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Review of *Cucurbita pepo* (Pumpkin) its Phytochemistry and Pharmacology

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Abstract

Cucurbita pepo, is widely used like food and in folk medicine around of the world. This aims a comprehensive of the pharmacological, chemical constituents, and clinical uses. Also have been identified the medicinally important phyto-constituents belonging mainly to cucurbitosides, multiflorane-type triterpenoids, carotenoids, ent-kaurane-type diterpene, and cucurbitaglycosides. Extracts and metabolites of this plant, particularly those from seeds and fruits possess useful pharmacological activities. A survey of the literature shows *C. pepo*, is mainly known for its improvement in prostatic hiperplasia (BPH), urinary dysfunction and cytotoxic properties, also has also been used extensively as a hypoglycaemic agent. Many pharmacological studies have demonstrated hepatoprotection, inhibit benign prostatic hiperplasia, antioxidant, anticancer, antimicrobial, antiinflamatory, antidiabetic, and antiulcer activities supporting its traditional uses.

Keywords: Antioxidant; Anticancer; Antimicrobial; Antiinflamatory; *Cucurbita pepo*; Curcurbiteae family

Introduction

The Curcurbiteae family, also referred as cucurbits form a very large group with approximately 130 genera and 800 species and can be cultivated in warmer region of worldwide and make popular food crop plants some of these species include squashes, pumpkins, melons and gourds. *Cucurbita pepo* is one of the oldest known cultivated species, with Mexican archaeological evidence from 7000 BC. Thus, it was widely cultivated by indigenous peoples throughout Mexico, Central, and North America before the arrival of Europeans. This plant is native of Northem Mexico and southwestern and eastern USA [1]. These family have medicinal and nutritional benefits. The immature fruits are consumed as a vegetable. The mature fruit is sweet and used to make confectionery, beverages are roasted, or cooked and can be incorporated into baked goods. The seeds, rich in oil, also are used in Mexico, with honey to prepare desserts known as palanquetas. Flower buds and flowers are also edible in Mexico to prepare quesadillas. Some fruit varieties are used with decorative purposes in Halloween party.

Uses in Traditional Medicine

Ethnopharmacological studies show that *Cucurbita pepo* is used in many countries for treating numerous diseases, e.g., as an anti-inflammatory, antiviral, analgesic urinary disorders, anti-ulcer, antidiabetic and antioxidant [1,2]. Traditional medicine, particularly Ayurvedic systems [3], and Chinese [4] have used different parts of the plant including flesh of the fruits and seeds [5] (Table 1). Reporting that pumpkin exhibiting important physiological properties as wound healing, tumour growth inhibition, hypoglycaemic effects and immunomodulating [4]. The seeds are used as a vermifuge, treat problems of the urinary system, hypertension, prevents the formation of kidney stones, alleviate prostate disesases, and enhanced the erysipelas skin infection [6-14].

Phytochemistry

Fruits

These are characterized by a low content of fat (2.3%, pumpkin pulp is not a rich source of oil), carbohydrates (66%), proteins (3%) [14], and by a high-carotenoids content with values of 171.9 to 461.9 $\mu g.g^{-1}$ [15]. Food value per 100 g is: Calories 80 kcal, crude fibre 11.46%, ash 16%. The mineral analysis indicated that pumpkin pulp contained high levels of Mn (0.5 mg/kg), Fe (1.37 mg/kg), Cu (3.9 mg/kg), Pb (0.29 mg/kg), P (11.38 mg/kg), Ni (0.5 mg/kg), Ca (179 mg/kg), Mg (190 mg/kg), Na (159 mg/kg) and K (160 mg/kg) [16]. The level of Pb (0.21-0.25 mg/kg), and Cu (2-5 mg/kg) are within the aceptable range to FAO [17].

Seeds

Seeds of pumpkin are consumed either roasted or raw and used in cooking and baking as an ingredient of cereals, bread, cakes and salads. Pumpkin seed oil is accepted as edible oil and as a nutraceutical. Pumpkin seed and seed oil are a rich natural source of phytosterols [18], proteins, polyunsaturated fatty acids [19], antioxidant vitamins, carotenoids and tocopherols [20] and various elements [21] due to these components are attributed providing many health benefits.

Seeds contain oil with the main fatty acid components being palmitic (C 16:0, 10.68%), palmitoleic (C 16: 1, 0.58%), stearic (C 18:0, 8.67%) Oleic (C 18: 1, 38.42%) Linoleic (C 18:2, 39.84%), Linolenic (C18: 3, 0.68%), Gadoleic (C20: 1, 1.14%), total saturated fatty acids (19.35%), and total unsaturated fatty acids (80.65%) [1]. Also contain various components such as *p*-aminobenzoic acid, γ-aminobutic acid, polysaccharides, peptides, proteins, carotenoids as lutein, lutein epoxide, 15-cis-lutein (central-cis)-lutein, 9(9')-cis-lutein, 13(13')-cis-lutein, α-carotene, β-carotene violaxanthin, auroxanthin epimers, flavoxanthin, luteoxanthin, chrysanthemaxanthin, α-cryptoxanthin, β-cryptoxanthin [22].

