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Anti-Hyperglycaemic and Anti-Hyperlipidemic Effect of Acacia Senegal Leaf Extract in Alloxan Induced Diabetic Rat

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ABSTRACT: Diabetes mellitus (DM), an endocrine syndrome characterized by high blood glucose levels due to abrogated insulin activity. The existing treatments for DM have side effects and varying degrees of efficacy. Therefore, it is paramount that novel approaches be developed to enhance the management of DM. Therapeutic plants have been accredited as having comparatively high efficacy with fewer adverse effects. The current study aims to elucidate the phytochemical profile, anti-hyperlipidemic, and anti-diabetic effects of methanolic extract Acacia senegal(leaves) in Alloxan-induced diabetic rats. Alloxan was injected intraperitoneally (150 mg kg-1, b.w), to induced diabetes in rats. The rats were divided into three groups (n=10). Group 1 (normal control) received normal food and purified water, Group II (diabetic control) received regular feed and clean water and group III (diabetic treated) received a methanolic extract of the plant (300 mg kg-1) for 28 days with a typical diet and clean water throughout the experiment. Blood samples were collected to checked serum glucose and concentration of LDL, TC, TG. The extract demonstrated significant antihyperglycemic activity ($P<0.05$), whereas improvements in rats's body weight and lipid profiles were observed after treatment with the extract. This study establishes that the extract has high efficacy with comparatively less toxicity that can be used for DM management.

KEYWORDS: Diabetes Mellitus, rats, anti-hyperglycaemic, antihyperlipidimic, blood, toxicity, Acacia senegal

I. INTRODUCTION

Diabetes mellitus (DM) is a serious, chronic, and complex metabolic disorder of multiple aetiologies with profound consequences, both acute and chronic [1]. Also known only as diabetes, DM and its complications affect rats both in the developing and developed countries, leading to a major socioeconomic challenge. It is estimated that 25% of the world population is affected by this disease [2]. Genetic and environmental factors contribute significantly to the development of diabetes [3]. During the development of diabetes, the cells of the body cannot metabolize sugar properly due to deficient action of insulin on target tissues resulting from insensitivity or lack of insulin (a peptide hormone that regulates blood glucose). The inability of insulin to metabolize sugar occurs when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. This triggers the body to break down its own fat, protein, and glycogen to produce sugar, leading to the presence of high sugar levels in the blood with excess by-products called ketones being produced by the liver [4,5]. Diabetes is distinguished by chronic hyperglycemia with disturbances in the macromolecules' metabolism as a result of impairments in insulin secretion, insulin action, or both. Diabetes causes long-term damage, dysfunction, and failure of various organ systems (heart, blood vessels, eyes, kidneys, and nerves), leading to disability and premature death [6]. The severity of damage triggered by hyperglycemia on the respective organ systems may be related to how long the disease has been present and how well it has been controlled. Several symptoms such as thirst, polyuria, blurring of vision, and weight loss also accompany diabetes [7].

Types of Diabetes, Prevalence, and Management

There are various types of diabetes of which type 1 DM (T1DM) and type 2 DM (T2DM) were the most usually discussed. The T1DM is also known as insulin-dependent diabetes. It is primarily due to pancreatic islet beta cell destruction and is characterized by deficient insulin production in the body [6]. Patients with T1DM are prone to ketoacidosis and need daily administration of insulin to control the amount of glucose in their blood. The majority of T1DM occurs in children and adolescents [5]. On the other hand, T2DM, also known as non-insulin-dependent diabetes, results from the body's ineffective use of insulin and hyperglycemia [8,9] and accounts for the vast majority of rats with diabetes around the world. Insulin resistance is due to a reduced responsiveness of target tissues to normal circulating levels of insulin [9]. Ethnicity, family history of diabetes, and previous gestational diabetes, older age, overweight and obesity, unhealthy diet, physical inactivity, and smoking increase diabetes risk. Most rats with diabetes

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are affected by T2DM diabetes (90%), usually occur nearly entirely among adults but, in these days, is increasing in children [5].

