Acta Poloniae Pharmaceutica – Drug Research, Vol. 71 No. 3 pp. 363–367, 2014 ISSN 0001-6837
Polish Pharmaceutical Society

A REVIEW ON ANTIDIABETIC ACTIVITY OF *CITRULLUS COLOCYNTHIS* SCHRAD.

CHENGHE SHI[1≠], SABIHA KARIM[2], CHUNYONG WANG[1], MINGJING ZHAO[3]* and GHULAM MURTAZA[4]*≠

[1]Department of Traditional Chinese Medicine, Peking University Third Hospital, 100190 Beijing, People's Republic of China
[2]University College of Pharmacy, The University of the Punjab, Lahore, Pakistan
[3]Beijing University of Chinese Medicine, Dongzhimen Hospital, People's Republic of China
[4]Department of Pharmaceutical Sciences, COMSATS Institute of Information Technology, Abbottabad 22060, Pakistan

Abstract: Current studies have elaborated diabetes mellitus as one of the most prevalent endocrine disorder throughout the world. *Citrullus colocynthis* (*C. colocynthis*) is one of the most common traditional plants used as remedy against diabetes mellitus. It is well recognized by its hypoglycemic effect, which is substantiated in current phytotherapy. Its undesired effects include the disturbance of gastrointestinal and urinary tracts. This review article encompasses various blood glucose lowering studies that have been carried out till date. Various parts of plants used in extract preparation were roots, fruits, seeds, rinds and leaves. The nature of these extracts was ethnolic, methanolic, or aqueous and their doses varied from 10 to 500 mg/kg body weight/ day. All these published articles elaborate *C. colocynthis* as a potential antiglycemic medicinal plant.

Keywords: hypoglycemia, *in vitro*, *in vivo*, traditional, extracts

Out of many endocrinal diseases, diabetes mellitus is one of the most commonly prevalent metabolic disorders which distresses over one billion population of world and cause extensive deaths. Various factors causing this disease have been observed including diet and age (1). World Health Organization (WHO) has revealed that three billion diabetic cases would be observed by the year 2025 (2). Due to abnormal metabolism of carbohydrates, diabetic person suffers from abnormally higher blood glucose level than normal, which may cause various complications such as nephrotoxicity and retinopathy as well as untimely, death (3). Chronic diabetic condition disturbs the metabolism of proteins and lipids as well (4) and promotes peroxidation of membrane lipid causing the disturbance in cell function. Hypergycemia also promotes non-enzymatic glycation of proteins leading to increased development of reactive oxygen species (5). There is important role of increased oxidative stress (IOS) in the progress of diabetes as well as its complication due to autocatalytic metabolism, which leads to production of more free radicals and reduction of antioxidants (6). IOS also causes the destruction of red blood cells in diabetic patients (7), this hematological complication disturbs the performance of erythrocytes (8).

Currently, substantial research for safe and efficacious hypoglycemic drugs is in progress, which could also protect diabetic patient from other complications of diabetes (9). In this context, WHO has suggested the utilization of herbal medicines (10).

There is a long history of herbal use as antidiabetic therapy. The validated antidiabetic potential of many plant remedies is available in literature showing controlled analyses in healthy and diseased animals as well as human in last ten years. The mode of antidiabetic effect of these plant remedies involves the modulation of carbohydrate metabolism by restoring integrity and function of the β cells (11, 12).

Citrullus colocynthis (*C. colocynthis*) Schrad. belongs to family Cucurbitaceae. *C. colocynthis*, also known as bitter apple and bitter cucumber, is famous for its medicinal value throughout the world,

* Corresponding authors: G. Murtaza: e-mail: gmdogar356@gmail.com; mobile: 00923142082826; fax: 0092992383441;
M. Zhao: e-mail: Linfengtingchan@foxmail.com

≠ Contributed equally.

especially in Asia and Africa (13). The appearance of *C. colocynthis* resembles that of watermelon, possessing herbaceous stems, triangular and hairy leaves, yellow flowers, and globular bitter fruit. Its fruit consists of an outer hard rind and an inner white spongy pulp. A large number of seeds are embedded in its pulp (14). Pectin, colocynthin, colocynthein, colocynthetin, and gum are main phytochemical constituents found in its pulp, while fixed oil and albuminoids have been isolated from its seeds. These medicinally potential compounds make the fruit pulp and seeds an important medicinal part of this plant. The root and leaf are other medicinal parts of *C. colocynthis* (15).