Also have been isolated from the seeds sterols which the most abundan was $\Delta^{7.22.25}$-stigmastatrienol with values of 18.8 to 35.1 g/100 g of the total sterol content, following by the Δ^{7} sterol spinasterol with values of 18.2-23.3 g/100 g of the total sterol content. β-sitosterol

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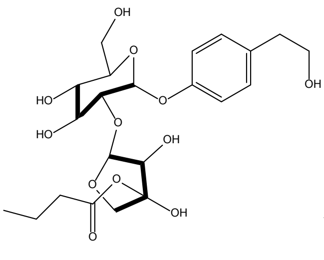
Place, Country	Part(s) used	Ethno medical uses	Preparation(s)	References
Mongolia	Fruits	Treat cold and alleviate ache	Infusion or decoction	[7]
Mexico	Seeds	Treat irritable bladder	Are eaten in the diet	[8]
Egypt	Seeds	Prostatic complains	Are eaten in the diet	[8]
Europe	Seeds	Micturition caused by the prostate	Are eaten in the diet	[9]
China	Seeds	Deworming medicine	Are eaten in the diet	[10]
Europe	Seeds	Treatment of urinary and prostate disease	Are eaten in the diet	[11]
China	Seeds	Anti-parasitic	Are eaten in the diet	[12]
China	Seeds	Beneficial to the spleen and lungs	Are eaten in the diet	[13]
Central and North America	Seeds	Taenicide, diuretic, Gastritis, burns, enteritis and Febrile diseases	Oil of the pumpkin seeds, in doses of 6 to 12 drops, several times a day	[14]
Centro America	Seeds	Headaches and neuralgia	Compress	[6]
Centro America	Leaves	Reduced fever	Infusion or decoction	[14]
Southwestern USA	Fruits	Cure fatigue and thirst and purify the blood	Infusion or decoction	[14]
Southwestern USA	Leaves	A treatment for nausea, and a boost to haemoglobin content of the blood.	Infusion or decoction	[6]
Northem Mexico	Seeds	Diuretic, a cure for bronchitis and fever. is effective against parasitic worms	Infusion or decoction	[14]

Table 1: Ethnobotanical uses of *Cucurbita pepo* found world wide.

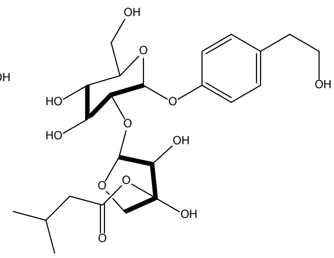
and spinasterol represented 41.1- 53.6 g/100 g of total sterol content. The third most abundants is the Δ^{7}-stigmasterol, with 12.5-20.3 g/100 and $\Delta^{7,25}$-stigmastadienol, with 5.8-8.0 g/100 g of total sterol content [23].

In seeds, the greatest concentrations of squalene were found with a ranged from 583.2 to 747 mg/100 g. Squalene is a triterpene produced by humans, animals and plants, is a precursor of steroid hormones, cholesterol, and vitamins D in their biosynthesis in the human body. Also, squalene is a compound that has positive effects in the treatment of certain types of cancer [23].

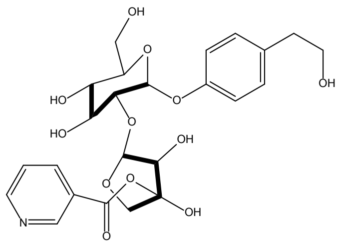
In addition, the seeds contain cucurbitosides which are acylated phenolic glycosides as well as cucurbitosides F-M [24].



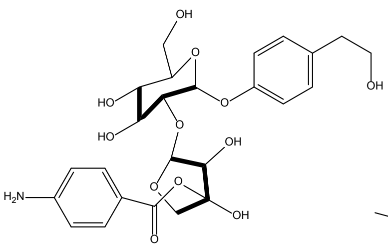
Cucurbitoside F



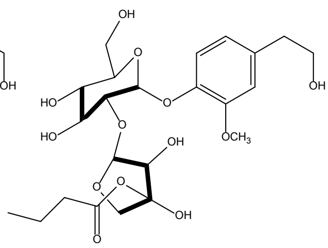
Cucurbitoside G



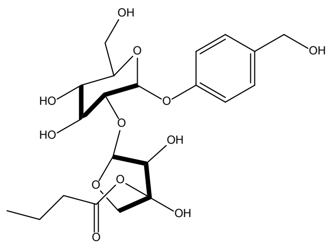
Cucurbitoside H



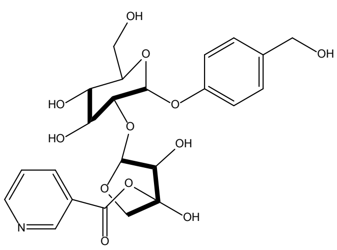
Cucurbitoside I



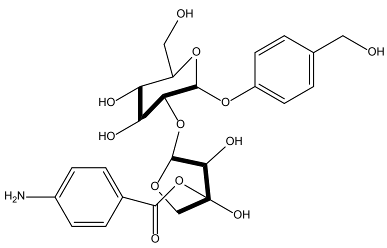
Cucurbitoside J



Cucurbitoside K



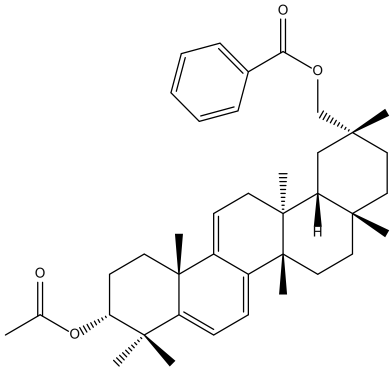
Cucurbitoside L



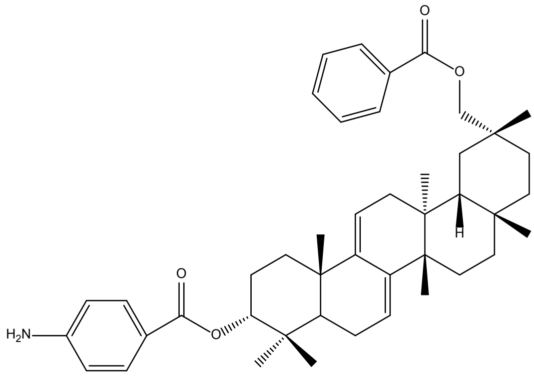
Cucurbitoside M

Examination of the seeds of *C. pepo* used HPLC leads to isolation of the following five multiflorane-type triterpenoids [25].

