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The Medicinal Properties of Anogeissus leiocarpus (African Birch Tree) and the Development of a Drug for Diabetes Mellitus and its Complications: A Review

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Abstract

The antidiabetic, sialoglycoconjugates, antidyslipidemic, antioxidant, anti-inflammatory, haematopoietic and wound-healing properties of Anogeissus leiocarpus are highlighted. Its purification and structure using nuclear magnetic resonance, for its mechanism of action are discussed. Its wide range of safety value and its lack of deleterious side effects on pregnancy, gestation, lack of teratogenic effects in pups (kitten) and impressive reproductive performance of Wistar rats are adequately emphasised. With information derived from search 'engines', such as Elsevier, Springer, PubMed, Science Direct, Medline, Google Scholar and a library search for articles published in peer reviewed journals, this review provides evidence for the development of a non-empirical and non-conventional alternative supporting drug from A. leiocarpus for diabetes mellitus and its complications.

The synergistic activities of anti-inflammatory Lupeol, coexisting with antidiabetic betulinic acid and trimethoxyellagic acid with their potent scavenging of glucose by glycosidation reactions support an economic development of the alternative drug. The inhibition of alpha-glucosidase by betulinic acid is an additional antidiabetic advantage.

The fertility assessment of the tree grown soils and the fast recovery of A. leiocarpus after stem bark harvest, following mild rainfall suggest its reduced vulnerability from climate change and an enhanced agricultural sustainability.

Keywords: *Anogeissus Leiocarpus; Stem Bark; Triterpenes; Lupeol; Anti-İnflammatory; Betulinic Acid; Trimethoxyellagic Acid; Glucose Scavenging Glycosidation; Alpha-Glucosidase İnhibition; Antidiabetic; Economic Drug Development.*

INTRODUCTION

Diabetes mellitus (DM) progressed dangerously worldwide and caused serious challenges for public health [1, 2] with severe health concerns budgets. Diabetes was considered as a world's major killer disease which by 2030, over 552 million people might be affected [3, 4] with a threatening scenario projected for 2035 [5]. The disease originated from chronic hyperglycaemia induced by metabolic disorders of carbohydrate, lipid and protein resulting from insulin secretory defect of the pancreatic ß-cells (type 1), insulin inaction or loss of insulin responsiveness in its target, like adipose and muscle (type 2) or both [6, 7].

Hyperglycaemia-induced injuries which led to the desialylation of endothelial and numerous other body cells [8] and oxidative stress [9] amongst others, explained partly, the multiple risk microvascular and macrovascular damages that resulted in numerous life-threatening complications, such as nephropathy, neuropathy and retinopathy that resulted in blindness [10]. Despite the budgets-destroying effects of DM on several nations, as essemplified by the worrisome risk factor of progression, prognosis and mortality of COVID-19, particularly patients with pre-existing type 2 diabetes [11, 12, 13] another long existing worrisome risk factor, injurious to national budgets, had been created by the serious diabetic disorder, the hyperglycaemia-induced delayed wound healing (or non-healing wounds, diabetic or foot ulcers) [14, 15, 16, 17] which in many instances led to embarrassing amputation of limbs, with accompanying social menace.

Between 2007 and 2013, in the United States alone, assessment of outpatient visits showed an estimated

6.7 million ambulatory care with diabetic foot cases in people with diabetes [15, 16] in addition to a worrisome unquantifiable scenario in Africa.

GLOBAL ESTIMATES OF DIABETES MELLITUS

By 2017, International Diabetes Federation (IDF) produced an IDF diabetes atlas that showed global estimates for prevalence of diabetes for 2015 with a projection for 2040, aimed at the national, regional and global impact of diabetes. The study which covered Africa, Europe, Middle East and North Africa, North America and Caribbean, South and Central America, South East Asia and Western Pacific 'against' the world was conducted using a systematic literature review that identified data sources from 1990 to 2015. The most appropriate studies from each country were retrieved using an analytic hierarchy process; from extrapolation of available data from such countries, estimates for similar countries without data were modelled. These processes generated smoothed age-specific estimates applied to United Nations (UN) population estimates [18]. From 111 countries, 196 sources were selected from 540 data sources reviewed in 2015, which showed that 415 million (uncertainty interval: 340–536 million) people with diabetes aged 20–79 years and diabetes accounted for 5 million deaths; with an incurred global health expenditures of 673 billion US dollars [18].

In addition, seventy-five percent of these patients lived in low and middle income countries and the 20–79 year-aged patients were predicted to rise to 642 million (uncertainty interval: 521–829 million) by 2040 [18]. Furthermore, the study produced the proportion in percentages and in the absolute values in millions of the 20–79 years patients with undiagnosed diabetes [18].

THE SCENARIOS OF DIABETES MELLITUS IN SOME SELECTED COUNTRIES

United States of America (USA)

Trends in the prevalence of type 2 diabetes and its association with abdominal obesity led to growing health disparities in the USA between 1999 and 2014 [19]. This study analysed data from the National Health and Nutrition Examination Surveys (NHANES) and estimated the prevalence of type 2 diabetes in association with abdominal obesity in individuals, 20 years and above in USA, from 1999 to 2014, with standardization to age, sex and ethnicity population [19]. In the US population, the prevalence of abdominal obesity increased from 47.4% in 1999/2000 to 57.2% in 2013/2014, with significant increase that occurred in all age groups [19].

The prevalence of type 2 diabetes also increased from 8.8% to 11.7% at the same periods and was limited to people with abdominal obesity, aged 45 years and above and no change in non-obese people and those aged 45 years and below [19]. These attached critical importance of abdominal obesity as a key contributor to type 2 diabetes progressing epidemic in USA and a priority target for public health interventions [19].

