ROLE OF DIET AND PLANTS ON DIABETIC PATIENTS - A CRITICAL APPRAISAL

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Large section of Afro-Asian population depends on the indigenous medicinal practices for the treatment of diabetes. These are largely based on the use of roots, leaves, fruits and flowers of different plants. Diabetes occurs due to inefficiency to produce insulin or the absence of proper function of insulin to maintain glucose in the body. This review aims to verify whether neem *leaves (Azadirachta indica) and mahogany seeds (Swietenia macrophylla) have any beneficial effect on diabetic patients. Neem leaves and mahogany seeds are used as traditional plant for treatment of diabetes. Hypoglycemic effect is observed with neem leaves when given as a leaf extract. The mahogany seeds revealed the presence of triterpenoids. These triterpenoids may serve as potential hypoglycemic agent in mahogany seeds.*

Introduction

Diabetes mellitus often has been referred to as a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormal of high blood sugar levels (hyperglycemia) [1].

Type I diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas leading to a deficiency of insulin. The majority of type-I diabetes is of the immune-mediated variety, where beta cell loss is a T-cell mediated autoimmune attack[2]. NAD(P)H oxidase activation may play an important role in the development of diabetic vascular complications, progressive pancreatic β-cell dysfunction and metabolic syndrome (Fig. 1). In general, the development of type II diabetes is associated with pancreatic beta-cell dysfunction occurring together with insulin resistance [3-6]. Abdominal fat is especially active hormonally, secreting a group of hormones called adipokines that may possibly impair glucose tolerance. Obesity is found in approximately 55% of patients diagnosed with type II diabetes [7]. See Table 1. for estimated Number of People with Diabetes**.**

Initial stage of diabetes is pre-diabetes which is the state in which blood glucose levels are above normal but have not reached those of diabetes. This state is also referred to as borderline diabetes, impaired glucose tolerance (IGT), and/or impaired fasting glucose (IFG). These are associated with insulin resistance and are risk factors for the development of type II diabetes mellitus. In addition, obesity, family history of type II diabetes mellitus, and certain ethnic groups are also at high-risk. Those in this stratum (IGT or IFG) are at increased risk of cardiovascular disease [8, 9, 10] .

Path Physiology of Pre-diabetes

The beta cells reduce their insulin output as blood glucose levels fall, with the result that blood glucose is maintained at approximately 5 mmol/L (mM) (90 mg/dL). In an insulin-resistant person, normal levels of insulin do not have the same effect on muscle and adipose cells, with the result that glucose levels stay higher than normal. It is often seen when hyperglycemia develops after a meal, when pancreatic β-cells are unable to produce sufficient insulin to maintain normal blood sugar levels. The inability

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Mechanism of Diabetes

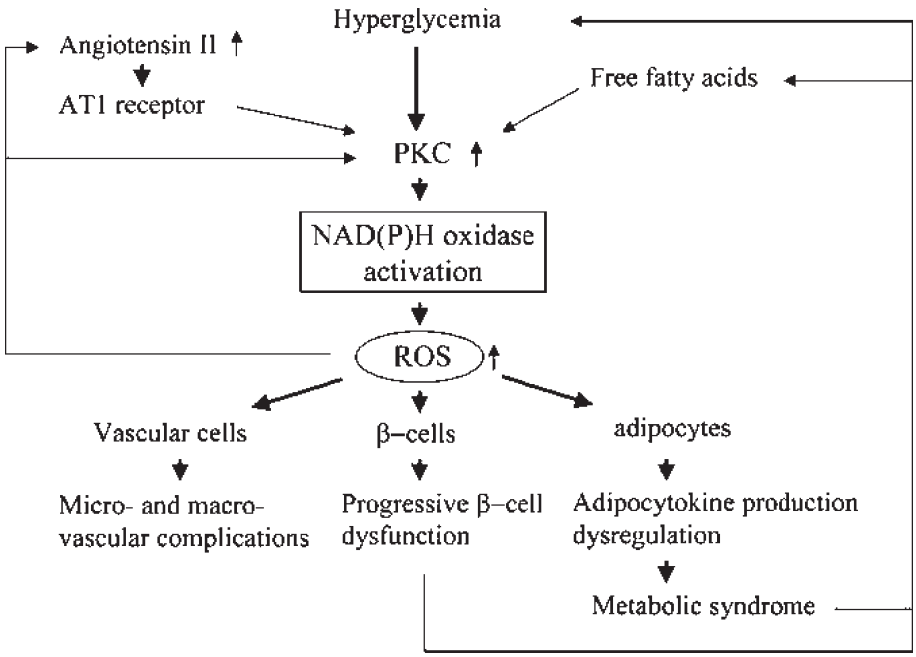

Fig.1. NAD (P) H oxidase activation as a therapeutic target for preventing diabetic vascular complications, progressive b-cell dysfunction and metabolic syndrome.