The objective of this review is to collect and summarize in one place all such data, which involve the study of antidiabetic effect of *C. colocynthis*.

METHODOLOGY

Using English language, various electronic data bases such as Medline (1966 to 2013) and EMBASE (1980 to 2013) were comprehensively used for literature survey using various terms like "*Citrullus colocynthis* Schrad." and "*Citrullus colocynthis* Schrad. and antidiabetic effect" as well as the terms mentioned in title, abstract and keywords were also used for searching. Bibliographies of all concerned publications were also carefully studied for the comprehensive review. Papers were dually checked to avoid duplication.

RESULTS AND DISCUSSION

Current studies have elaborated diabetes mellitus as one of the most prevalent endocrine disorder throughout the world. *C. colocynthis* is one of the most common traditional plants used as remedy against diabetes mellitus. To provide scientific grounds to medicinal use of *C. colocynthis* as antidiabetic remedy, various researchers have carried out scientific studies on its different parts. As far as the preparation of extract of the desired part is concerned, dried plant part (seeds, fruits, roots, rinds or leaves) is chopped to powder and a weighed amount of the powder is subjected to solvent extraction using suitable instrument such as Soxhlet apparatus and appropriate solvent/solvent system at appropriate temperature. The marc was entirely dried and weighed before and after every extraction followed by the concentration of extract to dryness at 40^{o}C under reduced pressure in a rotary vacuum evaporator (16).

We found two such studies in the literature, which involved the use of root extract of *C. colo-*

Table 1. Previous studies showing the animal, part of *Citrullus colocynthis*, and type and dose of extract used.

No.	Part used	Type of extract	Study subject	Dose (mg/kg b.w./ day)	Reference
1	Root	Aqueous extract	Rats	175–300	(16)
2	Root	Aqueous extract	Rats	50 & 100	(17)
3	Fruit pulp	Ethanolic extract	Rats	300	(12)
4	Fruit pulp	Petroleum ether extract	Rats	300 & 500	(18)
5	Fruit pulp and seed	Ethanolic extract	Male rabbits	100 & 200	(19)
6	Fruit pulp	Ethanolic extract	Rats	300	(20)
7	Fruit pulp	Ethanolic extract	Rats	50	(21)
8	Fruit pulp	Suspension	Rats	10 & 90	(22)
9	Fruit pulp	Ethanolic extract	Rats	300	(23)
10	Fruit pulp	Methanolic extract	Rats	250 & 500	(24)
11	Seeds	Ethanolic extract	Rats	250	(26)
12	Seeds	Ethanolic extract	Rats		(25)
13	Leaf	Suspension	Rats	250 & 500	(27)
14	Rind	Aqueous, glycosidic, alkaloidal and saponin extracts	Rabbits	10, 15, 20, 50 & 300	(28)
15	Rind	Aqueous extract	Rats	300	(29)
16	Rind	Ethanolic extract	Rats	300	(30)

cynthis. One of these was conducted by Agarwal et al. (16), who evaluated biochemical parameters of normal and alloxan-induced diabetic (AID) rats after administration of aqueous, chloroform and ethanolic extracts of *C. colocynthis* root to observe its therapeutic effect. The aqueous extract illustrated noteworthy hypoglycemic effect (58.70%) in comparison to chloroform (34.72%) and ethanol (36.60%) extracts. The aqueous extracts exhibited the improved serum levels of urea, protein and lipid as well as retrieved serum level of bilirubin, glutamate oxaloacetate transaminase, glutamate pyruvate transminase and alkaline phosphatase. In another experiment, the researchers distributed rats into three groups keeping one group as control and administered 50 mg and 100 mg of *C. colocynthis* root extract per kilogram of body weight of rat to other two groups for twenty eight days for evaluation of *C. colocynthis* therapeutic efficacy and safety in rats at its antidiabetic dosing amount. Standard kits were used for the study of hematology and biochemistry of rats on 29th day. The hematological, histopathological and biochemical data showed significant antidiabetic effect of *C. colocynthis* as well as were safe in rats at its antidiabetic dosing amount (17).

