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Effect of the combination of *Leptadenia hastata* (pers) decne and *Momordica balsamina* linn leaf extracts on lipid profile of streptozotocin-induced diabetic rats

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Abstract

Background: Changes in blood lipid level (dyslipidemia) play a central role in the onset and pathogenesis of macrovascular complications of diabetes mellitus. Traditional herbal healers commonly use anti-diabetic polyherbal formulations to provide a multi-therapeutic approach for the treatment of diabetes mellitus and its associated complications. The effect of the aqueous leaf extracts of *Leptadenia hastata* (pers) Decne, *Momordica balsamina* Linn and their combination on lipid profile of streptozotocin (STZ)-induced diabetic rats was therefore evaluated in the present study.

Results: We evaluated the serum lipid profile and blood glucose level of STZ-induced diabetic rats (60 mg/kg body weight) treated with the aqueous leaf extracts of *L. hastata* (400 mg/kg) and *M. balsamina* (200 mg/kg) alone and in combination (400 + 200 mg/kg) after a period of 4 weeks. A significantly decreased ($p < 0.05$) level of total cholesterol (TC), triglyceride (TG), very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) cholesterol levels and increased ($p < 0.05$) level of high-density lipoprotein (HDL) cholesterol was observed in all the treated groups when compared to the untreated diabetic rats. Furthermore, the combination treatment was potentially a more effective blood lipid-lowering ($p < 0.05$) agent when compared to the single treatments.

Conclusion: Results from this study demonstrated the blood lipid-lowering potential of the aqueous leaf extracts of *L. hastata*, *M. balsamina*, and their combination. However, the polyherbal combination could be more potent in controlling diabetes mellitus, associated dyslipidemia, and its complications.

Keywords: *Leptadenia hastata*, *Momordica balsamina*, Streptozotocin, Blood glucose, Lipid profile, aqueous extract

Background

Diabetes mellitus (DM) affects essential pathways of carbohydrate, protein, and lipid metabolism consequent to a deficiency of insulin secretion, insulin action, or both [1]. Hyperglycemia is the major hallmark of both type 1 and type 2 DM and it is the principal etiological factor for the pathogenesis of both macro- and microvascular complications. About 80% of type 2 DM is

reported to be associated with obesity, dyslipidemia and hypertension in addition to insulin resistance [2]. Dyslipidemia of diabetes mellitus has been linked with an increased risk of cardiovascular disease (CVD) development. However, the most common form of dyslipidemia associated with DM is hyperlipidemia; characterized by an elevated plasma triglyceride, cholesterol, small dense LDL, and low HDL cholesterol levels. Previous studies have indicated a strong positive correlation between high plasma lipids; notably of low-density lipoprotein (LDL) and incidence of CVD [3]. Increased lipid peroxidation that can damage cell membranes, lipoproteins and lipid containing

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structures is also linked with an increased CVD risk [4]. Potential mechanisms reported to most likely be responsible for diabetic dyslipidemia include defect in insulin action, hyperglycemia, and peripheral actions of insulin on adipose tissue, changes in liver apoprotein production, defective regulation and action of lipoprotein lipase (LPL), and cholesteryl ester transfer protein (CETP) [5]. In addition, increased adipocyte lipolysis due to poor insulinization results in increased free fatty acid flux from the adipocytes and transport to the liver which eventually causes an increased very low-density lipoprotein (VLDL) and triglyceride secretion in blood [6, 7].

While glycemic control tends to dominate the management of type 1 DM, the care for individuals with type 2 DM emphasizes the treatment of other co-morbid conditions associated with the disease such as life style modification, detection/management of obesity, hypertension, dyslipidemia, and related microvascular and macrovascular complications [7]. Diabetes thus, requires a multiple therapeutic approach to adequately control the multiple metabolic abnormalities and progressive nature of the disease. Recent therapeutic trends in the treatment of DM therefore use combination therapies involving different hypoglycemic drugs and/or insulin [8]. Furthermore, many diabetic patients have opted for alternative plant-based therapies alone or in combination to the conventional hypoglycemic drugs due to their increased cost, non-availability, contraindications, and the assumed safety of medicinal plants. As such, the use of medicinal plants would continue to be popular and common, hence the need to scientifically validate medicinal plants as safer alternatives to the conventional ones. Traditional herbal healers use different plant parts in combination with other plants for the treatment of diabetes with the hope that the combined plants would target different pathologies of the disease, despite that the safety and probable mechanism of action is unknown in addition to the consequences which could be increased morbidity and mortality.

