ISSN: 2347-467X, Vol. 08, No. (1) 2020, Pg. 01-11

Current Research in Nutrition and Food Science

www.foodandnutritionjournal.org

Effect of *Annona Muricata* L. on Metabolic Parameters in Diabetes Mellitus: A Systematic Review

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Abstract

In recent decades, numerous scientific investigations have been conducted to study the antidiabetic effects of *Annona muricata* L. However, no comprehensive evidence-based systematic review regarding this topic is available. Hence, this study was conducted to systematically evaluate the studies of the efficacy of *A. muricata* in diabetes management. Six online databases used to search for the related articles. The search terms used were *A. muricata/* soursop in combination with diabetes, glucose, and insulin. Seventeen studies were identified that fit the inclusion criteria (1 clinical, 10 *in vivo*, 4 *in vitro*, 1 *in vivo/ in vitro* and 1 in silico). A clinical study showed the positive adjuvant effect of *A. muricata* to glibenclamide in type 2 diabetes patients. In vivo studies reported beneficial effects of *A. muricata* in murine models to include decreasing fasting blood glucose level, attenuating diabetes-associated weight loss, increasing serum insulin, improving the lipid profile, normalizing the activity of antioxidant enzymes, and exerting pancreas-protective and hepatoprotective effects. *In vitro* studies of *A. muricata* demonstrated its potential for reducing post-prandial glucose level by inhibiting pancreatic α-amylase, lipase, and α-glucosidase and lowering oxidative stress by inhibiting glycation and lipid peroxidation. Additionally, the *in-silico* study suggested a positive effect of *A. muricata* in enhancing insulin sensitivity. *A. muricata* showed a promising effect on the metabolic parameters in diabetes mellitus. Considering that *A. muricata* is widely consumed worldwide, further exploration of its therapeutic potential is worthwhile.

Article History

Received: 29 August 2019
Accepted: 12 March 2020

Keywords

Annona Muricata;
Diabetes Mellitus;
Medicinal Plant;
Nutritional Food;
Soursop.

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Doi: http://dx.doi.org/10.12944/CRNFSJ.8.1.01

Introduction

Diabetes mellitus (DM) is a heterogeneous metabolic disorder indicated by chronic hyperglycemia in postprandial and fasting states due to the impairment of insulin production by pancreas β cells, insulin action at the selected tissues or both.[1] On a global scale, diabetes has reached epidemic proportions and is one of the significant contributors to the global economic burden of non-communicable disease. According to the International Diabetes Federation, the overall number of adult with diabetes worldwide in 2017 was approximately 425 million, and the number is estimated to be 629 million in 2045.[2] A recent report on the global economic burden of diabetes in adults aged 20–79 stated that the cost of diabetes globally was US$1.31 trillion in 2015, thus making it as one of the most expensive diseases to manage.[3] Due to the considerable cost associated with diabetes management, diabetes patients opted for complementary and alternative medicine (CAM) therapies to manage the disease. According to Dayeef, Karyono, Sujuti,[4] the prevalence of CAM namely medicinal plants in both developed and developing countries is attributable to its affordability, accessibility, and efficacy.

Annona muricata (Annonaceae) is one of the medicinal plants that has been widely studied for its therapeutic values. This widespread tree is local to tropical America but currently is planted worldwide. It is distributed for the most part in tropical and sub-tropical regions, including South and North America, Australia, India, Nigeria and Malaysia. *A. muricata* is known by different local names, for example soursop (English), graviola (Portuguese), Sirsak (Indonesia) and guanabana (Latin America).[5] Review of the literature indicated that all parts of *A. muricata* possess therapeutic values against numerous illnesses. The fruit has been reported to possess anti-depressive [6] and anti-cancer[7,8] effects. Leaves are effective against fever,[9] headache, sleep disorder, rheumatism,[10,11] viral infection,[12] breast cancer[13] and bacterial infection.[14] The stem bark may have adaptogenic[15] and antioxidant[16] potentials. In addition, the plant contains various phytoconstituents including alkaloids,[17] annonaceous acetogenins,[18] cyclopeptides,[19] megastigmanes,[20] flavonol triglycosides,[21] and phenolics.[22] Despite numerous studies of this plant and its properties, to date, no comprehensive evidence-based review has been conducted to establish the potential antidiabetic effect of *A. muricata*. Hence, this review aimed to summarize current and comprehensive studies of the efficacy of *A. muricata* as an antidiabetic agent.