Similarly, we found eight such studies in literature, which involved the use of fruit pulp extract of *C. colocynthis*. In order to assess the antioxidant effect of *C. colocynthis*, Dallak et al. (12) used extract of its fruit pulp in AID rats. The results exhibited significant reduction ($p < 0.05$) in total erythrocytes count, packed cell volume, thiobarbituric acid reactive substances, and activities of superoxide dismutase (SOD) and catalase (CAT) in the RBC's hemolysate of AID rats, and thus confirmed antioxidant features of *C. colocynthis* pulp extract. Jayaraman et al. (18) reported significant hypoglycemic effect of petroleum ether extract of *C. colocynthis* fruit pulp in STZID albino rats after oral administration of two different doses i.e., 300 and 500 mg of *C. colocynthis* fruit extract per kilogram of rat weight. In another study conducted on 36 white male New Zealand rabbits in Iran, antidiabetic effect of *C. colocynthis* fruit pulp as well as seed extract was determined using enzymatic kit through Elan Auto Analyzer. In comparison to the control group, significant hypoglycemic effect was observed after oral administration of 100 mg of pulp extract of *C. colocythis* per kilogram of rabbit weight, suggesting *C. colocythis* as an excellent antidiabetic drug (19). *C. colocynthis* pulp extract was once again used by Khalil et al., in the year 2010, to study its effect on liver of AID albino rats (20). Compared to the control group, histological study of liver of *C. colocynthis*-treated rats showed significantly lesser changes. Alternatively, AID rats regained normal histology of their liver after treating with *C. colocynthis* pulp extract. These results proved safe hypoglycemic effect of *C. colocynthis* pulp extract in AID rats.

El-Baky and Amin (21) reported that diabetic complications involving microvessels are reflected by nephropathy due to excessive filtration of various compounds like sugars. In this context, the effect of *C. colocynthis* fruits extract on the prevention of diabetic nephropathy was illustrated in STZID male albino rats. According to results, blood glucose¸ urea, creatinine, albumin and uric acid levels were significantly lowered. According to histopathological results, *C. colocynthis* fruit extract has nephroprotective effects concluding that fruit pulp of *C. colocynthis* may exert nephroprotective influences on the functioning of kidney tissues. Salami et al. (22) also observed significant hypoglycemic effects of suspensions of *C. colocynthis* fruit pulp in normal 12 h fasting rats after single dose of 30 mg/kg, while suspensions of *C. colocynthis* fruit pulp in the doses of 10 mg/kg and 90 mg/kg exhibited non-significant hypoglycemic effects. In Sudan, Babiker et al. (23) prepared the ethanolic extract of *C. colocynthis* fruit pulp and observed its influences in the oral dose of 300 mg/kg/mL of extract on fasting blood glucose level and glucose tolerance test. After 4 hours of administration, a swift decrease in blood glucose level of normal fasting rats was observed accompanied by few unwanted effects such as diarrhea, which resulted in death of two out of seven animals showing its toxic nature. Moreover, sub-acute treatment approach has been applied in STZID rats to test blood glucose level using the methanolic extract of *C. colocynthis* fruit pulp in the oral doses of 250 mg/kg and 500 mg/kg (24). There was non-significant ($p > 0.01$) and significant ($p < 0.01$) hypoglycemic effect of 250 mg/kg and 500 mg/kg dose.