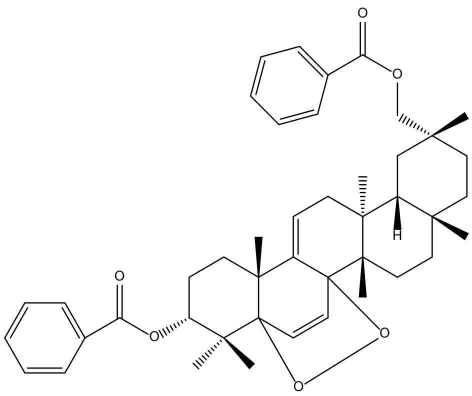
3α--Nitrobenzoylmultiflora-7:9(11)-diene-29-benzoate 3α -Acetoxymultiflora-7:9(11)-diene-29-benzoate



3α-Acetoxymultiflora-5(6):7:9(11)-triene-29-benzoate

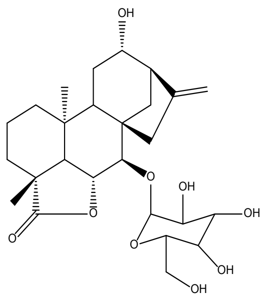


3α-p-AminobenzoylmultiJlora-7:9(11)-dien-29-benzoate

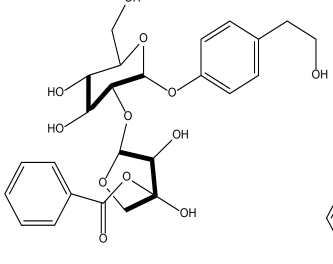


5α,8α-Peroxymultiflora-6:9(11)-diene-3α,29-dibenzoate

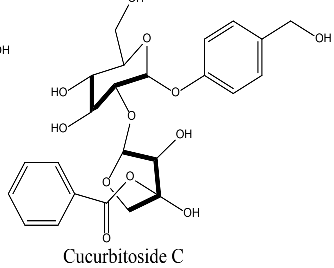
In another research thirteen compounds from *C. pepo* seeds, were isolated [26].



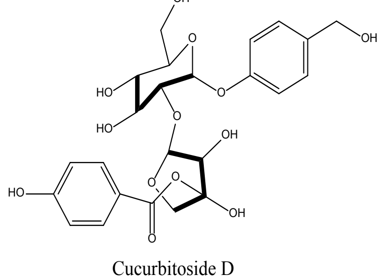
12α-(β-D-glucopyranosyloxy)- 7β-(β-D-glucopyranosyloxy)-12α-7β-hydroxykaurenolide hydroxykaurenolide