Data from adults with diabetes in the United States that participated in the NHANES were subjected to a cross-sectional analysis for national trends in diabetes treatment and risk-factor control aimed at providing public health policy and planning. Diabetes control improved from 1999 to early 2010, but stalled and declined subsequently. Between the periods 2007-2010 and 2015-2018, glycaemic control achieved a decline in diabetes from 57.4% to 50.5%; lipid control minimally improved diabetes between 2007-2010 and 2015-2018 [20].

United Kingdom

A review of type 2 diabetes in adult population in the UK dealt on the complex interplay of biological, lifestyle, social, clinical and healthcare systems factors that influenced disparities [21].

Type 2 diabetes was reported as a major UK public health priority, with an alarmingly higher prevalence among minority ethnic communities, about 3 to 5 times, higher than in the white British population and a worrisome earlier 10-12 years younger [21] with a significant proportion of cases diagnosed before the age of 40 years [21].

African Countries

Cases of diabetes surged in Africa, with an estimated 39,000 people that suffered from type 1 diabetes in 2013 and 6.4 new cases per 100,000 people per year in children less than 14 years old [22]. The age-categorized study revealed that among the 20-79 old people, type 2 diabetes prevalence was 4.9% with majority of diabetic patients less than 60 years old and the highest proportion, 43.2% aged 40-59 years [22]. Projection showed diabetic patients numbers increasing from 19.8 million in 2013 to 41.5 million in 2035, an absolute increase of 110% and the apparent increase in diabetes prevalence was associated with economic development, and inadequate response of local health systems to provide accessible, affordable and optimal care for diabetes [22].

Nigeria; South East Nigeria

In recognition of the rising prevalence of diabetes in Nigeria and Sub-Saharan Africa, a study investigated the prevalence of pre-diabetes and diabetes in people with low socio-economic status or in urban slums using the WHO STEP-wise approach to surveillance to non-communicable diseases [23]. Adults, 20 years and above in two urban slums, in Enugu, South East Nigeria, were investigated for prediabetes and diabetes. Of the 811 individuals, 605 (74.6%) participants provided prevalence of prediabetes and diabetes 7.6% and 11.7% respectively; newly detected cases accounted for 54.9%. the prevalence of diabetes peaked at 55 – 64 years, with considerations of contributory factors such as hypertension and stroke, and urban slam habitation [23].

Sudan

A prevalence of 3.4% for T2DM amongs Sudanese population accounted for 75% of all diagnosed cases in northern Sudan at 1996 [24]; this latter situation could have produced catastrophic increases in kidney and cardiovascular diseases prevalence [25] and the effects of the civil war, ravaging Sudan at this time, on these diseases are unquantifiable.

TREATMENT OF DIABETES MELLITUS

Insulin

Insulin, the conventional drug for DM, its withdrawal results in a rebound hyperglycaemia, notwithstanding its exorbitant cost for developing countries with reduced economic standing. With the increasing global threat of diabetes mellitus, and the need to reduce heightened pressure on insulin, the development of non-conventional treatment for DM is appropriately expected to receive urgent attention.

Medicinal Plants

The reduced economic resources, associated with some developing countries informed the interests of Traditionalists in managing diabetes mellitus with medicinal plants and their phytoconstituents, such as alkaloids and flavonoids. Numerous strong advocates for the use of medicinal plants and their phytoconstituents for the treatment of diabetes mellitus were recorded [26,27,28,29,30,31,32,33].

However, a thoroughly guided study using published and unpublished reports, universities' postgraduate theses, detailed search of literature databases (Pubmed, Web of science and Google) that systematically reviewed Algerian ethnobotanical treatments of diabetes mellitus identified 171 plants from 58 families of which *Asteraceae*, *Lamiaceae* and *Apiaceae* were the most often cited; in addition, the plants with the best evidence of activity were listed [34]. The use of traditional herbal medicines in Algeria continued but they remained poorly characterized and improperly in man, thus, systematic evaluation of the mechanism of their antidiabetic activity [34].

In addition, the aqueous extract of *Erythrina senegalensis* stem bark, produced results that suggested its possession of hypoglycaemic, antihypertensive, hypolipidaemic and antioxidant activities in experimentally-induced hypertensive, diabetic rats [35]. These active medicinal benefits were ascribed to the existence of Erysenegalesein, Warangalone,, senegalensein and 6,8-diprenylgenistein in the extract [35].

Amongst these medicinal plants, *Anogeissus leiocarpus* (African birch tree), common and widespread over Africa [36] received attention because it is endowed with numerous medicinal health benefits. *Anogeissus leiocarpus*, an evergreen tree, was placed in the kingdom *Plantae*, division *Magnoliophyta*, class *Magnolikiopsida*, family *Combretacae*, genus Anogeissus and species *A. leiocarpus* [37] with synonyms or binomial names of *Cononcarpus leiocarpus* DC, *Anogeissus leiocarpus* var *schimperi* Hochst [36,38] and common, vernacular names that included African birch tree in English, Kojoli in Fulani, Marike/marke in Hausa, abakiliki ataranin Igbo, anum in Kanuri, ayin or pako dudu in Yoruba [39], maaki in Tiv [40], n'galama in Bambara, Siigi in Moré, godoli in Peulh and Sahib in Shua Arab [36].