We also found two such studies in the literature, which involved the use of seed extract of *C. colocynthis*. Sebbagh et al. (25) compared the antidiabetic potential of *C. colocynthis*, sunflower or olive oils in streptozotocin (STZ)-induced diabetes (STZID) in rats and found that diet rich with *C. colocynthis* oil exerted significantly higher hypoglycemic effect in rats administered with or without insulin as compared to foods containing other oils. Conclusively, the results reported that antidiabetic effect of *C. colocynthis* oil occurs through the preservation or restoration of pancreatic β cells in STZIT rats. Lakshmi et al. (26) tested the ethanolic

extract (in the oral doses of 250 mg/kg body weight) of *C. colocynthis* seeds for its hypoglycemic feature in AID rats, which had elevated levels of biochemical parameters. After administration of extracts, the values of these biochemical parameters significantly reverted back to their approximately normal levels along with the improvement in their glycogen level. As a conclusion, *C. colocynthis* seeds extract has hypoglycemic activity similar to standard oral hypoglycemic drug, gliclazide.

We also found one such study in the literature, which involved the use of leaf extract of *C. colocynthis*. Gurudeeban and Ramanathan (27) investigated the hypoglycemic influence of *C. colocynthis* on hepatic hexokinase and gluconeogenic enzymes like glucose-6-phosphatase and fructose 1,6-bisphosphatase of control and AID rats after oral intake of its leaf suspension in the doses of 250 mg/kg and 500 mg/kg of body weight for sixty days and found a significant fall in blood glucose level from 381 ± 34 to 105 ± 35 mg/dL. There was a reduction in the activities of glucose-6 phosphatase and fructose 1,6-bisphosphatase, and an enhancement in liver hexokinase activity supporting the hypoglycemic importance of this medicinal plant.

Abdel-Hassan et al. (28) investigated the hypoglycemic potential of the aqueous, glycosidic, alkaloidal and saponin extracts of *C. colocynthis* rind in normal rabbits, while fasting AID rabbits were used also for the elaboration of the hypoglycemic effects of saponin extract. Orally administered aqueous extract in the dose of 300 mg/kg in normal rabbits provoked significant hypoglycemic effect after one hour and intensively significant during 1–6 hours, possibly due to the tertiary and quaternary alkaloids, glycoside and saponin components present in the aqueous extract of the rind of *C. colocynthis* at a dose of 50 mg/kg of body weight in normoglycemic rabbits. The same extent of hypoglycemic effect was observed from the glycosidic extract that significantly reduced the fasting glucose levels after two hours and highly significant ($p < 0.001$) after six hours. Orally administered alkaloidal extract in the dose of 300 mg/kg in normal rabbits provoked non-significant hypoglycemic effect even after 6 hours. The saponin extract, in the oral doses of 10, 15 and 20 mg/kg of AID rabbits, exerted more prominent hypoglycemic effect after one hour and strongly significant ($p < 0.001$) after 3 hours. Conclusively, the aqueous extract of the rind of *C. colocynthis* exhibited glucose lowering effect, possibly due to the presence of saponin and glycosides.

Jeyanthi et al. (29) measured the biochemical parameters in normal and AID rats to investigate the hypoglycemic influence of aqueous extract of *C. colocynthis* in the dose of 300 mg/kg body weight for twenty two days. According to observations, the activity of enzymes involved in carbohydrate metabolism as well as the increased blood glucose, insulin, hemoglobin, HbA1C and glycogen levels in AID rats reverted back to normal level after treating with extract, which indicates the hypoglycemic activity of this medicinal plant.

Aghanouri et al. (30) investigated the possible antihyperglycemic influence of *C. colocynthis* in STZID Wistar rats. According to results, there was a significant ($p < 0.05$) antihyperglycemic influence of this medicinal plant in the STZID rats after 10 days of drug administration, which elaborate *C. Colocynthis* as a suitable herbal medicine against diabetic condition.

CONCLUSION

This review article encompasses various blood glucose lowering studies that have been carried out till date. Various parts of the plant used in extract preparation were roots, fruits, seeds, rinds, and leaves. The nature of these extracts was ethanolic, methanolic, or aqueous and their doses varied from 10 to 500 mg/kg body weight/ day. All these published articles elaborate *C. colocynthis* as a potential antiglycemic medicinal plant, however, in depth toxicity studies of this plant are still to be done.