Ethnobotanic surveys have shown that plants such as *Leptadenia hastata* and *Momordica balsamina* used most commonly for dietary purposes have gained popularity as ingredients of polyherbal anti-diabetic formulations used by traditional herbal healers in Northern Nigeria [9–11]. *Leptadenia hastata* (Pers.) Decne, which belongs to the family Asclepiadaceae [12], and *Momordica balsamina* Linn, belonging to the family of Cucurbitaceae, are both used for multiple medicinal purposes in Africa [13, 14]. *L. hastata* and *M. balsamina* have both been reported as important sources of dietary nutrients including fatty acids, beta carotene, protein and minerals, and pharmacologically active phytoconstituents such as phenolic compounds, triterpenoids, and glycosides [15, 16]. Phytochemical screening of the leaves of *L. hastata* confirmed the

presence of major chemical compounds such as alkaloids, flavonoids, tannins, phenolic glycosides, triterpenes, and saponins [13]. The bark and leaves of *L. hastata* were found to contain mixtures of polyoxypregnane ester derivatives such as ester 12-O-aceylsarcostin, gagaminin, kidjolanin, metaplexigenin, and cyanforidin as well as triterpenes like lupeol, lupeol acetate, and lupeol palmitate [17, 18]. In a study by Bello et al. [19], the aqueous and methanolic leaf extracts of *L. hastata* reduced the level of blood glucose and blood lipids in both normal and alloxan-induced diabetic rats with a 37.02% and 69.81% alpha glucosidase inhibitory effect, respectively. In another study conducted by Gwarzo and Ameen [20], 3-week supplementation of the diet of hyperlipidemia-induced Wistar albino rats with the leaf powder of *L. hastata* was associated with a reduction in serum lipid profile and blood glucose level. Further to this, we conducted a bioassay-guided fractionation and characterization of the methanolic leaf extract of *L. hastata* and our results revealed 5-methyl genistein as one of the major bioactive compounds responsible for its anti-diabetic effect (unpublished).

In the same way, studies of the potential health benefits of the different plant parts of *M. balsamina* have indicated that it possesses activities like anti-microbial, anti-spasmodic, anti-inflammatory, analgesic, anti-HIV, anti-diabetic, anti-diarrheal, hepato-protective, anti-malarial, antioxidant, anti-cancer, and wound-healing properties [14]. These activities could be as a result of the presence of cucurbitane-type triterpenoids from the leaves of *M. balsamina* including balsaminapentaol, balsaminol A and B, cucurbalsaminol A and B [21], and a novel ribosome-inactivating protein (RIP), balsamin from the seeds of the balsam apple [18]. In our newly conducted work, we isolated a pentane type triterpenoid (betulinic acid) from the ethylacetate fraction of the leaves of *M. balsamina* which was found to contribute to its antidiabetic activity (unpublished). Combination of the plant leaves of *L. hastata* and *M. balsamina* could therefore provide a multi-therapeutic approach for the treatment of diabetes mellitus and its complications. Our previous study had demonstrated the acute and sub-acute anti-hyperglycemic effect of the aqueous leaf extracts of *L. hastata* and *M. balsamina* at a dose of 400 and 200 mg/kg body weight respectively (doses obtained from anti-hyperglycemic screening of the 1/5th, 1/10th, and 1/20th of the LD₅₀ dose; 2000 mg/kg) in STZ-induced diabetic [22]. The dose combination was therefore selected and used in the present study to further evaluate its effect on serum lipid profile in STZ-induced diabetic rats.

Methods

Plant material collection and preparation of aqueous leaf extracts

Fresh leaves of *L. hastata* and *M. balsamina* were obtained from natural vegetation in Kumbotso Local

Government Area of Kano State, Nigeria, in March 2013. Voucher specimens with number *L. hastata* (900220) and *M. balsamina* (1139) were deposited at the herbarium of the Department of Biological sciences, Ahmadu Bello University, Zaria, for future reference.

The leaves were rinsed with distilled water to remove dust and undesirable particles, air dried under the shade for 5 days, and grounded into a fine powder using mortar and pestle. The powdered leaves (500 g) of each plant were extracted with 2 L of distilled water (1:4; solute: solvent) using cold maceration method at room temperature ($25 \pm 2^\circ \text{C}$) for 48 h with constant intermittent shaking. The mixtures were filtered using muslin cloth followed by Whatman No. 1 filter paper and the filtrate was concentrated to dryness in a water bath set at 60°C . The aqueous extracts were stored at 4°C in an air tight container until required.