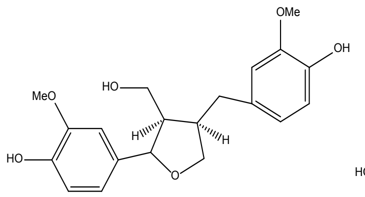
Cucurbitoside A



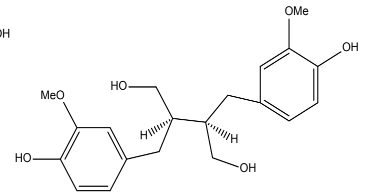
Cucurbitoside C



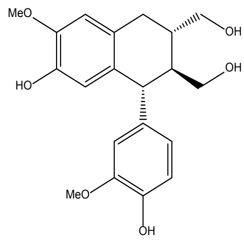
Cucurbitoside D



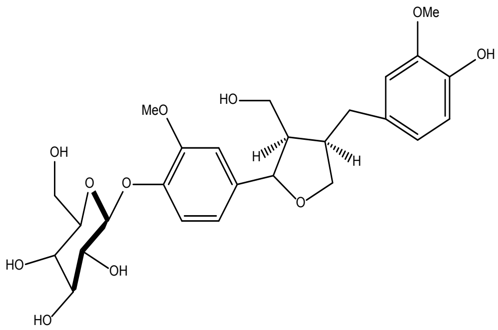
(+)-Lariciresinol



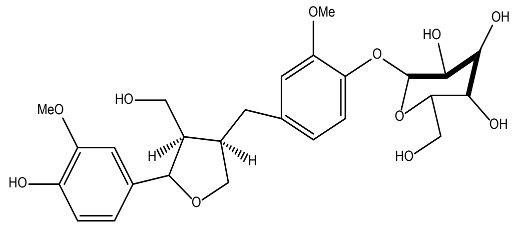
(−)-Secoisolariciresinol



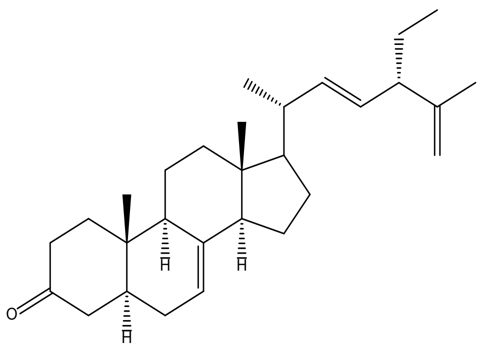
Isolariciresinol



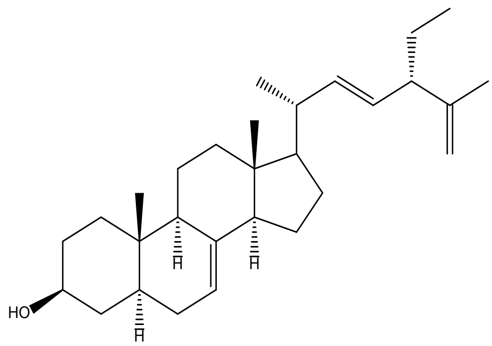
Lariciresinol-4′-O-β-D-glucoside



Lariciresinol-4-O-β-D- glucoside

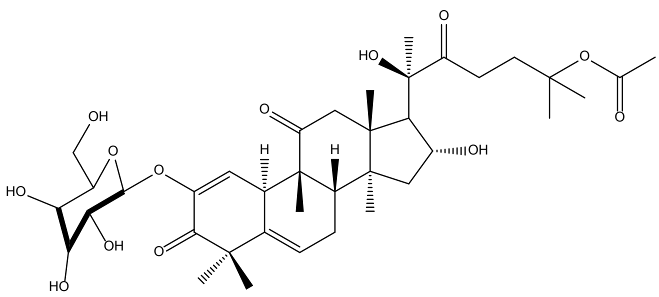


(24S)-stigmasta-7,22E,25-trien-3-one

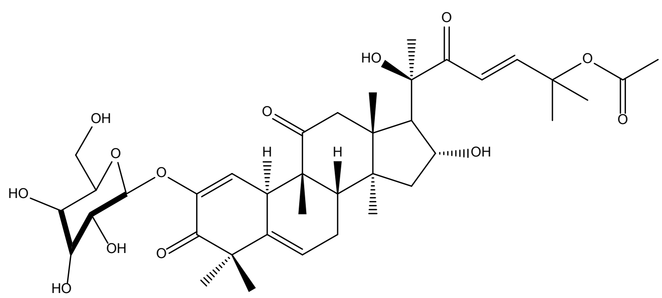


(24S)-stigmasta-7,22E,25-trien-3β-ol

Phytochemical study of the fruits of *C. pepo* cv dayangua has led to the isolation of two cucurbitane glycosides: cucurbitacin L 2-O-beta-D-glucopyranoside, and cucurbitacin K 2-O-beta-D-glucopyranoside [27].



Cucurbitacin L 2-O-beta-D-glucopyranoside



Cucurbitacin k 2-O-beta-D-glucopyranoside

Biological Activity

Scientific investigations on the medicinal properties of pumpkin dates back to the 1930s. A summary of the findings of these studies performed is presented below.

Antioxidant and free radical scavenger

Cellular damage or oxidative injury arising from free radicals or reactive oxygen species (ROS) now appears to be the fundamental mechanism underlying a number of human disorders including diabetes, digestive system disorders, viral infections, neurodegenerative disorders, autoimmune pathologies and inflammation. Free radicals are generated through environmental chemicals, xenobiotics, endogenous chemicals, as well as normal metabolism [28].

Tocopherols are non-glycoside are compounds of vegetable oil, and are natural antioxidants. Seeds oil of the pumpkin containing a mixture of isomers β and δ-tocopherol in range from 29.92 to 53.60 mg/100 g making 79% and 84% respectively of the total tocopherol content [23].

The antioxidant activity of pumpkin seeds methanol extract was determined using free radical DPPH (2,2-diphenyl-1-picrylhydryzyl) scavenging and soybean lipoxygenase [LOX] inhibition. Results expressed as EC_{50} values for scavenging activity on DPPH radical assay is 5.57 mg/ml. In addition, metanol extract inhibit 50% of LOX activity at concentrations ranging from 0.3 mg/ml to 1.02 mg/ml [29]. This extract contain higher amounts of phenolic compounds (5-11 μmol gallic acid 7-15% of total extractable phenolics). Radical scavenging effect depend on their total phenolic content. However, the lipoxygenase, inhibition and the phenolic content are not correlated.

In another study of a methanol seeds extract of varietes junona and Miranda both belonging to the species *C. pepo* had to higher total polyphenol content of 82.4 mgGA/100 g and 113 mgGA/100 g respectively [30]. In this study also was measured antioxidant activity from *C. pepo* by ABTS radical and ferric reducing antioxidant power (FRAO) assays. Results obtained with highest ranges from 0.443 to 1.220 μM Trolox/gFW (TEAC) for the hydrophilic form and lowest for lipophilic form of 3.33 to 0.1 TEAC. FRAP assay demonstrate a highest antioxidant effect of 1.83 nmol/100 g FW [30].

Pumpkin polysaccharides with different degree of substitution were phosphorylated using $POCl_3$ and pyridine. The antioxidant activity of the phosphorylated polysaccharides was determined using free radical DPPH, superoxide anion radical scavenging activity, reducing power and H_2O_2 -induced oxidative damages on rat thymic lymphocyte. All the phosphorylated polysaccharides derivatives tested showed higher antioxidant activities in both in cell system and *in vitro* due to highly phosphorylated derivatives have electron donating groups, capable of converting free radicals to stable compounds, indicating that connected moieties between the head and tail portions in electron donating groups have the ability to link using a negative interaction to allosteric sites. Pumpkin polysaccharide exhibiter higher cytoprotective effect than the unmodified polysaccharide *in vitro* models, indicating that chemical modification could enhance the cytoprotective effect [31].

