

Cucurbitacins – An insight into medicinal leads from nature

Ujjwal Kaushik, Vidhu Aeri, Showkat R. Mir

Department of Pharmacognosy and Phytochemistry, Phytochemistry Research Laboratory, Faculty of Pharmacy, New Delhi, India

Submitted: 05-03-2014

Revised: 27-03-2014

Published: 05-05-2015

ABSTRACT

Cucurbitacins which are structurally diverse triterpenes found in the members of Cucurbitaceae and several other plant families possess immense pharmacological potential. This diverse group of compounds may prove to be important lead molecules for future research. Research focused on these unattended medicinal leads from the nature can prove to be of immense significance in generating scientifically validated data with regard to their efficacy and possible role in various diseases. This review is aimed to provide an insight into the chemical nature and medicinal potential of these compounds exploring their proposed mode of action, probable molecular targets and to have an outlook on future directions of their use as medicinal agents.

Key words: Cucurbitaceae, cucurbitacin, triterpenoids

INTRODUCTION

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.^[1] 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, Datisceae, Primulaceae, Rubiaceae etc., The diversity of cucurbitacins lies in variety of its side chain derivatives that contribute to their disparate pharmacological actions.^[2,3] The bitter taste of plant species like cucumber have been attributed to the presence of cucurbitacins. 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.^[4] 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.

OCCURRENCE

Cucurbitacins are found in many cucurbitaceous plants. They are most common in species of the *Bryonia*, *Cucumis*, *Cucurbita*, *Luffa*, *Echinocystis*, *Lagenaria* and *Citrullus*. The plants of genera *Momordica* contain a special group of Cucurbitacins called momordicosides. The level of Cucurbitacins varies between tissues. They may be concentrated in fruits and roots of mature plants. In fruits where Cucurbitacins are produced, their highest concentration is achieved on maturity. Seeds generally contain very low concentration of Cucurbitacins. Cucurbitacin producing plants have also been identified outside the cucurbitaceae in the members of Scrophulariaceae, Begoniaceae, Primulaceae, Liliaceae, Tropaeolaceae and Rosaceae. The seeds of certain cruciferous plants, like *Iberis* species and *Lepidium sativum* also contain cucurbitacins.^[4] It is reported that Cucurbitacins are formed *in situ* and are not transported to other parts of the plant.^[5] The distribution of Cucurbitacins among various families of plant kingdom has been depicted in [Figure 1].

Address for correspondence:

Dr. Vidhu Aeri, Department of Pharmacognosy and Phytochemistry, Faculty of Pharmacy, Jamia Hamdard, New Delhi - 110 062, India.
E-mail: vidhuaeri@yahoo.com

Access this article online

Quick Response Code:



Website:

www.phcogrev.com

DOI:

10.4103/0973-7847.156314

CHEMISTRY AND CATEGORIES OF CUCURBITACINS

All cucurbitacins contain a basic 19-(10 \rightarrow 9 β)-abeo--10 α -lanost-5--ene ring skeleton. A common feature among all compounds in the category of Cucurbitacins is the presence of 5,(6)--double

bond. The difference of Cucurbitacins from steroidal nucleus lies in the fact that in basic structure of Cucurbitacins a methyl group is located at C-9 rather than C-10.^[6] Most of the Cucurbitacins are tetracyclic, but some representatives have an extra ring due to formal cyclization between C--16 and C--24 as in cucurbitacins S and T.^[7] The Cucurbitacins differ from most of the other tetracyclic triterpenes by being highly unsaturated and contains numerous keto-, hydroxyl-, and acetoxy--groups.^[8] Certain Cucurbitacins have been discovered in the form of glycosides and some of them lack C--11 carbonyl function.^[9] Chemically, Cucurbitacins are ranked according to presence of various functional groups on rings A and C, diversity in side chain and stereochemical considerations.^[10] The structural composition of following Cucurbitacins are known and have been designated by the letters: A, B, C, D, E, F, G, H, I, J, K, L, O, P, Q, R and S [Figure 2]. The term --“Cucurbitacin”-- refers to group of Cucurbitacins along with their glycosidic forms mentioned above, including those forms listed before.^[11] Cucurbitacin G and H have same structures but differ from each other in the configuration of the hydroxyl group at position 24 which is not yet established.^[12] Cucurbitacin R was demonstrated to be 23, 24-dihydrocucurbitacin D (DHCD) hence, its description has been moved to the group of Cucurbitacin D.^[13] Similarly Cucurbitacin J and K differ from each other only in the configuration of hydroxyl group at position 24 which is yet to be determined.^[14] A special group of Cucurbitacins are called as momordicosides, named after their occurrence in *Momordica charantia*. Momordicosides have never been identified in any other plant species. The common feature of momordicosides is that C₁₉ has been oxidized to an aldehyde group.

IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES

Cucurbitacins are derived from basic cucurbitane ring skeleton which is a triterpene hydrocarbon (IUPAC name 19 (10-9 β)-abeo-5 α -lanostane, which on modification by groups containing oxygen and double bonds produce manifold Cucurbitacins with distinctive features.^[15] The saccharide linkage

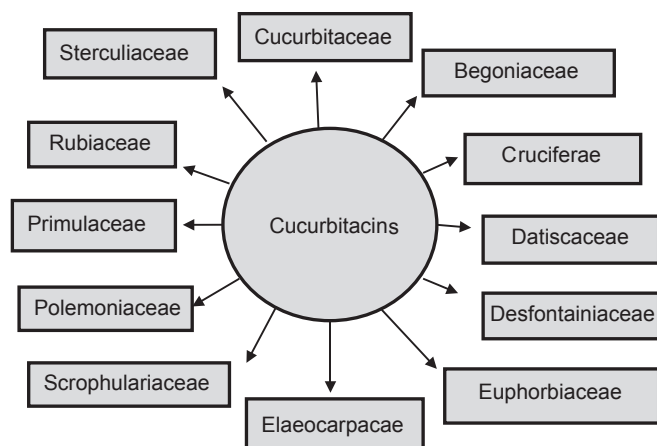


Figure 1: Occurrence of Cucurbitacins in various plant families

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.^[16] The molecular formulae and properties of all the known crystalline Cucurbitacins are given in Table 1.

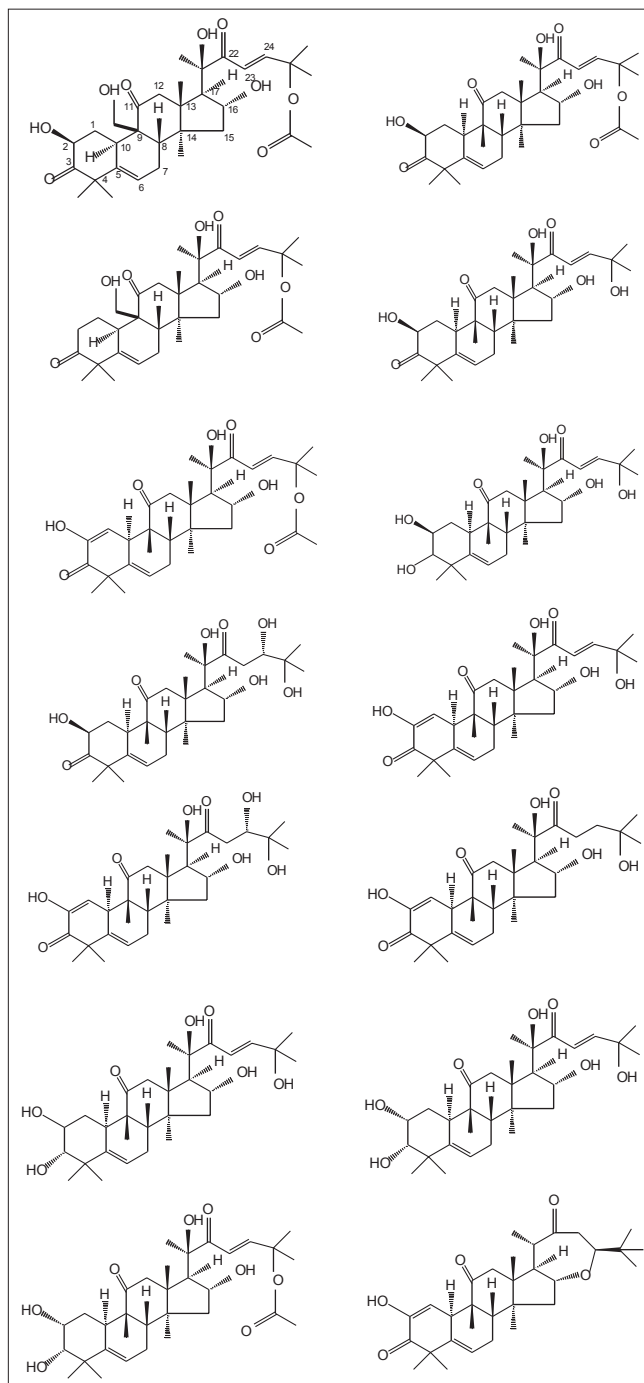


Figure 2: Chemical structures of cucurbitacin analogs

ANALYSIS OF CUCURBITACINS

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. 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.^[6,8] 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.^[17]

