Afr. J. Med. Med. Sci. (2022) **52,** 4 225-232

Synergistic effects of *Tetracarpidium conophorum* nuts (Nigerian walnuts) and *Gongronema latifolium* leaves (Utazi) on plasma lipid profile and blood glucose

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Abstract

Background: Herbal remedies or food supplements have increasingly become attractive alternatives to prevent or treat hyperglycemia and hypercholesterolemia. The study evaluates the synergistic effects of *Tetracarpidium conophorum (Tc) nuts and Gongronema latifolium (Gl)* leaves on plasma lipid profile and blood glucose.

Materials and Methods: The study was conducted on 60 apparently healthy subjects within the age range of 20-55years. 20 subjects consumed 5g of GI leaves, 20 consumed 75g of Tc nuts and 20 consumed 5g of GI leaves and 75g of Tc nuts daily for 6 weeks.

Results: The plasma Glucose and Lipid parameters were analyzed using standard laboratory methods. Statistically significant reduction was observed in the level of Plasma fasting blood glucose (FBG), Total cholesterol (TC), triglycerides (TG), LDL-C and LDL-C/ HDL-C ratio ($P<0.05$) of the subjects that consumed Gl leaves compared with their baseline values. Similar results were obtained in lipid parameters of participants that consumed Tc nuts with a significant increase in their HDL-C level ($P<0.05$). Also, subjects that consumed combined Gl leaves and Tc nuts recorded statistically significant reduction in the level of plasma FBG and the lipid parameters with a significant increase in HDL-C level ($P<0.05$) compared with their baseline values.

Conclusion: This study concluded that Gl has hypoglycemic and hypolipidemic effects while Tc has hypolipidemic effect. Furthermore, the synergistic hypolipidemic effect of Tc nuts and Gl leaves led to more significant reduction in the lipids and lipoprotein values.

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Keywords: *Tetracarpidium conophorum nuts, Gongronema latifolium leaves, Blood glucose, Lipid profile, cardiovascular diseases, Diabetes Mellitus.*

Résumé

Contexte : Les remèdes à base de plantes ou les compléments alimentaires sont devenus de plus en plus des alternatives intéressantes pour prévenir ou traiter l'hyperglycémie et l'hypercholestérolémie. L'étude évalue les effets synergiques des noix de *Tetracarpidium conophorum (Tc) et des feuilles de Gongronema latifolium* (Gl) sur le profil lipidique plasmatique et la glycémie. *Matériels et méthodes* : L'étude a été menée sur 60 sujets apparemment en bonne santé dans la tranche d'âge de 20 à 55 ans. 20 sujets ont consommé 5g de feuilles IG, 20 ont consommé 75g de noix Tc et 20 ont consommé 5g de feuilles IG et 75g de noix Tc quotidiennement pendant 6 semaines. *Résultats* : Les paramètres plasmatiques de glucose et de lipides ont été analysés à l'aide de méthodes de laboratoire standard. Une réduction statistiquement significative a été observée au niveau de la glycémie plasmatique à jeun (FBG), du cholestérol total (TC), des triglycérides (TG), du LDL-C et du rapport LDL-C/HDL-C ($P<0,05$) des sujets ayant consommé Feuilles de Gl comparées à leurs valeurs de base. Des résultats similaires ont été obtenus dans les paramètres lipidiques des participants ayant consommé des noix Tc avec une augmentation significative de leur taux de HDL-C ($P <0,05$). De plus, les sujets qui ont consommé des feuilles de Gl et des noix de Tc combinées ont enregistré une réduction statistiquement significative du niveau de FBG plasmatique et des paramètres lipidiques avec une augmentation significative du niveau de HDL-C ($P <0, 05$) par rapport à leurs valeurs de base.

Conclusion : Cette étude a conclu que Gl a des effets hypoglycémiques et hypolipidémiques tandis que Tc

a un effet hypolipidémique. De plus, l'effet hypolipidémiant synergique des noix Tc et des feuilles Gl a conduit à une réduction plus significative des valeurs de lipides et de lipoprotéines.

