Plant Archives Vol. 23, No. 2, 2023 pp.200-207 e-ISSN:2581-6063 (online), ISSN:0972-5210

Plant Archives

Journal homepage: http://www.plantarchives.org
DOI Url : https://doi.org/10.51470/PLANTARCHIVES.2023.v23.no2.034

CUCURBITACIN: A COMPREHENSION OF NATURE'S THERAPEUTIC BIOACTIVE COMPOUND

Mohammad Rashid[1, 3], Farhan J Ahmad[2], Sanjar Alam[3], Md. Azhar Iqbal[3] and Rakesh K Sindhu[1*]
[1]School of Pharmacy, Sharda University, Greater Noida, Uttar Pradesh, India - 201310
[2]School of Pharmaceutical Education & Research, Jamia Hamdard, New Delhi, India - 110062
[3]R.V. Northland Institute, G.B. Nagar, Dadri, Greater Noida. Uttar Pradesh, India- 203207
*Corresponding Author E-mail: rakesh.kumar7@sharda.ac.in
(Date of Receiving : 27-05-2023; Date of Acceptance : 05-08-2023)

ABSTRACT

Members of the Cucurbitaceae family, as well as the ones from other plant families, contain steroidal triterpenes called Cucurbitacins. These possess tremendous therapeutic potential due to their structural diversity found in their Bioactive compounds like Cucurbitacin. Potentially useful lead molecules for further study could be found within this wide variety of chemicals present in the fruits and other parts of plants. Scientifically valid evidences regarding the efficacy and likely relevance in many diseases can be generated by studying these neglected therapeutic leads from nature. This review will examine the suggested mode of action and possible molecular targets of these compounds in an effort to shed light on their chemical make-up and therapeutic potential.
Keywords **:** Cucurbitaceae, diabetes, Cucurbitacin, triterpenoids.

Introduction

The utilization of plant secondary metabolites holds significant potential for scientific and clinical investigations, as well as the discovery and development of novel pharmaceuticals. Cucurbitacins represent a broad range of chemically varied molecules that are abundantly oxygenated, and are primarily found in plants belonging to the Cucurbitaceae family (Kupchan, Meshulam and Sneden, 1978). These nonvolatile compounds possess a remarkable characteristic of exhibiting an exceptionally high level of bitterness, which can be detected by humans at a concentration as low as 1 part per billion (ppb) when dissolved in a solution (Horie *et al.*, 2007). The medicinal and poisonous qualities exhibited by these substances have engendered a persistent fascination and scholarly research across the nature of these substances.

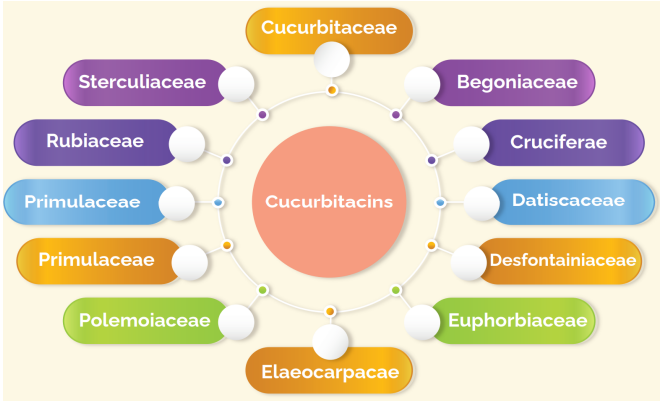

Fig. 1 : Various families enriched with Cucurbitacins.

The initial discovery of Cucurbitacin occurred in 1831, whereby a crystalline compound was identified and afterwards designated as α elaterin (Gry and Andersson, 2006). The depiction of the distribution of Cucurbitacins throughout different families within the plant world is presented in Fig. 1. Cucurbitacins are frequently found in several species, including *Bryonia, Cucumis, Cucurbita, Luffa, Echinocystis, Lagenaria,* and *Citrullus*. The plant species belonging to the genus *Momordica* are known to possess a distinct category of Cucurbitacins referred to as momordicosides. These chemicals have also been identified in other plant families such as Scrophulariaceae, Cruciferae, Datiscaceae, Primulaceae, Rubiaceae, and so on. Cucurbitacin-producing plants have been found in various plant families, including Scrophulariaceae, Begoniaceae, Primulaceae, Liliaceae, Tropaeolaceae, and Rosaceae, in addition to the cucurbitaceae family. Cucurbitacins are also present in the seeds of specific cruciferous plants, such as *Iberis* species and *Lepidium sativum* (Patel and Ghane, 2021). According to the literature, it has been stated that the formation of Cucurbitacins occurs in situ within the plant and does not involve their transportation to other plant tissues. The concentration of Cucurbitacins exhibits variation across different tissues. The compounds in question are likely to be found in high concentrations within the fruits and roots of fully developed plants. The production of Cucurbitacins in fruits occurs predominantly during the maturation stage, resulting in the attainment of their maximal concentration. In general, the content of Cucurbitacins in seeds is often quite low.