Materials and Methods

Search Strategy

Six online databases (PubMed, ScienceDirect, Web of Science, Scopus, Google Scholar and SpringerLink) were used to conduct a comprehensive search of articles published until December 2018 with no end date limit. The following keywords were chosen based on MeSH terms; *Annona*/ soursop in combination with diabetes, glucose, and insulin.

Study Selection And Inclusion/ Exclusion Criteria

The title and abstract of each article were assessed and the duplicated articles were removed. The remaining articles were further assessed to determine their compatibility with the inclusion criterion, which were studies of the antidiabetic activity of *A. muricata*. Review articles, conference proceedings, commentaries, and abstracts in symposiums and congresses were excluded. Additionally, a manual search was carried out from the reference list of included articles for additional data or forward citations. All remaining titles, abstracts, and full articles were independently reviewed by two collaborators (IAA and NAY).

Data extraction

The information extracted from the articles included the year of publication, country, study models (*in vivo, in vitro*, clinical, and *in silico*), plant part used, extraction solvent and parameters measured (level of blood glucose, insulin, bodyweight, antioxidants, enzymes, lipid profile and histological study of pancreas and liver).

Results and Discussion

Literature Search

The literature search yielded a total of 167 records (from the year 2002 to April 2018). The following are the numbers of articles extracted from the respective databases: Google Scholar (n = 68), ScienceDirect (n = 35), PubMed (n = 25), Web of Science (n = 19), Scopus (n = 10), and SpringerLink (n=10). No relevant study was obtained through a manual search of the references of included papers or from any other data sources. After removing the

duplicate articles, 132 articles remained, of which 91 were excluded based on the review of title and abstract. Forty-one articles were further assessed by reading the full text, and 24 of them were excluded. Ultimately, 17 articles met the inclusion criterion (Figure 1). Those articles were classified into five groups based on the study models; clinical (n = 1), *in vivo* (n = 10), *in vitro* (n = 4), *in vivo* and *in vitro* (n = 1), and *in silico* (n = 1).

Most of the studies were conducted by researchers from Nigeria (8 studies), followed by Indonesia (4 studies), then Brazil (2 studies), and Cameroon, Peru and India (1 study each). The number of studies per region is related to the geographical distribution of *A. muricata* as local researchers tend to focus on native plants with potential ethnomedicinal uses.[5] The application of traditional and complementary medicine to manage diabetes in these regions also prompted research activity focused on medicinal plants. The highest number of articles were published in 2015 and 2017 (4 studies for each year), followed by 2008 (3 studies) and 2010 and 2013 (2 studies in for each year).