Hepatoprotective effects

The hepatoprotective effect of an protein isolated of seeds from *C. pepo* was studied on Sprague-Dawley rat liver damage induced by acetoaminophen by monitoring serum transaminase including aspartate amino transferase (AST) and serum alanine amino transferase (ALT). The significant increased levels of plasma ALT and AST are the result of acetaminophen intoxication in the liver and kidney injury and leakage of cellular enzymes into the bloodstream as a result of the injury. The treatment with *C. pepo* seed protein isolate significantly reduced the levels of ALT and AST. In addition, seed protein isolated has good antioxidants effect as revealed by chelating effect, antixanthine oxidase properties, and free radical scavenging activity [32].

In another study, the effect of an protein isolated of seeds from *C. pepo* on CCl_4-induced injury in low-protein fed rats was studied. Administration of this protein caused significant increase en the enzymes antioxidant including catalase (CA), superoxide dismutase (SOD), glutathione peroxidase (GSHpx) as welll as glucose-6-phosphatase (G6Pase). However, was significantly decreased the lipid peroxidation (LPO-malondialdehyde-MDA) levels in liver homogenate [33]. Thesel studies have indicated the ability of seeds from *C. pepo* to reduce several parameters associated with liver injury.

Anti-hyperglycemic

Diabetes is a metabolic disease which is a serious problem of modern society due to the severe health complications associated with it. Pancreatic β-cells release insulin which is the hormone responsible for glucose homeostasis [34]. The inappropriate utilization of insulin leads to insulin resistance, which is characterised by the inability of cells to respond to normal levels of circulating insulin, thus leading to glucose metabolism disturbances are main factors leading to diabetes. For this reason therapeutic targets should lead a durable maintenance of glycemic control in the diabetic. Therefore, numerous herbal medicines, found to be effective in the long-term management of type 2 diabetes mellitus.

Tocopherol isomers (α, β, γ, and δ) from raw pumpkin seeds has been reported to be effective in the alleviation of diabetes through its antioxidant activities. Tocopherol was extracted and quantified of the seeds oil of *C. pepo* producing α- tocopherol ranged from 75 μg/g, 75 μg/g to 493 μg/g for γ-tocopherol, and from 35 μg/g to 1110 μg/g for δ-tocopherol. Tocopherol fraction of pumpkin seed oil was studied in hyperglycemia Wistar rats induced with nonionic copolymer PX-407 with impaired response and loss of β-cell sensitivity to glucose, which is considered as a appropriate model to study the activity of hypoglycemic drug. Results indicated a decreced of insulinemic, lipid profiles and glycemic levels. In addition, *in silico* constrained an noconstrained docking studies was performed using FRED and HYBRID programs to understand the mechanism of action with respect to three hypoglycemic proteins, PTP1 B, PPAR-γ, and DPP-IV with respect to 10 botanicals. In nonconstraint docking, all the tocopherols showed interaction in the active sites of the proteins [35]. A significantly reduction in oxidative markers and enhanced cecal and pancreatic characteristics were also observed.

Other Curcurbiteae as *Cucurbita ficifolia* Bouché (chilacayote) and *Cucurbita moshata* duch have properties hypoglycemic, increases serum insulin levels; produced a beta cell regeneration [36,37]. It has been shown that the bioactive component in *Cucurbita moshata* is a polysaccharide [38] though further research has been required to identify if this is true for all members of this family. It has been demonstrated that polysaccharides content in a water extract pumpkin produces higher hypoglycemic effects than those of the glibenclamide (GB) in alloxan-induced diabetic rats [38]. In addition, pumpkin fruit has high concentrations of pectin which is a fibre, when is consumed reduce the need for insulin and control glucose levels [39]. However, the protein-bound polysaccharides from pumpkin reduce the blood glucose levels, and improving the tolerance of glucose [40]. The structural characterization of the purified polysaccharide were evaluated as an acid heteropolysaccharide (Mw=27 kDa) including Ara, Gal, Glc and GalA in ratio of 2.6:3.6:2:1 with an α-configuration.

It has a backbone composed of (1 → 5)-linked Ara, (1 → 6)-linked Gal with three branches attached to O-3 of (1 → 6)-linked Gal and terminated with either Gal or Gal and Glc, and all of Glc and the majority of GalA are distributed in branches [41]. This polysaccharide (50 mg/kg) administered orally in alloxan-induced diabetic increase the body weight, reduce water intake, and blood glucose levels of diabetic mice group compared with diabetic control group.

In another studies also on alloxan-induced diabetic rats demonstrate that polysaccharide from pumpkins has hypoglycemic effect [42]. Furthermore, the administration of fruit powder for a month in diabetic rats significantly reduced C-reactive protein (CRP), colesterol, glucose, triglycerides while insulin was increased in diabetic rats [43].