Mots clés : *Noix de Tetracarpidiumconophorum, Feuilles de Gongronemalatifolium, Glycémie, Profil lipidique, Maladies cardiovasculaires, Diabète sucré.*

Introduction

Herbal remedies or food supplements have increasingly become attractive alternatives to prevent or treat hyperglycemia and hypercholesterolemia. Use of traditional Herbal remedies is steadily increasing in countries where its use was not recognized and has been used from ancient times for the prevention and treatment of chronic disease and also in health maintenance [1]. Thus, the development of new products from natural sources is encouraged because it is estimated that of the 300,000 plant species that exist in the world, only 15% have been evaluated to determine their pharmacological potential [2]. Therefore, such plants should be investigated for better understanding of their properties, safety and efficacy. In the past, several plants and plant products have been studied for their potential hypoglycemic and antihyperlipidemic effects [3-9]. Presently, there is an increasing interest in investigation of more plants for its therapeutic potentials in the management of hyperglycemia and hyperlipidemic which chiefly characterizes the pathophysiology of diabetes mellitus and cardiovascular diseases respectively. Diabetes mellitus (DM) is a chronic metabolic disease which results from diminished or absent secretion of insulin or even by reduced tissue sensitivity to insulin [10, 11].

Diabetes Mellitus has become a major public health problem in Nigeria accounting for a prevalence of 2.4% with total number of mortality amounting to 3028 deaths in 2017 [12]. On the other hand, cardiovascular diseases are a group of diseases that affect the heart and blood vessels. Cardiovascular diseases which include coronary heart disease and stroke are the most common non-communicable diseases globally, responsible for an estimated 17.8 million deaths in 2017, of which more than three quarters were in low-income and middle-income countries [13]. In Nigeria, CVDs accounted for 11% of all deaths in 2018 (WHO, 2018). Coronary artery disease and stroke account for 80 % of CVD death in males and 75 % of CVD deaths in females [14]. Dyslipidemia is associated with atherosclerosis and increases the risk of cardiovascular disease (CVD). Notably, both diabetes mellitus and CVDs are precipitated by a number of risk factors classified as modifiable and non-modifiable risk factors. Modifiable risk factors are those behavioural risk factors such as unhealthy diet, physical inactivity, harmful use of alcohol and smoking which lead to effects such as increased blood pressure, increased blood sugar levels, dyslipidemia, overweight and obesity [15]. These factors are preventable by way of healthy diet, physical activity and controlled lifestyle. Importantly several plants have been acclaimed to possess bioactive substances and photochemical properties capable of causing significant reductions in plasma glucose and lipid profile levels which is of utmost importance in the prevention and management of diabetes mellitus and cardiovascular diseases. Notable among these plants is *Tetracarpidium conophorum* nuts (Nigerian Walnuts) and *Gongronema latifolium* leaves (Utazi).

The tropical African walnut, known as *Tetracarpidium conophorum* belongs to the family Euphorbiaceae[16, 17] and is popularly known as African walnut, black walnut and Nigerian walnut [18, 19]. In Nigeria, among the Yoruba tribe, the walnut is known as *awusa* or *asala*, *ukpa*, or *okeokpokirinya* in Igbo and *gawudibairi* in Hausa; and it is known as *okhue*or *okwe* among the Bini tribe of Edo State [20, 21]. Studies have shown that Nigerian walnut contain biologically active substances and phytochemicals such as saponins, alkaloids, tannins, flavonoids, terpenoids, glycosides, reducing sugar, calcium, potassium, sodium, magnesium, phosphorus, iron, zinc, manganese, copper, vitamin A, vitamin C and vitamin E while containing other vitamins including vitamin D, K, B1, B2, B3, B5, B6, B9 and B12 in trace amounts [22]. It is also rich in polyunsaturated fatty acids such as α-linolenic acid and it contains mono-saturated fatty acids [21]. Several documented reports have shown the hypoglycemic and hypolipidemic effects of Nigerian walnut [8, 23].