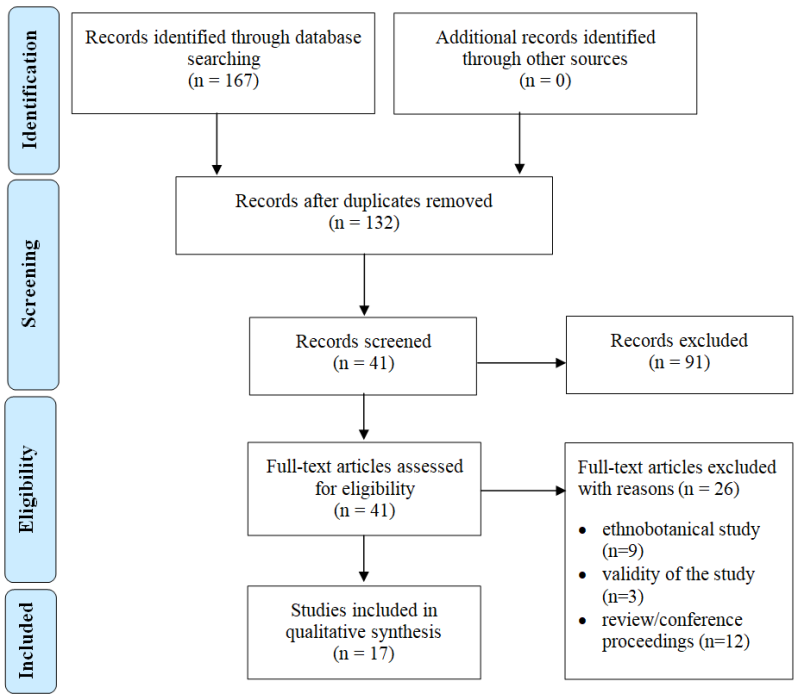

Fig.1: Method used for identification, screening, eligibility, and inclusion of the articles

Clinical Study

Based on the criteria, one clinical study was identified. Arroyo, Jaime, Ronceros Gerardo, Aníbal[23] evaluated the adjuvant effect of *A. muricata* in patients with type 2 diabetes mellitus. Three groups (n = 15) of patients were given 1, 2, and 3 capsules of ethanol extract of *A. muricata* leaves (180 mg) respectively, along with 5 mg of glibenclamide for a month. Three other groups were given glibenclamide only. A greater decrease in blood glucose level was observed in those who received *A. muricata* extract and glibenclamide, with 11% of them (5 patients) experienced side effects such as burning pain in epigastrium (two patients) and nausea (three patients).

***In Vivo* Studies**

The *in vivo* studies of *A. muricata* revealed that various parts of the plant showed potential antidiabetic effects when tested using rodent models (Table 1). Most of these studies tested the antidiabetic effect of leaf extracts (64%), whereas the other 27% focused on the seed extracts and only 9% examined the bark extract. Water and methanol

were the most frequently used solvents used to extract bioactive components of *A. muricata* (36% each), followed by ethanol (18%) and a mixture of methanol/ chloroform (10%). The studies show that polar solvents are preferable probably because they provide higher recovery yield of phenolic compounds than non-polar solvents.[24-26] Phenolic compounds from medicinal plants have been associated with various pharmacological activities of the medicinal plants, including anti-aging, antioxidant, anti-inflammatory, and anti-hyperglycemia.[27-29] The most common animal model used to study the antidiabetic activity of this plant was the streptozotocin (STZ)-induced diabetic rat models (64%). Other models used were alloxan-induced diabetic (9%), clozapine-induced diabetic (9%) and glucose preloaded models (9%). Ivorra, Paya, Villar[30] reported that the STZ-induced diabetic rat model is widely used because it is considered to be a good model for the preliminary screening of bioactive agents against diabetes.

Table 1: Effect of *A. muricata L.* on metabolic parameters determined through *in vivo* studies