A confirmatory test to determine the presence of Cucurbitacins in extracts and fractions has been reported whereby the sample is mixed with triphenyltetrazolium chloride. The occurrence of red precipitate of formazin indicates presence of Cucurbitacins.^[18] The thin layer chromatographic solvent mixtures reported in literature have been compiled in Table 2.^[17,19-24] 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.^[25] 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.^[26] 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.^[19,27] A general scheme for extraction and isolation of cucurbitacins from plants is summarized in Figure 3.

BIOACTIVITY

Various biological activities attributed to Cucurbitacins with probable mechanism of action (s) have been summarized in Table 3.

Anti-inflammatory activity

Cucurbitacin analogues viz. Cucurbitacin R and DHCB have been reported to possess anti-inflammatory potential and their action is reported to be mediated by inhibition of tumor necrosis factors (TNF)- α and other mediators of inflammation such as nitric-oxide synthase-2 and cyclo-oxygenase-2.^[45,46] Cucurbitacins B, D, E and I have been reported to inhibit cyclooxygenase (COX)-2 enzymes with no effect on COX-1 enzymes.^[34] The anti-inflammatory response of 23, 24-dihydrocucurbitacin D (DHCD) have been hypothesized to get mediated through blocking of NF- κ B activation thereby obstructing the release of nitrous oxide. DHCD can be taken up as probable lead and appraised for providing a promising anti-inflammatory agent.^[36,37]

Antitumor activity

Very less information is available on the role of Cucurbitacins at molecular level which has led to slow advancement in the development of Cucurbitacins as anti-cancer agents.^[4] In relation to cancer, targets of Cucurbitacin actions involve growth inhibition, arrest of cell cycle at G2/M phase and induction of apoptosis in cancer cell.^[47] The mechanisms underlying anti-tumorigenic potentials of Cucurbitacins involve inhibition of Janus kinase/Signal Transducer Activator of Transcription 3 (JAK/STAT3) signaling pathway whose activation is required for the proliferation and sustainment of cells.^[28-30] The role of Cucurbitacin I in suppressing phosphotyrosine STAT3 in cancer cell lines and cancerous lung

Table 1: Molecular formulae and physical properties of cucurbitacins

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	-

cells of humans has been reported.^[48] Although Cucurbitacin B, E, and I act by inhibiting the activation of both JAK2 and STAT3, Cucurbitacin A and I acts by inhibition of only JAK2 and STAT3 respectively.^[49] It has been reported that Cucurbitacin E inhibited tumor angiogenesis by inhibiting JAK-STAT3 and mitogen

activated protein kinases (MAPK)- signaling pathways.^[31] The role of interference with actin cytoskeleton has been attributed to anti-proliferative effects of Cucurbitacin B and E. The anti-proliferative activities have been correlated directly with the disruption of the F-actin cytoskeleton.^[32] It has been proposed that the combination of Cucurbitacin B with docetaxel may augment the chemotherapeutic effects by suppression STAT3 in patients with laryngeal cancer.^[47] It is expected that cucumber fruits have anti-tumor effects since they have been reported to contain Cucurbitacin C.^[50,51] It has been reported that cucurbitacin B exerts an anticancer effect by inhibiting telomerase via down-regulating both the human telomerase reverse transcriptase and c-Myc expression in breast cancer cells.^[33]

Table 2: List of TLC solvent mixtures reported in literature for cucurbitacins

Solvent system	Solvent ratio	Visualisation
Toluene: Ethyl acetate	40:60	Vanillin/orthophosphoric acid
Chloroform: Ethanol	95:5	Vanillin phosphoric acid reagent
Methanol: Water	55:45	UV 254 nm
EtOAc-C6H6	75:25	Vanillin-orthophosphate in EtOH
Ether: Hexane: Methanol	70:30:5	UV 254
Chloroform: Methanol	95:5	UV 254

TLC=Thin layer chromatography, UV=Ultra violet

Anti-atherosclerotic activity

There have been reports on Cucurbitacin B and E in glycosidic form to exhibit inhibitory effect on lipid

Table 3: Reported biological activities of cucurbitacins with probable mechanism of action

