in the Cucurbitaceae family but are also present in several other families of plant kingdom^{3,4}. Cucurbitacins have very strong bitter taste indeed they are probably bitterest compounds known. In addition these compounds exert a gibberlin-antagonistic activity, as well as both feeding and antifeedant effects for insects. Due to the strong bitter taste, the cucurbitacins act as purgative principle of different species of Cucurbitaceae by stimulating gastric secretion. Cucurbitacins are not usually used as medical agents because of their toxicity. However new drugs have demonstrated the potential of these natural products for treating different pathologies, including inflammation, cancer, or auto immune disease⁵⁷.

Many pharmacological and clinical investigations have verified that cucurbitacin B (CuB) and cucurbitacin E (CuE) possess various pharmacological activities, such as, antitumor, anti-hepatitis and immunopotentiating effects. The cucurbitacin preparation used clinically contains mostly CuB and CuE, which are obtained from the calyx of *Cucumis melo* L., a Chinese medicinal plant that is effective against chronic hepatitis and primary liver carcinoma. Seeds or fruit parts of some cucurbits are reported to possess purgative, emetic and antihelminthic properties due to the secondary metabolite cucurbitacin content⁵⁸.

Inhibitory effects of cucurbitacin B on laryngeal squamous cell carcinoma

Laryngeal squamous cell carcinoma is the most common squamous cell carcinoma of the head and neck. STAT3 plays important roles at all levels of tumorigenesis and has been identified as an oncogene. It has been documented that constitutively activated STAT3

participates in oncogenesis through upregulation of genes encoding apoptosis inhibitors (Bcl-2, Bcl-xL, and survivin), cell cycle regulators (cyclins and c-Myc), and inducers of angiogenesis (vascular endothelial growth factor). Cucurbitacin B is most widely used for in vivo and in vitro studies on tumor inhibition. Accumulated evidences have shown that cucurbitacin B inhibits the growth of numerous human cancer cell lines and tumor xenografts, including breast, prostate, lung, uterine cervix, liver, skin, and brain cancers. Combination therapy with multiple drugs is a common practice in the treatment of cancer to get an additive or synergistic effect and to reduce toxicity to the host^{59, 60}. The inhibitory effect of cucurbitacin B on laryngeal squamous cell carcinoma was studied by treating Hep-2 cells with different concentrations of cucurbitacin B for different time. Cell proliferation, cell cycle distribution, and cell apoptosis were evaluated using MTT assay, flow cytometry, and Fluorescent microscopy. Cucurbitacin B will inhibit cellular proliferation in a dose and time dependent manner. That is they can inhibit the growth of numerous human cancer cell lines. It also induced cell cycle arrest at G2/M phase, and apoptosis in a dose- and time-dependent manner. The possible mechanisms underlying the action is the suppression of STAT3 phosphorylation. It was shown that cucurbitacin B suppressed STAT3 activation in a dose- and time-dependent manner. Cucurbitacin B regulates cell cycle regulator such as cyclin B1 and antiapoptotic genes such as Bcl-2, Bcl-xL and BAX by suppressing the activation of STAT3. This investigation suggests a potential clinical application of cucurbitacin B for the treatment of laryngeal cancer patients^{59, 60}. Combined effects of cucurbitacin B and docetaxel against human laryngeal cancer cells shows that simultaneous exposure of Hep-2 cells to cucurbitacin B and docetaxel could significantly enhance the anticancer activity. The combination of cucurbitacin B and docetaxel produced greater efficacy in growth inhibition, cell cycle arrest at G2/M phase, and apoptosis induction. Compared with single treatment, combination treatment inhibited cell proliferation and viability more significantly. Moreover, simultaneous exposure to the combination produced greater therapeutic effect than that by single drug alone, suggesting that synergistic effect occurred on this tumor cell line, the anti-tumor efficacy mediated via the combination of cucurbitacin B and docetaxel was mainly due to the induction of cell cycle arrest as well as apoptosis. Cucurbitacin B might specifically block STAT3 signaling pathway by suppressing phosphorylation of STAT3, inhibiting STAT3-mediated gene expression⁵⁹.

The antitumor activities of Cucurbitacin Liposome for Injection (CLI)

Cucurbitacin Liposome for Injection (CLI) contains mostly CuB (85 %). The oral route for colloidal drug carrier systems remains the most convenient and popular way of administration. However, many anticancer drugs administered orally can be eliminated from the first pass extraction by the cytochrome P₄₅₀ dependent metabolic processes and the overexpression of plasma membrane

transporter P-glycoprotein (P-gp) in the physiological systems involved (intestine, liver, etc). It is suggested that CLI significantly inhibited the growth of tumor in vivo and in vitro in a dose-dependent manner. It is a potent and selective antitumor drug. CLI treatment arrested cells in G2/M phase. In in vivo experiments presented, CLI had strong antitumor activity even at relatively low doses⁵⁸

CONCLUSION

After the thorough literature review we have found that the plants in Cucurbitaceae Family have tremendous medicinal properties such as anti-HIV, anxiolytic, anti-pyretic, anti-diarrhoeal, carminative, antioxidant, anti-diabetic, antibacterial, laxative, anthelmintic, anti-tubercular, purgative and hepatoprotective. It is also employed as an abortifacient, diuretic, and cardiotoxic agent. They also show strong anti-inflammatory, antitussive, cytotoxic, and expectorant properties. Apart from biological profile Cucurbitaceae family possesses many therapeutically important chemical constituents which required further research to explore the medicinal value of this species. Seeds or fruit parts of some cucurbits are reported to possess purgative, emetic and anthelmintic properties due to the secondary metabolite cucurbitacin content. A number of compounds of this group have been investigated for their cytotoxic, hepatoprotective, anti-inflammatory and cardiovascular effects. Nevertheless some of the plants in this family need further study so that new biomolecules can be isolated and identified and ultimately one can develop new phytopharmaceutical agents which may be used as such or as a lead compound for synthesis and modification. The research and development of herbal formulation is highly relevant as it may be less toxic and can be used for mono or co-therapy with other drugs. The ultimate aim of all medical and pharmacological research is to cure diseases to maintain the health of the individual and to improve the quality of life.

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