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Complementary Therapeutic Effect of Polyherbal Supplement (Gasca D™) on Newly Diagnosed Type 2 Diabetic Patients on Lifestyle Modification: A Randomised Cohort Clinical Trial.

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ABSTRACT

Our previous studies have shown that Gasca D™; a polyherbal formulation made from three well known antidiabetic plants in Nigeria, possess anti-hyperglycemic, body weight and blood lipid lowering potentials in rats. In view of this, the present study was therefore designed to evaluate the complementary therapeutic efficacy of Gasca D™ supplementation with lifestyle modification in a clinical setting. The randomized cohort trial was conducted in sixty (60) newly diagnosed type 2 diabetic patients on life style modification as first-line therapy who willingly volunteered to participate. The subjects that satisfy our inclusion criteria were randomly assigned into Gasca D™ (GG) and lifestyle (LG) groups. The GG group received 2000 mg Gasca D™ capsules daily over a twelve weeks period whereas the LG group received none. Biochemical estimates were conducted on subjects to evaluate the safety and efficacy of the polyherbal supplement at the end of the intervention period. Mean fasting blood sugar (FBS) showed a decrease of 23.4% ($p < 0.05$) in the GG group contrary to a 9.6% mean FBS observed in the LG ($p < 0.05$) group. Variation in glycosylated hemoglobin (HbA1c) was in line with that of FBS. Safety of Gasca D™ was demonstrated by a normal renal and liver function profile in both groups. Our finding suggests that, Gasca D™ can successfully be used as an effective and safe complementary nutraceutical for the control of hyperglycemia in type 2 diabetic patients on life style modification.

Keyword: Type 2 diabetes mellitus, newly diagnosed, Gasca D, HbA1c, *Adansonia digitata*, FBS, HbA1c

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Introduction

Type 2 diabetes mellitus (T2DM) is a complex metabolic progressive disorder characterized by

relative deficiency of insulin caused by dysfunction of pancreatic β -cell and/or insulin resistance whose prevalence is increasing globally.

Incidence and prevalence of T2DM is observed to vary according to the geographical region, with more than 80% of patients living in low-to-middle-income countries. However, the overall trend is an increase in diabetes prevalence in every country since the 1980s [1].

Previous studies have documented the gradual worsening of glycemic control among T2DM patients as the disease progresses, necessitating the need for increasing numbers of hypoglycemic agents [2]. Additionally, with disease progression, many patients may require insulin therapy to achieve good glycemic control. Consequently, current treatment trend for T2DM is centered on drug interventions that stabilize hyperglycemia and manage cardiovascular risk factors, including blood pressure and lipids, to prevent associated symptoms and reduce the risk of vascular complications over time [3]. Interventions that work in some societies might not work in others, as a result of social, economic, and cultural influence of diet and exercise. Long term follow-up data from the United Kingdom Prospective Diabetes Study has shown that despite early successes, metabolic control progressively worsens with time, warranting exploration of alternative approaches for long term management of type 2 diabetes [5].

Observational studies have documented that intensive lifestyle modification; which is considered the frontline therapy for T2DM management before the commencement of pharmacotherapy can reverse or delay the development of type 2 diabetes [4], especially

among the newly diagnosed patients. Alternative therapies are therefore increasingly opted for by patient with diabetes especially since they are considered to be foods. Herbal medications are the most commonly used alternative therapy for blood sugar control. A lot of scientific researches are currently focusing on developing new drugs based on natural or nature-identical compounds of herbal origin to treat complicated diseases like diabetes. In contemporary research, plant-derived drugs are considered less toxic and more compatible with biological systems because of their lesser side effects as compared to the synthetic ones. However, their safety and efficacy needs to be further evaluated using well designed, controlled clinical trials. Furthermore, herbal medications have been shown to provide symptomatic relief and assist in the prevention of secondary complication of diabetes. Notably, some antidiabetic herbs have been shown to help in regeneration of β -cells and in overcoming resistance. Nearly 400 herbs and plant preparations are reported to have beneficial effects in the treatment of diabetes mellitus worldwide [6]. The surge for the use of natural agents and alternative therapies in diabetes management is therefore now on the increase to lower the overall financial burden on public health services [7,8].