Gongronema latifolium Benth belongs to the family Asclepiadaceae. It is an edible nutritional/ medicinal plant mostly found in the rain forest zones in Nigeria and other tropical African countries [24]. *Gongronema latifolium* is an herbaceous shrub, with yellow flowers [24]and a stem that yields characteristic milky exudates when cut. In Nigeria, it is commonly grown in gardens in Calabar, Cross River State. It is locally called "utasi" by the Efiks, Ibibio and Quas; "utazi" by the Igbos and "arokeke" by the Yorubas in Nigeria [25]. *Gongronema latifolium* is popularly known for its nutritional and medicinal values [26]. The health benefits of different

parts of this plant cannot be over emphasized especially in traditional medicine. The phytochemical evaluation of the plant has shown the presence of flavonoids, saponins, alkaloids, steroids, glycosides among others [27, 28]. Furthermore, Egbung*et al.* reported the presence of phytochemicals (tannins, saponins, alkaloids, flavonoids and hydrocyanide), mineral elements (Cr, Cu, Se, Zn and Fe) and vitamins (A, C,riboflavin, niacin and thiamine) in the root bark and twig extracts of *Gongronema latifolium*[29]. The nutritional composition of the plant includes carbohydrates, protein, amino acids, vitamins, minerals and fats [28]. On the other, the pharmacological activities of the plant such as antioxidant, hypoglycemic, hypolipidemic, hepatoprotective and antimicrobial are well documented [8-9; 30-32].The use of *G. latifolium* leaves in folklore medicine by different ethnic groups for treatment of diseases such as malaria, nausea, anorexia, diabetes, hypertension, constipation, dysentery, etc., had earlier been reported [26, 33-34]. It is traditionally used in the South-Eastern part of Nigeria for the management of diseases such as diabetes, high blood pressure and others [35]. However, despite the numerous acclaimed benefits of Nigerian walnut and *G. latifolium*, there is paucity of information on the synergistic effects of both Nigerian walnut and *G. latifolium* (Utazi). Hence, the need for this study.

Materials and methods

Ethical Consideration

This was obtained from Ethics Committee of NnamdiAzikiwe University Teaching Hospital, Nnewi (NAUTH/CS/66/VOL8/127).

Subjects

The study was conducted on 60 apparently healthy subjects within the age range of 20-55years. Participants were informed about the study and only those who gave their consent were randomly recruited for the study. They were neither diabetic nor hypertensive nor on any medication at the time of the study. Of the total 60 participants recruited, 20 subjects consumed 5g of *G. latifolium (*GI) leaves (group A), 20 consumed 75g of *T.conophorum (*TC) nuts (group B) and 20 consumed combined 5g of GI leaves and 75g of TC nuts (group C) daily for 6 weeks in addition to their normal diet.

Collection and preparation of G. latifolium leaves and T.conophorum

Fresh leaves of *G. latifolium* were plucked from the farm in Nnewichi village of Nnewi town and a sample was authenticated by a certified Botanist (Prof R.N. Okigbo) in NnamdiAzikiwe University, Awka. The mature husk of *Tetracarpidium conophorum*nuts were purchased from Afor Nnobi market which is a local market close to Nnewi town and authenticated by Prof R.N. Okigbo of Botany Department of NnamdiAzikiwe University, Awka. The nuts were obtained by breaking the pod. The walnuts were boiled at 100^{o}C for 2 hours. The leaves of GI were washed and allowed to drain completely; 5 g/day was weighed and served to each subject in group A. Group B participants received 75g of *T.conophorum (*TC) nuts while group C participants received both 5g of GI leaves and 75g of TC nuts (group C) daily for 6 weeks in addition to their normal diet. In an attempt to maximize the medicinal value and to minimize delayed absorption, each subject consumed their portion of the leaves raw between 8am and 10am (before breakfast) each day for a period of six weeks. It was believed that six weeks would be enough for the leaves to exert its full medicinal effect on the subjects.

