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CUCUMBER IS A CHAMBER OF BITTER TO BETTER STEREOCONSTITUENTS

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ABSTRACT

Cucurbitacins are highly oxygenated, tetracyclic triterpenes present in the fruits and roots of cucurbits such as watermelon, squash, and zucchini at 0.1–0.3% concentrations. These non-volatile compounds are notable for their extreme bitterness with a detection level for humans of about 1 ppb in solution. Cultivated cucumbers all contain cucurbitacin B and cucurbitacin C, compounds that are supposed to make their leaves bitter and less tasty to munching animals. These compounds are usually confined to the leaves and stems of the plants, parts of the plant humans don't eat, so we are not aware they are there. It is only when they move into the fruits that we start detecting a bitter taste.

KEYWORDS: Cucurbitacins, bitterness, cucumbers.

Overview: Plant secondary metabolites represent tremendous resources for scientific and clinical research as well as for new drug development. Cucurbitacins are multiplex category of diverse compounds found in the plants of family cucurbitaceae. Medicinal and toxic properties of these compounds have stimulated a continuing interest in them. Many genus of cucurbits viz. Trichosanthes, cucurbita, cucumis and citrullus are affluent in cucurbitacins. These compounds have also been discovered in other plant families like scrophulariaceae, cruciferae, datiscaceae, primulaceae, rubiaceae etc., the diversity of cucurbitacins lies in variety of its side chain derivatives that contribute to their disparate pharmacological actions. The bitter taste of plant species like cucumber have been attributed to the presence of cucurbitacins.[1]

Figure-1: Cucumber.

The first cucurbitacin was isolated as a crystalline substance in 1831 and was named α-elaterin. Certain plant species rich in cucurbitacins like momordica hold coveted position in different system of traditional medicines for curative effects in metabolic disease like diabetes. Plants from genus trichosanthes have been used in china by herbal drug practitioners. The purpose of this review is to gather the information related to these highly diverse group of compounds which may be useful in future research.[2]

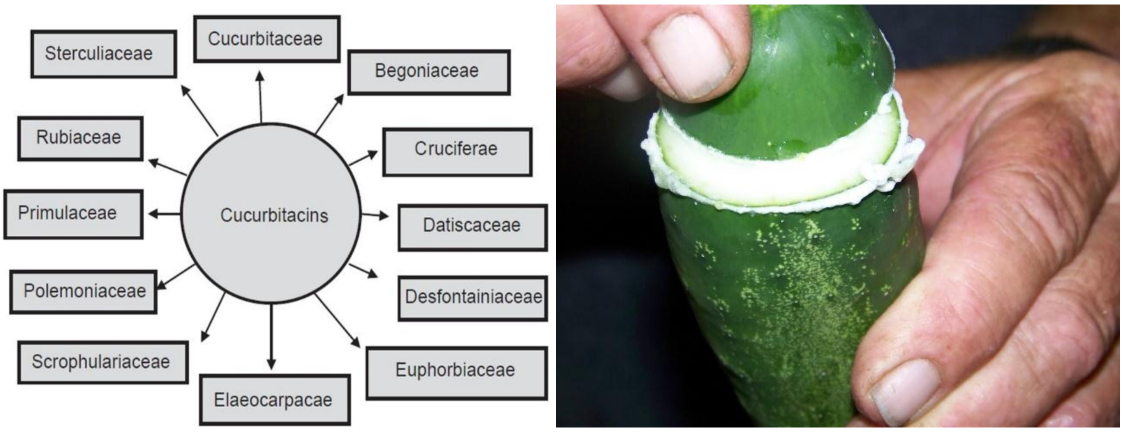


Figure-2: Family of Cucurbitacins.

Chemistry: Cucumber (*Cucumis sativus*) is a widely-cultivated creeping vine plant that bears usually cylindrical fruits, which are used as vegetables. Considered an annual plant, there are three main varieties of cucumber — slicing, pickling, and burpless/seedless — within which several cultivars have been created. Raw cucumber (with peel) is 95% water, 4% carbohydrates, 1% protein, and contains negligible fat. A 100-gram (3+1⁄2-ounce) reference serving provides 67 kilojoules (16 kilocalories) of food energy. It has a low content of micronutrients: it is notable only for vitamin K, at 16% of the Daily Value. Depending on variety, cucumbers may have a mild melon aroma and flavor, in part resulting from unsaturated aldehydes, such as (E,Z)-nona-2,6-dienal [CAS: 557-48-2], and the cis- and trans-isomers of 2-nonenal [2-Nonenal is an unsaturated aldehyde. The colorless liquid is an important aroma component of aged beer and buckwheat. CAS: 18829-56-6 (trans), 60784-31-8 (cis)].[3]

Figure-3: (E,Z)-nona-2,6-dienal and 2-noneal.