Activity	Mechanism	Reference
Antitumor activity	inhibition of Janus kinase/Signal Transducer Activator of Transcription 3 (JAK/STAT3) signaling pathway disruption of F-actin cytoskeleton	[28-31] [32] [33]
Anti-inflammatory	Down-Regulation of the c-Myc/hTERT/Telomerase Pathway and Obstruction of the Cell Cycle inhibit the expression of TNF and proinflammatory mediators such as nitric-oxide synthase-2 and cyclooxygenase-2	[34,35] [36,37]
Artherosclerosis	inhibition of NO generation through blocking NF- κ B activation Inhibition of lipid-oxidation products malonaldehyde (MAD) and 4-hydroxynonenal (4-HNE)	[38-40]
Blood circulation promoter	Inhibition of Na ⁺ /K ⁺ -ATPase	[41]
Immunosuppressant	By inhibiting expression of surface markers CD69 and CD25 required for activation of lymphocytes	[42]
Antidiabetic	Activation of AMPK pathway (a major regulatory pathway for GLUT4 translocation)	[43,44]

TNF=Tumor necrosis factor, AMPK=5'-adenosine monophosphate-activated protein kinase, GLUT4=Glucose transporter type 4

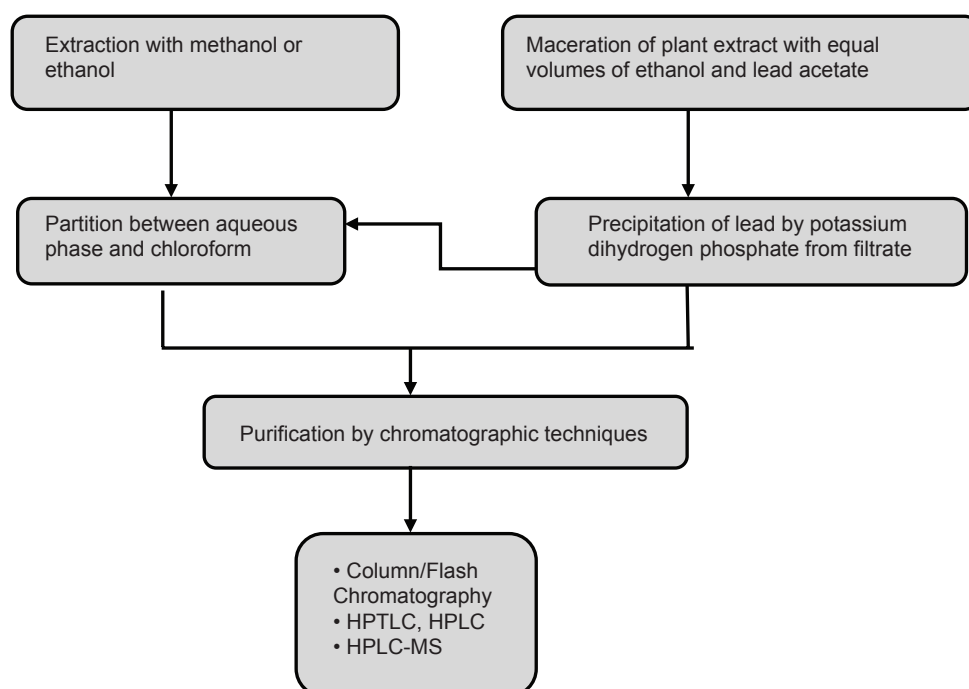


Figure 3: Scheme for extraction and isolation of cucurbitacins. HPTLC= High performance thin layer chromatography; HPLC= High performance liquid chromatography; HPLC-MS= High performance liquid chromatography- Mass spectroscopy

oxidation products like- malonaldehyde (MDA) and 4-hydroxynonenal (4-HNE).^[38,39] These reports bolster the therapeutic role of Cucurbitacins in atherosclerosis, which involves modification of lipoproteins by involvement of- MDA and 4-HNE.^[40]

Antidiabetic activity

There have been a plethora of reports on the role of Cucurbitacins for their cytotoxic, hepatoprotective, cardiovascular, and antidiabetic effects.^[36] Cucurbitane triterpenoids present in momordica fruits are noted for antidiabetic and anticancer activities, this may provide leads as a class of therapeutics for diabetes and obesity.^[52-55] The 5'-adenosine monophosphate-activated protein kinase (AMPK) pathway is suggested as a probable mechanism for the stimulation of GLUT4 translocation by triterpenoids from *M. charantia*. It is particularly interesting in relation to diabetes and obesity because activation of AMPK increases fatty acid oxidation, inhibits lipid synthesis, and can improve insulin action.^[43,44] An analogue of 23,24-dihydrocucurbitacin F from *Hintonia latiflora* has been reported to possess significant hypoglycemic and antihyperglycemic effects. The probable mechanism underlying-- antihyperglycemic effect could be stimulation of insulin release and regulation of hepatic glycogen metabolism.^[56]