of the β-cells to produce sufficient insulin in a condition of hyperglycemia characterizes the transition from insulin resistance to type II diabetes [11] .

Insulin itself can lead to insulin resistance, every time a cell is exposed to insulin, the production of GLUT4 (type four glucose receptors) on the cell's membrane is decreased[12]. In pre-diabetes, fasting glucose is higher than normal but hepatic glucose output (HGO) is normal. Fasting plasma insulin is elevated and is inappropriately normal to the degree of insulin milieu thus indicating existence of hepatic insulin resistance. In pre-diabetes, the rapid oscillations of insulin secretion are lost and the amplitude of large pulses is decreased. Thus the loss of oscillations may be markers of pre-diabetes and contributes to IFG and IGT by decreasing the efficiency of the action of insulin on the liver and muscle [13, 14]. In IGT, the glycemic excursion after each meal are high and early insulin response to meal tend to be lower than normal but the second phase is delayed and prolonged [14] .

Fasting Insulin Level : When fasting serum insulin level is greater than 60 pmol /L, it is considered as evidence of insulin resistance.

Glucose tolerance test (GTT) : During a glucose tolerance test, which may be used to diagnose diabetes mellitus, a fasting patient takes a 75 gms oral dose of glucose. Blood glucose levels are then measured over the following 2 hours.

Interpretation is based on WHO guidelines. After 2 hours a Glycemic less than7.8 mmol/L is considered normal,

Estimated Top 10: Number of People with Diabetes

TABLE 1. ***Diabetes Atlas Second Edition.*** **© International Diabetes Federation 2003.**

(20–79 Age Group), 2003 and 2025

2003		2025	
Country	Persons (millions)	Country	Persons (millions)
1. India	35.5	1. India	73.5
2. China,People's Republic of	23.8	2. China,People's Republic of	46.1
3. USA	16	3. USA	23.1
4. Russia	9.7	4. Pakistan	11.6
5. Japan	6.7	5. Russia	10.7
6. Germany	6.3	6. Brazil	10.7
7. Pakistan	6.2	7. Mexico	9.0
8. Brazil	5.7	8. Egypt	7.8
9. Mexico	4.4	9. Japan	7.1
10. Egypt	3.9	10. Germany	7.1

a glycaemia of between7.8 to 11.0 is considered as Impaired Glucose Tolerance (IGT) and a glycemic of greater than or equal to 11.1 is considered Diabetes Mellitus.

Diabetic diet and treatment : Certain dietary components have been reported to potentially suppress the initiation of experimental insulin-dependent diabetes mellitus (IDDM) in animal models. In the present study, we have shown that dietary soybean prevents induction of experimental hyperglycemia by retaining β cell activity. In rat's feed raw soybean, expression of insulin m-RNA in pancreatic β cells is significantly increased compared to those feed with normal diet [15]. A low-calorie diet extends median and maximum life span in human. This effect may involve a reduction in oxidative stress [16]. Diet high in fruit and vegetables, which are high in antioxidant, promote health and reduce the effect of ageing [17, 18].

Best choice of food depends on glycemic-index which is a measure of the effects of carbohydrates on blood glucose levels. Carbohydrates that break down rapidly during digestion releasing glucose rapidly into the bloodstream have a high GI; carbohydrates that break down slowly, releasing glucose gradually into the bloodstream, have a low GI. For most people, foods with a low GI have significant health benefits where found out which foods are best for people with diabetes [19]. A lower glycemic response is often thought to equate to a lower insulin demand, better long-term blood glucose control and a reduction in blood lipids [20]. Several lines of recent scientific evidence have shown that individuals who followed a low GI diet over many years are at a significantly lower risk for developing both type 2 diabetes and coronary heart disease than others[21].