The aqueous leaf extracts of *L. hastata* (400 mg) and *M. balsamina* (200 mg) per kilogram body weight was combined to obtain the combination dose; LHMB.

Experimental animals and induction of diabetes

The animals were purchased from the personal farm of Mr. Yakubu Otaro of the Department of Zoology, Bayero University, Kano, and were housed and maintained in the animal house of the same department for this experiment. The animals were allowed to acclimatize for 2 weeks prior to study commencement. They were housed in wire meshed cages under laboratory condition of temperature $25.0 \pm 2^\circ \text{C}$, 12 h natural light and dark cycle and were allowed free access to commercial pellet diet (Vital feeds®, Jos) and tap water ad libitum. The animals received human care in accordance with the requirements of the guide for care and use of laboratory animals [14]. Apparently healthy albino rats (Wistar strain) of both sexes weighing between 240 and 250 g were injected intraperitoneally with freshly prepared single dose of streptozotocin (60 mg/kg) (Tocoris Bioscience, UK) in 0.1 M cold citrate buffer after overnight starvation as described by Sankar and Pari [23]. Four hours after induction, the diabetic induced rats were maintained on 5% glucose solution for 24 h to prevent initial STZ induced hypoglycemia. Diabetes was confirmed in rats after 72 h post-STZ injection with blood obtained from rat tail vein using a one touch glucometer (Accuchek Roche, Germany) and rats with blood glucose level of $> 250 \text{ mg/dl}$ were used for the study.

Experimental design

A total of 48 rats comprising of diabetic and normal Wistar albino rats were randomly assigned into 8 groups of 6 rats per group as follows:

Group I: served as normal control and were orally administered water only.

Group II: served as diabetic controls and were orally administered water only.

Group III: were normal rats treated orally with *M. balsamina* (MB) (200 mg/kg body weight)

Group IV: were diabetic rats treated orally with *M. balsamina* (MB) (200 mg/kg body weight).

Groups V: were normal rats treated orally with *L. hastata* (LH) (400 mg/kg body weight)

Group VI: were diabetic rats treated orally with *L. hastata* (LH) (400 mg/kg body weight).

Group VII: were normal rats treated orally with LHMB.

Group VIII: were diabetic rats treated orally with LHMB.

After 4 weeks treatment, the experimental animals were sacrificed by cervical decapitation in the fasted state and blood samples were collected from the jugular vein [24]. Blood glucose level was immediately tested with the whole blood collected using a glucometer (Accuchek, Roche Germany) and serum was obtained thereafter from the clotted blood after centrifugation at 3000 rpm for 10 min for lipid profile estimation.

Biochemical estimations

Serum total cholesterol and triglyceride levels were determined using commercial kits (Fortress Diagnostic Limited, UK). Serum HDL-C was determined using the polyvalent-anion precipitation method as described by Burstein et al. [25] and Lopes-virella et al. [26] while serum LDL-C and VLDL-C levels were calculated using Friedewald's equation; $\text{LDL-C (mg/dl)} = \text{Total Cholesterol} - (\text{Triglycerides}/5 + \text{HDL-C})$; $\text{VLDL-C (mg/dl)} = \text{Triglyceride}/5$ described by Friedewald et al. [27]. All reagents used in the present study were of analytical grade.

Statistical analysis

Data obtained was expressed as mean and their standard deviations. Analysis of variance (ANOVA) followed by Tukey's post hoc tests were used to compare experimental groups. Statistical analysis was performed using R studio software. Values of $P < 0.05$ were considered significant.

Results

Treatment of STZ-induced diabetic rats with the aqueous leaf extracts of *L. hastata*, *M. balsamina* and their combination exerted a 52%, 61%, and 64% decrease in blood glucose respectively at the end of 4 weeks period (Table 1). *M. balsamina* alone and the combination treatments exerted the same anti-hyperglycemic effect as evidenced by the non-significant difference ($p > 0.05$) observed in their percentage decrease in blood glucose level.