The universal prevalence of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population. Moreover, the prevalence of diabetes has also been found to steadily increase for the past 3 decades and has risen faster in low- and middle-income countries compared to high-income countries. The increase in the prevalence of diabetes is parallel with an increase in associated risk factors such as being overweight or obese. If not properly treated or controlled, diabetes may cause blindness, kidney failure, lower limb amputation, and other long-term consequences that impact significantly on the quality of life [10]. Interestingly, the WHO also projects that diabetes will be the seventh leading cause of death in 2030 [11]. The incidence and prevalence of diabetes have continued to increase globally, despite a great deal of research with the resulting burden resting more heavily on tropical developing countries [12,13]. Based on demographic studies, by 2030, the number of rats older than 64 years with diabetes will be greater in developing countries (≥82 million) in comparison to that in developed countries (≥48 million). The greatest relative increases are projected to occur in the Middle East crescent, sub-Saharan Africa, and India [14,15].

Amongst all rats with diabetes, T2DM accounts for the majority (90%) of cases, and these can be prevented as well as treated easily, while T1DM cannot be prevented with current knowledge. Since management of diabetes is complex and multidisciplinary, it should include primary prevention through promotion of a healthy diet and lifestyle (such as exercise). Dietary management and exercise represent important pillars of care and are crucial in the treatment of T2DM, and both may be adequate to attain and retain the therapeutic goals to normolipidemic and normoglycemia.[1,2,3]

Antidiabetic Drugs and Their Side Effects

There are several classes of oral hypoglycemic drugs that exert antidiabetic effects through different mechanisms, namely sulfonylureas, biguanides, α-glucosidase inhibitors, thiazolidinediones, and non-sulfonylureas secretagogues. Oral sulfonylureas, such as glimepiride and glyburide, act to reduce blood sugar, mainly by elevating insulin release from islets of Langerhans. This is achieved through binding with the sulfonylurea receptor on β cells resulting in adenosine triphosphate-dependent potassium channels closure. As a result, the cell membrane depolarizes and the following calcium influx accompanied by secretion of stored insulin from secretory granules within the cells takes place. This mechanism works only in the presence of insulin [16,17].

Another oral hypoglycemic drug, the biguanides, acts to reduce hepatic gluconeogenesis and to replenish peripheral tissues' sensitivity to insulin, actions that are achieved through elevation of insulin-stimulated uptake and use of sugar. Nevertheless, biguanides are ineffective in insulin absence. The best example of this class is metformin.

The α-glucosidase inhibitors, such as acarbose and miglitol, impede certain enzymes responsible for the breakdown of carbohydrates in the small intestine. This class of hypoglycemic agents acts mostly by reducing the absorption rate of carbohydrates in the body. Also, acarbose reversibly inhibits both pancreatic α-amylase and α-glucosidase enzymes by binding to the carbohydrate-binding region and by interfering with their hydrolysis into monosaccharides, which leads to a slower absorption together with a reduction in postprandial blood sugar levels [16,18].

Another important class of oral hypoglycemic agents is the thiazolidinediones (TZDs), such as pioglitazone and rosiglitazone, of which the mechanism of action primarily includes improving muscle and adipose tissue sensitivity to insulin and, to a smaller extent, reducing liver glucose production. TZDs also are potent and selective agonists to the nuclear peroxisome proliferator-activated receptor gamma (PPARγ) present in liver, skeletal muscle, and adipose tissue. Activation of PPARγ receptors controls the transcription of insulin-responsive genes involved in the regulation of transportation, production, and glucose use. Also, TZDs have been reported to augment β-cell function by lowering free fatty acid levels that ultimately lead to β-cell death [19].

The last class of oral hypoglycemic agents is the non-sulfonylureas secretagogues, which include meglitinide and repaglinide and which increases the secretion of insulin from active β cells by a similar mechanism as sulfonylureas. However, this class of oral antidiabetic agents binds to different β-cell receptors [20].