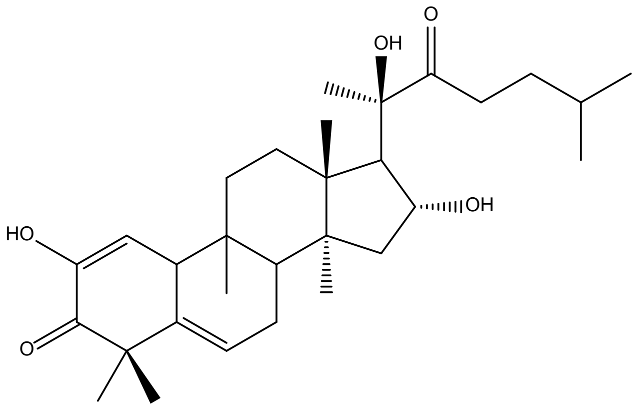
Protein-bound polysaccharides (PBPP) are isolated from water extract from pumpkin fruits to consist of 10.13% protein and 41.21% polysaccharides. Administration of this protein-bound polysaccharides to alloxan-induced diabetic rat model reduced significantly glucose levels [44]. All these studies indicate that polysaccharides and protein-bound polysaccharides are the bioactives antidiabetic of pumpkin. In clinical study, thirty T2DM diabetic patients were treated with pumpkin polysaccharide granules for four weeks. After treatment there is a reduction in both urination and plasma glucose [45].

Numerous plants are used in South Africa for the treatment of type II diabetes among them they is *C. pepo* which was evaluated using *in vitro* α-glucosidase and α-amylase activity. The results demonstrated inhibitory activity against both enzyme systems adding evidence to the traditional use in the management of the type II diabetic post-prandial hyperglycemia [46].

C. pepo may therefore be beneficial for the prevention of **complications related to diabetes**, also since its traditional use in diabetes is well established.

Anti ulcer activity

Cucurbitacin derivative was isolated from metanol extract of powdered seeds of *C. pepo* which showed dose dependent antiulcer activity decreasing ulcerative index indicated the ability of the compound to protect the gastric mucosa [47].



Cucurbitacin derivative

Prostatic hiperplasia (BPH) and urinary function

Benign prostatic hyperplasia (BPH) result of gradual overgrowth of the prostate gland, which is located at the base of tbe bladder and and surrounds the urethra. The enlarged prostate affects the urethra, and therefore BPH is associated with diminution in urinary function [48]. Management of this disease to include pumpk seeds suggested that the actions of pumpkin seed oil may be attributed to the content of phytosterols, which are known to interfere with the actions of dihydrotestosterone. This is a potent androgen produced in the prostate, from testosterone by the enzyme 5α-reductase that lead growth of the prostate. This androgens playing an considerable part in the disease process of BPH, so dihydrotestosterone inhibition reduced growth of the prostate.

In one study, hiperplasia of the rat prostate was induced by a subcutaneous injection of testosterone at a dose of 0.3 mg/100 g daily for 20 days. Administration of pumpkin seeds oil (14 mg/kg) daily for 30 days inhibited testosterone-induced hyperplasia of the rat prostate involving a direct inhibition of growth of the prostate [48].

In a double-blind, placebo controlled study with curbicin isolated from *C. pepo* seeds in the treatment of patients with symptoms of prostatic hiperplasia over a three month period. The cubicin dose administered to 55 patients was of 160 mg of standardized extract from *C. pepo* (80 mg). After treatment with cubicin micturition time, frequency of micturition, urinary flow, and residual urine were significantly improvement [49].

In another study forty five patients with urinary dysfunction (overactive bladder, OAB) were orally treated with *C. máxima* seeds oil (10 g/oil/day) for 12 weeks. Treatment with oil significantly reduced the degree OABSS in patients [50]. OABSS, a self-assessment of OAB symptoms, is recognized as a standard tool for diagnosis and evaluation of the severity of OAB, and has been used in clinical studies [51].

Furthermore, the pumkin seeds oil (10%) were investigated on citral induced BPH in Wistar rats. Citral significantIy increased prostate weight. However, seeds oil significantIy inhibited enlarged prostate, decrease of protein binding prostate (PBP) levels, weight of ventral prostate size, and amelioration histology of testis. Thus, indicate that seeds oil may be beneficial in the management of mild stage of benign prostatic hiperplasia [52].

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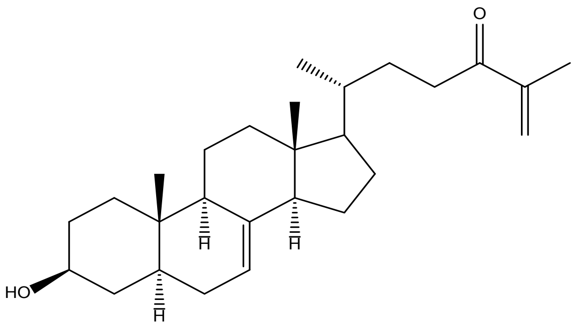
These finding suggested that pumkin seeds oil have the potential to be developed as new chemotherapeutic agents to prevent or to inhibit benign prostatic hiperplasia.

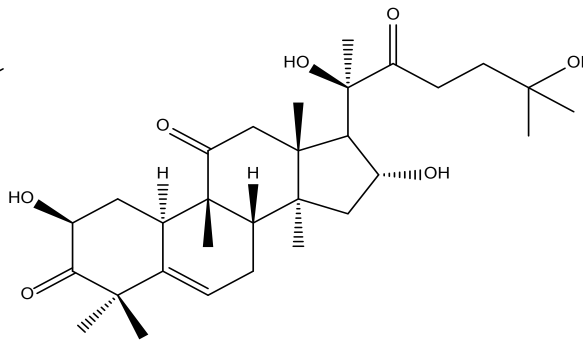
Anti-inflammatory activity

3β-hydroxycholest-7-en-24-one from *C. pepo* seeds, was isolated and evaluated for macrophage activation by the inhibitory assay of NO production in RAW264.7 mouse macrophages stimulated by LPS. 3β-hydroxycholest-7-en-24 one exhibited inhibitory effects on macrophage activation at 3-30 μM (produced NO: 81.3% at 3 μM, 61.2% at 10 μM, and 33.9% at 30 μM). Triterpene exhibited low cytotoxicity at 30 μM (cell viability: 85.9% at 30 μM), but not at effective concentrations, namely 3 and 10 μM. These results suggested that isolated steroid has potential as an anti-inflammatory agent [26].

