Pharmacognosy Communications, 2023; 13(4):163-168.
https://www.phcogcommn.org

Review Article

Potential Use of *Helicteres isora* L. in Diabetes Mellitus: A Systematic Review of Scientific Literature

Kamatchi Sundara Saravanan*, Radhakrishnan Gowri, Karthik Kumar Ramesh, Sanjana Shetty, Soubhagya Maity

Department of Pharmacognosy, Faculty of Pharmacy, M S Ramaiah University of Applied Sciences, Bangalore, Karnataka, INDIA.

ABSTRACT

Introduction: Plant-based medicines have been in use over the years for the management and treatment of various ailments including diabetes. The current study was undertaken to explore and compile the research evidence on *Helicteres isora* L. (*Sterculiaceae*) in the management of diabetes. **Materials and Methods:** Peer-reviewed literature was retrieved during January 2023 from databases comprising of PubMed, Science Direct, Springer and LILACS. The obtained literature was initially subjected to title and abstract screening, followed by full-text screening. **Results:** The study includes 12 articles that were chosen among a total of 111 articles retrieved through various sources. The selected articles reported either *in vitro* assay or *in vivo* evaluation of various extracts of *H. isora* bark, fruit, or root for its anti-diabetic property. The duration of the *in vivo* evaluation studies were up to 30 days in Wistar rat/Swiss albino mice/C57BL mice. The diabetogenic agents used were either Streptozotocin (STZ) or alloxan, while the reference drugs used comprised of tolbutamide, pioglitazone, glibenclamide, insulin, or metformin. A significant anti-diabetic property of various parts of *H. isora* were reported in the reviewed studies. **Conclusion:** The available evidence demonstrates the potential of *H. isora* against diabetes as it holds significant glucose-lowering effects in the reported screened models. Bioactivity-guided fractionation followed by elucidation of the mechanism of action will be useful in establishing the application of the plant species in diabetes.

Keywords: *Helicteres isora*, Diabetes, Root, Bark, Fruit.

Correspondence:
Dr. Kamatchi Sundara Saravanan
Department of Pharmacognosy, Faculty of Pharmacy, M S Ramaiah University of Applied Sciences, Bangalore-560054, Karnataka, INDIA.
Email: sundarksharan@gmail.com

Received: 03-08-2023;
Revised: 15-09-2023;
Accepted: 10-10-2023.

INTRODUCTION

Diabetes Mellitus (DM) is a chronic, serious, complex metabolic disorder that poses a public threat across the globe.[1,2] It is estimated and reported that around 25% of the population belonging to developing and developed countries were affected by this disorder.[3] Moreover, DM is one of the top 10 disorders in adults that not only lead to socioeconomic challenges but also cause almost four million deaths per annum universally.[2] Furthermore, according to WHO, diabetes will be the seventh most common cause of mortality by 2030.[4] Owing to numerous problems including affordability, inadequate healthcare system, dearth of suitable facilities etc., the effective treatment of diabetes and its related consequences continue to be a significant challenge for the developing countries.[5]

There are numerous treatment options available such as synthetic pharmaceuticals, insulin therapy, etc., but they have advantages and disadvantages in terms of efficacy and adverse effects.[6] Plant-based medicines are useful in diabetes management[3] as they are considered to be the storehouse for a diverse class of phytoconstituents including alkaloids, flavonoids, phenolics, and tannins that helps to improve the efficiency of pancreatic tissues.[7]

Helicteres isora L. is one of the important plants with proven medicinal properties. The species is a small tree or a sub-deciduous shrub and is commonly known as the East Indian screw tree.[8] Ethnomedicinal use claims that the leaf paste is used to treat eczema and scabies.[9] The root juice and bark are said to be used in the treatment of intestinal infections, colic, diarrhoea, dysentery, diabetes, asthma, blood disorders, snake bites, emphysema, and as a urinary astringent, expectorant, and anti-galactagogue.[8,9] Fruits were used as an astringent, refrigerant, demulcent, vermifuge, anti-spasmodic, and in constipation.[8,10]