Table 1 Percentage decrease in fasting blood glucose (FBG) of normal and STZ-induced diabetic rats treated with aqueous leaf extracts of *L. hastata* and/or *M. balsamina* for 4 weeks

Treatment	Fasting blood glucose (FBG) (mg/dL)
Normal control	95 ± 1.7 ^b (2)
Diabetic control	428 ± 5.8 ^f (-3)
Normal LH (400 mg/kgbw)	91 ± 1.0 ^b (6)
Diabetic LH (400 mg/kgbw)	187 ± 10.4 ^e (52)
Normal MB (200 mg/kgbw)	88 ± 3.8 ^a (8)
Diabetic MB (200 mg/kgbw)	156 ± 20.9 ^d (61)
Normal LHMB (400 + 200 mg/kgbw)	82 ± 3.5 ^a (11)
Diabetic LHMB (400 + 200 mg/kgbw)	145 ± 15.0 ^c (64)

As shown in Fig. 1, the persistent hyperglycemia observed in the untreated diabetic rats was accompanied with significantly elevated ($p < 0.05$) levels of blood total cholesterol, triglyceride and VLDL-C and significantly decreased ($p < 0.05$) level of HDL-C when compared to the normal controls. However, the high blood lipids observed in the diabetic rats was ameliorated by the treatment with *L. hastata*, *M. balsamina*, and their combination with significantly decreased ($p < 0.05$) levels of total cholesterol, triglyceride and VLDL-C and increased ($p > 0.05$) level of HDL-C when compared to the untreated diabetic rats. Additionally, significantly higher levels of total cholesterol, triglyceride, VLDL-C, and LDL-C were observed in the diabetic rats treated singly with the extracts when compared to the combination-treated diabetic rats. This indicates potent lipid-lowering effect of the polyherbal combination on the diabetic rats. In contrast, no significant ($p > 0.05$) change in HDL-C level was observed between diabetic rats treated with single and combination treatments (Fig. 1).

With respect to the normoglycemic rats, a significantly lower ($p < 0.05$) levels of total cholesterol, triglyceride, and LDL-C, and insignificantly higher ($p > 0.05$) HDL-C level was observed in the rats treated singly with *L. hastata* and *M. balsamina* as compared to the normal control and combination treated group (Fig. 1).

STZ Streptozotocin, LH *Leptadenia hastata*, MB *Momordica balsamina*, LHMB combination of *L. hastata* and *M. balsamina*. Values expressed are means with their standard deviations for six animals each per group. Values with different a–f superscripts within the same column are statistically significant (Tukey's post hoc test, $P < 0.05$). Figures in parentheses show percentage decrease over experimental period

Discussion

Severity of hyperlipidemia observed in diabetes appears to depend on the extent of insulin deficiency and interaction of lipids with free radicals which play important roles in tissue damage and consequently diabetic complications [28]. With the progression of diabetes mellitus in patients, treatment is usually modified to contain two or more hypoglycemic agents, despite their major drawbacks of having side effects when used alone and in combination, necessitating the search for safer alternatives. Plants contain a large compound-base that can provide hypoglycemic substitutes that can be safely combined and without drastic side effects, hence the need for scientific validation of traditionally used plants.

Plant extracts or their isolated phytochemicals have been used for decades to ameliorate high blood glucose level. In consistent to the present study, several other studies have confirmed the ability of streptozotocin using a single dose of 60 mg/kg to induce hyperglycemia [29] via the selective necrosis of the pancreatic beta cells which results in diminished insulin secretion and suppressed hormone sensitive lipoprotein lipase of triacylglycerol activity [30]. Hyperglycemia induced using streptozotocin is reported to be accompanied by hypoinulinemia, dyslipidemia, kidney damage, cataract formation, and weight loss [31, 32]. These pathologies are usually accompanied with a markedly elevated glycated hemoglobin level for up to 23 weeks post-induction of diabetes [33]. In this perspective, researchers worldwide have used streptozotocin-induced model of diabetes as an inexpensive, simple, and available method to study diabetes. Streptozotocin-induced type 1 diabetes models are well-accepted in practice as animal models that recapitulate the different types of human diabetes and can therefore be used for the elucidation of diabetic pathogenesis and screening of potential glucose-lowering agents [34]. Furthermore, hyperglycemia of streptozotocin is reported to be stable for up to 24 weeks without intervention [35].

The hypoglycemic and lipid-lowering effect of *L. hastata* and *M. balsamina* observed in the present study is consistent to studies by Karumi and Bobboi [36], Karumi et al. [14], Bello et al. [19], Ayoub et al. [37], and Gwarzo and Ameen [20]. Treatment with *M. balsamina* alone depicted the same anti-diabetic efficacy as the combination treatment; this could have been due to the length of the study period. The anti-hyperglycemic efficacy could have been higher in the combination group if the study period was extended. However, the results validate the traditional use of the anti-diabetic polyherbal combination. As observed in the present study, glycemic control appears to be paramount for the control of high blood lipid level; as blood lipid levels were ameliorated with lower blood glucose level.