Many studies show that low-carbohydrate diet is a very valuable prevention and treatment tool in diabetes and pre-diabetes [22, 23]. The American Diabetes Association (ADA) only recently agree that low-carbohydrate diets can be a good way to help people with diabetes, pre-diabetes, or those who are insulin resistant lose weight. The previous advice is focus on low-fat approach[24].

Fat : High fat diets promote insulin resistance have a greater rate of development of IGT and progression of type II Diabetes Mellitus [25] .In epidemiology studies a high saturated fat intake has been found to be associated with higher fasting insulin and glucose levels [26] and greater rates of glucose intolerance[27]. Fats are a combination of fatty acid: PUFA n-6 (linoleic acid) and n-3 (α linolenic acid) which are obtained from diet and not synthesized *in vivo.* High n-3 and lower n6/n3 ratio has marked effects on insulin sensitivity[27]. They have anti-inflammatory properties and have potent lipid modifying effect with consistent reduction in fasting triglycerides of 25-30% of patient groups [28].

Carbohydrate : Diets proportionately higher in complex carbohydrates tend to be associated with a reduced risk of obesity and hence decreased rate of diabetes.

Dietary Fibre : Consumption of soluble dietary fibre (DF) is reducing postprandial glucose responses after carbohydrate-rich meals, as well as lowering total cholesterol and LDL cholesterol levels[29]. However, it is not soluble DF, but mainly the consumption of insoluble cereal DF and whole grains that are consistently associated with reduced risk of type II diabetes in large prospective cohort studies [30, 31]. DF is highly complex substances that can be described as any no digestible carbohydrates and lignins not degraded in the upper gut [32].

Antioxidant and diabetes : Antioxidants are compound that protect cells against the damaging effects of reactive oxygen species, such as singlet oxygen, superoxide, peroxyl radicals, hydroxyl radicals and peroxynitrite. An imbalance between antioxidants and reactive oxygen species results in oxidative stress, leading to cellular damage. Oxidative stress has been linked to cancer, ageing, atherosclerosis, ischemic injury, inflammation and neurodegenerative diseases (Parkinson's and Alzheimer's)[33.]

Antioxidant is classified into two broad divisions, depending on whether they are soluble in water (hydrophilic) or in lipid (hydrophobic). In general, water-soluble antioxidant react with oxidants in the cell cytosol and the blood plasma, while lipid-soluble antioxidants protect cell membrane from lipid per oxidant [34].These compound may be synthesized in the body or obtained from diet [35].There are some compounds that contribute to antioxidant defense by chelating transition metals and preventing them from catalyzing the production of free radicals in the cell [36].Antioxidant that are reducing agents can also act as pro-oxidant. Such as vitamin C has antioxidant activity when it reduces oxidizing substance such as hydrogen peroxide [37].

Antioxidants are also widely used as ingredients in dietary supplements in the hope of maintaining health and preventing diseases such as cancer and coronary heart disease [38]. The role of antioxidants in biology is focus in preventing the oxidation of unsaturated fats, causing rancidity[39]. Antioxidant activity can be measured simply by placing the fat in a close container with oxygen and measuring the rate of oxygen consumption. It is the

identification of vitamins A, C, and E as antioxidants that revolutionized the field and led to the realization of the importance of antioxidants in the biochemistry of living organisms [40, 41.]

Groups of compound are react differently with different reactive oxygen species. In food science, the oxygen radical absorbance capacity (ORAC) has become the current industry standard for assessing antioxidant strength of whole foods, juice and food additives [42, 43], Other test includes the Foline-ciocalteu reagent [44]. Antioxidants are found in varying amount in foods such as vegetables, fruits, grain-cereals legumes and nuts. Some antioxidants such as lycopene and ascorbic acid can be destroyed by long term cooling or storage [45, 46]. Other antioxidant compound is more stable such as polyphenolic antioxidant in food [47].

Diabetes improves with plant extract : *1. Neem :* *Neem* (*Azadirachta indica*), is a tree in the mahogany family Meliaceae. *Neem* has two closely related species: A. indica A. Juss and M. azedarac, the former is popularly known as Indian *neem* (margosa tree) or Indian lilac, and the other as the Persian lilac [48]. It is evergreen and is native to India, Myanmar, Bangladesh, Sri Lanka and Pakistan growing in tropical and semi-tropical regions. Very young leaves are reddish to purplish in colour. The shape of mature leaflets is more or less asymmetric.