The species, a tall tree, that could reach up to 70ft (21.336m) in height (typically, 15-18m) with light green foliage [37], with a wider base trunk, dense crown and drooping branches. The beige to grey bark gets blackish with age and fibrous with thin scales. The stems are finely pubescent. The leaves are elliptic to ovate-lanceolate in shape and are arranged alternate to sub-opposite. Individual trees growing in dry areas tend to have smaller leaves and hairier flowers, with inflorescence spherical, axillary and terminal cluster [41]. The flowers scented with white hairs coloured yellow-green, with yellowish to reddish brown trapezium samaras broadly winged and beaked fruits by a persistent tubular portion of the receptacle to contain one seed small in size but produced in high numbers [36]. At the growing period, the plant appears shrub-like (see Figs. 6 to 10).

The distribution of *Anogeissus leiocarpus* started from the borders of the Sahara up to the humid tropical forests found in West African countries of Mali, Senegal, Ivory Coast, Ghana, Nigeria (from North through to the South), Cameroon, Sudan and Upper Nile region [38] extending into Ethiopia in East Africa [36] and favoured by the dry forests, fringing forests and semi-arid Savanah areas, including swamps, valleys and forests galleries, usually forming pure dense and closed stands. Though with very slow initial growth, low re-growth ability and very sensitive to bush fire, in addition to the poor germination of its seeds were observed as adverse factors for long term conservation and sustainable uses of the species [38], these factors were not encountered in some areas, as shown in Figs 6 to 10

BENEFICIAL BOTANICAL USES OF *ANOGEISSUS LEIOCARPUS*

The wood of *A. leiocarpus* served commonly for carving constructions and tool handles because of its fair resistance to insects and termites. In addition it was used for firewood and charcoal production and the ashes for tanning leathers. From the leaves and bark yellow dyes were produced for fabrics and leather while it made ink more viscous, glued leather or occasionally replaced Arabic gum. The roots served as chewing sticks for cleaning teeth, furthermore the leaves as fodder for small ruminants [41,42,43].

The genus *Anogeissus* (axlewood, ghatti, button and chewing stick trees) of the Combretaceae, with eight species and of wide distribution in Asia and Africa had received attention. Under the context of traditional management of diabetes mellitus, more attention had been focused on two of the its species, but more on *Anogeissus leiocarpus* [44].

BENEFICIAL MEDICINAL USES OF *A. LEIOCARPUS*

Antibacterial Effects

Extracts of the leaf, stem and root bark of *A. leiocarpus* exhibited antibacterial effects on *Staphylococcus aureus*, *Streptococcus pyogenes*, *Eschericia coli* and *P. vulgaris* [39].

Antiprotozoan Activities

Sequel to the use of the mixture of the barks of *A. leiocarpus*, *Khaya senegalensis* and potash, by Nigerian Pastoralists, to treat animal African trypanosomosis, the antitrypanosomal activity of the mixture was investigated; the mixture significantly and dose-dependently reduced parasite motility and completely immobilized the parasites at higher doses and all the mice with complete parasite immobilization became aparasitaemic during the next month of observation [45].

The study suggested that cytotoxic effect of the combination led to the death of the trypanosomes [45]. However, one medicinal benefit of both *A. leiocarpus* and *K. senegalensis* in the treatment of anaemia-inducing diseases could be traced to their enhanced haematopoietic properties [8, 9, 40,46,47].

Antidiabetes:

Under the context of the aim and objectives of this review *A. leiocarpus* as a non-conventional drug for DM has exhibited numerous medicinal properties that effectively treated DM. These medicinal properties, antidiabetic, sialoglycoconjugate, antidyslipidaemic, antioxidant, wound-healing anti-inflammatory, and the potential glucose scavenging properties are summarized on Table 6.

Over a two-week period, oral administration of ethanolic extract of the stem bark of *Anogeissus leiocarpus* reduced blood glucose and improved blood by enhanced haemotopoiesis in normal Wistar rats [40] which betrayed the plant's ability to manage naturally occurring diabetes, characterized by hyperglycaemia, with accompanying anaemia and leukopenia in human patients [48,49,50] characteristics that similarly occurred in experimental alloxan-induced diabetes in dogs [8,46] without a rebound hyperglycaemia when the *A. leiocarpus* extract was withdrawn, which further endowed the plant with an ability to prevent a progression to type 2-diabetes mellitus and the associated organic damages.

Table 1. Effect of administration of insulin and crude ethanolic extract of *A. leiocarpus* on serum biochemical values in alloxan-induced diabetes mellitus in dogs

Pre-induction		ND	DU	DI	DE
AST (IU/L)	17.30 ± 0.14	17.33 ± 0.13	18.11 ± 0.69	16.30 ± 0.22	16.83 ± 0.46
ALT (IU/L)	4.13 ± 0.10	4.21 ± 0.09^a	7.07 ± 0.10^b	6.19 ± 0.178^a	4.07 ± 0.23^a
ALP(IU/L)	60.98 ± 1.24	61.77 ± 1.48^a	67.86 ± 1.67^b	60.94 ± 2.14^a	58.06 ± 1.15^a
PROT (g/dl)	7.15 ± 0.10	7.10 ± 0.24^a	8.79 ± 0.26^b	5.77 ± 0.18^c	6.01 ± 0.23^c
Album (g/dl)	3.74 ± 0.08	3.80 ± 0.06^a	4.40 ± 0.31^b	3.60 ± 0.18^a	3.30 ± 0.08^a
Na^+ (mmol/L)	146.00 ± 14.65	150.00 ± 18.68^a	120.00 ± 12.35^b	144.00 ± 15.86^a	140.00 ± 7.75^a
K^+ (mmol/L)	4.80 ± 0.60	4.90 ± 0.58^a	8.00 ± 1.78^b	4.50 ± 0.05^a	5.00 ± 0.58^a
Cl^-(mmol/L)	112.00 ± 7.80	111.00 ± 7.75^a	128.00 ± 15.86^b	119.00 ± 7.75^a	112.00 ± 7.75^a
HCO_3^- (mmol/L)	26.80 ± 1.08	27.00 ± 1.05^a	18.00 ± 2.08^b	48.00 ± 6.51^c	24.00 ± 3.06^a
Urea (mg/dl)	0.56 ± 0.04	0.50 ± 0.01^a	4.50 ± 0.58^b	1.00 ± 0.33^a	1.20 ± 0.64^a