The slightly bitter taste of cucumber rind results from cucurbitacins. Trans, cis-2,6-Nonadienal is an organic compound that is classified as a doubly unsaturated derivative of nonanal. The molecule consists of a α,β-unsaturated aldehyde with an isolated alkene group. The compound has attracted attention as the essence of cucumbers, but it is also found in bread crust and freshly cut watermelon. The bitterness in cucumbers is produced by the compound cucurbitacin. Cucurbitacins are normally found in the leaves, stems, and roots of cucumber plants. The cucurbitacins spread from the vegetative parts of the plant into the cucumber fruit when plants are under stress. Cucurbitacin is a class of biochemical compounds that some plants – notably members of the pumpkin and gourd family, Cucurbitaceae – produce and which function as a defense against herbivores.[4]

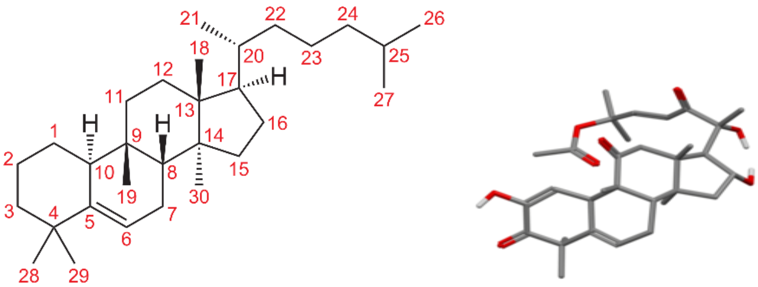
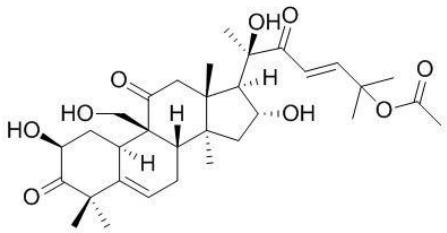


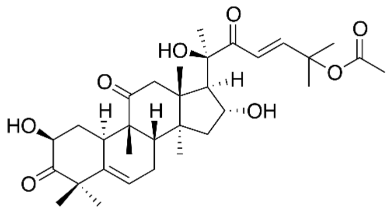
Figure-4: Cucurbeta-5-ene.

Cucurbitacins are chemically classified as triterpenes, formally derived from cucurbitane, a triterpene hydrocarbon – specifically, from the unsaturated variant cucurbit-5-ene, or 19(10→9β)-abeo-10α-lanost-5-ene. They often occur as glycosides. They and their derivatives have been found in many plant families (including Brassicaceae, Cucurbitaceae, Scrophulariaceae, Begoniaceae, Elaeocarpaceae, Datiscaceae, Desfontainiaceae, Polemoniaceae, Primulaceae, Rubiaceae, Sterculiaceae, Rosaceae, and Thymelaeaceae), in some mushrooms (including Russula and Hebeloma) and even in some marine mollusks. Cucurbitacins may be a taste deterrent in plants foraged by some animals and in some edible plants preferred by humans, like cucumbers and zucchinis. In laboratory research, cucurbitacins have cytotoxic properties and are under study for their potential biological activities.[5]

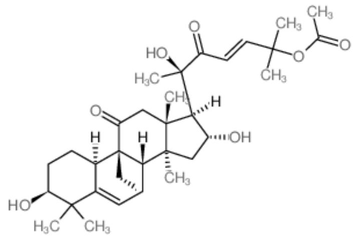
Cucurbitacin-A: 22-hydroxy-23,24,25,26,27-pentanorcucurbit-5-en-3-one $C_{25}H_{40}O_2$, white powder found in Cucumis.