The diversity of Cucurbitacins is attributed to the wide range of side chain derivatives they possess, which play a significant role in determining their distinct pharmacological effects (Dai *et al.*, 2023). The presence of Cucurbitacins has been associated with the bitter taste observed in plant species such as cucumber. Several plant species, such as *Momordica*, which are abundant in Cucurbitacins, are highly regarded in

several traditional medicinal systems due to their therapeutic properties in treating metabolic disorders like diabetes (Jian *et al.*, 2005). The utilisation of plants belonging to the *Trichosanthes* genus has been observed in traditional Chinese medicine practices (Çiçek, 2022). The objective of this review is to compile pertinent information pertaining to a wide range of chemicals, with the aim of potentially facilitating future research endeavours. Traditional remedies comprise of the building blocks of plants like *Begonia heracleifolia* and *Picrorhiza kurrooa* as well as *Echinocystis fabaceae* and *Wilbrandiae bracteata* and *Trichosanthes kirilowii* all of these have Cucurbitacin-B (Chen *et al*., 2005).

Chemistry and Categories of Cucurbitacins

The structural framework of all Cucurbitacins consists of a fundamental 19-(10-9β)–abeo 10α–lanost–5-ene ring. The presence of a 5,(6)-double bond is a shared characteristic among all molecules classified as Cucurbitacins. The distinguishing characteristic between Cucurbitacins and steroidal nuclei is the presence of a methyl group at carbon 9 in the basic structure of Cucurbitacins, as opposed to carbon 10 (Kaushik, Aeri and Mir, 2015). The majority of Cucurbitacins exhibit a tetracyclic structure, while certain examples possess an additional ring resulting from formal cyclization between carbon atoms 16 and 24, as observed in Cucurbitacins **S** and **T**.

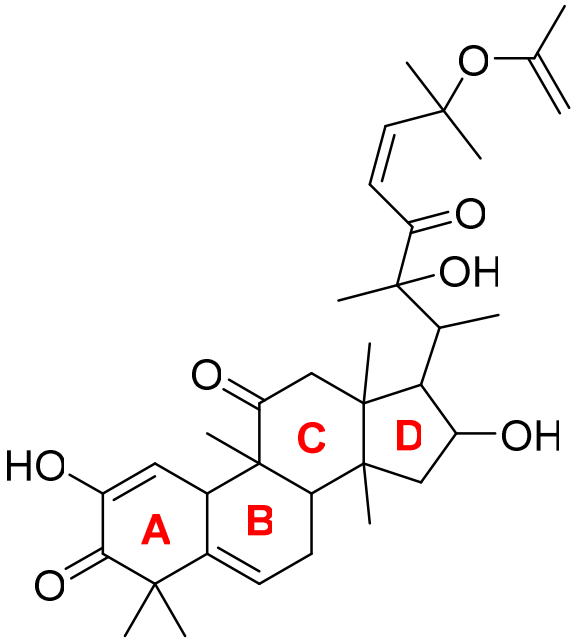

Fig. 2 : Basic Structure of Cucurbitacin

The Cucurbitacins exhibit a notable distinction from the majority of other tetracyclic triterpenes due to their high degree of unsaturation and the presence of several keto, hydroxyl, and acetoxy functional groups. Certain Cucurbitacins have been identified as glycosides, with some of them exhibiting an absence of the C 11 carbonyl functionality (Patel and Ghane, 2021).

Cucurbitacins are classified based on the presence of different functional groups on rings **A** and **C**, the diversity in the side chain, and considerations of stereochemistry (Jayaprakasam, Seeram and Nair, 2003). The structural makeup of the Cucurbitacins mentioned in Fig: 2. Now various kind of it has been identified and designated by the letters **A, B, C, D, E, F, G, H, I, J, K, L, O, P, Q, R**, and **S** (Fig. 3). The name "Cucurbitacin" encompasses a collection of Cucurbitacins, including both their glycosidic forms stated previously and those forms listed earlier (Ven Subbiah, 105 Bella Vista Dr., Edenton, 1996). Cucurbitacin G and H possess identical structures, although they exhibit dissimilarities in the arrangement of the hydroxyl group at position 24, the determination of which remains unresolved. Cucurbitacin R has been identified as 23, 24 dihydrocucurbitacin D (DHCD), leading to its reclassification within the Cucurbitacin D group (Jian *et al.*, 2005). Cucurbitacin J and K exhibit a notable distinction in their chemical structures, namely in the arrangement of the hydroxyl group at position 24.

According to reports on structural features, triterpenoids compounds indicated bitterness, and the strength of bitterness reflected the distances between three oxygen atoms and the hydrophobic methyl groups, playing a significant role in generating bitterness in the triterpenoids components (Sakamura, 1988). The Cucurbitacins are traditionally arbitrarily split into a total of twelve variants. We stick with this nomenclature all throughout this review for the sake of clearness and since it is generally accepted in the relevant literature.

The categories of Cucurbitacins can be as- (Jian Chao Chen, a Ming Hua Chiu,*a Rui Lin Nie, no date)- Only Cucumis species are composed of the extremely rare component Cucurbitacin A.