Miscellaneous activity

It has been reported that the concentration of Cucurbitacin C in the leaves is an important parameter in spider mite resistance in *Cucumis sativus*, perhaps by acting as an antagonist of a spider mite ecdysteroid receptor.^[57] The steroid like resemblance of Cucurbitacin D may possess therapeutic effects via inhibition of Na⁺/K⁺-ATPase.^[41] The role of Cucurbitacins as preventive and radical scavenging antioxidant has also been reported.^[58] Cucurbitacins have also been reported to possess adaptogenic activity. Cucurbitacins have been reported to increase the rat capillary permeability and to demonstrate antifertility effects in female mice.^[25,59,60] Cucurbitacin D has been reported to inhibit ovulation in mice. There has been protective role of Cucurbitacins acting as allomones in many plant species. Role of Cucurbitacins as anti-feedants for few insects, birds and as kairomones (Cucurbitacin B, E, D, I and L) for diabroticite beetles have been reported.^[11] It is reported that Cucurbitacins act via Cuc receptors located on the maxillary palpi. They arrest the searching behavior of diabroticite beetles and produce a compulsive feeding behavior.^[24] Role of Cucurbitacin B and D in controlling diabrotic beetles can be an interesting approach.^[35,61,62]

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.^[63] 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.^[64] 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.^[65] The presence of a double bond at C-23 and acetyl group at C-25 have been found to augment the toxicity of Cucurbitacins.^[66] Cucurbitacin's strong biological activity was found to be very close to their toxic dose, which renders them unlikely to be biological agents.^[48] 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.^[8] Cucurbitacins are found to be fatal when fruits of *Luffa cylindrical* (L.) were consumed.^[67] Gastrointestinal symptoms have also been reported in a Japanese population consuming the bottle gourd, which contained Cucurbitacin D.^[68] 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.^[17] 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.^[42]

CONCLUSION

Although Cucurbitacins are highly toxic compounds and often their biological activities are close to their toxic dose level, these compounds possess immense pharmacological potential. Apart from their toxic nature cucurbitacins have been proved to possess pharmacological effectiveness against inflammation, cancer, atherosclerosis and diabetes. The reports on their toxicity must not overshadow the potential use of these compounds as potent medicinal agents. The chemical modification of various functional groups of these compounds to reduce toxic effects may provide important lead compounds for future research. Various Cucurbitacin analogues have been explored and are well established for toxic nature and their effectiveness against tumor cell lines. In modern drug discovery from medicinal plants, the importance of Cucurbitaceae species has been markedly recognized in empirical control of diabetes. It is interesting to find most of the traditionally used herbal plants against diabetes especially from genus *Momordica* are rich in triterpenoids, Cucurbitacins and related compounds momordicosides. Their occurrence is believed to be more in roots and fruits of such plants. The information on absorption, distribution, metabolism and excretion of these compounds is scarce and can be an area of exploration keeping in concern their toxic effects in mammals. Research focused on these unattended medicinal leads from the nature may prove to be of immense significance in generating scientifically validated data regarding their efficacy.

ACKNOWLEDGEMENT

Author, Ujjwal Kaushik, acknowledges the financial assistance by Council of Scientific and Industrial Research (CSIR), Government of India as SRF.