Cucurbitacin A



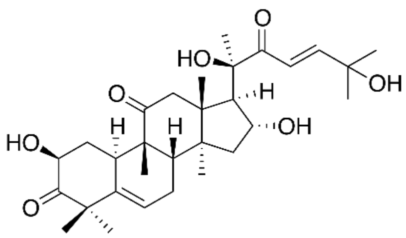
Cucurbitacin B



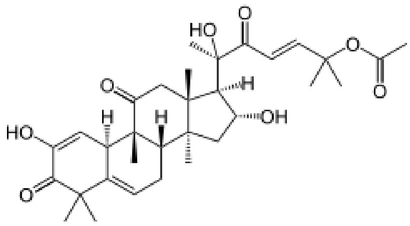
Cucurbitacin C

Cucurbitacin B: Cucurbitacin B from *Hemsleya endecaphylla* (62 mg/72 g) and other plants (e.g. *Cucurbita andreana*); anti-inflammatory, any-hepatotoxic.

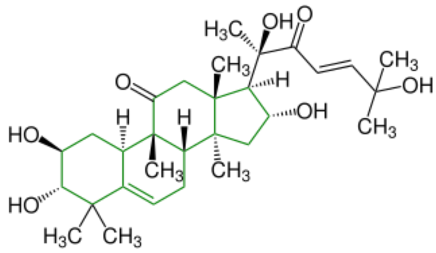
Cucurbitacin C: Cucurbitacin C, from *Cucumis sativus* (cucumber)



Cucurbitacin D



Cucurbitacin E



Cucurbitacin F

Cucurbitacin D: Cucurbitacin D [CAS: 3877-86-9; IUPAC: (1R,2R,3aS,3bS,8S,9aR,9bR,11aR)-1-[(2R,4E)-2,6-Dihydroxy-6-methyl- 3-oxohept-4-en-2-yl]-2,8-dihydroxy- 3a,6,6,9b,11a-pentamethyl-2,3,3a,3b,4,6,8,9,9a,9b,11,11a- dodecahydro-1H-cyclopenta[a] phenanthrene-7,10-dione], from *Trichosanthes kirilowii* and many other plants (e.g. *Cucurbita andreana*)

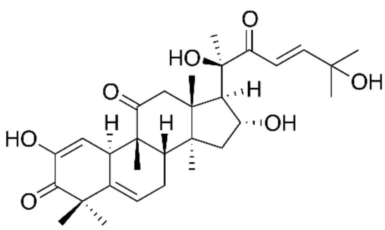
Cucurbitacin E: Cucurbitacin E [CAS: 18444-66-1; IUPAC: (3E,6R)-6-[(1R,2R,3aS,3bS,9aR,9bR,11aR)-2,8-Dihydroxy-3a,6,6,9b,11a-pentamethyl-7,10-dioxo-2,3,3a,3b,4,6,7,9a,9b,10,11,11a- dodecahydro-1H-cyclopenta[a] phenanthren-1-yl]-2-methyl-5-oxohept-3-en-2-yl acetate] (α-Elaterin), from roots of *Wilbrandia ebracteata*. Strong antifeedant for the flea beetle, inhibits cell adhesion (also in e.g. *Cucurbita andreana*)

Cucurbitacin F from *Elaeocarpus dolichostylus*

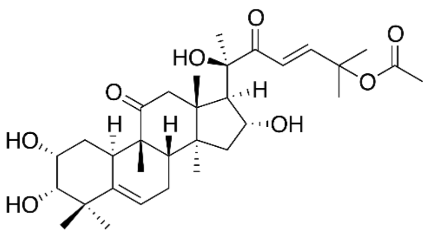
Cucurbitacin F 25-acetate from *Helmseya graciliflora*
23,24-Dihydrocucurbitacin F from *Helmseya amabilis*
25-Acetoxy-23,24-dihydrocucurbitacin F from *Helmseya amabilis (hemslecin A)*
23,24-Dihydrocucurbitacin F glucoside from *Helmseya amabilis*
Cucurbitacin II glucoside from *Helmseya amabilis*
Hexanorcucurbitacin F from *Elaeocarpus dolichostylus*
Perseapicroside A from *Persea mexicana*
Scandenoside R9 from *Hemsleya panacis-scandens*
15-Oxo-cucurbitacin F from *Cowania mexicana*
15-oxo-23,24-dihydrocucurbitacin F from *Cowania mexicana*
Datiscosides B, D, and H, from *Datisca glomerata*

Cucurbitacin G from roots of *Wilbrandia ebracteata*

Cucurbitacin H, stereoisomer of cucurbitacin G, from roots of *Wilbrandia ebracteata*.