Sample collection

Initial collection of 6mls of fasting Blood samples were obtained from all the participants. 2ml was dispensed into fluoride oxalate containers while 4ml was dispensed into plain containers and this serve as baseline samples. The subjects fed on their normal diet in addition to 5g of Gl, 75g/day of cooked walnuts and both 5g of Gl and 75g Tc daily respectively for six weeks based on the group to which each subject belonged to and fasting blood samples were similarly collected from the subjects at the end of the six weeks feeding period. The blood samples in the plain containers were allowed to clot, retracted and was centrifuged at 4000 revolutions per minutes for 5 minutes and the serum separated into plain sample containers. The plasma obtained from the blood samples in fluoride oxalate containers were used for the determination of blood glucose while the serum obtained from the blood samples in plain containers were used for the determination of total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol using standard laboratory methods.

Laboratory methods

Lipid profile was determined using enzymatic colorimetric methods. Total Cholesterol was determined by the method described by Roeschlaw *et al.* [36]. Serum triglyceride was determined by using the method described by Schettler and Nussel [37]. High density lipoprotein cholesterol (HDL-C)

was determined using the method described by Assmann [38]. Low density lipoprotein cholesterol (LDL-C) was estimated by calculation according to the formular of Friedewald *et al.* [39]. Serum fasting blood sugar was determined using the method described by Trinder [40] which involves the enzymatic oxidation of glucose in the presence of glucose oxidase.

Statistical analysis

Results were expressed as mean ± SD and the data obtained were analyzed using the Statistical Package for Social Sciences (SPSS) version 23.0 software. Significance Mean difference between two related variables was assessed using the paired t-test. Confidence limit was chosen at 95% ($P<0.05$) and $P< 0.05$ was regarded as significant.

Results

There were significant decreases in the mean fasting plasma glucose (FBG) concentration (3.85±0.14 Vs 4.92±0.31), serum total cholesterol (3.60±0.43 Vs 4.56±0.67), triglyceride (0.73±0.19 Vs 0.96±0.20), low density lipoprotein cholesterol (1.97±0.48 Vs 2.70±0.67) and the ratio of low density lipoprotein cholesterol to high density lipoprotein cholesterol (1.32±0.44 Vs2.11±0.72) in subjects that consumed *G. latifolium* leaves 6 weeks post treatment compared with baseline values (p=0.000; 0.000, 0.001, 0.000, 0.000) respectively. However, there was a statistically significant increase in the mean serum level of high density lipoprotein cholesterol in subject who consumed *G. latifolium* leaves 6 weeks post treatment compared with baseline values (1.55±0.27 Vs 1.35±0.27; p=0.000). See table 1.

Table1: Mean ± SD of glucose and lipid parameters of the subjects that consumed *Gongronema latifolium* leaves

Parameters	FBG (mmol/L)	Total chol (mmol/L)	Triglyceride (mmol/L)	HDL-Chol (mmol/L)	LDL-Chol (mmol/L)	LDL-Chol/ HDL-Chol Ratio
Baseline (n= 20)	4.92±0.31	4.56±0.67	0.96±0.20	1.35±0.27	2.70±0.67	2.11±0.72
6 weeks post treatment (n= 17)	3.85±0.14	3.60±0.43	0.73±0.19	1.55±0.27	1.97±0.48	1.32±0.44
t-value	14.962	15.612	4.043	-3.256	7.537	7.111
p-value	0.000*	0.000*	0.001*	0.003*	0.000*	0.000*

**p-value at <0.05 is statistically significant.*

There were significant decreases in the mean serum total cholesterol (3.43±0.60 Vs 4.44±0.82), triglyceride (0.70±0.19 Vs 0.92±0.23), low density lipoprotein cholesterol (1.70±0.51 Vs 2.76±0.67) and the ratio of low density lipoprotein cholesterol to high density lipoprotein cholesterol (0.61±0.21 Vs 2.24±0.54) in subjects that consumed *T. conophorium* nuts 6 weeks post treatment compared with baseline values (p=0.000; 0.004, 0.000, 0.000) respectively. However, there was a statistically significant increase in the mean serum level of high density lipoprotein cholesterol in subject who consumed *T. conophorium* nuts 6 weeks post

Table2: Mean ± SD of Glucose and Lipid Parameters of the Subjects that consumed *Tetracarpidium conophorum* nuts