Biological activity of some neem compounds : Nimbidin, a major crude bitter principle is extracted from the oil of seed kernels of *Azadirachta indica* demonstrated several biological activities. From this crude principle some tetranortriterpenes, including nimbin, nimbinin, nimbidinin, nimbolide and nimbidic acid have been isolated [48].

Biological activity of neem compounds : Anti-inflammatory; Antiarthritic; Antipyretic; Hypoglycaemic; Antigastric ulcer; Spermicidal; Antifungal; Antibacterial; Diuretic; Antimalarial; Antitumour; Immunomodulatory etc.Aqueous extracts of neem leaves have demonstrated significant antidiabetic potential[48].

Antioxidant activity : The chemopreventive potential of *Azadirachta indica (neem)* leaf fractions base on *in vitro* antioxidant assays, and *in vivo* inhibitory effects on 7, 12 dimethylbenz[a] anthracene (DMBA)-induced hamster buccal pouch (HBP) carcinogenesis is evaluated. In addition the major constituents in *neem* leaf fractions are also identified by HPLC. Analysis of the free radical scavenging activities and reducing potential of crude ethanolic extract (CEE), ethyl acetate fraction (EAF) and methanolic fraction (MF) of *neem* leaf is revealed a concentration-dependent increase in antioxidant potential that is in the order EAF>MF>CEE. Administration of *neem* leaf fractions is reduced the incidence of DMBA-induced HBP carcinomas at a lower concentration compared to the crude extract. Chemoprevention by *neem* leaf fractions is associated with modulation of phase I and phase II xenobiotic-metabolising enzymes, lipid and protein oxidation, up regulation of antioxidant defences, inhibition of cell proliferation and angiogenesis, and induction of apoptosis. However, EAF is more effective than MF in terms of antiproliferative and antiangiogenic effects, and expression of CYP isoforms. The greater efficacy of EAF may be due to higher content of constituent phytochemicals as revealed by HPLC analysis. The results of the present study suggest that the antioxidant properties of *neem* leaf fractions may be responsible for modulating key hallmark capabilities of cancer cells such as cell proliferation, angiogenesis and apoptosis in the HBP carcinogenesis model[49].

Neem leaf aqueous extract, flower and stem bark ethanol extracts is exhibited higher free radical scavenging effect on the DPPH assay with 50% scavenging activity. The total antioxidant activity of these extracts is found to be 0.959, 0.988 and 1.064 mM of standard trolox, respectively. At 100 µg /ml, the flower ethanol and leaf aqueous extracts is significantly decreased malondialdehyde (MDA) levels by the TBARS method. The results suggest that extracts from leaf, flower and stem bark of the[50] Siamese *neem* tree have strong antioxidant potential.

Neem's effects on degenerative diseases : Standardize aqueous extract of *neem (Azadirachta indica)* leaves (AIE) has been reported to show both ulcer protective and ulcer healing effects in normal as well as in diabetic rats. AIE is found to inhibit acid-pepsin secretion in 4 hr pylorus ligated rats. Continuous infusion of PENTA is significantly increased the acid secretion after 30 to 180 min or in the total 3 hr acid secretions in rat stomach perfusate while, AIE pretreatment significantly decreased them. AIE is inhibited the rat gastric mucosal proton pump activity and the effect is comparable with that of omeprazole (OMZ). Further, AIE do not show any effect on mucin secretion though it enhanced life span of mucosal cells as evidenced by a decrease in cell shedding in the gastric juice. Thus, our present data suggest that the ulcer protective activity of AIE may be due to its anti-secretary and proton pump inhibitory activity rather than on defensive mucin secretion[51]. Effect of petroleum ether extracts of kernel (NSK) and husk (NSH) of *neem (Azadirachta indica* A.