Preliminary phytochemical analysis of the species revealed the presence of alkaloids, phytosterols, sugars, saponins, lignin's, phlobotannins, triterpenoids, isorin, and their acetates, isocucurbitacin B, cucurbitacin B, flavonoid glucuronides, flavonoids, neolignans, rosmarinic acid derivatives, daucosterol, betulic acid, tannins, triterpenes anthraquinones, cardiac glycosides, α- and β-amyrin, sterols, ridelin, lupeol, taraxerone, volatile oil and β-sitosterol.[9,10] 4,49-O-di-b-D-glucopyranosyl

DOI: 10.5530/pc.2023.4.26

rosmarinic acid, 49-O-b-D-glucopyranosyl rosmarinic acid, 49-O- b-D glucopyranosyl isorinic acid and rosmarinic acid were reported from the fruits.[10] Various parts of this species have been evaluated and reported to possess anti-hyperglycemic, anti-HIV, hypolipidaemic, antioxidant, anti-bacterial, anti-plasmid, anti-cancer, anti-nociceptive and hepatoprotective activity.[11] Despite the popularity of *H. isora* in folk medicines for its potential use in diabetes, few scientific validations have been reported.

Herein we present a systematic review that aims to identify, collect, evaluate, and summarize the findings of all relevant individual literature[12] about the beneficial effects of *H. isora* in diabetes. Although a challenging endeavour, systematic review is considered to be a valuable resource for researchers[13] as it comprehends and critically appraise the available literature on a specific domain.[14] In recent years, systematic reviews including meta-analyses have been more popular across a variety of disciplines, including pharmacy. The significance of systematic reviews has also been emphasized in the field of pharmacognosy which focuses on pharmaceuticals originating from natural sources. Moreover, it is also expected that the present review on *H. isora* will provide a platform to investigate the phytobioactives that could be attributed to anti-diabetic properties alongside the involved mechanism of action.

MATERIALS AND METHODS

Search strategy

Literature pertinent to the proposed study was collected online using the keywords *H. isora* and diabetes during January 2023. The primary scientific databases such as PubMed, Science Direct, Springer, and LILACS were utilized to retrieve the published articles. Thus, obtained research papers through the aforementioned search criteria were combined to remove the duplicates. This was followed by a preliminary examination that involved reading the paper's title and then the abstracts.

Exclusion/inclusion criteria

The studies with inadequate information, species other than *H. isora*, and activity not related to diabetes were excluded. Only the research papers that utilized the extracts of any of the morphological parts and/or reported phytoconstituents of *H. isora* were included. Some of the research articles were gathered by examining the bibliography of retrieved publications. The articles eligible for inclusion were limited to the English language. Literature that did not satisfy the set inclusion criteria was excluded at this stage.

Data extraction

Three independent authors scrutinized the title and abstract of the retrieved studies. Later, full-text screening for data extraction was performed to compile the details from the selected full texts for analysis. Any differences among these three authors were resolved by the other two authors.

RESULTS

Following are the number of articles retrieved from various databases, PubMed (n=13), Science Direct (n=46), and Springer (n=49), while from LILACS no literature was retrieved. Three more articles were identified through a manual search from the reference lists of included papers. All the literature was combined to remove the duplicates. Later title, abstract, and full-text screening were performed. Finally, 12 articles were included in the current review. Figure 1 presents the search strategy followed in selecting the articles.

Study characteristics

The following are the details in brief regarding the data retrieved from the 12 studies included in this review. There were four studies reported on bark; three on fruit, and five on root. The aforementioned plant parts have been used in the form of extract prepared using any one of the solvents such as ethanol, methanol, chloroform, and/or water. Bark extract was used in the dose level of 100 mg/kg and 200 mg/kg, while 100 mg/kg, 125 mg/kg, 250 mg/kg, and 300 mg/kg of root extract were utilized among various studies reviewed. Fruit extracts were screened by *in vitro* methods at the dose level of 2 mg/mL and 200 µg/mL.

Ten studies included *in vivo* evaluation with duration up to 30 days that used any one of the following animals such as Wistar rats, Swiss albino mice, or C57BL mice; on the other hand, two articles encompassed *in vitro* evaluation. The diabetogenic agents used are either Streptozotocin (STZ) or alloxan, while the reference drugs used comprised of tolbutamide, pioglitazone, glibenclamide, insulin, or metformin.

Serum glucose, plasma glucose, total cholesterol, triglycerides, urea, insulin levels, glycogen content, and insulin sensitivity were the key parameters assessed among others. Only one study involved histopathological studies of organs such as the kidney, pancreas, and liver.