The Cucurbitaceae family has various plants that contain cucurbitacin B. It protects against CCl4-induced hepatotoxicity and even reverses its effects in certain cases. It also has potent anti-inflammatory & antidiabetic properties.The most common form of cucurbitacin is cucurbitacin D, which differs from cucurbitacin B by lacking an acetyl group at the 25-OH. Cucurbitcin E (aelaterin), dihydrocucurbitacin E, and dihydrocucurbitacin E 2-glucoside were isolated from the roots of *Wilbrandiae bracteata*. Two compounds, isocucurbitacin E and 23, 24-dihydroisocucurbitacin E, were identified from the *Cucumis phrophetarum* plant (Cucurbitaceae). *Elaeocarpus dolichostylus* (Elaeocarpaceae) yielded cucurbitacin F, which was proven to be cytotoxic against human tumour cells. The stereochemistry difference at C-24 between cucurbitacins G and H has not been verified, yet the molecular structures are identical in nature. *Wilbrandiae bracteata* (Cucurbitaceae) is a plant whose roots have recently been observed for the cucurbitacins G and H, as well as 3-epi-isocucurbitacin G. Cucurbitacin I (elatericin B) and hexanorcucurbitacin I were first isolated from *Ecballium elaterium*. The cytotoxicity of cucurbitacin L (23,24-dihydrocucurbitacin I, isolated from *Catullus colocynthis* was similar to that of cucurbitacin I, but cucurbitacin I was more potent.Both Cucurbitacin J and Cucurbitacin K were discovered in *Iberis amara* (Brassicaceae).The only real distinction between them is the orientation of the 24th hydroxyl group.The cytotoxicity of Cucurbitacins O, P, and Q isolated from *Brandegea bigelovii* (Cucurbitaceae) against Eagle's KB human cancer of the nasopharynx was evaluated. Since Cucurbitacin R was identified as 23,24-dihydrocucurbitacin D, the latter's characterization has been transferred to the Cucurbitacin D class. Cucurbitacin S was extracted from *Bryonia dioica*.

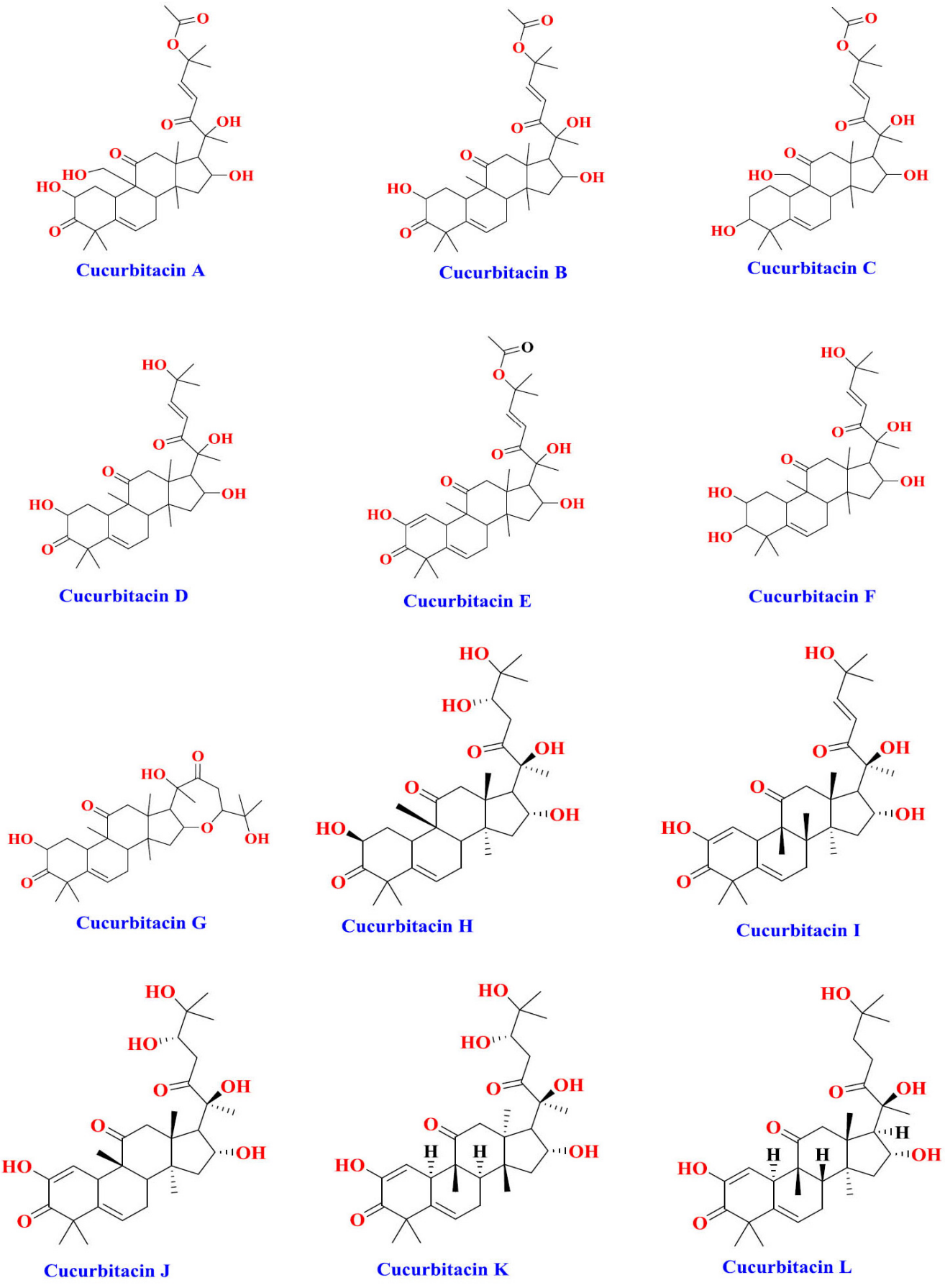

Fig. 3 : Structure of some common Cucurbitacins

However, the precise configuration of this hydroxyl group has not yet been established (Charan and Haryana, 2019). A specific subset of Cucurbitacins is referred to as momordicosides, a nomenclature derived from their presence in Momordica charantia. No other plant species have been found to contain momordicosides. A shared characteristic of momordicosides is the presence of an aldehyde group resulting from the oxidation of C19.