In response to these public health challenges of T2DM management in Nigeria, a new polyherbal formulation listed with the National Agency for Food and Drug Administration and Control (NAFDAC) as “Gasca D” with

registration no: A7-2639L was developed. Gasca D is a polyherbal formulation containing active constituents of various plant parts of *Adansonia digitata*, *Hyphaenae thebaica*, *Vernonia amygdalina*. Individually, the aqueous extracts of the aforementioned plants have documented antidiabetic effects in Africa based-researches [9-11].

Gasca D herbal supplement was obtained by the researchers from Green leaf Herbal Product company Nigeria. The polyherbal drug presents works on the aqueous extracts of the different plant parts of *Adansonia digitata* as the main functional ratio while having *Hyphaenae thebaica* and *Vernonia amygdalina* in smaller ratios. The baobab (*Adansonia digitata*) tree has been referred to as a small pharmacy or chemist tree and many authors have reported that all Baobab plant parts are valuable [12, 13]. In addition to being a source of food, the plant parts are used as astringent, demulcent, diaphoretic and for diarrhea, dysentery, haemoptysis, rheumatic pain, inflammatory ulcers, intermittent fever, antitrypanosome, anti-diabetic, anti-cancer, diuretic agents [14]. The pulp fruits of *Adansonia digitata* are traditionally used for dietary as well as for medicinal purposes, such as management of diabetes mellitus in Hausa land of Northern Nigeria.

The pre-clinical efficacy of Gasca D™ on hyperglycemia and associated complications such as hyperlipidemia has been confirmed using in vitro studies and in animal models of type 1 and 2 diabetes mellitus and the activity

was found to be comparable to that of conventional hypoglycemic drugs (metformin) [15]. In this regard, the present study was aimed to evaluate the complementary therapeutic efficacy of Gasca D™ supplementation with lifestyle modification in newly diagnosed T2DM patients.

MATERIAL AND METHODS

Study design and Study Subjects

The study is a randomized cohort clinical trial on newly diagnosed patients with type 2 diabetes mellitus on life style modification only. Patients were assessed by an endocrinologist and confirmed to be type 2 diabetic according to WHO diagnosis criteria of FBS and HbA1c levels at two different times. Subjects diagnosed with non-insulin dependent type 2 diabetes, HbA1c > 6.5%, who had been following a steady lifestyle modification regime (in terms of diet and exercise) with no previous history of use of hypoglycemic medication and were willing to continue the same without any changes during the study period, those with body mass index (BMI) of 18.5–35 kg/m²were included in the study. Subjects were excluded from the study if they consume other types of herbal supplement for any condition, take any glucose lowering medication or drug that is known to affect blood sugar level, alcohol drinkers, and have major systemic disorders, known cases of renal impairment or cardiac disorders and women who were pregnant/lactating.

Sixty newly diagnosed type 2 diabetic patients on lifestyle modification and after the study objectives were explained to them and have met our inclusion criteria were enrolled in the study. The subjects were randomly assigned into two groups: thirty five (35) volunteered to willingly receive Gasca D™ herbal supplement and were grouped as Gasca D Group (GG) and 25 opted not to receive the supplement and were assigned to the lifestyle modification only (LG) group. Life style modification in this study was defined as dietary modification and increased physical activity of at least 4 times weekly. The glycemic indices (FBS and HbA1c), lipid profile, liver enzymes and electrolytes, urea and creatinine of the intervention arm and non intervention arm were assessed at baseline. The intervention group received 4 capsules of 500 mg of Gasca D as a twice daily dosing for 90 days. Follow-up of the patients was done at two (2) weeks interval to monitor compliance and for clinical evaluation for any adverse effects. The supplements to last two weeks were given to each subject at each follow-up clinic visit. To be assured of the consumption of supplement by the subjects, the subjects were asked to first deliver the empty boxes of capsules and then receive the new ones needed for the next two weeks. The participants were also advised against further dietary modifications during the study period.

The primary outcome of the present study was to determine the effect of Gasca D™ supplementation on glycemic control as measured using Fasting blood sugar (FBS) and HbA1c. On the other hand, the secondary

outcome was to determine the efficacy and safety of Gasca D supplementation on lipid profile, anthropometric measurements and liver and kidney function profiles respectively.