Plant part-extract used	Dose-route of administration	Test Model	Duration	Findings of study	Reference
Leaves-methanol extract	100mg/kg – i.p.	STZ-induced diabetic rats	10 weeks	↑ Bodyweight, ↓ glucose level	(33)
Leaves-methanol extract	25, 50, 100, 200, 400mg/kg – i.p.	STZ-induced diabetic rats	10 weeks	↓ TC, TG, LDL, VLDL ↑ HDL and AAI	(31)
Leaves-aqueous extract	100, 200mg/kg – p.o.	STZ-induced diabetic rats	5 hours 4 weeks	Both doses: ↓ glucose level Both doses: ↓ glucose level, LDL, creatinine, AST, ALT, MDA, nitrites, restored TG, TC, SOD, CAT content	(32)
Seeds-methanol extract	600, 800 mg/kg – p.o.	Clozapine-induce diabetic rats	10 days	↓ Glucose level	(39)
Seeds- ethanol extract	100, 200, 400 mg/kg – p.o.	Glucose pre -loaded rat	120 minutes	↓ Glucose level	(38)
Bark-ethanol extract	150, 300 mg /kg – p.o.	Alloxan-indu -ced diabetic rats	6 hours 14 days	↓ Glucose level ↑ Bodyweight, ↓ glucose level ↓ TC, TG, LDL, VLDL ↑ HDL	(42)
Leaves-methanol extract	100 mg/kg – i.p.	STZ-induced diabetic rats	10 weeks	↑ Bodyweight, ↓ glucose level, regenerate pancreatic β-cells	(34)
Leaves- aqueous extract	100 mg/kg – p.o.	STZ-induced diabetic rats	60 days	No change in bodyweight ↓ glucose, ROS, MDA, TC, TG, LDL ↑ insulin level and antioxidant enzymes, enhance pancreas protective effect	(36)
Leaves- aqueous extract	100 mg/kg orally – p.o.	STZ-induced diabetic rat	8 hours	Normalize bodyweight, ↓ glucose level, ↑ insulin, ↑ antioxidant enzymes, protect pancreatic β cells	(35)
Leaves- aqueous extract	100 mg/kg orally – p.o.	STZ-induced diabetic rats	60 days	No change in body and liver weight, ↓ glucose	(43)

				level, TC, TG, LDL, normalize hexokinase and glucokinase activities , ↑ antioxidant enzymes	
Seed oil	1.0 mL/kg – p.o.	STZ induced T1D BALB/c mice	48 days	↓ Glucose level, ↑ insulin levels, preserve panc-reatic islets area, hepato -protective effect	(37)

i.p. (intraperitoneal), p.o. (per oral), STZ (streptozotocin), TC (total cholesterol), TG (triglyceride), LDL (low density lipoprotein), VLDL (very low density lipoprotein), HDL (high density lipoprotein), AAI (advanced atherogenic index), AST (aspartate aminotransferase), ALT (alanine aminotransferase), ROS (reactive oxygen species), SOD (superoxide dismutase), MDA (malondialdehyde), CAT (catalase).

Leaf extracts of *A. muricata* have been shown to have positive effects on the metabolic parameters of diabetes. For example, the leaf extracts in various doses were found to significantly decrease blood glucose levels, increase bodyweight, improve the serum lipid profile by decreasing total cholesterol (TC), triglycerides (TGs), low density lipoprotein-cholesterol (LDL-C), and very low density lipoprotein-cholesterol (VLDL-C), and increase the level of high density lipoprotein-cholesterol (HDL-C) and the percentage of anti-atherogenic index (AAI). They also altered the activity of the antioxidant enzymes such as glutathione, superoxide dismutase (SOD), and catalase.[31-33] Adeyemi, Komolafe, Adewole, Obuotor, Abiodun, Adenowo[34] and Adewole, Caxton-Martins[35] suggested that leaf extract of *A. muricata* might contain bioactive compounds that exert anti-hyperglycemic effect by stimulating and enhancing the secretion and action of insulin. This premise was supported by Adewole, Ojewole 36 who reported that leaf extracts of *A. muricata* could prevent degeneration of β-cells and to regenerate and proliferate the pancreatic β-cells destructed by STZ, thus replacing damaged cells and increasing the area of insulin immunoreactive β-cells and insulin production.