Cucurbitacins are created from a fundamental cucurbitane ring skeleton, which is a triterpene hydrocarbon with the IUPAC name 19 (10-9β)-abeo-5α lanostane. Through modifications involving groups containing oxygen and double bonds, many Cucurbitacins with unique characteristics are produced(Stuppner, Müller and Wagner, 1991). In Cucurbitacin glycosides, the saccharide linkage is typically observed at the C-2 position, specifically in the form of 2-O-β glycosides.

The majority of Cucurbitacins typically exhibit a crystalline structure or exist in the form of needle-like structures when maintained at room temperature, with the exception of Cucurbitacin H, which is characterized as an amorphous solid. The solubility of most Cucurbitacins is observed in petroleum ether, chloroform, benzene, ethyl acetate, methanol, and ethanol, while they exhibit insolubility in ether. These substances exhibit limited solubility in aqueous solutions. Cucurbitacins typically exhibit absorption maxima within the UV light spectrum, specifically ranging from 228 to 234 nm (Delgado-Tiburcio *et al*., 2022). This study aims to investigate the molecular formulas and characteristics of all documented crystalline structures and mentioned in Table: 1. the aglycone component of most Cucurbitacins has notable solubility in moderately polar solvents such as chloroform. The utilisation of a partition between water and chloroform is a conventional method employed for the purification of Cucurbitacins obtained from plant extracts, which have been initially extracted using methanol.

Chromatographic techniques, such as open-column chromatography on silica gel, alumina, or florisil, as well as thin layer chromatography, have been employed in the purification process of Cucurbitacins from plant extracts (Patel *et al*., 2020).

The extraction of Cucurbitacins has also been attempted by the process of maceration, involving the combination of plant material with equal amounts of absolute ethanol and lead acetate. The filtrate is subjected to filtration, followed by the addition of an aqueous solution of potassium dihydrogen phosphate to induce the precipitation of lead. The Cucurbitacins are extracted from the aqueous phase using the chloroform solvent in a triple extraction process, followed by concentration of the resulting extract at a temperature of 70 degrees Celsius (Alara *et al*., 2018).

Table 1 : Plant Source, Molecular formulae and physical properties of Cucurbitacins (CBT)

CBT	Plant Source *(B. Names & C. Names)*	Physical State	Emp. Formula	UV-λ_{max}. (ethanol)	Molecular Mass	Melting Point
A	*Trichosanthes cucumerina.* (Snake gourd)	Crystals	$C_{32}H_{46}O_9$	229,290	574.314	207-208°C
B	*Trichosanthes cucumerina.* (Snake gourd), *Cucurbita andreana* (Buttercup squash). *Wilbrandiae bracteata.* *Luffa operculata.* (Sponge Cucumber)	Crystals	$C_{32}H_{46}O_8$	-	558.3192	184-186°
C	*Cucumis sativus*(cucumber)	Needles	$C_{32}H_{48}O_8$	231,298	560.3348	207-207.5°C
D	*Trichosanthes kirilowii* (Chinese Cucumber) *Cucurbita andreana* (Winter Squash)	Needles	$C_{30}H_{44}O_7$	230	516.3087	151-153°C
E	*Bacopa monnieri* (Water hyssop) *Cucurbita andreana* (Winter Squash) *Citrullus colocynthis*. (Bitter cucumber)	Crystals	$C_{32}H_{44}O_8$	234,268	556.3035	234.5°C
F	*Elaeocarpus dolichostylus*	Needles	$C_{30}H_{46}O_7$	-	518.3243	244-245°C
G	*Roots of Wilbrandiae bracteata*	Crystals	$C_{30}H_{52}O_9$	-	534.3192	150-152°C
H	*roots of Wilbrandiae bracteata*	Amorphous solid	$C_{30}H_{46}O_8$	-	534.3192	150-152°C
I	*Momordica balsamina L* (Balsam pear). *Cayaponia tayuya.* (Tayuya) *Cucurbita andreana.* (Winter Squash) *Citrullus colocynthis*. (Bitter cucumber)	Needles	$C_{30}H_{42}O_7$	234,266	514.293	148-148.5°C
J	*Iberis amara*	Crystals	$C_{30}H_{44}O_8$	270	532.3036	200-202°C
K	*Trichosanthe stricuspidata*	Needles	$C_{30}H_{44}O_8$	270	532.3036	200-202°C
L	*Bryonia dioica*	Needles	$C_{30}H_{44}O_7$	270	516.3087	137-142°C
O	*Wilbrandiae bracteata,* *Picrorhiza kurrooa,* *Brandegea bigelovii*	-	$C_{30}H_{46}O_7$	-	518.3243	122-127°C
P	*Picrorhiza scrophulariaeflora*	-	$C_{30}H_{48}O_7$	-	520.3399	-
Q	*Cayaponia tayuya.* (Tayuya)	-	$C_{32}H_{48}O_8$	-	560.3348	-
R*	*Cayaponia tayuya.* (Tayuya)		Dihydrocucurbitacin D			
S	*Bryonia dioica*	-	$C_{30}H_{42}O_6$	-	498.298	-
T	*Citrullus colocynthis*					

* Cucurbitacin R is actually 23, 24-dihydrocucurbitacin D.** Cucurbitacin D is also called as (Elatericin A)