In this study, we reviewed the effect of various morphological parts and/or reported constituents of *H. isora* on blood glucose levels. The schematics represented in Figure 2 provide an outline of the different parts used, various extracts, and their fractions along with the screened models.

DISCUSSION

As traditional medicine research has recently advanced and accelerated, it is now obvious that plant-based remedies are one of the most important sources to find potential lead compounds in the drug development process. Moreover, the availability, affordability, and cost burden of conventional medicines along with other reasons make a huge population in developing

countries rely on plant-based medicines to treat diabetes.[1] *H. isora* is one of the most widely used medicinal plants in the traditional system of medicine to manage diabetes besides its use in emphysema, and snakebite among others.[15] The following section provides an insight into the antidiabetic activity of bark, fruit, and root of *H. isora* retrieved from the selected literature.

Bark

Glucose Tolerance Test (GTT) performed on normal rats with 10 g glucose raised the sugar level by 138.5% after 30 min. This elevated level was reduced by 15.68% and 19.64% at 1 and 2 hr post-administration of 100 mg/kg dose, while 200 mg/kg reduced the elevated level by 20.74% and 28.05% at 1 and 2 hr post-administration of aqueous extract. Moreover, the study revealed a reduction of 24.8% and 29.5% of fasting blood glucose levels in normal rat's 2 hr post-administration of aqueous extract at 100 mg/kg and 200 mg/kg respectively and was reported to be higher than the level in tolbutamide-treated animals. Also, an increase in a 3-fold level of blood glucose owing to STZ administration in rats was reversed by 100 mg/kg and 200 mg/kg of aqueous extract to 56.3% and 64.9%, respectively over 21 days of administration.[16]

Kumar G *et al.*,[17] reported a reduction in plasma glucose levels in STZ-induced diabetic male Wistar albino rats that were orally administered with aqueous extract of 100 mg/kg and 200 mg/kg. The levels decreased by 9.60% and 22.04% on the 15th day, 19.18%, and 33.93% on the 30th day. Furthermore, it was reported that the extract treatment elevated the decreased level of enzymes encompassed in carbohydrate metabolism such as hexokinase, glucokinase, fructose-1, 6-bisphosphatase, and phosphofructokinase.

Ganesan Kumar *et al.*,[18] demonstrated that aqueous extract at 100 mg/kg and 200 mg/kg administered for 14 days to STZ-induced diabetic rats displayed a dose-dependent reduction in the fasting blood glucose levels. The fasting blood sugar level was reduced by 67.1% and 68.4% at the dose of 100 mg/kg and 200 mg/kg respectively on the 14th day of treatment.

Kumar G *et al.*,[19] reported the effect of aqueous extract on urine and blood sugar levels in rats induced with STZ for diabetes. The animals treated with 100 mg/kg and 200 mg/kg of extract per oral showed a decrease in blood and urine glucose levels. Concurrently, an elevation in hepatic hexokinase activity and a decrease in hepatic glucose-6-phosphatase activity has also been reported.

Root

Chakrabarti R *et al.*,[20] evaluated the effect of roots collected from three different geographical locations. Ethanol extract (300 mg/kg) was administered orally to db/db mice for 15 days. The percentage plasma glucose level reduction offered by the root from three different locations was reported to be 14, 64, and 41.

Treatment of db/db mice with 300 mg/kg ethanol extract orally for 10 days reduced the plasma glucose by 62%, and insulin level by 61%, while the extract did not display plasma glucose lowering properties at a single dose in the studied model. The extract was