REFERENCES

- Kupchan SM, Meshulam H, Sneden AT. New cucurbitacins from *Phormium tenax* and *Marah oreganos*. *Phytochem* 1978;17:767-9.
- Stuppner H, Muller EP. Cucurbitacins with unusual side chains from *Picrohiza kurroa*. *Phytochem* 1993;37:1483-5.
- Dinan L, Whiting P, Girault JP, Lafont R, Dhadialla TS, Cress DE, *et al.* Cucurbitacins are insect steroid hormone antagonists acting at the ecdysteroid receptor. *Biochem J* 1997;327:643-50.
- Kee HC, Hongtao X. Methods of inducing apoptosis in Cancer treatment by using Cucurbitacins. US2008/0207578A1; Aug 28, 2008.
- Frohne D. A coloured Atlas of poisonous plants. London: Wolf; 1983.
- Dinan L, Harmatha J, Lafont R. Chromatographic procedure for the isolation of plant steroids. *J Chromatogr A* 2001;935:105-23.
- Gamlath CB, Leslie GA. Cucurbitacins of *Colocynthis vulgaris*. *Phytochem* 1998;27:3225-9.
- Jorn G, Inge S, Hans CA. Cucurbitacins in plant food. *TemaNord* 2006:556.
- Stuppner H, Muller EP, Wagner H. Cucurbitacins from *Picrohiza kurroa*. *Phytochem* 1991;30:305.
- Zheng CH, Fu HW, Pei YH. A new Cucurbitacin from *Bolbostemma paniculatum* Franguent. *J Asian Nat Prod Res* 2006;9:187-90.
- Subbiah. Method of isolating Cucurbitacin. US1999/5,925,356. Jul. 2011, 1999.
- Chen JC, Chiu MH, Nie RL, Cordell GA, Qiu SX. Cucurbitacins and cucurbitane glycosides: Structures and biological activities. *Nat Prod Rep* 2005;22:386-99.
- Roa MM, Meshulam H, Lavie D. Constituents of *Ecballium elaterium* XXIII: Cucurbitacins and hexanorcucurbitacin. *J Chem Soc* 1974;22:2552.
- Stecher PG. The Merc index-An encyclopedia of Chemicals and drugs. Rahway: Merck and Co., Inc; 2009. p. 296-7.
- Teuscher E, Lindequist U. Triterpene. In: *Biogene Gifte-Biologie, Chemie, Pharmakologie*, 2. Auflage. New York: Gustav Fischer Verlag, Stuttgart, Jena; 1994. p. 159-75.
- Enslin PR, Joubert FJ, Rehm S. The distribution and biogenesis of the Cucurbitacins in relation to the taxonomy of the Cucurbitaceae. *J Sci Food Agric* 1956;7:646.
- Njoroge GN, Leonard EN. Edible and poisonous species of cucurbitaceae in the central highlands of Kenya. *J East Afr Nat Hist* 1994;83:101-15.
- Lavie D, Willner D, Merenlender Z. Constituents of *Citrullus colocynthis* (L.) Schard. *Phytochem* 1964;3:51-6.
- Bartalis J, Halaweish FT. Relationship between Cucurbitacins reversed-phase high-performance liquid chromatography hydrophobicity index and basal cytotoxicity on HepG2 cells. *J Chromatogr B Analyt Technol Biomed Life Sci* 2005;818:159-66.
- Gorski PM, Jaworski A, Shannon S, Robinson RW. Cucurbit. *Genet Coop Rep* 1985;8:69.
- Oleszek WA. Chromatographic determination of plant saponins. *J Chromatogr A* 2002;967:147-62.
- Rice CA, Raymal KA, Chambliss OL, Johnson FA. Chromatographic and mass spectral analysis of Cucurbitacins of three *Cucumis sativus* cultivars. *J Agric Food Chem* 1981;29:194-6.
- Gorski PM, Jaworski A, Shannon S, Robinson RW. Rapid TLC and HPLC quantification of Cucurbitacin C in cucumber cotyledons. *Hortic Sci* 1986;21:1034-6.