A previously documented method has been employed to conduct a confirmatory test for the detection of Cucurbitacins in extracts and fractions. In this procedure, the sample is combined with triphenyltetrazolium chloride. The presence of Cucurbitacins is shown by the occurrence of a red precipitate of formazin (Attar and Ghane, 2018). Table 2. presents a compilation of the solvent mixes used in thin layer chromatography as documented in various academic sources Frequently (Njoroge and Newton, 1994; Bartalis and Halaweish, 2005; Chen *et al*., 2012) (Metcalf, Metcalf and Rhodes, 1980; Gorski *et al*., 2022), the consistent existence of α, β unsaturated ketones, whether located in the side chain or in the A-ring of the cucurbitane skeleton, leads to the manifestation of UV-absorbance at 230 nm in the majority of Cucurbitacins. However, numerous other Cucurbitacin analogues do not exhibit UV-absorbance over 210 nm (Bajcsik, Pfab and Pietsch, 2017). A chromatographic system, namely reversed phase high performance thin layer chromatography (HPTLC), has been documented for the quantification of Cucurbitacins. This system employs a mobile phase composed of ethyl acetate and benzene in a ratio of 25:75 (Chanda *et al*., 2020). The examination of various Cucurbitacin analogues, which are frequently present in plants, has been extensively reported utilizing a high-performance liquid chromatography (HPLC) technique. This chromatographic method involves gradient elution of acetonitrile in water (Sturm and Stuppner, 2000). The extraction and isolation process of Cucurbitacins from plants is outlined in Fig. 3.

Table 2 : Solvent Ratios reported to be used for Cucurbitacins

Solvent	Ratios
Chloroform: Methanol	95:05
Toluene: Ethyl acetate	40:60
Chloroform: Ethanol	95:05
Ether: Hexane: Methanol	70:30:05
Methanol: Water	55:45

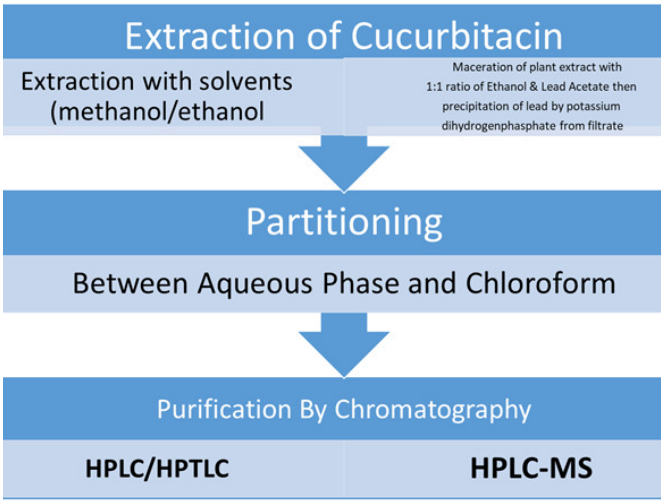

Fig. 3: Layout of Isolation process of Cucurbitacins

Bioactivity

Numerous studies have been conducted to investigate the various impacts of Cucurbitacins, including their cytotoxic, hepatoprotective, cardiovascular, and antidiabetic properties (Attar *et al.*, 2022). This review cumulates diverse biological activities corresponding to Cucurbitacins, along with their potential mechanisms of action.

Anti-diabetic activity

The *Momordica* fruits contain cucurbitane triterpenoids, which have been observed to possess antidiabetic and anticancer properties. These findings suggest that these compounds could potentially serve as a promising class of medicines for the treatment of diabetes and obesity (Rahman *et al.*, 2022). The potential mechanism for the stimulation of GLUT4 translocation by triterpenoids from *M. charantia* is hypothesized to include the 5'-adenosine monophosphate-activated protein kinase (AMPK) pathway. The activation of AMPK holds particular relevance in the context of diabetes and obesity due to its ability to enhance fatty acid oxidation, suppress lipid synthesis, and perhaps enhance insulin sensitivity (Sang, Dhakal and Lee, 2021). Significant hypoglycemic and antihyperglycemic actions have been seen in an analogue of 23, 24-dihydrocucurbitacin F derived from *Hintonia latiflora*, as reported in the literature. The potential mechanism responsible for the antihyperglycemic effect may involve the stimulation of insulin secretion and the modulation of hepatic glycogen metabolism (Kim *et al.*, 2018).

Adipocytes, skeletal myoblast cells, and hepatocytes share biochemical properties in which many cucurbitane triterpenoids activate AMPK (Adenosine monophosphate activated protein kinase) and AMPK signaling. When it comes to hunger regulation and metabolic impacts, AMPK was found to be a key mediator in the endocrine system. Metformin, a hypoglycemic drug, stimulated the p-AMPK in NCI-H716 cells but had no direct effect on GLP-1 (glucagon-like peptide-1) secretion. When metformin was infused intra-duodenaly, it activated AMPK in the duodenal mucosa, which in turn helped reduce glucose levels in a mouse model of obesity and diabetes. Our team, however, found that p-AMPK expression varied depending on whether or not the cells were differentiated. In the undifferentiated state, NCI-H716 cells expressed conserved p-AMPK, but in the differentiated state, this p-AMPK was drastically down regulated. Our data demonstrated that Cucurbitacin B enhanced GLP-1 secretion in a dose- and time-dependent manner in a differentiated NCI-H716 cell line (Kim *et al.*, 2018).