ND = Non-diabetic (control), DU = diabetic untreated, DI = diabetic insulin-treated, DE = diabetic extract-treated, AST = Aspartate amino transferase, ALT = Alanine amino transferase, ALP = Alkaline phosphatase, PROT = Protein, Album = Albumin, Na^+ = Sodium, K^+ = Potassium, Cl^- = Chloride, HCO_3^- = Bicarbonate. Values are expressed as mean ± SEM.
^{a,b,c} = Values in the same row with different superscript letters are significantly ($P < 0.05$) different.
i. *b* = DU compared with ND, DI and DE. (Significant level of hepato-renal damage in the development of DM in DU).
ii. *c* = DI and DE compared with DU and ND. (Efficacy of treatments with insulin and extract).
(i and ii are based on Tukey's post-hoc tests which statistically analyse differences within/between groups).

(Reference 46)

In addition, earlier reports showed that extracts of *A. leiocarpus* guill and perr leaf positively affected the hyperglycaemia and associated dyslipidaemia in alloxan-induced diabetic rats [51] while total extract and fractions of *A. leiocarpus* exhibited antihyperglycaemia activity in mice [52]. Recently, ethanolic extract of *A. leiocarpus* as a non-conventional treatment for DM and associated diabetic disorders received more credence by its antidiabetic and antioxidant properties in alloxan-induced diabetic Wistar rats [9] and its attenuation of dyslipidaemia in alloxan-induced diabetic dogs [53], while some enhanced pro-synthetic antidiabetic drugs did not effectively control dyslipidaemia, induced by diabetes, in addition to toxicity and resistance experienced by patients [28].

Table 2. Percentage weight changes in dogs.

	ND (kg)	DU(kg)	DI (kg)	DE (kg)
Week 0	10.03	12.05	10.2	9.01
Week 1	12.20 (21.64%) [a]	10.01 (16.93%)[a]	9.07 (11.08%) [a]	7.7 (14.54%) [a]
Week 2	14. 25(42.07%) [a]	7.03 (41.66%) [a]	8.90 (12.75%) [b]	6.86 (23.86%) [b]
Week 3	14.50 (44.57%) [b]	7.01 (41.81%) [a]	9.30 (8.2%)[b]	8.75 (2.89%) [b]
W eek 4	14.74(46.96%)[a]	6.0 (50.21 %) [a]	12.60 (23.53%) [a]	11.92 (32.30%) [a]

[ab]= P < 0.05, ND = Non-diabetic (control), DU = Untreated diabetic, DI = Diabetic insulin treated, DE= Diabetic extract treated. (Crude ethanolic extract-stembark)

(Reference 53)

Table 3. Lipid profiles in dogs.

TC (mmol/L)	3.1 ±0.08	6.6 ± 0.12	3.4 ± 0.53	3.02 ±0.45
HDL (mmol/L)	1.2 ±0.01	0.2 ±0.17	1 ± 0.15	1.28 ± 0.31
LDL (mmol/L)	2.7 ± 0.14	5.8 ± 0.23	2.9 ±0.57	1.4 ± 0.50
TG (mmol/L)	1.5 ±0.01	3 ±0.29	1.8 ±0.40	1.54 ±0.38

ND = Non diabetic, DU= Diabetic untreated, DI = Diabetic insulin treated, DE = Diabetic extract treated, TC = Total cholesterol, HDL = High density lipoprotein, LDL = Low density lipoprotein, TG = Triglyceride. (Crude ethanolic extract-stembark)

(Reference 53)

More significantly, ethanolic extracts of *A. leiocarpus* exhibited sialoglyco-conjugate, erythrocyte surface and free serum sialic acids modulating effects, which exposed elevated serum sialic acids as potent biomarker of alloxan-induced type 1 diabetes in dogs [8]. Indeed, elevated serum sialic acids was predictive of the DM and the administration of the ethanolic extracts of *A. leiocarpus* was effective in the prognosis of the eventual outcome of the DM [8]; the latter suggested an enhanced sialyltransferase activity [8]. In addition, it was recommended that laboratory investigation of obese patients and dogs [8] should include assay of plasma or serum sialic acid to diagnose prediabetes for early control of DM.