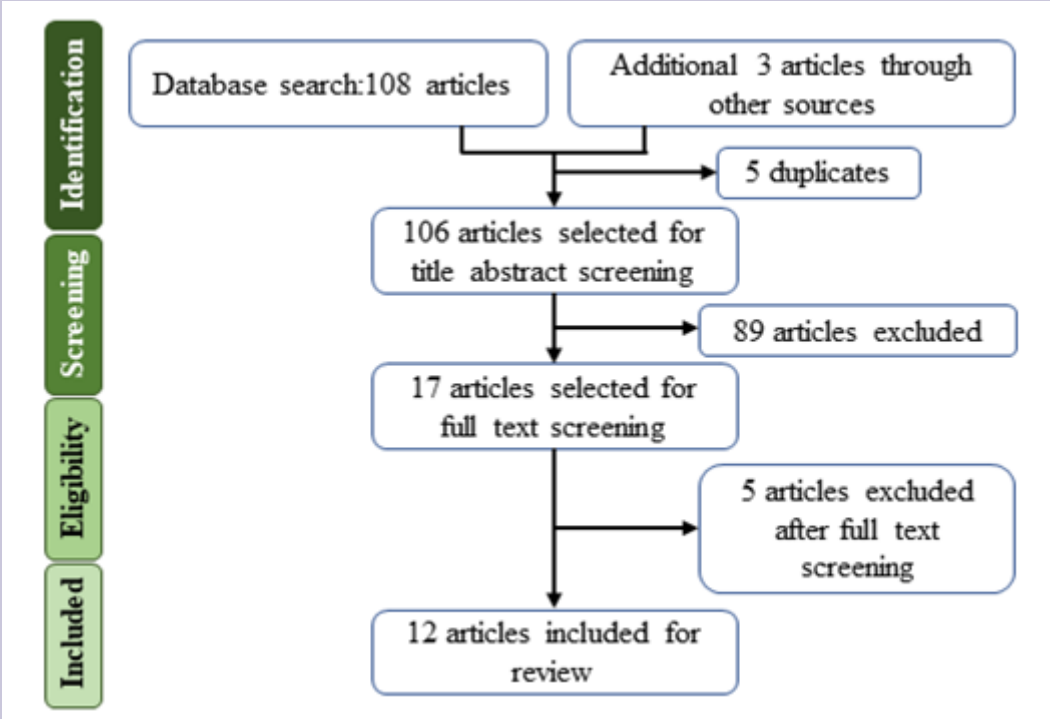

Figure 1: Work flow of screening process.

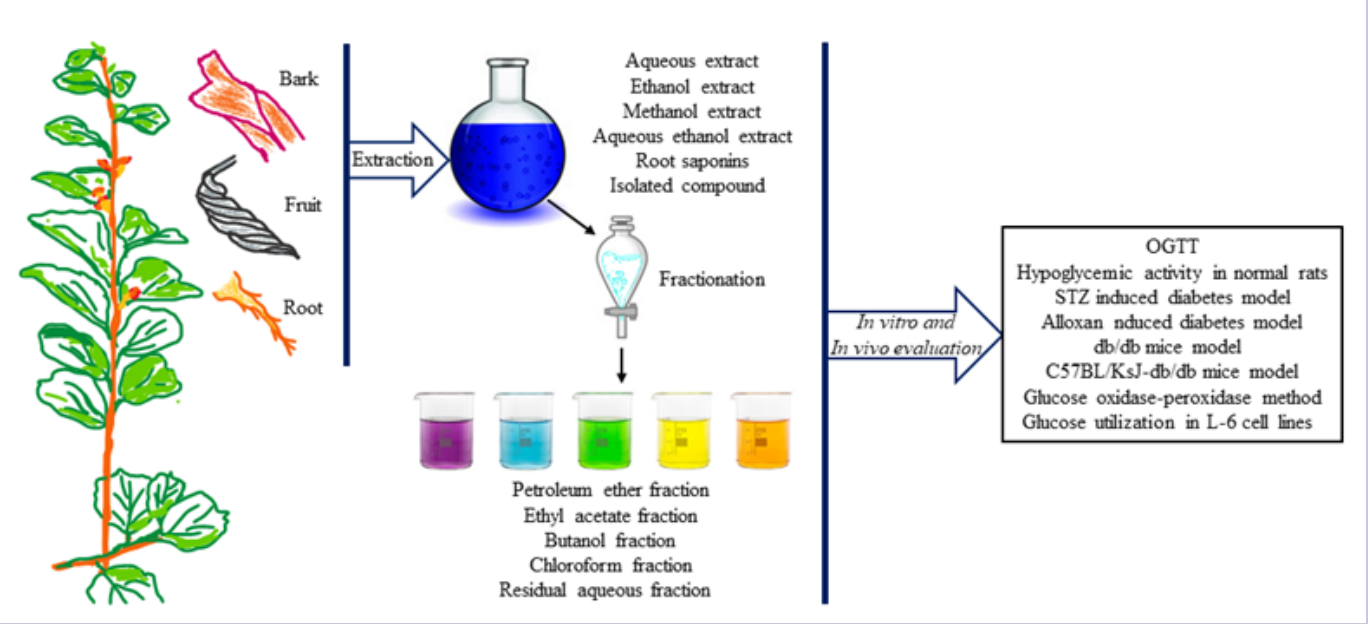

Figure 2: Schematic representation of plant parts and its extracts screened for diabetes.

claimed to possess a similar effect to that of troglitazone at 400 mg/kg, p.o., and an insulin-sensitizing drug.