Anti-inflammatory activity

Cucurbitacin analogues, including Cucurbitacin R and DHCB, have been documented to have anti-inflammatory properties. Their mechanism of action involves the suppression of tumour necrosis factors (TNF)-α, as well as other (Dai *et al.*, 2023)mediators such as nitric oxide synthase-2 and cyclooxygenase-2 .Previous studies have indicated that cucurbitacins B, D, E, and I had inhibitory properties against cyclooxygenase (COX)-2 enzymes, while exhibiting no discernible impact on COX-1 enzymes (Jayaprakasam, Seeram and Nair, 2003). The hypothesised mechanism of action for the anti-inflammatory effects of 23, 24-dihydrocucurbitacin D (DHCD) involves the inhibition of NF-κ B activation, leading to the suppression of nitrous oxide emission. The potential of DHCD to serve as a viable candidate for evaluation as a promising anti-inflammatory agent can be considered (Wang *et al.*, 2008).

Anti-tumor activity

There is a scarcity of information regarding the molecular mechanisms underlying the involvement of Cucurbitacins, which has impeded progress in the use of Cucurbitacins as potential anti-cancer drugs. In the context of cancer, the activities of Cucurbitacin primarily entail inhibiting growth, causing cell cycle arrest during the G2/M phase, and inducing death in cancer cells (Attar *et al.*, 2022). The anti-tumorigenic properties of Cucurbitacins are attributed to their ability to disrupt the Janus kinase/Signal Transducer Activator of Transcription 3 (JAK/STAT3) signaling pathway, which is essential for cell proliferation and maintenance. Previous studies have documented the inhibitory effects of Cucurbitacin I on phosphotyrosine STAT3 in both cancer cell lines and malignant lung cells in humans. Although Cucurbitacin B, E, and I function through the suppression of both JAK2 and STAT3 activation, Cucurbitacin A and I specifically inhibit JAK2 and STAT3, respectively. According to reports, the inhibition of tumour angiogenesis by Cucurbitacin E is attributed to its ability to inhibit the JAK-STAT3 and mitogen activated protein kinases (MAPK) signaling pathways (Iqbal *et al.*, 2020). The anti-proliferative actions of Cucurbitacin B and E have been ascribed to their interference with the actin cytoskeleton (Zhao *et al.*, 2016). The correlation between the disruption of the F-actin cytoskeleton and the anti-proliferative activity has been observed. There has been a proposal suggesting that the co-administration of Cucurbitacin B and docetaxel could potentially enhance the therapeutic outcomes by inhibiting STAT3 in individuals diagnosed with laryngeal cancer(Attar and Ghane, 2018).The presence of Cucurbitacin C in cucumber fruits has been discovered to potentially confer anti-tumor properties (Horie *et al.*, 2007). According to the available study, there is evidence suggesting that cucurbitacin B demonstrates anti-cancer properties by decreasing telomerase activity. This inhibition is achieved by reducing the expression levels of two key factors involved in telomerase function, namely human telomerase reverse transcriptase and c-Myc, within breast cancer cells (Dai *et al.*, 2023).

Anti-atherosclerotic activity

Previous studies have documented the inhibitory effects of glycosidic forms of Cucurbitacin B and E on lipid oxidation products, specifically malonaldehyde (MDA) and 4-hydroxynonenal (4-HNE) (Karimi *et al.*, 2010) (Tannin-Spitz, Bergman and Grossman, 2007). These results provide additional support for the therapeutic potential of Cucurbitacins in the treatment of artherosclerosis, a condition characterised by the change of lipoproteins through the involvement of MDA and 4-HNE(Bhusal, 2014).

Miscellaneous activity

According to reports, the level of Cucurbitacin C concentration in the foliage of Cucumis sativus is a significant factor in determining resistance to spider mites. This may be attributed to its potential role as an antagonist of the ecdysteroid receptor in spider mites. The compound known as Cucurbitacin D exhibits a structural similarity to steroids and has the potential to have therapeutic effects by inhibiting the activity of Na^+/K^+-ATPase. The preventative and radical scavenging antioxidant properties of Cucurbitacins have been documented in previous studies. Furthermore, it has been documented that Cucurbitacins exhibit adaptogenic properties. Previous studies have documented the ability of Cucurbitacins to enhance capillary permeability in rats and exhibit antifertility properties in female mice (Almeida, Rao and Matos, 1992). According to existing literature, it has been documented that cucurbitacin D exhibits inhibitory effects on ovulation in mice. Cucurbitacins have been observed to serve as allomones, playing a protective role in numerous plant species. The literature has documented the role of Cucurbitacins, specifically Cucurbitacin B, E, D, I, and L, as anti-feedants for some insects and birds, as well as their function as kairomones for diabroticite beetles. According to the paper, the mechanism of action of Cucurbitacins involves the activation of Cuc receptors present on the maxillary palpi. The diabroticite beetles' searching behaviour is inhibited, leading to the manifestation of a compulsive feeding behaviour. The potential efficacy of Cucurbitacin B and D in the management of diabrotic beetles is an intriguing avenue for investigation(Bruno *et al.*, 2023).