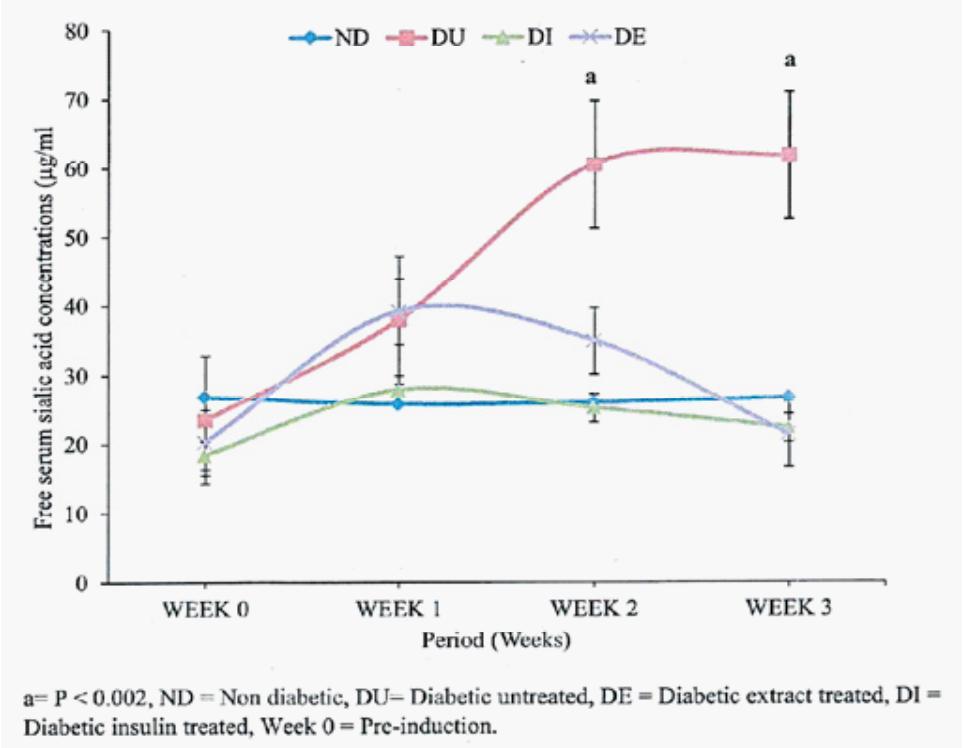

Fig. 1. Effect of administration of insulin and crude ethanolic extract of *A. leiocarpus* on free serum sialic acid concentrations in alloxan-induced diabetic dogs

(Reference 8)

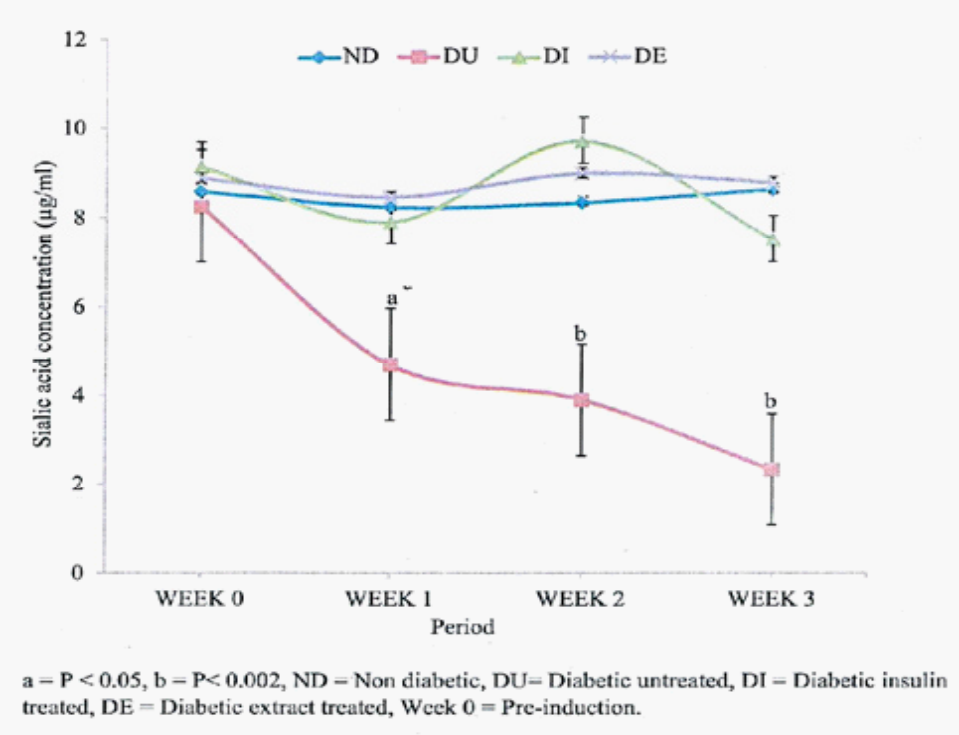

Fig. 2. Effects of administration of insulin and crude ethanolic stem bark extract of *A. leiocarpus* on erythrocyte surface sialic acid concentrations in alloxan-induced diabetic dogs

(Reference 8)

In addition, ethanolic extract of *A. leiocarpus* stem bark markedly improved healing of surgically-induced skin wounds on alloxan-induced diabetic dogs [54].

Table 4. Effect of treatment with ethanolic extract of *A. leiocarpus* stem bark on wound dimensions in alloxan-induced diabetic and surgically wounded dogs.

Group	Dimension (cm)	Day 0 (cm^2)	Dimension (cm)	Day 7 (cm^2)	Dimension (cm)	Day 14 (cm^2)	Dimension (cm)	Day 21 (cm^2)
A (NDW)	L 2 W 2	4	1.4 1.8	2.52	0.9 1.3	1.17	0.1 0.2	0.02
B (DWI)	L 2 W 2	4	1.6 1.8	2.88	1.4 1.5	2.1	1.1 1.3	1.43
C (DWE)	L 2 W 2	4	1.4 1.5	2.1	0.6 0.6	0.36	0.1 0.2	0.02
D (DWU)	L 2 W 2	4	1.8 1.8	3.24	1.6 1.7	2.72	1.4 1.6	2.24

(Reference 54)

Table 5. Effect of treatment with ethanolic extract of *A. leiocarpus* stem bark on wound contraction percentage in alloxan-induced diabetic and surgically wounded dogs.

Group	Day 0	Day 7	Day 14	Day 21
A (NDW)	0%	37%	71%	100%
B (DWI)	0%	28%	48%	64%
C (DWE)	0%	48%	91%	100%
D (DWU)	0%	19%	32%	44%

(Reference 54)

These medicinal properties made *A. leiocarpus* a strong "candidate" for drug development requiring further technological development; the first being maximum purification followed with the investigation of its structure using Nuclear Magnetic Resonance (NMR)for the elucidation of its mechanism of actions.