Ethical considerations

This study was performed in accordance to the Declaration of Helsinki and subsequent revisions (WMA, 2008) and was approved by the Ethical Sub-committee of Health Operational Research Unit of Ministry of Health, Kano State, Nigeria with ethical approval no **MOH/Off.797/T.1/389**. All patients provided written informed consent for participation in the study.

Anthropometric and Biochemical measurements

Demographic data, including patient's age, sex, height, weight, BMI and results of blood and urine glucose tests were obtained from subjects using checklists developed by the authors. Weight and height were measured in the fasting state with minimal clothing on standard weighing scale to the nearest 100 g. Standing height was measured by a stadiometer to the nearest 1–2 mm. Blood samples were collected on Days 0 (at base line) and 90 from subjects after a 10- to 12-hours overnight fast. The blood samples were centrifuged after clot retraction at 3000 X g for 10 minutes at 20°C to obtain serum samples which were used for biochemical analysis.

Biochemical tests included FBG, HbA1c, triglyceride (TG), total cholesterol and its components (low-density lipoprotein cholesterol (LDL) and high density lipoprotein cholesterol

(HDL), electrolytes, urea and creatinine and liver enzymes. Fasting blood glucose was analyzed using the glucose oxidase method using a commercially available kit (Randox Ltd, UK). Similarly, HbA1c, serum TG, HDL-C and cholesterol levels were evaluated by the enzymatic colorimetric method using commercially available kits (Randox, UK) following manufacturer's instructions. LDL-C was calculated using Friedewald's formula (2004).

Data analysis

Data was analyzed using statistical software package, SPSS version 20.0. Data was presented as mean \pm SD. For comparison of means, student t-test was used to determine the significance between groups and ANOVA across groups. P-value of <0.05 was considered statistically significant.

RESULTS

The mean ages of the study subjects was found to be 47.1 ± 13.4 years with subjects being majorly males. Significantly lower FBG was

observed in the Gasca D supplementation group when compared with both the baseline and diabetic group on lifestyle modification only. Additionally, Gasca D intervention resulted in an average decrease of 1.28 mmol/L of FBG relative to the diabetic group on lifestyle modification only. On the other hand, the intervention group had an average decrease of 2.16 mmol/L of FBG when compared with the baseline values (Table 1).

Furthermore, significant improvement in glycemic control as indicated by glycated hemoglobin level (HbA1c) was observed in diabetic group taking Gasca D supplementation when compared with baseline values. Conversely, an average of 1.7% decrease in HbA1c level was observed in the intervention group relative to the non-intervention group on lifestyle modification only. However, no significant difference in BMI was observed between diabetic group taking Gasca D supplementation, diabetic group on lifestyle modification only and baseline (Table 1).

Table 1: Effect of Gasca D supplementation on Glycemic control and body mass index of newly diagnosed diabetic patients on lifestyle modification

| Parameters | Baseline | Lifestyle Modification | Lifestyle Modification + |
|--------------|-----------------|------------------------|--------------------------|
| | | Only | Gasca D |
| FBG (mmol/L) | 9.4 ± 0.7 | 8.5 ± 1.3^a | $7.2 \pm 0.8^{a,b}$ |
| HbA1c (%) | 7.7 ± 1.1 | 6.6 ± 1.9^a | 6.0 ± 1.2^a |
| BMI | 32.7 ± 10.3 | 27.8 ± 6.9 | 27.2 ± 6.3 |

Values expressed are Mean \pm S.D (n=60).

Abbreviations: FBG: Fasting Blood Glucose, HbA1c: glycated hemoglobin, BMI: Body Mass Index,

^ap<0.05, vs Baseline (pretreatment) ^bp<0.05 vs Lifestyle modification

Liver enzymes; AST and ALT level were observed to be significantly ($p < 0.05$) decreased in diabetic groups that received Gasca D intervention and lifestyle modification only

when compared with pre-intervention group. However, no significant difference in the level of ALP was observed in all three groups (Table 2).

Table 2: Liver function parameters before and after Gasca D supplementation and Lifestyle modification only

| Parameters | Baseline | Lifestyle Modification Only | Lifestyle Modification + Gasca D |
|------------|----------------|-----------------------------|----------------------------------|
| AST (U/L) | 16.3 \pm 4.1 | 11.5 \pm 5.5 ^a | 11.2 \pm 3.8 ^a |
| ALT (U/L) | 11.9 \pm 4.0 | 8.6 \pm 3.2 ^a | 9.0 \pm 2.7 ^a |
| ALP (U/L) | 12.7 \pm 3.6 | 10.5 \pm 2.0 | 13.8 \pm 6.2 |

Values expressed are Mean \pm S.D. (n=60).