Parameters	FBG (mmol/L)	Total chol (mmol/L)	Triglyceride (mmol/L)	HDL-Chol (mmol/L)	LDL-Chol (mmol/L)	LDL-Chol/ HDL-Chol Ratio
Baseline (n= 20)	4.56±0.36	4.44±0.82	0.92±0.23	1.24±0.12	2.76±0.67	2.24±0.54
6 weeks post t reatment (n= 20)	4.44±0.18	3.43±0.60	0.70±0.19	1.52±0.14	1.70±0.51	0.61±0.21
t-value	1.575	11.218	3.227	-10.477	15.842	18.611
p-value	0.132	0.000*	0.004*	0.000*	0.000*	0.000*

**p-value at <0.05 is statistically significant.*

treatment compared with baseline values (1.52±0.14 Vs 1.24±0.12; p=0.000); although the mean plasma glucose level did not differ significantly when baseline values were compared with 6 weeks post treatment values (p= 0.132). (table 2).

There were significant decreases in the mean plasma glucose concentration (3.94±0.16 Vs 4.73±0.30), serum total cholesterol (3.35±0.28 Vs 4.39±0.62), triglyceride (0.62±0.07 Vs0.91±0.11), low density lipoprotein cholesterol (1.48±0.43 Vs 2.55±0.66) and low density lipoprotein cholesterol to high density lipoprotein cholesterol (0.85±0.25 Vs 1.85±0.62) ratio in subjects that consumed combined *G. latifolium* leaves and 75g of T. conophorum nuts 6 weeks post treatment compared with baseline values (p=0.000; 0.000, 0.000, 0.000, 0.000) respectively. However, there was a statistically significant increase in the mean serum level of high density lipoprotein cholesterol in subject who consumed combined *G. latifolium* leaves and *T. conophorum* nuts 6 weeks post treatment compared with baseline values (1.72±0.10 Vs1.43±0.22; p=0.000) . (table 3).

Discussion

Non communicable diseases such as diabetes mellitus and cardiovascular diseases continue to be on the rise especially in the developing countries of the world like Nigeria. Medicinal plants and foods play vital roles in the prevention and management of a number of non-communicable diseases and thus there is need for continuous evaluation of the various principles, toxicities and efficacy of medicinal plants in the prevention and management of non-communicable diseases.

The present study showed a significant decrease in fasting plasma glucose (FBG) level in subjects that consumed *G. latifolium* leaves 6 weeks post treatment when compared to baseline values. This implies that *G. latifolium* has antidiabetic or hypoglycemic properties which may have resulted from the bioactive substances or principles present in it. *G.latifolium* is known to contain phytochemical agents such as saponins and alkaloids which are known for their hypoglycemic effects [27]. The hypoglycemic potentials of *G. latifolium* may be attributed to the ability of *G.latifolium* to potentiate insulin secretion from pancreatic beta cells or sensitize insulin receptors. Evidences from previous similar studies point to the hypoglycemic effects of *G.latifolium*[8, 41]. Furthermore, this study revealed significant decreases in serum total cholesterol, triglyceride, low density lipoprotein cholesterol and low density lipoprotein cholesterol to high density lipoprotein cholesterol ratio in subjects that consumed *G. latifolium* leaves 6 weeks post treatment compared with baseline values respectively. However, there was a significant increase in the level of high density lipoprotein cholesterol in subject who consumed *G. latifolium* leaves 6 weeks post treatment compared with baseline values. These findings suggest that consumption of *G. latifolium* leaves have the ability to help in preventing cardiovascular diseases through its ability to reduce fat deposits in the arteries and prevent blood clot formation. It is possible that the hypolipidemic effects of GI stem from the antioxidant properties of the plant which are mediated through the bioactive substances such as terpinoids and flavonoids present in the plant. Other studies have reported hypolipidemic effects of Gl which are in line with this study [8, 42].