Various fractions of aqueous ethanol extract obtained using petroleum ether, ethyl acetate, and butanol showed 10%, 20%, and 44% reduction in the plasma glucose level at 15-day post-treatment with 300 mg/kg in db/db mice.

The left-over aqueous residue possessed a 25% reduction while the semi-purified butanol extract through chromatography displayed a reduction of 45%.

A reduction of 63% in plasma insulin level with no alteration in plasma glucose level was noticed in moderate hypertriglyceridemic normoglycemic Swiss albino mice at 300 mg/kg treated orally for 10 days.

Venkatesh S *et al.*,[21] in their study reported that the administration of aqueous ethanol extract and its n-butanol fraction at 250 mg/kg in alloxan-induced diabetic rats for 10 consecutive days displayed a progressive reduction in serum glucose levels. Aqueous ethanol extract and n-butanol fraction displayed a serum glucose reduction of 36.01%, 39.64%, 43.98%, 51.14% and 49.48%, 55.88%, 62.26%, 69.13% respectively on 3rd, 5th, 7th, and 10th day.

Venkatesh S *et al.*,[22] evaluated the aqueous ethanol, chloroform, ethyl acetate, n-butanol, and left-over aqueous extract for their possible effect on glucose tolerance in glucose-induced hyperglycemic rats. The above-mentioned extracts were orally administered at a dose of 250 mg/kg and later the animals were loaded with glucose (2 g/kg). Among the extracts screened ethyl acetate, aqueous ethanol, and butanol extracts were observed to significantly prevent the elevation in blood glucose followed by glucose challenge, and a maximum glucose tolerance was displayed by butanol extract at 1 hr post-dosing.

Bhavsar SK *et al.*,[23] reported the effect of root saponins and methanol extract on glucose metabolism. Treatment of C57BL/KsJ-db/db mice with root saponins and methanol extract at 100 mg/kg for a duration of 14 days displayed a percentage serum glucose change of -16.1 and -30.3 respectively. Concurrently, the insulin percentage change was observed to be -27.91 and -15.09 upon administration of methanol extract and saponins respectively.

Also, Oral GTT on overnight fasted mice administered with 3 g/10 mL of glucose/kg revealed an improvement in fasting glucose levels as well as reduction at 60 and 120 min.

Zareen N *et al.*,[24] reported the effect of the butanol fraction of ethanol extract in STZ-induced diabetic rats. A single administration of butanol fraction at 125 mg/kg resulted in the reduction of plasma glucose by 29.49%, 39.85%, and 14.66% at 1, 3, and 5 hr post-dosing respectively, while a reduction of 32.23%, 47.26% and 14.24% was reported with 250 mg/kg at 1, 3 and 5 hr post-administration. Concurrently, the effect was studied in

animals that were administered with the same dose of extracts for 10 days. The low-dose group displayed a glucose reduction of 24.84% and 41.88%, while the high-dose group revealed a reduction of 34.82% and 54.18% on day 1 and day 10 respectively.

Fruit

Govindasami Chandirasegaran *et al.*,[25] evaluated the isolated berberine chloride, together with commercially available sanguinarine and muscimol, the major compounds of methanol fruit extract for anti-diabetic activity using oral GTT in normal and STZ induced diabetic rats. STZ-induced diabetic male albino rats were treated with sanguinarine (50 mg/kg), berberine chloride (50 mg/kg), and muscimol (50 mg/kg) followed by 2 g/kg of oral glucose challenge. The outcome revealed that berberine chloride exerted a significant decrease in blood glucose levels at 30, 60, 90, and 120 min compared to sanguinarine and muscimol-treated animals.

A moderate anti-diabetic property of hot aqueous fruit extract was reported by Suthar M *et al.*[15] The study was performed using isolated rat hemidiaphragm and the glucose content was measured following the glucose oxidase-peroxidase method. It was reported that the extract at 1 mL (2 mg/mL) displayed a glucose uptake of 4.85 mg/g/30 min. No demonstrable increase in glucose uptake was observed with extract in combination with insulin (0.62 mL of 0.4 IU/mL).