Although synthetic oral hypoglycemic drugs alongside insulin are the main route for controlling diabetes, they fail to reverse the course of its complications completely and further worsen it by the fact that they also demonstrate prominent side effects. This forms the main force for discovering alternative sources of antidiabetic agents [21]. Despite the significant progress made in the treatment of diabetes using oral antidiabetic agents in the past three decades, the results of treatment of diabetic patients are still far from perfect. Several disadvantages have been reported

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related to the use of those oral hypoglycemic agents, including drug resistance (reduction of efficiency), adverse effects, and even toxicity. For example, sulfonylureas lose their effectiveness after 6 years of treatment in approximately 44% of patients, whereas glucose-lowering drugs are reported to be not able to control hyperlipidemia [22]. Due to the several limitations associated with the use of existing synthetic antidiabetic drugs, the search for newer antidiabetic drugs from natural source continues [23].

Acacia senegal as an Alternative Source of Antidiabetic Agents

Natural products, particularly of plant origin, are the main quarry for discovering promising lead candidates and play an imperative role in the upcoming drug development programs [24,25,26]. Ease of availability, low cost, and least side effects make plant-based preparations the main key player of all available therapies, especially in rural areas [27]. Moreover, many plants provide a rich source of bioactive chemicals, which are free from undesirable side effects and possess powerful pharmacological actions [28,29,30,31,32,33,34]. Plants also have always been an exemplary source of drugs with many of the currently available drugs being obtained directly or indirectly from them [2,29,30,31]. The recent review of Durazzo et al. [35] gives a current snapshot of the strict interaction between the main biologically active compounds in plants and botanicals by giving a mini overview of botanicals features, a definition of the study, and examples of innovative (i.e., an assessment of the interaction of bioactive compounds, chemometrics, and the new goal of biorefineries) and a description of existing databases (i.e., plant metabolic pathways, food composition, bioactive compounds, dietary supplements, and dietary markers); in this regard, the authors marked the need for categorization of botanicals as useful tools for health research [35].

For centuries, many plants have been considered a fundamental source of potent antidiabetic drugs. In developing countries, particularly, Acacia Senegal are used to treat diabetes to overcome the burden of the cost of conventional medicines to the population [2]. Nowadays, treatments of diseases including diabetes using Acacia senegalare recommended [36] because these plants contain various phytoconstituents such as flavonoids, terpenoids, saponins, carotenoids, alkaloids, and glycosides, which may possess antidiabetic activities [37]. Also marked by Durazzo et al. [35], the combined action of biologically active compounds (i.e., polyphenols, carotenoids, lignans, coumarins, glucosinolates, etc.) leads to the potential beneficial properties of each plant matrix, and this can represent the first step for understanding their biological actions and beneficial activities. Generally, the main current approaches of study [38,39] of the interactions of phytochemicals can be classified: (i) model system development of interactions [40,41,42]; (ii) study of extractable and nonextractablecompounds [43,44]; or (iii) characterization of biologically active compound-rich extracts [45,46].

The antihyperglycemic effects resulting from treatment with plants are usually attributed to their ability to improve the performance of pancreatic tissue, which is done by increasing insulin secretions or by reducing the intestinal absorption of glucose [2].

The number of rats with diabetes today has been growing and causing increasing concerns in the medical community and the public. Despite the presence of antidiabetic drugs in the pharmaceutical market, the treatment of diabetes with Acacia senegalis often successful. Herbal medicines and plant components with insignificant toxicity and no side effects are notable therapeutic options for the treatment of diabetes around the world [47]. Most tests have demonstrated the benefits of Acacia senegalcontaining hypoglycemic properties in diabetes management. Ríos et al. [48] described Acacia senegal(i.e., aloe, banaba, bitter melon, caper, cinnamon, cocoa, coffee, fenugreek, garlic, guava, gymnema, nettle, sage, soybean, green and black tea, turmeric, walnut, and yerba mate) used for treating diabetes and its comorbidities and the mechanisms of natural products as antidiabetic agents, with attention to compounds of high interest such as fukugetin, palmatine, berberine, honokiol, amorfrutins, trigonelline, gymnemic acids, gurmarin, and phlorizin. The current review of Bindu and Narendhirakannan [49] has categorized and described from literature 81 plants native to Asian countries with antidiabetic, antihyperglycemic, hypoglycemic, anti-lipidemic, and insulin-mimetic properties.[4,5,6]