Toxicity Reports:

The examination of substitution patterns on different Cucurbitacins offers valuable insights towards discerning and delineating the contrasting harmful effects and therapeutic properties of these compounds.Cucurbitacins are known to possess significant toxicity, and there is ample documentation of severe poisoning and fatalities in sheep and calves who have ingested bitter fruits from the *Cucumis* and *Cucurbita* genera. Based on a limited number of in-vivo toxicity reports, it has been shown that the toxicity range of Cucurbitacins is between 2 and 12.5 mg/kg. A report documenting the toxicity of Cucurbitacin R at doses of 375 mg/Kg p.o and 67 mg/kg i.p has been published. The toxicity of Cucurbitacins has been observed to be enhanced by the presence of a double bond at C-23 and an acetyl group at C-25. The biological activity of cucurbitacin was discovered to be in close proximity to its hazardous threshold, hence diminishing the likelihood of its utilisation as a biological agent. The pronounced acrimony exhibited by Cucurbitacins should dissuade individuals from subjecting themselves to significant amounts of these substances. However, there have been reported cases of poisonings following the ingestion of plants belonging to the Cucurbitaceae family.Cucurbitacins have been identified as potentially lethal compounds when ingested in the fruits of *Luffa cylindrica* (L.). In a study conducted on a Japanese population, it was observed that those who consumed bottle gourd, including Cucurbitacin D, experienced gastrointestinal complaints. The toxicity of Cucurbitacins C, D, E, and I has been evaluated, and it has been determined that these compounds are highly dangerous. It is imperative to refrain from consuming plants containing Cucurbitacins C, D, E, and I, since their ingestion can result in severe illness or fatality (Jian *et al.*, 2005). The manifestation of toxic symptoms exhibits variation among different animal species employed in the experimental setting, as well as in relation to the method of drug administration and the dosage delivered (Dai *et al.*, 2023)

Conclusion

Cucurbitacins have tremendous pharmacological promise despite being highly toxic chemicals. Many of their biological effects occur at or near their toxic dose threshold. The therapeutic benefit of Cucurbitacins against inflammation, cancer, atherosclerosis, and diabetes

outweighs their toxicity. The potential for these chemicals to be used as effective therapeutic agents should not be overshadowed by reports of their toxicity. Potentially useful lead compounds for future study could be derived from the chemical modification of different functional groups of these compounds in order to lessen their hazardous effects. The poisonous nature of Cucurbitacin analogues and their efficacy against tumour cell lines have been thoroughly investigated. The Cucurbitaceae family of plants has been given a lot of attention in recent years because to the recognition of their potential in the empirical management of diabetes through medication discovery from plants. Triterpenoids, Cucurbitacins, and similar substances called momordicosides can be found in abundance in the genus Momordica, which contains many of the herbal plants traditionally used to treat diabetes. The roots and fruits of these plants are where you're most likely to find them. Considering the toxicity of these substances to mammals, it would be useful to learn more about how they are absorbed, distributed, metabolized, and excreted by the body. The generation of scientifically accurate data regarding the efficiency of these unexplored therapeutic leads from nature could be of enormous value.

References

Almeida, F.R.C., Rao, V.S.N. and Matos, M.E.O. (1992). 'Antiinflammatory, antitumour and antifertility effects in rodents of two nor-cucurbitacin glucosides from Wilbrandia species', *Phytotherapy Research*, 6(4): 189–193.

Attar, U.A. *et al.* (2022). Simultaneous detection of anticancer compounds (Cucurbitacin I, B and E) and some pharmacological properties of Indian Blastania species, *South African Journal of Botany*, 147: 871–881.

Attar, U.A. and Ghane, S.G. (2018). Optimized extraction of anti-cancer compound – cucurbitacin I and LC–MS identification of major metabolites from wild Bottle gourd (*Lagenaria siceraria* (Molina) Standl.), *South African Journal of Botany*, 119: 181–187.

Bajcsik, N., Pfab, R. and Pietsch, J. (2017). Simultaneous determination of cucurbitacin B, E, I and E-glucoside in plant material and body fluids by HPLC–MS, *Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences*, 1052: 128–134.

Bartalis, J. and Halaweish, F.T. (2005). Relationship between cucurbitacins reversed-phase high-performance liquid chromatography hydrophobicity index and basal cytotoxicity on HepG2 cells, *Journal of chromatography. B, Analytical technologies in the biomedical and life sciences*, 818(2): 159–166.

Bhusal, A. (2014). Evaluation of Antioxidative and Antidiabetic Activity of Bark of Holarrhena Pubescens Wall', *Journal of Clinical and Diagnostic Research*, 8(9): 5–9.

Bruno, P. *et al.* (2023). Sequestration of cucurbitacins from cucumber plants by Diabrotica balteata larvae provides little protection against biological control agents., *Journal of pest science*, 96(3): 1061–1075.

Chanda, J. *et al.* (2020). Determination of cucurbitacin E in some selected herbs of ayurvedic importance through RP-HPLC, *Journal of Ayurveda and Integrative Medicine*, 11(3): 287–293.

Charan, C. and Haryana, S. (2019). The Merck index : an encyclopedia of chemicals, drugs, and biologicals Links to this item Find a copy in the library Enter your location : Chaudhary Charan Singh Haryana Agricultural Tamil Nadu Veterinary and Animal Science Genre / Form : Material Type', pp. 5–8.

Chen, X. *et al.* (2012). Biological activities and potential molecular targets of cucurbitacins: A focus on cancer, *Anti-Cancer Drugs*, 23(8): 777–787.

Çiçek, S.S. (2022). Momordica charantia L.-Diabetes-Related Bioactivities, Quality Control, and Safety Considerations, *Frontiers in Pharmacology*, 13(May): 1–9.