23, 24-dihydrocucurbitacin D [53] blocked NO production from peritoneal macrophages activates with lipopolysaccharides and interferon γ, with values of ED_{50} of 13 μM and the effect might occur via inhibiting NF-KB activation and iNOs gene transcription. However, did not show cytotoxic to peritoneal macrophages [54].



3β-hydroxycholest-7-en-24-one



23, 24-dihydrocucurbitacin D

Antimicrobial activity

Antimicrobial chemotherapy has revolutionized modern medicine and has significantly reduced death and ailments from infectious diseases. Nevertheless, microorganisms have progressively diminished the effectiveness of previously successful antibiotics by developing resistance. Certain bacterias can secrete an extracelular polymer layer (biofilm) that accumulates and surrounds bacterial cells to resist to antibiotics. Bacteria in a biofilm present more resistance to multiple antibiotics that planktonic bacteria. In intracellular infections most antibiotic have poor cellular penetration and limited intracelular retention. Therefore develop of novel bioactive are of a high interest. The infection caused by multidrug-resistant and pandrug-resistant stains are often hard to treat due therapeutic options. Currently there is a great interest on natural antimicrobial molecules in hope that they may provide useful leads into anti-infective drug candidates.

Extracts of leaves from *C. pepo* displayed the largest spectra of activity against *Providencia stuartii, Pseudomonas aeruginosa, K. pneumoniae, Escherichia coli, Enterobacter aerogenes* and *Enterobacter cloacae*. The extract from *C. pepo* was more active than chloramphenicol used as positive control on at least one of the tested MDR bacteria. The activity of chloramphenicol increased in the presence of PAβN in the majority of the tested bacteria. The extract from *C. pepo* leaves showed the best MBC spectrum with the values below to 1024 μg/ml recorded on 58.62% (17/29) of the studied microorganisms [55].

In another research, the methanolic extract of fruit of *C. pepo* were evaluated for antimicrobial activity against bacterial strains *Bacillus cereus, Bacillus subtilis, Escherichia coli, Enterobacter aerogenes, Enterobacter agglomerans, Salmonella enteritidis, SalmoneIla cholerasius, Staphylococcus aureus, Pseudomonas aeruginosa, Candida albicans, Penicillium chrysogenum, Enterobacter faecalis, Klebsiella pneumonia, Bisphericus, B. thruengenesis* and *Cryptococcus meningitis*. The extract showed moderate to high activity against all the investigated microbial strains [56].

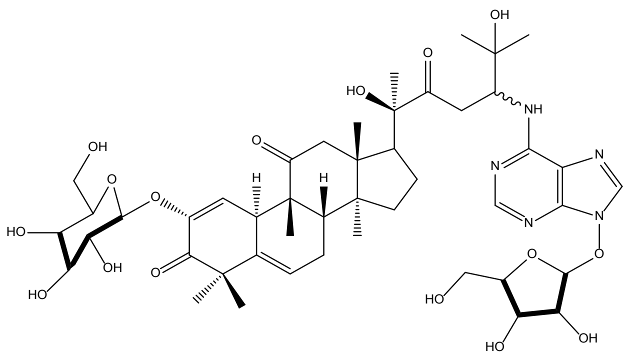
Anticancer/antitumour effects

Cancer is one of the main health problems of all the world. Cancer is responsible for 12% of the world's mortality. Treatments include chemotherapy surgery, and radio-theraphy. However, chemotherapy suffers limitations of drug resistance, toxicity, side-effects and lacking specificity toward tumor cells [57]. Therefore, there is a strong interest in the use of plants as a promising source of more efficient anticancer drugs.

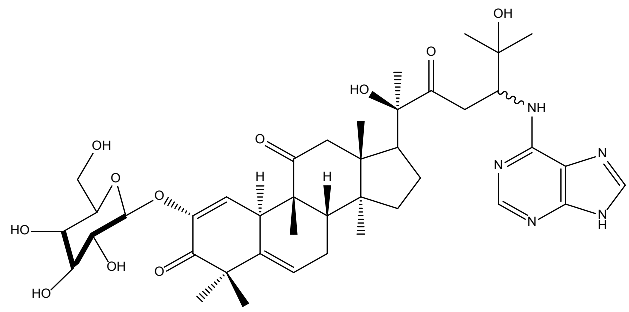
Currently more than 40 cucurbitacin-derived compounds and cucurbitacins and have been isolated from the Cucurbitaceae family and from other species of the plant. The apoptotic effects of cucurbitacins is due of their ability to modify the genes, transcriptional activities via nuclear factors and mitochondrial trans-membrane potential and their capability to activate or inhibit pro- or anti-apoptotic proteins. Cucurbitacins are selective inhibitors of the JAK/STAT pathways; also, other mechanisms are implicated in their apoptotic effects, such as PARP cleavage, MAPK pathway, expression of active caspase-3, decreased JAK3 and pSTAT3 levels, as well as decreases in various downstream STAT3 targets such as Bcl-2, Mcl-1, cyclin D3, and Bcl-xL, all of which are implicated in the cell cycle control [58].