Traditional knowledge of antidiabetic Asian plants: (1) Review in Iran [50,51,52,53,54]; (2) Review in Jordan [55,56,57]; (3)Review in Malaysia [58,59]; (4) Review in Mongolia [60]; (5) Review in Philippines [61,62]; (6) Review in Saudi Arabia [63,64,65]; (7) Review in Korea [66,67,68]; (8) Review in Sri Lanka [69]; (9) Review in Syria [70]; (10) Review in Thailand [71,72,73,74,75]; (11) Review in Turkey [76,77,78,79,80,81,82]; (12) Review in Vietnam [83,84,85]; (13) Review in India [86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105]; and (14) Review in China [99,106,107,108,109,110,111,112].

The biological activities considered in this review are antidiabetic, antihyperglycemic, and hypoglycemic activities as well as α-amylase and α-glucosidase inhibition. A majority of the plant species was tested for antidiabetic activity. The

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methodology followed while collecting the plant species should influence the treatment of diabetes. Accordingly, the plants screened from the Asian region were selected.

II. DISCUSSION

THE particular purpose of this research was to assess the antidiabetic, antihyperlipidemic and antioxidant activities of Acacia senegal methanol extract. In addition, a phytochemical study for A. senegal has been performed. Isolation and identification of pure compounds were carried out by different chromatographic and spectroscopic techniques. Quercetin, kaempferol and their glycosides have been isolated from A. senegal leaves. Structures of the isolated compounds have been estimated by 1D/2D 1H/13C-NMR spectroscopy. Methanolic extract of the leaves of A. senegal improved the diabetes status, and it showed antidiabetic, antihyperlipidimic and antioxidant effects in rats. These findings suggest that A. senegal leaves may be used as hypolipidemic and normo-glycemic agents, additionally; A. senegal is a rich source of phenolic compounds.[7,8,9]

Medicinal plants are considered an alternative therapy for diabetes mellitus as they regulate glucose levels. Moreover, a variety of plants offer a rich source of bioactive compounds that have potent pharmacological effects without any negative side effects. The present study aimed to clarify the effects of Arabic gum/Gum Acacia (GA) on the biochemical, histopathological, and immunohistochemical changes observed in diabetic rats. Further, the anti-inflammatory activity of GA in response to diabetes, through inflammatory mediators analysis. Male rats were divided into four groups: untreated control, diabetic, Arabic gum-treated, and Arabic gum-treated diabetic rats. Diabetes was induced using alloxan. Animals were sacrificed after 7 and 21 days of treatment with Arabic gum. Body weight, blood and pancreas tissue samples were collected for analysis. Alloxan injection significantly decreased body weight, increased glucose levels, decreased insulin levels, and caused depletion of islets of Langerhans and β-cell damage in the pancreas. Arabic gum treatment of diabetic rats significantly increased body weight, decreased serum glucose levels, increased insulin levels, exerts anti-inflammatory effect, and improved the pancreas tissue structure. Arabic gum has beneficial pharmacological effects in diabetic rats; therefore, it might be employed as diabetic therapy to reduce the hyperglycemic damage and may be applicable for many autoimmune and inflammatory diseases treatment. Further, the new bioactive substances, such as medications made from plants, have larger safety margins, and can be used for a longer period of time.[10,11,12]