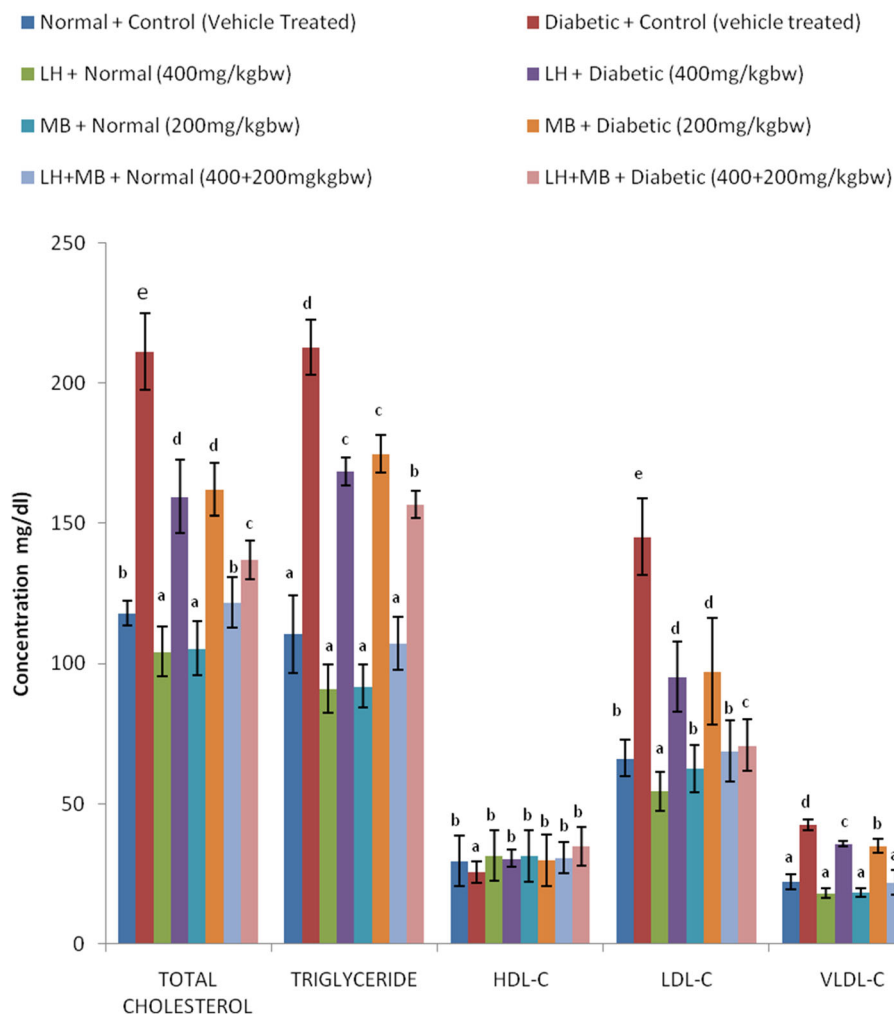


Fig. 1 Effect of aqueous leaf extracts of *L. hastata*, *M. balsamina* and their combination on lipid profile of normal and STZ-induced diabetic rats. Values expressed are means with their Standard Deviations represented as error bars for six animals per group. Different superscripts a–d for each parameter indicate statistical significance at value of $P < 0.05$ (Tukey's post hoc test)

Insulin has an important role in the regulation of lipid metabolism most especially its effect on the activity of hormone sensitive lipoprotein lipase. Low insulin level that accompany hyperglycemia has been reported to significantly promote the conversion of free fatty acids into phospholipids and cholesterol which are released into the blood resulting in high blood cholesterol levels of diabetic patients [6, 7]. This is consequent to the activation of lipoprotein lipase and inhibition of lecithin cholesterol acyl-transferase which causes an elevated blood VLDL, LDL, and triglyceride levels with a concomitant decrease in HDL [38]. In agreement with our results, increased serum triacylglycerol and cholesterol concentration due to their increased production by the liver and increased VLDL-C and LDL have been reported in many studies [7, 38]. Furthermore, long-term hyperglycemia of diabetes mellitus causes small dense LDL particles to be more atherogenic because they are easily glycosylated and

susceptible to oxidation as such increases the risk of developing cardiovascular diseases in diabetic patients [3, 6]. Glycation of lipoproteins and apolipoproteins have been shown to play significant role in the development of atherosclerosis [39]. The hypolipidemic activity of the polyherbal combination containing *L. hastata* and *M. balsamina* could therefore be an indication of its anti-atherogenic potential and consequently potential for lowering the risk of CVD.