After maximum fractionation and ethyl acetate and n-Hexane purification, using column chromatography and thin layer chromatography the analysis of the NMR spectra and the resultant structure confirmed fraction A as lupeol [55], a pentacyclic pharmacologically active tripenoid [56].

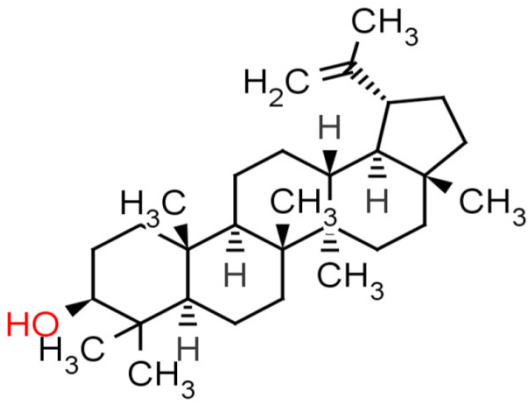

Figure 3. Structure of Lupeol. Purified extract; stembark. (Reference 55).

This first report that lupeol exists in *A. leiocarpus* joined the latter with other plant sources of lupeol [56]. The finding of lupeol in the purified extract of *A. leiocarpus* stem bark gave a boost to the claims of its efficacy in the treatment of the complications of diabetes mellitus, such as improved inflammatory response in the accelerated healing of diabetic wound [54] and the hepato-renal damages of alloxan-induced diabetic dogs [46] due to hepato protective property of lupeol [56]. Hepatic damage similarly occurred in alloxan-induced diabetic albino rats [57].

Therefore, *A. leiocarpus* with its constituent lupeol can effectively treat T2DM with its accompanying organic damages; this was premised from the anti-inflammatory activity of lupeol [56], as inflammation accompanies diabetes mellitus, exemplified by the significantly higher cytokine associated acute phase reaction and a maker of inflammation, highly sensitive Creative Protein (hs-CRP) in T2DM diabetic people [58,59,60,61], with a report of slight variability [62]. Lupeol activity could be optimized [56], through synthesis along its hydroxyl group and double bond.

Numerous other notable pharmacological activities of lupeol were detailed as antiprotozoal, antimicrobial, antitumor and chemopreventative [56,63], and the therapeutic advantages in the treatment of diabetes were enumerated [55]. The trypanocidal effect of *A. leiocarpus* [45] could have manifested through the lupeol component found in purified extract of *A. leiocarpus* stem bark [55] from its antiprotozoal activity [56,63].

The antidiabetic compounds were located in the interface after maximum purification [64]. Five (5) each of adult male and female Wistar rats and the revised limit test dose of 2000mg/kg.bd.wt. were used to evaluate the acute and delayed oral toxicity and effects on reproductive characteristics of the purified extracts on Wistar rats. The median lethal Dose (LD_{50}) is > 2000mg/kg./bd.wt. The rats were monitored for instant death and 24hours later, 3 each of male and female rats were humanely sacrificed. On day 0 and 24hours later biomarkers of liver damage, AST, ALT, and ALP and that of kidney, urea, were assayed. The remaining 4 rats (2 males and 2 females) were monitored for additional 14days and thereafter for any effect of the limit dose on reproductive activities.

No death within the first 24hours and no hepato-renal damages. Pregnancy, gestation, parturition, pups (kitten) and reproductive performance were normal [64].

The purified extracts of *A. leiocarpus* stem bark as a non-conventional drug for diabetes mellitus, had no effects on pregnancy and reproductive performance. There was no teratogenic effect on pups. The compound has a wide range of safety value [64].

Optimization studies showed that daily administration of 5 mg/kg/bd.wt. of the extract (interface) of *A. leiocarpus* stem bark was therapeutically hypoglycaemic as it reduced random blood glucose (RBG) significantly ($P<0.05$) up to day 12 in Wistar rat [65]. The clinical application of the lower doses was suggested to maintain normoglycaemia for a while after "crashing" down the hyperglycaemia of DM with a much higher therapeutic dose [65].

The shelf life/expiry date of the extract (interface) of *A. leiocarpus* stem bark was found greater than seventeen (17) months, when stored at room temperature [65].

The interface that possessed the antdiabetic activity was subjected to nuclear magnetic resonance (NMR) and the spectral and structural outputs from the NMR confirmed Betulinic acid and Trimethoxyellagic acid as the antidiabetic compounds in the stem bark of *A. leiocarpus* [66].

In addition, the details of the chemical shift data of proton and carbon NMR of the betulinic acid and trimethoxyellagic acid were described adequately [66].

Potent chemical reaction of betulinic acid through carboxylic group, with glucose at its reactive hydroxyl group, a glycosidic linkage, leads to betulinic acid glycoside, an ester, to scavenge glucose molecules in the circulation of diabetic patients and animals. Additionally, the hydroxyl group on the betulinic acid is through glycosidic linkage with another molecule of glucose to form betulinic acid glycoside, an ether achieved after a chemically saturated reaction with the betulinic acid carboxylic group. These two ester and ether productions would scavenge more glucose molecules from

the circulation of diabetic patients and animals, which gives betulinic acid further support for its contribution, partly, for the amelioration of diabetes mellitus.