Juss, Meliaceae) seeds on the prevention of oxidative stress cause by streptozotocin (STZ) is investigated. Serum creatine phosphokinase (CPK) is increased in diabetic rats and significantly decreased on insulin, NSK, and NSH treatments. The decrease in activities of superoxide dismutase (SOD) and catalase (CAT) and increase in lipid peroxidation (LPO) of erythrocytes as observe in diabetes is regained after insulin, NSH, and NSK treatments. However, there is insignificant improvement in SOD, CAT, and LPO of kidney on NSK and NSH treatment. In spite of increase CAT and SOD activities in liver and heart, LPO is also increased in diabetic rats. Insulin, NSH, and NSK treatments is significantly protected animals from cardiac damage but not hepatic. NSH and NSK prevent oxidative stress is caused by STZ in heart and erythrocytes. However, no such preventive effect is observed on renal and hepatic toxicity [52].

Combination (1:1) of water extract of dried powder of root and leaves (200 mg/kg body wt) of *A. augusta* and *A. indica* respectively is administered orally to alloxan diabetic rats once a day for 8 weeks. This treatment is caused significant lowering of blood sugar in fasted as estimated by glucose tolerance test. The treatment is resulted in a significant reduction in serum lipids. Aqueous extract is also decreased the formation of lipid peroxides estimated as thiobarbituric acid reactive substance, (TBARS), and increased antioxidants (superoxide dismutase, catalase, and glutathione peroxides and glutathione transferase) in erythrocytes. There is reduction in LPO as TBARS in heart, liver, kidney, and muscles [53].

Hypoglycemic effect : Hypoglycemic effect is observed with *Azadirachta indica* when given as a leaf extract and seed oil, in normal as well as diabetic rabbits. The effect, however, is more pronounced in diabetic animals in which administration for 4 weeks after alloxan induced diabetes, significantly reduced blood glucose levels. Hypoglycemic effect is comparable to that of glibenclamide. Pre-treatment with *Azadirachta indica* leaf extract or seed oil administration, started 2weeks prior to alloxan, partially is prevented the rise in blood glucose levels as compared to control diabetic animals.

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Mahogany (Swietenia macrophylla) : The name *mahogany* is used when referring to numerous varieties of dark-colored hardwood, originally the wood of the species *Swietenia macrophylla*, known as West Indian or Cuban *mahogany* [55]. There are 3 species of *mahogany. Mahogany* tree are large trees 20 to 40 m of height and more than 2 m in diameter. Mature fruit turn from green to reddish brown.[56, 57.]

From *Swietenia macrophylla* seeds many kind of tetranortriterpenoids or limonoids, namely, Swietinine [58], Swietenolide [59], 8,30-epoxy-swietenine acetate [60], Swietenolide diacetate [61], augustineolide and 3β,6-dihydroxydihydrocarapin [62, 63] ,as well as known fatty acid and terpenoids [61], namely γ-Himachalene, germacrene D & A, Hexadecanoic acid and ethyl hexadecanoate, are isolated and identified. *Swietenia macrophylla* is non-toxic upto 1.2 gm/kg body weight upto 24 hours.[64]

The seeds have been used for leishmaniasis and abortion medicine by Amazonian Bolivian ethnic group[65] and for treatment of hypertention, diabetes and malaria[66]. The seeds has antimalarial activity[66], antibabesial activity[66]and antidiarrhoeal activity[67].

Anti-diarrhoeal activity : The *swietenia macrophylla* seed are used in traditional medicine for the treatment of diarrhoea and produce a significant antidiarrhoeal activity when given in a single dose of 100 mg/kg B.Wt. [67]

Hypoglycaemic effect : The anti-diabetic effect of *swietenia macrophylla* seeds is evaluated in Streptozotocin induced type II diabetic rat. The extract is found more effective at the dose of 300 mg/kg body weight and it is lowered fasting blood glucose level (FBG) levels is statistically significant ($P < 0.010$) (32.78%) in diabetic rats at day 12. Extract at the same dose is also significantly reduced ($P < 0.01$) the elevated level of serum total cholesterol (18.56%) and triglyceride (10.41%), and increased ($P < 0.01$) (46.27%) the reduced liver glycogen level. Though statistically non-significant the extract at both the doses is found to improve the body weight of diabetic rat [68].