Low HDL cholesterol level is also implicated as an underlying risk of CVD development. This finding is consistent with our results and could be due to an increased non-enzymatic glycation of HDL-C resulting in its increased clearance [40]. While our study did not observe a significant improvement of HDL level after treatment with the plant extracts alone and in combination, the finding is however in agreement with the study of Ighodaro et al. [41]. This emphasizes the need for long-

term research in order to ascertain the lipid-lowering mechanism of action of the medicinal plants as potential drug candidates.

Phytochemical compounds reported to be found in *L. hastata* and *M. balsamina* [13, 21] may be responsible for their anti-diabetic activities. The blood lipids-lowering effect exerted by the aqueous leaf extracts might have worked synergistically or additively in the polyherbal combination. Emerging research on mechanism of action of phytochemical compounds with hypolipidemic and anti-hyperglycemic potentials are reported to be through the inhibition of cholesterol synthesis, lipoprotein lipase, HMG-CoA reductase, or reduction in the NADPH required for fatty acids synthesis [7]. Plants rich in flavonoids, alkaloids, and tannins are reported to have significant blood lipid-lowering effects [42]. Cucurbitane type triterpenoids [15] and pentacyclic type triterpenoids; betulinic acid (unpublished) reported in *M. balsamina* and lupeol palmitate [16] and isoflavone; 5-methyl genistein (unpublished) in *L. hastata* could therefore be responsible for their blood lipid- and glucose-lowering effects. The anti-diabetic, antioxidant, inhibitory intestinal glucose and lipid absorption, and insulinomimetic activities of the compounds in *L. hastata* and *M. balsamina* [16, 19, 43, 44] have been reported. Recent studies have demonstrated the ability of betulinic acid found in *M. balsamina* to effectively ameliorate hyperglycemia as well as to exert hypolipidemic, antioxidant, anti-AGE, and anti-obesity activities [45]. Genistein on the other hand found in *L. hastata* has been shown to be a strong antioxidant capable of removing damaging free radicals and reduce lipid peroxidation through increases in activity of antioxidant enzymes including glutathione peroxidase, superoxide dismutase, and glutathione reductase [30].

Maceration extraction procedure used in the present study, which uses low temperature and produces a product without the degradation of the heat labile compounds found in the plant leaves, could have preserved the potency of the lipid-lowering phytochemicals [46]. The use of aqueous extract in the present study is in consonance to how these plant extracts are used by the traditional herbal healers. However, further studies using non polar solvent extracts of *L. hastata* and *M. balsamina* could provide more potent hypolipidemic agents to exert an enhanced anti-diabetic and anti-hyperlipidemic effect of the polyherbal combination. An aspect for future study is to unravel the mechanism of anti-diabetic action of *L. hastata* and *M. balsamina* and to produce a polyherbal supplement for diabetics.

Conclusion

Our findings demonstrated the potential anti-hyperglycemic and blood lipid-lowering effects (hypolipidemia) of *L. hastata* and *M. balsamina* alone and in combination. The

hypolipidemic activity could be consequent to an improved glycemia as such could be beneficial for managing diabetes mellitus and its associated complications. Thus, this research validates the traditional usage and efficacy of the polyherbal combination in exerting both anti-hyperglycemic and lipid lowering effects.

Abbreviations

HDL: High-density lipoprotein cholesterol; VLDL: Very low-density lipoprotein; LDL: Low-density lipoprotein; FBG: Fasting blood glucose; STZ: Streptozotocin; DM: Diabetes mellitus; CVD: Cardiovascular disease

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Plant authentication

The plant leaves used for this study were authenticated by Musa Muhammad of the herbarium, Department of Biological Sciences, Ahmadu Bello University, Zaria.

Authors' contributions

NK, UIA, DBJ, and HMI conceived and designed the study. NK, UIA, DBJ, HMI, and MKA were responsible for acquisition of data, analysis and interpretation of data obtained, and drafting of manuscript. UIA, DBJ, HMI, and MKA supervised the work and NK, UIA, and MKA revised and corrected the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data used to generate the findings of this study are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Faculty of Life Sciences scientific and biochemical ethics committee, Ahmadu Bello University, Zaria, under registration number Ph.D/Scie/3691/2011–2012.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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