The seeds of *A. muricata* have also been reported to possess promising antidiabetic effects. Pinto, Cerqueira-Lima, dos Santos Suzarth, de Souza, Tosta, da Silva, de Oliveira Pires, de Almeida Queiroz, Teixeira, Dourado[37] found that diabetic mice treated with the extract of seed oil had lower glucose levels, higher insulin concentrations and a well-preserved pancreatic islet area, compared to untreated diabetic rats. Additionally, the histology of the liver tissues suggested the presence of a hepatoprotective effect, as the *A. muricata*-treated group had the normal architecture of hepatocytes with partial recovery of glycogen storage compared to the STZ-induced group. In addition to that, Hasanah, Sundhani, Nurulita[38] found that 400 mg/kg of ethanol seed extract to be effective in reducing blood glucose of glucose preloaded rats. In another study, a significant effect on the blood glucose level was observed at higher doses of the methanolic seed extract (600 and 800mg/kg) in clozapine-induced diabetic rats.[39] The observed hypoglycemic effect might be due to the secondary metabolites presented in *A. muricata* seed extracts like alkaloids, flavonoids, triterpenoids and tannins.[40,41] As for the bark extract, Ahalya, Shankar, Kiranmayi[42] demonstrated that 300 mg/kg of the ethanolic bark extract significantly reduced blood glucose level of alloxan-induced diabetic rats. The same extract also resulted in a significant improvement in the rat lipid profile by lowering TG, LDL, and TC and increasing HDL.

***In Vitro* Studies**

All of the *in vitro* studies of *A. muricata* demonstrated a significant effect of different parts of the plant on inhibition of α-amylase and α-glucosidase activities and on strengthening antioxidant capacities (Table 2). α-amylase is an enzyme that catalyzes the hydrolysis of polysaccharide (e.g., starch) into oligosaccharides (e.g., sucrose, maltose and lactose). These oligosaccharides are further degraded into absorbable monosaccharides (e.g., glucose, fructose, and galactose) by α-glucosidase

in the intestine.[43] Therefore, inhibition of these enzymes will eventually lead to suppression of postprandial hyperglycemia as the amount of glucose being absorbed into the blood circulation is delayed.[44] Oxidative stress plays a major role in the development of diabetes complications both in the microvascular and macrovascular systems. Oxidative stress in diabetics occurs primarily due to excessive oxygen free radical production from auto-oxidation of glucose, glycated protein, and glycation of antioxidative enzymes.[45] Oxygen free radicals are responsible for oxidative damage to macromolecules such as proteins, lipids, and nucleic acids in diabetic patients.[46] Most of these side effects can be prevented by the presence of antioxidants.[47]

A study conducted by Berawi, Shidarti, Nurdin, Lipoeto, Wahid[48] on the leaf of *A. muricata* demonstrated a potential inhibitory activity of the methanol extract against α-amylase and α-glucosidase while the water extract showed high total phenolic content. In another study, Justino, Miranda, Franco, Martins, da Silva, Espindola[49] reported that, the ethyl acetate and n-butanol fractions of the ethanolic extract of *A. muricata* leaves had potent antioxidant capacity, suppressed the activities of α-amylase, α-glucosidase, and pancreatic lipase, inhibited formation of advanced glycation end-products and reduced lipid peroxidation in the liver as compared to the other fractions. Lipid peroxidation is known to be induced in type 2 diabetes mellitus due to hyperglycemia-induced free radicals production.[50] Thus, Justino et al.'s findings suggested a promising use of the *A. muricata* leaf, particularly its polyphenol-enriched fractions, as a therapy for treating diabetes. Same finding was reported by Hardoko, Wijoyo, Halim[51] on the aqueous extract of leaf in terms of suppressing α-glucosidase activity. The pericarp, pulp and seeds of *A. muricata* have also been reported to possess promising enzyme inhibitory effects. Aqueous extract of these parts inhibited the activity of α glucosidase and α amylase in a concentration dependent manner.[52]

Table 2: Effect of *A. muricata L.* on metabolic parameters determined through *in vitro* studies