- Metcalf RL, Metcalf RA, Rhodes AM. Cucurbitacins as Kairomones for diabroticite beetles. *Proc Natl Acad Sci U S A* 1980;77:3769-72.
- Lavie D, Glotter E. The Cucurbitacins, a group of tetracyclic triterpenes. *Fortschr Chem Org Naturst* 1971;29:307-62.
- Halaweish FT, Tallamy DW. Quantitative determination of Cucurbitacins by high performance thin layer chromatography. *J Liq Chromatogr* 1993;16:497-511.
- Bauer R, Wagner H. Cucurbitacinhaltige Drogen. *Dtsch Apoth Ztg* 1983;123:1313-21.
- Bowman T, Yu H, Sebti S, Dalton W, Jove R. Signal transducers and activators of transcription: Novel targets for anticancer therapeutics. *Cancer Control* 1999;6:427-35.
- Turkson J, Jove R. STAT proteins: Novel molecular targets for cancer drug discovery. *Oncogene* 2000;19:6613-26.
- Bowman T, Garcia R, Turkson J, Jove R. STATs in oncogenesis. *Oncogene* 2000;19:2474-88.
- Dong Y, Lu B, Zhang X, Zhang J, Lai L, Li D, *et al.* Cucurbitacin E, a tetracyclic triterpenes compound from chinese medicine, inhibits tumor angiogenesis through VEGFR2 mediated JAK2/STAT3 signaling pathway. *Carcinogenesis* 2010;31:2097-104.
- Duncan KL, Duncan MD, Alley MC, Sausville EA. Cucurbitacin E-induced disruption of the actin and vimentin cytoskeleton in prostate carcinoma cells. *Biochem Pharmacol* 1996;52:1553-60.
- Duangmano S, Dakeng S, Jiratchariyakul W, Suksamra A, Smith DR, Patmasiriwat P. Antiproliferative effects of cucurbitacin B in breast cancer cells: Down-regulation of the c-myc/htert/telomerase pathway and obstruction of the cell cycle. *Int J Mol Sci* 2010;11:5323-38.
- Jayaprakasam B, Seeram NP, Nair MG. Anticancer and anti-inflammatory activities of Cucurbitacins from *Cucurbita andreana*. *Cancer Lett* 2003;189:11-6.
- Escandell JM, Recio MC, Manez S, Giner RM, Cerda-Nicolas M, Gil-Benso R, *et al.* Dihydrocucurbitacin B inhibits delayed type hypersensitivity reactions by suppressing lymphocyte proliferation. *J Pharmacol Exp Ther* 2007;322:1261-8.
- Park CS, Lim H, Han KJ, Baek SH, Sohn HO, Lee DW, *et al.* Inhibition of nitric oxide generation by 23,24-dihydrocucurbitacin D in mouse peritoneal macrophages. *J Pharmacol Exp Ther* 2004;309:705-10.
- Yuan G, Mark LW, Guoqing H, Min Y, Li D. Natural products and anti-inflammatory activity. *Asia Pac J Clin Nutr* 2006;15:143-52.
- Esterbauer H. Cytotoxicity and genotoxicity of lipid oxidation products. *Am J Clin Nutr* 1993;57 Suppl 5:779S-85S; discussion 785S-86S.
- Tannin-Spitz T, Bergman M, Grossman S. Cucurbitacin glucosides: Antioxidant and free-radical scavenging activities. *Biochem Biophys Res Commun* 2007;364:181-6.
- Saba AB, Oridupa AO. Search for a novel antioxidant, anti-inflammatory/analgesic or anti-proliferative drug: Cucurbitacins hold the ace. *J Med Plants Res* 2010;4:2821-6.
- Chen RJ, Jin TR, Chen YC, Chung TY, Yang WH, Tzen JT. Active ingredients in many Chinese medicines promoting blood circulation are Na⁺/K⁺-ATPase inhibitors. *Acta Pharmacol Sin* 2010;32:141-51.
- Yaowalak U, Usaneeporn L, Weena J, Tanawan K.