Alcoholic extract of *Cucurbita pepo* showed IC_{50} values on cancer cell lines HepG2 and CT26 of 132.6 and 167.2 μg/ml respectively. The ethanolic extract of fruits of *C. pepo* was observed to exhibit a significant dose-dependent inhibitory effect against HeLa cell growth [59].

Cucurbitacins have been reported mainly in the Cucurbutacea, are a class of highly oxidized tetracyclic triterpenoids possess the biogenetically unusual 10α-cucurbit-5-ene[19(10 →19β)*abeo*-10α-lanostane skeleton which are well known for their cytotoxic activity. The ethanolic extract of air-dried fruits of *C. pepo* was subjected to chromatography to give cucurbitaglycosides A and B. *In vitro* assay both compounds showed weak cytotoxic activity against HeLa cells with IC_{50} values of 17.2 and 28.5 μg/ml respectively [60].



Cucurbitaglycosides A



Cucurbitaglycosides B

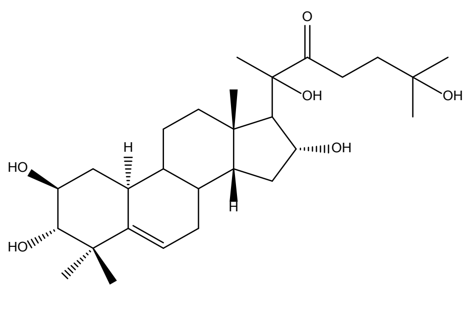
Feng et al. [53] found that *C. pepo* cv dayangua contain 23, 24-dihydrocucurbitacin F, 23, 24-dihydrocucurbitacin D, cucurbitacin B and cucurbitacin E.

The antiproliferative effect of 23, 24-dihydrocucurbitacin F, on human PCa cells might occur to the induction of the cofilin-actin rod formation and actin aggregation producing to cell cytokinesis failure, inhibited cell growth cycle arrest at G2/M phase and apoptosis [61]. In addition, 23,24-dihydrocucurbitacin F have been inhibitory activity on Epstein-Barr virus (EBV) activation induced by the tumor promoter, 12-O-tetradecanoyl-phorbol-13-acetate (TPA) and also exhibit significantly anti-tumor-promotion activity on mouse skin tumor promotion [62].

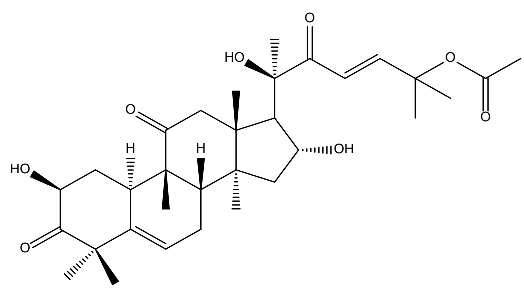
Cucurbitacin B and cucurbitacin E characterized from *C. pepo* cv dayangua has been shown antiproliferative in breast (MCF-7), colon (HCT-116), brain (SF-268), lung cancer cells (A549) and lung (NCI-H460) cancer cell lines, among them cucurbitacin B demonstrated more than 80% proliferation inhibitory activity [63].

Treatment with cucurbitacins B and E showed growth inhibition accompanied by apoptosis and cell cycle arrest in breast cancer cell lines (MDA-MB-231 and MCF-7) [64]. They also modulated the expression of proteins involved in cell-cycle regulation in both of the estrogen-independent (MDA- MB-231) and estrogen-dependent (MCF-7) in human breast cancer cell lines [65]. Growth inhibition and cytotoxic effect of cucurbitacin B on breast cancer cell lines SKBR-3 and MCF-7 were attributed to G2/M phase arrest and apoptosis. Cucurbitacin B treatment inhibited Cyclin D1, c-Myc, and β-catenin expression levels, translocation to the nucleus of β-catenin and galectin-3. Western blot analysis showed increased PARP cleavage suggesting induced caspase activity and decreased mitogenic Wnt-associated signaling molecules galectin-3, β-catenin, c-Myc, and cyclin D1 with changes in phosphorylated GSK-3β levels [66].

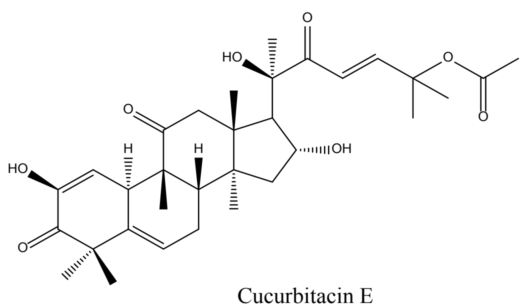
Cucurbitacin E caused disruption of the cytoskeleton structure of actin and vimentin inhibing the proliferation of prostate cancer cells [67]. Moreover, cucurbitacins also inhibited proliferation of endothelial cells accompanied by a disruption of the F-actin and tubulin microfilaments cytoskeleton, normal mitogen-induced T-lymphocytes [68] and reduced cell motility suggest an anti-angiogenesis and anti-metastasis role for cucurbitacins [67]. In addition is capable of inducing and maintaining high proliferation rates in lymphocytes [69].



23, 24-dihydrocucurbitacin F



Cucurbitacin B



Cucurbitacin E

These finding suggested that *C. pepo* extracts have the potential to be developed as new chemotherapeutic agents to prevent or to inhibit the growth of tumours and cancers.

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