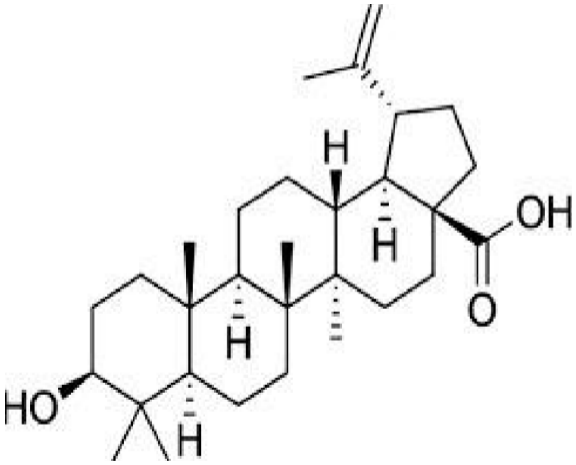

Figure 4. Chemical Structure of Betulinic Acid. Purified extract; stembark-Interface. (Reference 66).

The potent chemical reaction of trimethoxyellagic acid through its hydroxyl group with glucose, at its reactive hydroxyl group, a glycosidic linkage, leads to trimethoxyellagic acid glycoside, an ether, to scavenge glucose molecules in the circulation of diabetic patients and animals.

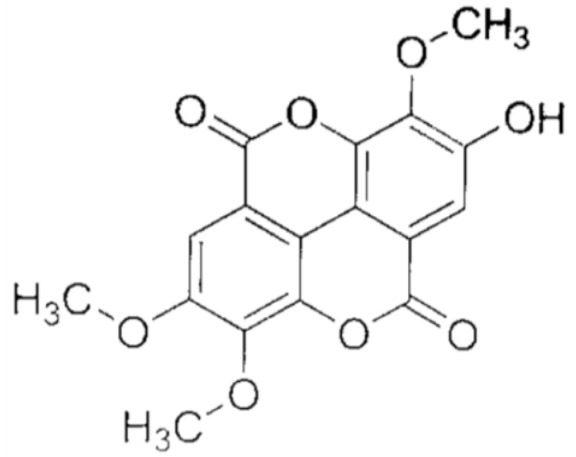

Figure 5. Chemical Structure of Trimethoxyellagic Acid. Purified extract; stembark-Interface. (Reference 66).

These glycosidation processes in part ascribed trimethoxyelllagic and betulinic acids as the antidiabetic compounds in the interface of ethyl acetate and n-hexane purified extracts of *A. leiocarpus* stem bark and that these compounds, acted synergistically, to produce water into the circulation [66].

Leukopenia and anaemia occurred in human diabetic patients [48,49,50] and diabetic dogs [8,46] and the anaemia was macrocylic and regenerative that was restored to normal values by enhanced haematopoiesis by ethanolic extracts of *A. leiocarpus* Paradoxically, limit dose of 2,000 mg/kg bd.wt of purified interface extracts *A. leiocarpus* stem bark produced normocytic normochromic anaemia in Wistar rats over a 24hr period. The normocytic normochromic anaemia was ascribed to hydraemia, due to an expanded plasma volume in the absence of an immediate erythropoiesis [64]; reticulocytosis/macrocytosis, hence an enhanced erythropoiesis and haematopoiesis occurred thereafter.

Therefore, elimination and production of water molecules from the glycosidation processes of betulinic acid and trimethroxyellagic acid occurred in the circulation and an indirect evidence of intact entries of betulinic and trimethoxyellagic acids into the circulation from oral administration of the purified interface extracts [66].

These clinical observations implied that for human or animal patients presenting with advanced diabetes mellitus and anaemia, requiring Physician's or veterinary Clinician's discretion for a higher therapeutic dose of these betulinic and trimethoxyellagic acids, a further deterioration or exacerbation of the anaemia within the first 24hrs must be avoided. Much lower dose was recommended to maintain normoglycaemia for a while, after "crashing" down DM with a higher dose [65].

Urea evaluation showed an enormous and advantageous detoxification effect from the oral administration of the purified interface to the Wistar rats but no adverse effects from ester or ether [64].

Other chemical reactions of betulinic acid supporting its medicinal antidiabetic property included the effect of betulinic acid on the potent insulin secretagogue, an antidiabetic activity mediated by potassium and chloride channels; this novel *in vitro* study showed that betulinic acid triggered calcium influx, partly, through ATP-dependent potassium channels and partly, a calcium-dependent chloride channels, an intricately interwoven process that allowed betulinc acid to stimulate insulin secretion [67]. This latter mechanism of antidiabetic activity is supported by the hyperkalemia and the hyperchloridaemia in diabetic dogs which were restored by crude ethanolic extract of *A. leiocarpus* containing betulinic acid [46,66]

In addition, betulinic acid derivatives exhibited a management tool for type 2 diabetes mellitus by inhibiting alpha-glycosidase activity, and preventing of hydrolysis of carbohydrates; this regulation of blood glucose of postprandial hyperglycaemia and the risk of complications of diabetes [68,69,70,71,72,73].

Derivatives of ellagic acid glycosides had been reported to possess anti-inflammatory activity [74,75]. The antitrypanosome activity of *A. leiocarpus* [45] might be ascribed, partly, to depletion of glucose in peripheral circulation by betulinic acid and trimethoxyellagic acid through glycosidation [66] because of trypanosomes enormous requirement of glucose for glycolysis [76].

Table 6. Effects of *Anogeissus leiocarpus* on Diabetes Mellitus and other Diabetic Metabolic Disorders and Complications.