Cucurbitacin I



Cucurbitacin Q

Cucurbitacin I: Cucurbitacin I (elatericin B) from Hemsleya endecaphylla, 10 mg/72 g, also from *Ecballium elaterium, Citrullus colocynthis, Cucurbita andreana,* deters feeding by flea beetle.
Cucurbitacin J: Cucurbitacin J from *Iberis amara*: Cucurbitacin J 2-O-β-glucopyranoside from *Trichosanthes tricuspidata.*
Cucurbitacin K: Cucurbitacin K, stereoisomer of cucurbitacin J, from *Iberis amara*. Cucurbitacin K 2-O-β-glucopyranoside from *Trichosanthes tricuspidata*.
Cucurbitacin L: Cucurbitacin L, or 23,24-dihydrocucurbitacin I. Brydioside A from *Bryonia dioica.*
Constituents of the colocynth fruit and leaves (*Citrullus colocynthis*) include cucurbitacins. The 2-O-β-D-glucopyranosides of cucurbitacins K and L can be extracted with ethanol from fruits of *Cucurbita pep*o cv dayangua. Pentanorcucurbitacins A and B can be extracted with methanol from the stems of *Momordica charantia*. Cucurbitacins B and I, and derivatives of cucurbitacins B, D and E, can be extracted with methanol from dried tubers of *Hemsleya endecaphylla*. Cucurbitacins impart a bitter taste in plant foods such as cucumber, zucchini, melon and pumpkin.
Cucurbitacin O: Cucurbitacin O from *Brandegea bigelovii*. Cucurbitacin Q 2-O-glucoside, from *Picrorhiza kurrooa.*
Cucurbitacin P: Cucurbitacin P from *Brandegea bigelovii*. Picracin from *Picrorhiza scrophulariaeflora.*
Cucurbitacin Q: Cucurbitacin Q from *Brandegea bigelovii*. 23,24-Dihydrodeacetylpicracin 2-O-glucoside from *Picrorhiza kurrooa*. Cucurbitacin Q1 from Cucumis species, actually Cucurbitacin F 25-acetate.
Cucurbitacin R: Cucurbitacin R is actually 23,24-dihydrocucurbitacin D.
Cucurbitacin S: Cucurbitacin S from *Bryonia dioica*.
Cucurbitacin T: Cucurbitacin T, from the fruits of *Citrullus colocynthis*.

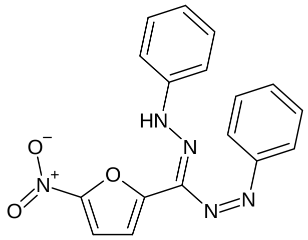
Occurrence and bitter taste
Constituents of the colocynth fruit and leaves (*Citrullus colocynthis*) include cucurbitacins. The 2-O-β-D-glucopyranosides of cucurbitacins K and L can be extracted with ethanol from fruits of *Cucurbita pepo* cv dayangua. Pentanorcucurbitacins A and B can be extracted with methanol from the stems of *Momordica charantia*. Cucurbitacins B and I, and derivatives of cucurbitacins B, D and E, can be extracted with methanol from dried tubers of *Hemsleya endecaphylla*. Cucurbitacins impart a bitter taste in plant foods such as cucumber, zucchini, melon and pumpkin.[6-10]

Identity, physical and chemical properties: Cucurbitacins are derived from basic cucurbitane ring skeleton which is a triterpene hydrocarbon (IUPAC name 19 (10-9β)-abeo-5α-lanostane, which on modification by groups containing oxygen and double bonds produce manifold Cucurbitacins with distinctive features. The saccharide linkage is generally present at C-2 (2-O-β-glycosides) in Cucurbitacin glycosides. Majority of Cucurbitacins are usually crystalline in nature or present in the form of needles at room temperature except Cucurbitacin H which is an amorphous solid. Most Cucurbitacins are soluble in petroleum ether, chloroform, benzene, ethyl acetate, methanol and ethanol, but are insoluble in ether. They are only slightly soluble in water. Cucurbitacins usually have absorption maxima for ultraviolet light between 228-234 nm.[11,12]