Plant part	Dose/ concen -tration	Test Model	Extract/ fraction	Effect	Reference
Leaves	0.3, 0.6, 0.9, 1.2, 1.5 mg/ml	α-amylase assay	Methanol extract	Inhibited α-amylase activity	(49)
		α-glucosidase assay	Methanol extract	Inhibited α-glucosidase activity	
		Total phenol content	Aqueous extract	High total phenol content	
Leaves	20, 40, 60, 80 µg/ml	α-amylase assay	Ethanol extract and n-butanol fraction	Inhibited α-amylase activity	(50)
	500, 1000, 1500 µg/ml	α-glucosidase assay		Inhibited α-glucosidase activity	
	500, 1500, 2000 µg/ml	Pancreatic lipase inhibition		Inhibited pancreatic lipase activity	
	0.15, 1.5 and 15 µg/ml	Lipid peroxidation		Reduced liver lipid peroxidation	
Pericarp, pulp and seed	0.2, 0.4, 0.6, 0.8 mg/ml	α-amylase assay	Aqueous extract	Concentration-dependent inhibition	(53)
		α-glucosidase assay		Concentration-dependent inhibition	
Leaves	6.25, 12.5, 22 and 50 ppm	α-glucosidase assay	Aqueous extract	Concentration-dependent inhibition	(52)

mg/ml (milligram per milliliter), µg mL-1 (microgram per milliliter), IC_{50} (concentration required to reduce the rate of reaction by 50%), DPPH (2,2-diphenyl-1-picrylhydrazyl), ORAC (oxygen radical absorbance capacity), FRAP (ferric reducing antioxidant power).

***In Silico* Study**

One computational study has been carried out to study the effect of *A. muricata* on metabolic parameters related to diabetes condition.[53] In that study, the effect of selected *A. muricata* active compounds (rutin, muricatocin A, anonaine, isolaureline, xylopine, and kaempferol 3-O-rutinoside) on inhibition of the Forkhead Box O1 (FOXO1) protein was evaluated. The FOXO1 protein plays a crucial role in the proliferation process of pancreatic β-cells and inhibition of the FOXO1 protein activity in the nucleus will enhance insulin sensitivity, as previously reported.[54,55] The study revealed that active compounds in *A. muricata* leaves had similar or less free binding energy than the control. Muricatocin A and rutin were found to have a same binding effect against 66% of amino acid residues, whereas the other four active compounds had the equal binding ability of 33% of amino acid residues as compared to the control with hydrogen bonds.

Possible Mechanism Underlying the Antidiabetic Action of *A. Muricata* L.

Review of the literature indicated that the observed blood-glucose-lowering effect of *A. muricata* might be due to the following several possible mechanisms of action

Pancreatic β-cell protection/ regeneration

Pancreatic β-cells are responsible for the restoration and secretion of insulin, a hormone that is important for the metabolism of carbohydrate, fat, and protein. Reduced β-cell mass and impaired insulin secretion are responsible for the progression of hyperglycemic conditions to diabetes; therefore, preservation of β-cells is an important therapeutic goal to prevent diabetes development and progression. Several studies have reported the pancreas protective effects of *A. muricata* which include regeneration of pancreatic β-cells after STZ destruction,[34] preservation of pancreatic islet area,[37] proliferation or renewal of β-cells,[32] and inhibition of FOXO1 protein.[53] These pancreas protective effects resulted in significant improvement in insulin secretion and action[33,34,39] that eventually lead to the normalization of the blood glucose level in diabetic rat models.

Hepatoprotective Effect

The liver plays a vital role in the glucose homeostasis by controlling numerous pathways of glucose metabolism, namely gluconeogenesis, glycogenesis and glycolysis. Thus, the hepatoprotective effect of *A. muricata* could bring a significant contribution to its observed antidiabetic effect. Histology of the liver tissues showed a typical architecture of hepatocytes in the *A. muricata* treated group, with partial recovery of glycogen storage, compared to the STZ-induced group.[32] Justino, Miranda, Franco, Martins, da Silva, Espindola[49] also demonstrated the effect of this plant in reducing liver lipid peroxidation.