III. RESULTS

This study was designed to investigate the effect of an aqueous methanol extract of Acacia Senegal pods Anp) on various biochemical parameters, namely blood glucose levels, total cholesterol, High density lipids (HDLs), triglycerides, Serum Glutamate Oxaloacetate and Pyruvate Transaminase (SGOT, SGPT) and serum creatinine clearance in alloxan-induced diabetic rats. Rats were divided into three experimental groups: control, diabetic and Anp treated. The Anp treated group was further subdivided into three different groups based on the dose administered. This showed that a dose of 400 mg/kg body weight maximally reduced the blood glucose levels as compared to the diabetic group ($p<0.001$). This dose also significantly ($p<0.05$) lowered the plasma total cholesterol, triglyceride and Low-density lipids (LDLs) in treated rats as compared to diabetic rats. Furthermore, the same dose also significantly increased the plasma HDL levels of the treated group when compared with the diabetic group. Whereas the activity of SGOT and SGPT were decreased significantly ($p<0.001$). Anp extract in treated diabetic rats. Anp treatment showed no significant effect on creatinine clearance. For interest a paper with similar aims, but using water extract of Nigella stiva L. appeared in this journal in 2004, (Merel et at, 31 (1), 49-53). Diabetes is an endocrine disorder associated with high blood glucose levels and irregular metabolism. Long-lasting high levels of glucose are related to numerous problems, such as cardiovascular disease, kidney disease and visual defects (SINGH et al., 2016) Existing treatments for diabetes have numerous adversities (Mukundi et al., 2015). Therefore, the exploration of safe, accessible and low-priced antidiabetic substances needs to be sustained (Rajagopal and Sasikala, 2008). Plant derivatives have been demonstrated as being active and effective in treating DM. The WHO estimates that 80% of people worldwide utilize plant remedies for the treatment of different types of diseases (Alarcon Aguilar et al., 2000). [13,14,15]The consumption of plant extracts and their active compounds has increased worldwide owing to the evident benefits. In this investigation, diabetes was induced by the administration of an inducing agent called Alloxan monohydrate. This drug destroys and decreases the pancreatic β-cell population in the islets of Langerhans by the production of reactive oxygen species i.e. nitric oxide (Szkudelski, 2001). The oral administration of a methanolic leaf extract of Acacia Senegal in diabetic rats revealed glucose-lowering activities, indicating that the plants constituents have glucose-lowering compounds. The blood glucose reducing activity of the extract may be due to an increase in the use of glucose by marginal cells in muscles, liver and fat cells owing to increased insulin sensitivity and upregulation of insulin receptors or short activation of β-cells of the pancreas lead to insulin release (Ayodhya et al., 2010). The anti-hyperglycemic activity of