Cucurbitacin	Nature	Formula	UV max. (ethanol) nm	Mass	m.p.
A	Crystals	$C_{32}H_{46}O_9$	229, 290	574.314	207-208°
B	Crystals	$C_{32}H_{46}O_8$	-	558.3192	184-186°
C	Needles	$C_{32}H_{48}O_8$	231, 298	560.3348	207-207.5°
D	Needles	$C_{30}H_{44}O_7$	230	516.3087	151-153°
E	Crystals	$C_{32}H_{44}O_8$	234, 268	556.3035	234.5°
F	Needles	$C_{30}H_{46}O_7$	-	518.3243	244-245°
G	Crystals	$C_{30}H_{52}O_9$	-	534.3192	150-152°
H	Amorphous solid	$C_{30}H_{46}O_8$	-	534.3192	150-152°
I	Needles	$C_{30}H_{42}O_7$	234, 266	514.293	148-148.5°
J	Crystals	$C_{30}H_{44}O_8$	270	532.3036	200-202°
K	Needles	$C_{30}H_{44}O_8$	270	532.3036	200-202°
L	Needles	$C_{30}H_{44}O_7$	270	516.3087	137-142°
O	-	$C_{30}H_{46}O_7$	-	518.3243	122-127°
P	-	$C_{30}H_{48}O_7$	-	520.3399	-
Q	-	$C_{32}H_{48}O_8$	-	560.3348	-
S	-	$C_{30}H_{42}O_6$	-	498.298	-

Figure-5: Cucurbitacin constituents chemistry.

Analysis of cucarbitacins: Cucurbitacins are secreted in very minute quantities in plants and due to difficulties in isolating these compounds in large quantities many of their potential uses remain unexplored. Cucurbitacins are moderately polar compounds and have been isolated using solvents like methanol. The solubility of aglycone portion of most Cucurbitacins is significant in moderately polar solvents like chloroform. Partition between water and chloroform is customarily used for purification of Cucurbitacins isolated from plant extracts which are extracted with methanol.[13]



(*Z*)-1-[(*E*)-(5-nitrofuran-2-yl)(2-phenylhydrazinylidene)methyl]-2-phenyldiazene

Figure-6: Formazine.

The chromatographic techniques like open-column chromatography on silica gel, alumina or florisil, or thin layer chromatography have been utilized for purification process of Cucurbitacins from plant extracts. Extraction of cucurbitacins have also been tried using maceration of the plant material with absolute ethanol and lead acetate in equal quantities. The mixture is filtered and after aqueous potassium dihydrogen phosphate is added to precipitate lead. The Cucurbitacins are extracted from the aqueous phase with chloroform three times and finally the extract is concentrated at 70°C. A confirmatory test to determine the presence of Cucurbitacins in extracts and fractions has been reported whereby the sample is mixed with triphenyltetrazolium chloride.[14]