Antioxidant Properties

It has been shown that in the diabetic states, antioxidant defenses are altered due to the presence of chronic hyperglycemia, which results in reduced antioxidant levels, increased free radical regeneration, and increased oxidative stress.[56] Oxidative stress plays a significant role in the development of diabetes complications both in the microvascular and macrovascular systems. Oxidative stress in people with diabetes occurs primarily due to excessive oxygen free radical production from auto-oxidation of glucose, glycated protein, and glycation of antioxidative enzymes.[45] Oxygen-free radicals are responsible for oxidative damage to macromolecules such as proteins, lipids, and nucleic acids in diabetic patients.[46] Most of these side effects can be prevented by the presence of antioxidants.[47] Hence, plants with antioxidant ingredients have the potential to fight against oxidative stress and contribute to the amelioration of hyperglycemia condition. *In vivo* studies using diabetic rat model have shown that administration of *A. muricata* extracts can lower blood glucose level and simultaneously restored antioxidant enzymes namely superoxide dismutase (SOD), catalase and nitrite oxide and also reduced lipid peroxidation by suppressing malondialdehyde and transaminase activities.[32,35,36,57] In accordance with *in vivo* findings, *in vitro* studies using DPPH, FRAP and ORAC assays demonstrated the ability of *A. muricata*'s extracts to scavenge free radicals.[49] Furthermore, phytochemical analysis of *A. muricata* revealed the presence of total phenolic compounds such as tannins and flavonoids that are known for their antioxidant properties.[48,58] These findings suggested the protective role of this plant's extracts against oxidative stress and associated their activities with the observed anti-hyperglycemic effect.

Intestinal α-Glucosidase and α-Amylase Inhibitory Effect

All the *in vitro* studies of *A. muricata* showed inhibitory activities against the enzymes α-amylase and α-glucosidase. α-amylase is an enzyme that catalyzes the hydrolysis of polysaccharide (e.g., starch) into oligosaccharides (e.g., sucrose, maltose and lactose). These oligosaccharides are further degraded into absorbable monosaccharides (e.g., glucose, fructose, and galactose) by α-glucosidase in the intestine.[43] Therefore, inhibition of these enzymes will eventually lead to suppression of postprandial hyperglycemia as the amount of glucose being absorbed into the blood circulation is delayed.[44] These findings might explain the low blood glucose level after *A. muricata* ingestion.

Conclusion

A. muricata L. is a coveted tropical tree that has been widely used in traditional medicine to treat different medical conditions. A literature review indicates *A. muricata* to be a potential therapeutic agent for the management of diabetes mellitus and its complications. It promotes better glycemic control, normalizes lipid parameters, stimulates insulin secretion and action and improves the morphology of pancreas and liver. Though past studies seem to provide sound pharmacological confirmation of the folkloric usage of this plant, they suffered from several limitations. We conclude with the critical caveat that; many questions still need to be addressed regarding *A. muricata* as a safe antidiabetic agent. Firstly, further investigations are required to identify and characterize the active principle ingredients responsible for its antidiabetic effect, establish its safety profile, and determine the therapeutic index of all active ingredients. The conclusion must be made as to whether the antidiabetic effect is due to a single compound or the synergistic effect of multiple compounds. Secondly, studies on the mechanism of action at the cellular and molecular levels should be conducted because available data does not fully explain the observed effect. By knowing the target pathway, specific effect of the extract or its active principle could be monitored, thus, enabling dosage adjustment. Metabolic studies are also needed to determine the effect of the hepatic first-pass and digestive enzymes on the bioactivity of the extract or its active principle. Thirdly, there is a lack in a clinical validation as most of the preclinical data retrieved has not been clinically validated. Despite a body of preclinical evidence suggesting its potential use for managing diabetes, it is necessary to conduct well-designed clinical trials that are randomized and systematic to validate the efficacy and safety of this plant further. Also, trials should test and compare whether the extract/ active compound of *A. muricata* is useful as a single therapy or, at best, as an adjuvant therapy with concurrent oral hypoglycemic agents. Considering that *A. muricata* is widely consumed worldwide, further exploration of its potential is worthwhile.

Author Disclosure Statement

The authors declared there is no potential conflict of interest concerning the research, authorship, and publication of these articles.

Acknowledgments

This work was supported by the short-term research grant (304/CIPPT/6315187) from Universiti Sains Malaysia.

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