Gupta RN *et al.*,[26] reported the effect of aqueous extract on glucose utilization in L-6 cell lines *in vitro*. The results indicated that the extract at 200 µg/mL augmented the uptake of glucose by 28.99%. The extract in combination with insulin exhibited a glucose uptake in L-6 cells by 149.28%, however no synergistic activity was noted.

CONCLUSION

The current review reiterates that the bark, fruit, and root of *H. isora* exhibited a significant antidiabetic effect in the screened models supporting its traditional claim. However, extensive research on the isolation of phytobioactive substances responsible for the antidiabetic activity, as well as an evaluation of their toxicity profile and mechanism of action needs to be carried out. This research effort may make the drug one of the therapeutic options, either alone or in combination with other herbs to manage DM.

ACKNOWLEDGEMENT

The authors wish to thank Dr. Saraswathy GR, Professor and Head, Department of Pharmacy Practice, Faculty of Pharmacy, Ramaiah University of Applied Sciences, Bangalore for her suggestions and inputs on the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Salehi B, Ata A, Kumar VA N, Sharopov F, Ramírez-Alarcón K, Ruiz-Ortega A, *et al.* Antidiabetic potential of medicinal plants and their active components. Biomolecules. 2019;9(10):551.
2. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, *et al.* Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 9th ed. 2019;157:107843. doi: 10.1016/j.diabres.2019.107843, PMID 31518657.
3. Arumugam G, Manjula P, Paari N. A review: anti diabetic medicinal plants used for diabetes mellitus. J Acute Dis. 2013;2(3):196-200. doi: 10.1016/S2221-6189(13)60126-2.
4. Kakkar R. Rising burden of Diabetes-Public Health Challenges and way out. Nepal J Epidemiol. 2016; 30;6(2): 557-9. doi: 10.3126/nje.v6i2.15160, PMID 27774342.
5. Viswanathan V, Rao VN. Problems associated with diabetes care in India. Diabetes Manag. 2013;3(1):31-40. doi: 10.2217/dmt.12.62.
6. Tripathy B, Sahoo N, Sahoo SK. Trends in diabetes care with special emphasis to medicinal plants: advancement and treatment. Biocatal Agric Biotechnol. 2021;33:102014. doi: 10.1016/j.bcab.2021.102014, PMID 35342487.
7. Kooti W, Farokhipour M, Asadzadeh Z, Ashtary-Larky D, Asadi-Samani M. The role of medicinal plants in the treatment of diabetes: a systematic review. Electron Phys. 2016; 15;8(1): 1832-42. doi: 10.19082/1832, PMID 26955456.
8. Deshpande HA, Bhalsing SR. Isolation and characterization of diosgenin from *in vitro* cultured tissues of *Helicteres isora* L. Physiol Mol Biol Plants. 2014;20(1):89-94. doi: 10.1007/s12298-013-0205-3, PMID 24554842.
9. Dayal R, Singh A, Ojha RP, Mishra KP. Possible therapeutic potential of *Helicteres isora* (L.) and it's mechanism of action in diseases. J Med Plants Stud. 2015;3(2):95-100.
10. Loganayaki N, Siddhuraju P, Manian S. Antioxidant activity and free radical scavenging capacity of phenolic extracts from *Helicteres isora* L. and *Ceiba pentandra* L. J Food Sci Technol. 2013;50(4):687-95. doi: 10.1007/s13197-011-0389-x, PMID 24425970.
11. Kumar N, Singh AK. Plant profile, phytochemistry and pharmacology of Avartani (*Helicteres isora* Linn.): a review. Asian Pac J Trop Biomed. 2014;4;Suppl 1:S22-6. doi: 10.12980/APJTB.4.2014C872, PMID 25183085.
12. Gopalakrishnan S, Ganeshkumar P. Systematic reviews and meta-analysis: understanding the best evidence in primary healthcare. J Fam Med Prim Care. 2013;2(1):9-14. doi: 10.4103/2249-4863.109934, PMID 24479036.
13. Russell R, Chung M, Balk EM, *et al.* Issues and challenges in conducting systematic reviews to support development of nutrient reference values: workshop summary: nutrition research series. Rockville, (MD): Agency for Healthcare Research and Quality. US. 2009;2:2. Systematic Review Methods. Available from: https://www.ncbi.nlm.nih.gov/books/NBK44088/.
14. Owens JK. Systematic reviews: brief overview of methods, limitations, and resources. Nurse Author Ed. 2021;31(3-4):69-72. doi: 10.1111/nae2.28.
15. Suthar M, Rathore GS, Pareek A. Antioxidant and antidiabetic activity of *Helicteres isora* (L.) fruits. Indian J Pharm Sci. 2009;71(6):695-9. doi: 10.4103/0250-474X.59557, PMID 20376228.
16. Kumar G, Banu GS, Murugesan AG, Pandian MR. Hypoglycaemic effect of *Helicteres isora* bark extract in rats. J Ethnopharmacol. 2006;107(2):304-7. doi: 10.1016/j.jep.2006.05.007, PMID 16839725.
17. Kumar G, Sharmila Banu G, Murugesan AG. Attenuation of *Helicteres isora* L. bark extracts on streptozotocin-induced alterations in glycogen and carbohydrate metabolism in albino rats. Hum Exp Toxicol. 2009;28(11):689-96. doi: 10.1177/0960327109350797, PMID 19812119.
18. Kumar G, Banu GS, Murugesan AG. Antidiabetic activity of *Helicteres isora* L. bark extracts on streptozotocin-induced diabetic rats. Int J Pharm Sci Nanotechnol. 2009;1(4):379-82.
19. Kumar G, Murugesan AG, Rajasekara Pandian M. Effect of *Helicteres isora* bark extract on blood glucose and hepatic enzymes in experimental diabetes. Pharmazie. 2006;61(4):353-5. PMID 16649554.
20. Chakrabarti R, Vikramadithyan RK, Mullangi R, Sharma VM, Jagadheshan H, Rao YN, *et al.* Antidiabetic and hypolipidemic activity of *Helicteres isora* in animal models. J Ethnopharmacol. 2002;81(3):343-9. doi: 10.1016/s0378-8741(02)00120-4, PMID 12127235.
21. Venkatesh S, Madhava Reddy B, Dayanand Reddy G, Mullangi R, Lakshman M. Antihyperglycemic and hypolipidemic effects of *Helicteres isora* roots in alloxan-induced diabetic rats: a possible mechanism of action. J Nat Med. 2010;64(3):295-304. doi: 10.1007/s11418-010-0406-9, PMID 20238178.
22. Venkatesh S, Dayanand Reddy G, Reddy YS, Sathyavathy D, Madhava Reddy B. Effect of *Helicteres isora* root extracts on glucose tolerance in glucose-induced