S/N	Diabetes and Disorders	Effects/Section of Plant/Experimental animal model/Outcome	References
I	Hyperglycaemia	Hypoglycaemic/Crude ethanolic extract of stem bark/Wistar rats Hypoglycaemic/Crude ethanolic extract of stem bark/Wistar rats Hypoglycaemic/guill and perr leaf/rats Hypoglycaemic/total extracts and fractions/mice Hypoglycaemic/crude ethanolic extract of stem bark/dogs **Antidiabetic**	No.9 No. 40 No. 51 No. 52 Nos. 8, 46, 54
II	Organic damages/ deranged Electrolytes/ deranged Acid-base balance	Ameliorated organic damages; ameliorated deranged electrolytes and acid-base inbalance. (Regeneration of damaged organs)/crude ethanolic extract of stem bark/ dogs and rats **Prevention of progression into type 2 diabetes mellitus** **Marked detoxifying effects, from plasma urea evaluation/purified extract (Interface) Wistar rats** **Regeneration of tissues**	Nos. 9, 46, 54 Nos. 64, 65
III	Anaemia, Leukopenia and Thrombocytopenia (Pancytopenia)	Improved haematopoiesis/crude ethanolic extract of stem bark/dogs and rats **Haematopoiesis**	Nos. 8, 9, 40, 46, 54
IV	Sialoglycoconjugate	Elevated serum sialic acids served as a biomarker of diabetes mellitus, predictive of DM and *A. leiocarpus* exhibited prognostic value/ crude ethanolic extract of stem bark/dogs **Biomarker, predictive, prognostic**	No. 8
V	Obesity	a) Effectively controlled cholesterolaemia and lipid metabolism/ethanolic extract of stem bark/dogs b) ……../guill and perr leaf/rats **Antidyslipidaemic**	Nos. 53, 54 No. 51
VI	Oxidative stress/Lipid Peroxidation	a) Effective against lipid peroxidation/oxidative stress/ethanolic extract of stem bark/rats b) ……../total extracts and fractions/mice **Antioxidant**	No. 9 No. 52
VII	Delayed Wound Healing (Diabetic ulcers)	Improved granulation, epithelialization and wound contraction. Thrombocytosis/crude ethanolic extract of stem bark/dogs **Accelerated Wound Healing**	No. 54
VIII	Inflammation Perioxidation; Oxidatives stress	Fraction A of purified extracts of stem bark is **Lupeol** Hepato-protective **Anti-inflammatory; Antioxidant**	No. 55 No. 56
IX	Hyperglycaemia	a) Betulinic acid **(in the interface of purified extract)**; marked potential of scavenging glucose molecules from diabetic patients and animals, through glycosidic linkage to form betulinic glycosides (ester, at the carboxylic group and ether at the hydroxyl group respectively of betulinic acid) b) Stimulates insulin secretion. **Antidiabetic** c) Betulinic acid inhibits intestinal α-glucosidase to control postprandial hyperglycaemia/mice. A good management of glucose metabolism **Alleviates postprandial hyperlycaemia**	No. 66 No. 67 Nos. 68, 69, 70, 71, 72, 73
X	Hyperglycaemia; Inflammation	Trimethoxyellagic acid **(in the interface of purified extract)**; marked potential of scavenging glucose molecules from diabetic patients and animals, through glycosidic linkage to form trimethoxyellagic glycoside (ether, at the hydroxyl group of the trimethoxyellagic acid) **Antidiabetic** Ellagic glycosides were reported to exhibit antiinfllamtory activity	No. 66 Nos. 74, 75

The Plant; *Anogeissus leiocarpus* (African Birch Tree)

The soil contents and fertility are very favourable and supportive to the plant [64] hence not affected by biodiversity and does not appear vulnerable by climate change. When the stem bark is harvested for traditional medicinal purposes, the plant apparently withers off, but with time, particularly with the approach of the rainy season, the plant blossoms perfectly (see Figs. 6 to 10).

Fig 6a. Shrub-like; immediately before the harvest of stem bark (18th Dec., 2021 – Dry season)

Fig 6b. Shrub-like; immediately before the harvest of stem bark (18th Dec., 2021 – Dry season)

Fig 7a. Shrub-like; withering effects from stem bark harvest; (27th April, 2022). 109 days post-harvest of stem bark

Fig 7b. Shrub-like; withering effects from stem bark harvest; (27th April, 2022). 109 days post-harvest of stem bark. Towards the right, arrowed unharvested plant with regular plumage.

Fig 8a. Shrub-like; during the rainy season; recovery from the withering effects of stem bark harvest (27th Sept., 2022)

Fig 8b. Shrub-like; during the rainy season; recovery from the withering effects of stem bark harvest (27th Sept., 2022)

Fig 9a. Tall-tree shape. (10th Dec., 2021)

Fig 9b. Tall-tree shape. (10th Dec., 2021)

Fig 10. Leaves for Botanical Identification and voucher numbering. (10th Dec., 2021) ABU01756

CONCLUSION

From an extensive use of the library complex for articles published in peer reviewed journals, in combination with other search facilities, such as Elsevier, Google Scholar, Medline, PubMeb, Science Direct and Springer, this review has highlighted the numerous benefits of *Anogeissus leiocarpus* as an industrial and economic tree. The antibacterial and antiprotozoal medicinal properties of *A. leiocarpus* were addressed, in addition. Marked harvesting of stem bark subjects the shrub-like "variety" of *A. leiocarpus* to withering; the full "evergreen" plumage returns after mild rain fall, supported by fertility assessment of the tree grown soils. The latter suggest lack of vulnerability to climate change.

With emphasis on the focus of this review, spectral and structural identification of anti-inflammatory lupeol and antidiabetic betulinic acid and trimethoxyellagic acid along with their mechanisms of action on diabetes mellitus and complications are adequately reviewed.

The synergistic performance of these compounds, coexisting *A. leiocarpus* requires economic and agricultural sustainability of *A. leiocarpus* for drug development.

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