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the extract may also be due the interference of nutritive carbohydrates and disaccharide absorption in the small intestines of rats resulting in digestive flexibility and pouring (Esmaeili and Yazdanparast, 2004). This could also be due to renewed β-cells (Sharma et al., 2006; Lombardo and Chicco, 2006), and/or increased sensitivity to insulin. The extract of the plant may also enhance liver function such as the uptake of glucose, facilitating the transportation of serum glucose to outlying tissue and consumption (Ikmal et al. 2013). The glucose reducing influence of our plant extract is similar to that observed in previous studies. For example, the aqueous leaf extracts of Acacia showed anti-diabetic action by improving either the secretion of pancreatic insulin from the β-cells or the discharge of attached insulin (Njagi et al., 2015). A chemical component present in garlic has also been shown to exert anti-oxidative action by removing reactive oxygen species and enhancing cellular antioxidant enzymes like superoxide dismutase, catalase, and glutathione peroxidase (Njagi et al., 2015). Murugi et al., (2012) demonstrated that acacia leaf extracts show a glucose lowering effect in Alloxan-induced diabetic rats at dosage of 50, 100 and 150 mg kg-1 by weight the administration of Acacia senegal orally at a dosage of 300 mg kg1body weight also reduced the fasting blood glucose levels in rats(Xu et al., 2015). There is a higher anti-diabetic effect observed when anti-hyperglycemic plant extracts are administered intraperitoneally as compared to the oral route, potentially due to the relatively reduced rate of assimilation (Meezan et al., 2005). The plant extract in our study may be absorbed by active transport at a dosage of 300 mg kg-1of body weight. The lesser glucose levels in rats orally and intraperitoneally administered with extracts can be a consequence of high glycolysis (Meezan et al., 2005).[16,17,18] The methanolic leaf extract of Acacia Senegal indicates insulin-mimetic action and at times worked better than traditional medicines orally administered, these may be due to the element that increases absorption of glucose by marginal mediation of GLUT-4 or the extracts might be effortlessly immersed in the intraperitoneal cavity and gastrointestinal mucosa. The anti-hyperglycemic influence of the extracts of the Acacia senegal might also be accredited to the existence of numerous phytochemical ingredients it contains sterols, tannins, saponins, alkaloids, terpenoids, flavanoids, free and bound anthraquinones etc, that have been related with anti-diabetic influence (Modak et al., 2007). The conclusion of the anti-diabetic effects of Acacia senegal could be attributed therefore to these detected components. The polyhydroxylated flavonol improves lipid production and glucose absorption in the adipocyte's tissues, likewise, flavonoid and myricetin have insulin-mimetic activities (Modak et al., 2007). Epicatechin and its active ingredients have been shown to enable insulin discharge through the conversion of proinsulin to insulin in vitro. It has been revealed that the flavonoid component from Acacia could be indicated for pancreatic beta-cell regeneration (Li et al., 2009). Flavonoid glycosides such as isostrictinin, pedunculagin, and strictinin are the active ingredients of Acacia, which are being used in the clinical management of diabetes due to increased insulin secretion (Li et al., 2009) and this is also observed in our studied plant. At 50-150 mg kg-1 flavonoids isolated from the leaf of Acacia decreases lipid and glucose level in Alloxan-induced diabetic rats (Shukla et al., 2012) corroborating with the outcome of our study where blood glucose and lipid levels, were improved. The aqueous leaf extract of Acacia senegal consists of alkaloids, which are recognized to have blood glucose level lowering capacity, also found in the plant Acacia senegal El-Mahmood et al., (2008). An alkaloid fraction from Acacia senegal exhibits hypoglycemic prospective in rats (Sharma et al., 2010), the same component was found in our studied extract. Alkaloids and tetrandrine show antioxidant actions attributable to many natural actions related to this plant's anti-diabetic influence. The alkaloids l-of Acacia senegal plant has shown glucose-lowering action in rats with diabetes due to restoration and renewal of atrophied pancreatic cells that discharge insulin (Piero et al., 2015; Alarcon-Aguilar et al., 2000). Similar constituents were also investigated in the Acacia senegal plant, which has confirmed glucose reducing effects. The aqueous leaf extract of Acacia senegal contains saponins that have been shown to exhibit glucose-lowering effects (Arika et al., 2015). The intraperitoneal dosage of 100, 200 mg kg-1b.w of the leaf extract of Acacia senegal in Alloxan-induced diabetic rats showed the presence of saponins (that are also present in Acacia senegal) that lower blood glucose and adrenaline levels without effecting the blood glucose levels in untreated rats. Kumari et al.confirmed that 50% of Acacia senegal consists tannins which have been shown to reduce blood glucose in diabetic rats (Kumari et al., 2014). The methanolic leaf extract of Acacia senegal also consists of tannins that are known to have anti-diabetic effects. In medical reports, all kinds of tannins may contribute to managing sugar concentration in blood.[19]

IV. CONCLUSION

The methanolic leaf extracts of Acacia senegal has antidiabetic potential due to the existence of important phytochemicals that confer the anti-diabetic actions. The oral administration of methanolic extract was however found to be very active in lowering the blood glucose, normalizing weight as well as marginally improving lipid profiles. The anti-diabetic potential of the plant extract investigated may be due to the occurrence of phytochemicals. Therefore, this work proves the medicinal use of Acacia senegal and demonstrates its effectiveness in controlling DM. Further investigations need to be carried out focusing on the molecular underpinnings leading to its use in treating DM. Investigation and utilization of this plant in advanced wildlife or human subject experiments should also be planned to determine its full drug potential.[20]

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