hyperglycemic rats. Fitoterapia. 2004;75(3-4):364-7. doi: 10.1016/j.fitote.2003.12.025, PMID 15158996.

23. Bhavsar SK, Singh S, Giri S, Jain MR, Santani DD. Effect of saponins from *Helicteres isora* on lipid and glucose metabolism regulating genes expression. J Ethnopharmacol. 2009;124(3):426-33. doi: 10.1016/j.jep.2009.05.041, PMID 19505560.
24. Zareen N, Venkatesh S, Bolleddu R, Dayanand RG, Ramesh M. Antidiabetic effect of *Helicteres isora* Root in streptozotocin induced diabetic rats. Austin J Endocrinol Diabetes. 2019;6(1):1067.
25. Chandirasegaran G, Elanchezhiyan C, Ghosh K, Sethupathy S. Determination of antidiabetic compounds from *Helicteres isora* fruits by oral glucose tolerance test. J App Pharm Sci. 2016;6(2):172-4. doi: 10.7324/JAPS.2016.60227.
26. Gupta RN, Pareek A, Suthar M, Rathore GS, Basniwal PK, Jain D. Study of glucose uptake activity of *Helicteres isora* Linn. fruits in L-6 cell lines. Int J Diabetes Dev Ctries. 2009;29(4):170-3. doi: 10.4103/0973-3930.57349, PMID 20336200.

Cite this article: Saravanan KS, Gowri R, Ramesh KK, Shetty S, Maity S. Potential Use of *Helicteres isora* L. in Diabetes Mellitus: A Systematic Review of Scientific Literature. Pharmacognosy Communications. 2023;13(4):163-8.