REFERENCES

1. Zimmet P.Z.: Diabetologia 42, 499 (1999).
2. Pradeepa R., Mohan V.: Indian J. Med. Res. 116, 121 (2002).
3. Aravind K., Pradeepa R., Deepa R.: Indian J. Med. Res. 116, 163 (2002).
4. Rao B.K., Kesavulu M.M., Giri R., AppaRao C.H.: J. Ethnopharmacol. 67, 103 (1999).
5. Nishikawa T., Edelstien D., Du X.L.: Nature 404, 787 (2000).
6. Baynes J.W.: Diabetes 40, 406 (1991).
7. Rice-Evans C., Omorphos S.C., Baysal E.: J. Biochem. 237, 265 (1986).
8. Comazzi S., Spagnolo V., Bonfanti U.: J. Comp. Clin. Pathol. 12, 199 (2004).
9. Krishna B., Nammi S., Kota M.K., Krishna Rao R.V., Koteswara Rao N., Annapurna A.: J. Ethnopharmacol. 91, 95 (2004).
10. WHO. Expert Committee on Diabetes mellitus, Second Report. World Health Organ Tech. Rep. Ser. 646, 1–80 (1980).
11. Mansi K., Lahham J.: J. Basic Appl. Sci. 4, 57 (2008).

12. Dallak M., Bin-Jaliah I.: Pak. J. Physiol. 6, 1 (2010).
13. Rahimi R., Amin G., Ardekani M.R.S.: J. Altern. Complement. Med. 18, 551 (2012).
14. Shahabi S., Hassan Z.M., Mahdavi M.: J. Altern. Complement. Med. 14, 147 (2008).
15. Ardekani M.R.S., Rahimi R., Javadi B.: J. Trad. Chin. Med. 31, 27 (2011).
16. Agarwal V., Sharma A.K., Upadhyay A., Singh G., Gupta R.: Acta Pol. Pharm. Drug Res. 69, 75 (2012).
17. Atole S.K., Jangde C.R., Philip P., Rekhe D.S., Aghav D.V., Waghode H.J.: Veterinary World 2, 423 (2009).
18. Jayaraman R., Shivakumar A., Anitha T., Joshi V.D., Palei N.N.: Rom. J. Biol. Plant Biol. 54, 127 (2009).
19. Dashti N., Zamani M., Mahdavi R., Rahimi O.: J. Jahrom Univ. Med. Sci. 9, 13 (2012).
20. Khalil M., Mohamed G., Dallak M., Al-Hashem F., Sakr H, et al.: Am. J. Biochem. Biotechnol. 6, 155 (2010).
21. El-Baky A.E.A., Amin H.K.: Int. J. Pharm. Stud. Res. 2, 1 (2011).
22. Salami M., Aqanouri Z., Karimian M., Enshai M.: Ethnopharmacology 3, 50 (2004).
23. Babiker H.A., Eldin I.M.T., Abd-Elwahab H.M.: Gezira J. Health Sci. 8, 1 (2012).
24. Jayaraman R., Kumar G.A.S., Raj P.V., Nitesh K., Naryanan K.: Biomed. 4, 269 (2009).
25. Sebbagh N., Cruciani-Guglielmacci C., Ouali F., Berthault M.F., Rouch C. et al.: Diabetes Metab. 35, 178 (2009).
26. Lakshmi B., Sendrayaperumal V., Subramanian S.: Int. J. Pharm. Sci. Rev. Res. 19, 47 (2013).
27. Gurudeeban S., Ramanathan T.: Ethnopharmacology 11, 10 (2010).
28. Abdel-Hassan I.A., Abdel-Barry J.A., Mohammeda S.T.: J. Ethnopharmacol. 71, 325 (2000).
29. Jeyanthi K.A., Mary C.A.: IUP J. Biotechnol. 3, 30 (2009).
30. Aghanouri Z., Noureddini M., Salami M.: Feyz J. Kashan Univ. Med. Sci. 12, 1 (2009).

Received: 24. 06. 2013