Abbreviations: AST: Aspartate amino Transferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, ^a $p < 0.05$, vs Baseline (pretreatment) ^b $p < 0.05$ vs Lifestyle modification

Significantly decreased the level of urea and creatinine were observed in the Gasca D intervention and non-intervention group when compared with baseline values. Furthermore, even though both the levels urea and creatinine in the intervention and non intervention groups were within normal reference limit, an average

of 1.49mmol/L increase in urea level was observed in diabetic group supplemented with Gasca D when compared with diabetic group on lifestyle modification only. Conversely, an average of 0.32 mmol/L urea was found to have increased in diabetic group taking Gasca D relative to the baseline (Table 3).

Table 3: Effect of Gasca D supplementation on Electrolyte Urea and Creatinine of diabetic patients on life style modification only

| Parameters | Baseline | Lifestyle Modification Only | Lifestyle Modification + Gasca D |
|--|-----------------|-----------------------------|----------------------------------|
| UREA (mmol/L) | 4.4 \pm 1.4 | 4.4 \pm 1.5 | 5.9 \pm 2.3 ^{a,b} |
| Creat. (mg/dl) | 0.8 \pm 0.3 | 1.0 \pm 0.2 ^a | 1.3 \pm 0.3 ^{a,b} |
| HCO ₃ ⁻ (mmol/L) | 23.4 \pm 2.0 | 27.1 \pm 11.9 | 23.1 \pm 2.6 |
| Na ⁺ (mmol/L) | 134.4 \pm 3.9 | 134.9 \pm 7.2 | 133.6 \pm 3.5 |
| K ⁺ (mmol/L) | 3.7 \pm 0.4 | 3.4 \pm 0.6 | 3.5 \pm 0.7 |
| Cl ⁻ (mmol/L) | 99.7 \pm 3.3 | 95.2 \pm 3.8 ^a | 101.2 \pm 5.3 ^b |

Values are expressed as Mean \pm S.D. (n=60).

Abbreviations: Creat: Creatinine, HCO₃⁻: bicarbonate, Na⁺: sodium, K⁺: Potassium, Cl⁻: chloride, ^ap<0.05, vs Baseline (pretreatment) ^bp<0.05 vs Lifestyle modification

No significant difference (p>0.05) was observed in the levels of serum electrolytes; sodium, potassium and bicarbonate. However, significantly higher chloride was observed in the Gasca D intervention group when compared to the lifestyle modification only and baseline groups.

With regards to the lipid profile, the levels of total cholesterol (p < 0.05), TG (p < 0.05) and

LDL-C (p <0.05) were found to be significantly decreased in the Gasca D supplemented and lifestyle modification only group when compared with baseline (pre-treatment) values. On the contrary, HDL-C level was found to be significantly (p<0.05) increased in Gasca D supplementation when compared with diabetic group on life style modification only and baseline (Table 4).

Table 4: Effect of Gasca D supplementation on Lipid profile and renal function of type 2 diabetic patients on life style modification

| Parameters | Baseline | Lifestyle Modification Only | Lifestyle Modification + Gasca D |
|----------------------|--------------|-----------------------------|----------------------------------|
| T.Chol. (mg/dl) | 211 ±13.5 | 183.7 ± 18.5 ^a | 170.7 ±14.6 ^a |
| Triglyceride (mg/dl) | 158.2 ±19.8 | 122.5 ± 18.1 ^a | 113.8 ±19.2 ^a |
| HDL (mg/dl) | 52.2 ± 9.7 | 57.3 ± 9.7 ^a | 68.8 ± 12.1 ^{a,b} |
| LDL (mg/dl) | 136.1 ± 20.4 | 93.1 ± 41.5 ^a | 100.1 ±18.7 ^a |

Values expressed are Mean ± S.D (n=60).