Increase in liver glycogen can be brought about by an increased in glycogenesis and or inhibited

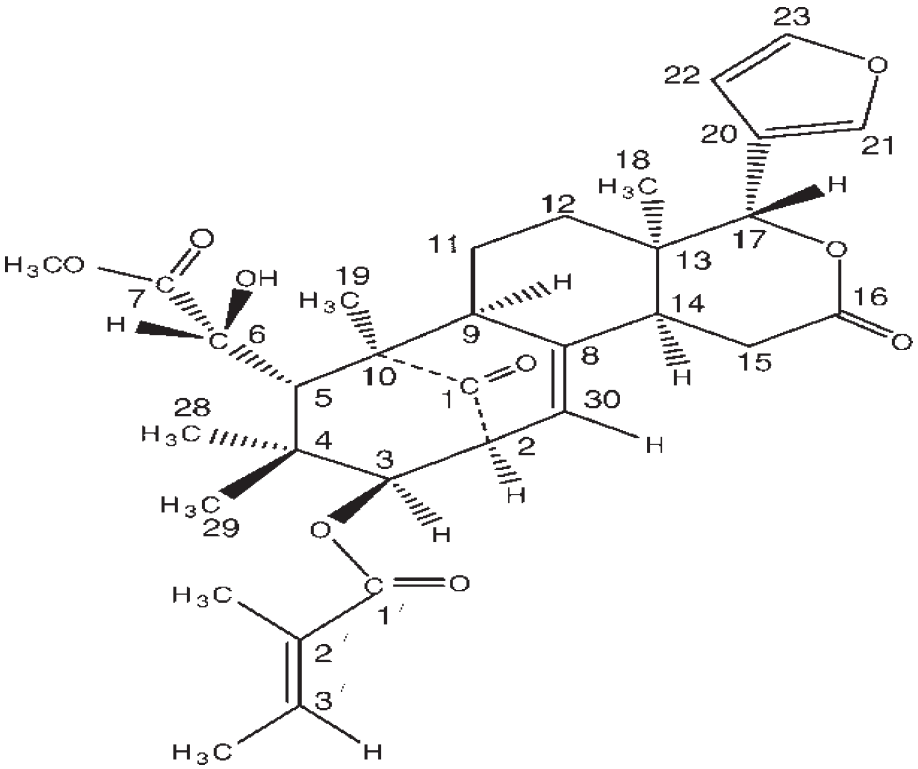

Fig.2. Structure of isolated product (swietenine).

glucogenolysis. Excessive hepatic glycogenolysis and gluconeogenesis is associated with decreased utilization of glucose by tissues is the fundamental mechanism underlying hyperglycemia in the diabetic state[69]. This may be due to the lack of or resistance to insulin, which is essential to trigger the activation of glycogen synthase systems[70].

Diabetes is associated with hyperlipidemia[71].The serum total cholesterol and triglycerides have been decreased significantly in type II diabetic rats after the extract supplementation. This effect may be due to low activity of cholesterol biosynthesis enzymes and or low level of lipolysis which are under the control of insulin[72].

In another study show that various type of phytoconstituent are present in in *swietenia macrophylla*. Such type of phytoconstituent is swietenine **(Fig.2)**. The switenine is identified by physiochemical and spectrometric analysis. Isolated phytoconstituent which is improved peripheral glucose utilization in diabetic rat due to an insulin nimicking effect of plant [73].

Anti-bacterial activity : Two limonoids from *swietenia macrophylla* are 2 hydroxy 3-swietenolide and 2 hydroxy-3-O-tigloylswietenolide shows significant anti bacterial activity against eight multi-drug resistant (MDR) bacterial strains.[74]

Anti-inflammatory activity : *Swietenia macrophylla* seed extract inhibits carrageenan-induce paw edema by 7.35% at a dose of 50mg/kg, higher dose of 100 mg/kg produce 47.06% that is comparable to the 54.4% inhibition produce by the standard drug ibuprofen.[64] It is well known that there is a close relationship between inflammation and cancer[75, 76].

Conclusion

This review aims to focus on the anti-diabetic activity of *neem* leaves and *mahogany* seeds. The data suggest that *neem* leaves and *neem* seed have benefit in diabetes mellitus in controlling the blood sugar or may also be helpful in preventing or delaying the onset of the disease. Quantitative phytochemical assay is indicated the presence of triterpenoids in *mahogany* seed. These triterpenoids may serve as potential hypoglycemic agent.

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