Dai, S. *et al.* (2023). Cucurbitacin B: A review of its pharmacology, toxicity, and pharmacokinetics, *Pharmacological Research*, 187(September 2022).

Delgado-Tiburcio, E.E. *et al.* (2022). Pharmacokinetics and Biological Activity of Cucurbitacins, *Pharmaceuticals*, 15(11).

Gorski, P.M. *et al.* (2022). Rapid TLC and HPLC Quantification of Cucurbitacin C in Cucumber Cotyledons, *HortScience*, 21(4), pp. 1034–1036.

Gry, J. and Andersson, H.C. (2006) *Cucurbitacins in plant food*, *TemaNord*.

Horie, H. *et al.* (2007) Cucurbitacin C-Bitter principle in cucumber plants, *Japan Agricultural Research Quarterly*, 41(1): 65–68.

Iqbal, M.A. *et al.* (2020). Design, synthesis, and biological evaluation of imidazopyridine-linked thiazolidinone as potential anticancer agents, *Archiv der Pharmazie*, 353(10).

Jayaprakasam, B., Seeram, N.P. and Nair, M.G. (2003). Anticancer and antiinflammatory activities of cucurbitacins from Cucurbita andreana, *Cancer Letters*, 189(1): 11–16.

Jian, C.C. *et al.* (2005) 'Cucurbitacins and cucurbitane glycosides: structures and biological activities', *Natural product reports*, 22(3): 386–399.

Jian Chao Chen, a Ming Hua Chiu,*a Rui Lin Nie, a G.A.C. and S.X.Q. (no date) *Cucurbitacins and cucurbitane glycosides: structures and biological activities - PubMed*. Available at: https://pubmed. ncbi.nlm. nih. gov/16010347/ (Accessed: 25 July 2023).

Karimi, E. *et al.* (2010). Evaluation of *Crocus sativus* L. stigma phenolic and flavonoid compounds and its antioxidant activity', *Molecules*, 15(9): 6244–6256.

Kaushik, U., Aeri, V. and Mir, S.R. (2015). Cucurbitacins – An insight into medicinal leads from nature, *Pharmacognosy Reviews*, 9(17): 12.

Kim, K.H. *et al.* (2018). Cucurbitacin B Induces hypoglycemic effect in diabetic mice by regulation of AMP-activated protein kinase alpha and glucagon-like peptide-1 via bitter taste receptor signaling, *Frontiers in Pharmacology*, 9(SEP): 1–13.

Kupchan, S.M., Meshulam, H. and Sneden, A.T. (1978). New cucurbitacins from Phormium tenax and Marah oreganus, *Phytochemistry*, 17(4): 767–769.

Metcalf, R.L., Metcalf, R.A. and Rhodes, A.M. (1980). Cucurbitacins as kairomones for diabroticite beetles, *Proceedings of the National Academy of Sciences of the United States of America*, 77(7 II): 3769–3772.

Njoroge, G.N. and Newton, L.E. (1994). Edible and Poisonous Species of Cucurbitaceae in the Central Highlands of Kenya, *Journal of East African Natural*

History, 83(2): 101–115.

Patel, S.B. *et al.* (2020). Efficient extraction of cucurbitacins from *Diplocyclos palmatus* (L.) C. Jeffrey : Optimization using response surface methodology, extraction methods and study of some important bioactivities, *Scientific Reports*, pp. 1–12.

Patel, S.B. and Ghane, S.G. (2021). Phyto-constituents profiling of Luffa echinata and in vitro assessment of antioxidant, anti-diabetic, anticancer and anti-acetylcholine esterase activities, *Saudi Journal of Biological Sciences*, 28(7): 3835–3846.

Rahman, M.M. *et al.* (2022). 'Exploring the plant-derived bioactive substances as antidiabetic agent: An extensive review', *Biomedicine & Pharmacotherapy*, 152: 113217.

Sakamura, S. (1988). Bitterness and Structure Relationship of the Triterpenoids from Ganoderma lucidum (Reishi) group at C-3 by the', 52(7): 1791–1795.

Sang, J., Dhakal, S. and Lee, Y. (2021). Cucurbitacin b suppresses hyperglycemia associated with a high sugar diet and promotes sleep in drosophila melanogaster, *Molecules and Cells*, 44(2): 68–78.

Stuppner, H., Müller, E.P. and Wagner, H. (1991). Cucurbitacins from Picrorhiza kurrooa, *Phytochemistry*, 30(1): 305–310.

Sturm, S. and Stuppner, H. (2000). Analysis of cucurbitacins in medicinal plants by high-pressure liquid chromatography-mass spectrometry, *Phytochemical Analysis*, 11(2): 121–127.

Tannin-Spitz, T., Bergman, M. and Grossman, S. (2007). Cucurbitacin glucosides: Antioxidant and free-radical scavenging activities, *Biochemical and Biophysical Research Communications*, 364(1): 181–186.

Ven Subbiah, 105 Bella Vista Dr., Edenton, N.C. 27932 (1996) 'Method of isolating cucurbitacin'.

Wang, X. *et al.* (2008). Enhancing anti-inflammation activity of curcumin through O/W nanoemulsions, *Food Chemistry*, 108(2): 419–424.

Zhao, W. *et al.* (2016). Development and validation of a UPLC-MS/MS method for the determination of cucurbitacin B in rat plasma and application to a pharmacokinetic study, *Biomedical Chromatography*, 30(4): 503–507.