T.Chol: Total cholesterol, HDL: High density lipoprotein, LDL: low density lipoprotein: ^ap<0.05, vs Baseline (pretreatment) ^bp<0.05 vs Lifestyle modification

Discussion

In the present study the efficacy and safety of daily consumption of 2g of Gasca D poly herbal formulation by type 2 diabetic patients for 12 weeks complementary to lifestyle modification was demonstrated. In agreement with our results of improved body mass index; a marker of obesity, a study conducted by Rajkumar et al. [16] suggested that *Adansonia digitata*; the main active ingredient of Gasca D, caused an improved weight in diabetic rats. Several human

and animals studies have also demonstrated the vast antidiabetic effects of the different plant parts of *Adansonia digitata* by different mechanisms of action to reduce high blood glucose [17, 20]. Additionally, in a study conducted by Margarida *et al.* [18] to verify the effect of *Adansonia digitata* L. (Baobab) fruit on postprandial glycaemia levels on non-diabetic adults, they found that the fruit extract acted beneficially on postprandial glycaemic control which is in line with our fasting glucose

results. The reduction in elevated blood glucose along with HbA1c levels indicated that Gasca D can improve insulin sensitivity through an improved glycemic control thus can effectively manage newly diagnosed diabetic patients in addition to lifestyle modification. Furthermore, studies by Stefania *et al.* [19] reported that baobab leaves possess potent inhibitory glucose uptake activity via its inhibitory effect on alpha-amylase and alpha-glucosidase enzymes. These could provide therefore another probable mechanism of action of Gasca D in addition to its beta cell stimulatory effects as evidenced by an improved glycemic control.

Several studies have demonstrated the serum lipid-lowering effects of the methanolic and aqueous extracts of the leaves of *Adansonia digitata*, *Vernonia amygdalina* and *Hyphaena thebaica* in rats [21, 23, 24]. This could be consequent to its potential phytochemical-induced stimulatory effect on insulin secretion. Over the years therapeutic properties of medicinal plants has been scientifically validated to be due to the presence of mixtures of different biologically active phytochemicals. These phytochemical are shown to act synergistically, or additively to produce beneficial health effects. The decrease in glycemic and lipidemic index by Gasca D can therefore be attributed to the presence of phytoactive constituents present in different plant parts of *Adansonia digitata*, *Hyphaena thebaica* and *Vernonia amygdalina*. Phytochemical studies of the three plant in Gasca D (*Adansonia digitata*, *Vernonia*

amygdalina and *Hyphaena thebaica* have reported them to be rich in flavonoids among others. Flavonoids which include catechin, epicatechin, quercetin, quercetrin, rutin, kaempferol and leuteol. Flavonoids such as kaempferol, catechin, and quercetin has been reported to bind to HMG-Co AR [25], thereby bringing about reduction in blood cholesterol level. Flavonoids are of pharmacological importance for the management and/or prevention of type 2 diabetes [26]. Isolated flavonoids from other medicinal plants with antidiabetic activity have been found to stimulate secretion of insulin [27]. Quercetin an important flavonoid also found in the pulp and fruit of *Adansonia digitata* and *Hyphaena thebaica* respectively has been found to increase insulin secretion by enhancing hepatic glucokinase activity [28]. Similarly, the inhibition of α -amylases and α -glucosidases activities has been reported to be effective in controlling hyperglycemia [29] because hydrolytic activity of amylase and glucosidase on carbohydrates contributes to postprandial blood glucose level [30].

Furthermore, our results are suggestive of the fact that Gasca D is a potentially safe herbal supplement as no toxicity was evident on the liver and kidney. When used appropriately, Gasca D supplement is safe for use as the main plants used, have a long traditional usage history as medicines and food. Additionally, aqueous extracts were used for Gasca D formulation in consonance to how they are used in traditional

medicine practice. This traditional approach makes Gasca D safe as the potentially toxic compounds are mostly not extracted when water is used for extraction [21]. Our result further buttresses the safety and potential use of Gasca D for the management of diabetes and its complication outside the boundaries of cultural use.

Limitation

The limitations of the present study, was that it was a short period of supplementation (3 months) was used for the study and crude extracts of the plant parts were used. Hormones and other metabolic parameters pertinent to inflammation were not assessed.

Conclusion

This study demonstrated the safety and ability of Gasca D supplementation in addition to lifestyle modification to be used for achieving good glycemic control. Our results further suggest that Gasca D is a safe and standardized polyherbal drug that has the potential efficacy to help in the management of patients with type 2 diabetes mellitus and could be use as a complementary nutraceutical by newly diagnosed type 2 diabetic patients.

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