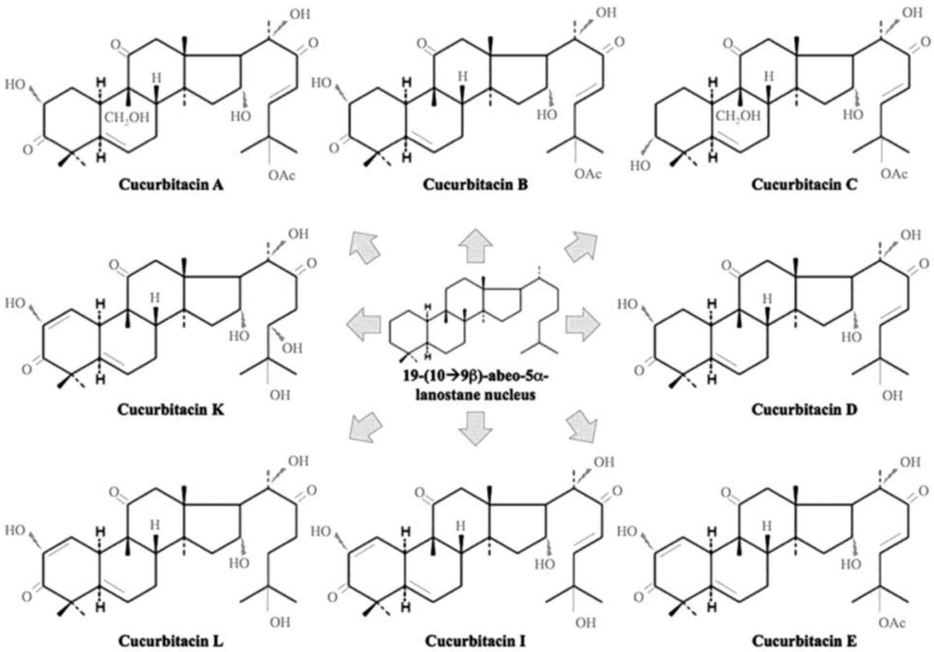


Figure-7: Stereochemistry of cucurbitacin.

The occurrence of red precipitate of formazin is indicates presence of Cucurbitacins. The thin layer chromatographic solvent mixtures reported in literature have been compiled. Often invariable presence of α, β-unsaturated ketones either in the side chain or in the A-ring of cucurbitane skeleton results in the UV-absorbance at 230 nm for most Cucurbitacins, yet for many other Cucurbitacin analogues UV-absorbance does not go above 210 nm. Chromatographic system such as reversed phase high performance thin layer chromatography (HPTLC) using mobile phase composition of ethyl acetate and benzene (25:75) have been reported for quantifying Cucurbitacins. A high-performance liquid chromatography (HPLC) chromatographic technique using gradient elution of acetonitrile in water have been documented for the analysis of a number of Cucurbitacin analogues commonly found in plants.[15]

Toxicity reports: Substitution pattern on various Cucurbitacins provides the lead to understand and trace out clear distinction between the toxic effects and curative role of Cucurbitacins. Cucurbitacins have been reported as highly toxic compounds and instances of severe poisoning and death in sheep and cattle that consumed bitter fruits of Cucumis and Cucurbita are well documented. The range of toxicity of Cucurbitacins based on few *in-vivo* toxicity reports, has been found to be between 2 -12.5 mg/kg. Although a report on toxicity of Cucurbitacin R at level as high as 375 mg/Kg p.o and 67 mg/kg i.p is available. The presence of a double bond at C-23 and acetyl group at C-25 have been found to augment the toxicity of Cucurbitacins. Cucurbitacin's strong biological activity was found to be very close to their toxic dose, which renders them unlikely to be biological agents. The extreme bitterness of Cucurbitacins should deter humans from being exposed to substantial quantities of the compounds. Nevertheless, some poisonings have been reported after consumption of Cucurbitaceous food plants. Cucurbitacins are found to be fatal when fruits of Luffa cylindrical (L.) were consumed. Gastrointestinal symptoms have also been reported in a Japanese population consuming the bottle gourd, which contained Cucurbitacin D. The toxicity of Cucurbitacins C, D, E, and I have been assessed and these compounds ascertained to be lethal. Plants with Cucurbitacins C, D, E and I must be avoided as their consumption can lead to illness or even death. The appearance of toxic symptoms varies with the animal species used in the experiment, the route of administration of the compound, and the quantity that has been administered.[16,17]

CONCLUSION

As a member of the Cucurbitaceae family of plants, cucumbers contain high levels of bitter-tasting nutrients known as cucurbitacin. According to an article in the International Journal of Health Services, cucurbitacins may help prevent cancer by stopping cancer cells from reproducing. Cucurbitacins are under basic research for their biological properties, including toxicity and potential pharmacological uses in development of drugs for inflammation, cancer, cardiovascular diseases, and diabetes, among others. The toxicity associated with consumption of foods high in cucurbitacins is sometimes referred to as "toxic squash syndrome". In France in 2018, two women who ate soup made from bitter pumpkins became sick, involving nausea, vomiting, and diarrhea, and had hair loss weeks later. Another French study of poisoning from bitter squash consumption found similar acute illnesses and no deaths. The high concentration of toxin in the plants could result from cross-pollination with wild cucurbitaceae species, or from plant growth stress due to high temperature and drought.

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