- Immunosuppressive effects of Cucurbitacin B on human peripheral blood lymphocytes. *J Med Plants Res* 2010;4:2340-47.
43. Ye JM, Ruderman NB, Kraegen EW. AMP-activated protein kinase and malonyl-CoA: Targets for treating insulin resistance? *Drug Disc Today Ther Strateg* 2005;2:157-63.
 44. Iglesias MA, Ye JM, Frangioudakis G, Saha AK, Tomas E, Ruderman NB, *et al.* AICAR administration causes an apparent enhancement of muscle and liver insulin action in insulin-resistant high-fat-fed rats. *Diabetes* 2002;51:2886-94.
 45. Escandell JM, Kaler P, Recio MC, Sasazuki T, Shirasawa S, Augenlicht L, *et al.* Activated kRas protects colon cancer cells from Cucurbitacin-induced apoptosis: The role of p53 and p21. *Biochem Pharmacol* 2008;76:198-207.
 46. Ri'os JL, Giner RM, Jime'nez MJ, Wickman G, Hancke JL. A study on the anti-inflammatory activity of *Cayaponia tayuya* root. *Fitoterapia* 1990;61:275-8.
 47. Liu T, Zhang M, Zhang H, Sun C, Deng Y. Inhibitory effects of Cucurbitacin B on laryngeal squamous cell carcinoma. *Eur Arch Otorhinolaryngol* 2000;265:1225-32.
 48. Blaskovich MA, Sun J, Cantor A, Turkson J, Jove R, Sebti SM. Discovery of JSI-124 (Cucurbitacin I), a selective Janus kinase/signal transducer and activator of transcription 3 signaling pathway inhibitor with potent antitumor activity against human and murine cancer cells in mice. *Can Res* 2003;63:1270-9.
 49. Sun J, Blaskovich MA, Jove R, Livingston SK, Coppola D, Sebti SM. Cucurbitacin Q: A selective STAT3 activation inhibitor with potent antitumor activity. *Oncogene* 2005;24:3236-45.
 50. Higashio H. Value adding technologies to commodities in vegetable production. *Res J Food Agric* 2002;25:8-22.
 51. Rehm S. Bitter principles of the Cucurbitaceae. VII. The distribution of bitter principles in this plant family. *J Sci Food Agric* 1957;8:679-86.
 52. Tan MJ, Ye JM, Turner N, Hohen Behrens C, Ke CQ, Tang CP, *et al.* Antidiabetic activities of triterpenoids isolated from bitter melon associated with activation of the AMPK Pathway. *Chem Biol* 2008;15:263-73.
 53. Harinantenaina L, Tanaka M, Takaoka S, Oda M, Mogami O, Uchida M, *et al.* Momordica charantia constituents and antidiabetic screening of the isolated major compounds. *Chem Pharm Bull (Tokyo)* 2006;54:1017-21.
 54. Zhu ZJ, Zhong ZC, Luo ZY, Xiao ZY. Studies on the active constituents of Momordica charantia L. *Yao Xue Xue Bao* 1990;25:898-903.
 55. Jianchao C, Renrong T, Qiu M, Lu L, Yongtang Z, Zhang Z. Trinorcucurbitane and cucurbitane triterpenoids from the roots of Momordica charantia. *Phytochem* 2008;69:1043-48.
 56. Jose' GA, Omar MC, Fernando B, Robert B, Jose' PC, Andre's N, *et al.* Antidiabetic properties of selected Mexican copalchis of the Rubiaceae family. *Phytochem* 2007;68:2087-95.
 57. Balkema-Boomstra AG, Zijlstra S, Verstappen FW, Inggamer H, Mercke PE, Jongsma MA, *et al.* Role of Cucurbitacin c in resistance to spider mite (*Tetranychus urticae*) in Cucumber (*Cucumis sativus* L.). *J Chem Ecol* 2003;29:225-35.
 58. Noguchi N, Komuro E, Niki E, Wilson RL. Action of cucurmin as an antioxidant against lipid peroxidation. *J Jpn Oil Chem Soc* 1994;43:1045-51.
 59. Shohat B, Beemer AM, Gitter S, Lavie D. Antifertility activity of dihydroelatericin A in the female mouse. *Experientia* 1972;28:1203-5.
 60. Behle RW. Consumption of residue containing Cucurbitacin feeding stimulant and reduced rates of carbaryl insecticide by western corn rootworm (Coleoptera: Chrysomelidae). *J Econ Entomol* 2001;94:1428-33.
 61. Martin PA, Blackburn M, Schroder RF, Matsuo K, Li BW. Stabilization of Cucurbitacin E-glycoside, a feeding stimulant for diabroticite beetles, extracted from bitter Hawkesbury watermelon. *Insect Sci* 2002;2:19.
 62. Martin PA, Blackburn M. Inhibition of seed germination by extracts of bitter Hawkesbury watermelon containing Cucurbitacin, a feeding stimulant for corn rootworm (Coleoptera: Chrysomelidae). *J Econ Entomol* 2003;96:441-45.
 63. Watt JM, Breyer-Brandwijk MG. The medicinal and poisonous plants of Southern and Eastern Africa. Edinborough and London: E. and S. Livingston; 1962. p. 336-41.
 64. Rixos JL, Escandell JM, Recio MC. New insight on the bioactivity of Cucurbitacins, In: Atta-Ur-Rahman, editor. *Studies in Natural Products Chemistry: Bioactive Natural Products*. Vol. 32. New Insight on the Bioactivity of Cucurbitacins: Amsterdam; 2005. p. 429-69.
 65. Musza LL, Speight P, McElhiney S, Barrow CJ, Gillum AM, Cooper R, *et al.* Cucurbitacins, cell adhesion inhibitors from *Conohea scoparioides*. *J Nat Prod* 1994;57:1498-502.
 66. Storrs AE, Pearce GD. Don't Eat These: A Guide to some local poisonous plants. Forest Department, Ndola, Zambia; 1982.
 67. Tamura Y, Maki T, Kan K, Nagayama T, Naoi Y. Outbreaks of food poisoning through chemicals and natural toxicants in Tokyo. I. 1980-1982. *Ann Report Tokyo Metro Res Lab Public Health* 1983;34:171-7.
 68. Edery H, Schatzberg-Porath G, Gitter S. Pharmacodynamic activity of elatericin (Cucurbitacin D). *Arch Int Pharmacodyn Ther* 1961;130:315-35.

How to cite this Article: Kaushik U, Aeri V, Mir SR. Cucurbitacins - An insight into medicinal leads from nature. *Phcog Rev* 2015;9:12-8.

Source of Support: Nil, **Conflict of Interest:** None declared