In this study, there was no significant difference in blood glucose level following the consumption of *T. conophorium nuts* (Nigerian walnuts) for a period of 6 weeks when compared with baseline value. This shows that Nigerian walnuts

Table3: Mean ± SD of glucose and lipid parameters of the subjects that consumed combined *Gongronema latifolium* leaves and *Tetracarpidium conophorum* nuts

Parameters	FBG (mmol/L)	Total chol (mmol/L)	Triglyceride (mmol/L)	HDL-Chol (mmol/L)	LDL-Chol (mmol/L)	LDL-Chol/ HDL-Chol Ratio
Baseline (n= 20)	4.73±0.30	4.39±0.62	0.91±0.11	1.43±0.22	2.55±0.66	1.85±0.62
6 weeks post treatment (n= 18)	3.94±0.16	3.35±0.28	0.62±0.07	1.72±0.10	1.48±0.43	0.85±0.25
t-value	9.536	9.782	8.626	-7.999	11.043	8.795
p-value	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*

**p-value at <0.05 is statistically significant.*

may not possess antidiabetic effects. This result corroborates with previous findings of similar studies [7].

There were significant decreases in total cholesterol, triglyceride, low density lipoprotein cholesterol and ratio of low density lipoprotein cholesterol to high density lipoprotein cholesterol and a significant increase in the level of high density lipoprotein cholesterol in subjects that consumed *T. conophorium* nuts 6 weeks post treatment compared with baseline values. These results indicate that Nigerian walnuts possess hypolipidemic properties which is vital in mitigating the impacts of cardiovascular diseases such as heart attack and stroke which is characterized by hyperlipidemia. This is in line with results of several previous studies. Ezealisiji*et al*. [43] reported on the anti-cholesterol activity of the ethyl acetate and n-hexane extracts of the *T. conophorum* seed and showed that a 2.00 mg/kg dose of both extracts decreased low density lipoprotein (LDL) and increased high density lipoprotein (HDL) cholesterol when compared with atorvastatin (a standard cholesterol-lowering agent), which could be attributed to the oleic acid and α-linolenic acid. Analike *et al*. investigated the effects of cooked walnuts on blood lipids, lipoprotein and glucose among adult Nigerians and reported that there was a significant reduction in plasma cholesterol, triglycerides, LDL-C and the ratio of LDL-C to HDL-C of the subjects when compared with their baseline values [7]. It was concluded that the reduction could prevent hyperlipidaemia complications and also improve lipid metabolism. Nwaichi*et al*. also reported on the nutraceutical potential of *T. conophorum*and *Buchholziacoriacea*in diet-induced hyperlipidaemia [18]. The hyperlipidaemic rats were subsequently treated with normal feed supplemented at 500 mg/kg and 1000 mg/kg of *T. conophorum*and *B. coriacea*for two weeks. In comparison to test control animals, there was a reduction in weight gain, total cholesterol (TC), triglycerides (TG), plasma contents of LDL, very low density lipoprotein (VLDL), non-HDL and atherogenic indices in a dose-dependent fashion.

In the present study, there were significant decreases in blood glucose concentration, total cholesterol, triglyceride, low density lipoprotein cholesterol levels and ratio of low density lipoprotein cholesterol to high density lipoprotein cholesterol and importantly, there was also a significant increase in the serum level of high density lipoprotein cholesterol in subjects that consumed combined *G. latifolium* leaves and 75g of Nigerian walnuts 6 weeks post treatment compared with baseline values. These results showed that the combined consumption of *T.conophorum* nuts and *G. latifolium* leaves exhibited synergistic effect on blood glucose and lipid profile levels and this contributed to a better improvement observed in the level of glucose and lipids profile following 6weeks intake. Thus, combined use of *T.conophorum* nuts and *G. latifolium*leaves could be of greater benefits in prevention and management of diabetes mellitus and cardiovascular diseases.

Conclusion

The results of this study show that Gl has hypoglycemic and hypolipidemic effect while Tc has hypolipidemic effect. Furthermore, combination of the two plants might have potentiated the hypolipidemic action noticeable in the result obtained after consumption. Therefore, the synergistic hypolipidemic effect of Tc nuts and Gl leaves when consumed together contributed to a more significant reduction observed in the lipids and lipoprotein values and the reduction in the ratio of LDLc to HDLc will be of immense benefit in reducing the risk of Heart attack and stroke.

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Received = 27/05/2021
Accepted = 14/07/2021