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Modulatory Roles of Clove and Fermented Ginger Supplements on Lipid Profile and Thyroid Functions in High Fat Diet Induced Insulin Resistance in Rabbits

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Authors' contributions

This work was carried out in collaboration between all authors. Author AA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors TY and MA managed the analyses of the study. Author DAAU managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To evaluate the effects of clove buds and fermented ginger rhizome supplements on Lipid profile and thyroid functions in high fat diet induced insulin resistance in rabbits.
Study Design: High fat diet was fed to rabbits for eleven weeks to ascertain diabetic animal model (DAM), thereafter, DAM were treated with supplements for six weeks.
Place and Duration of Study: Department of Human Physiology, Ahmadu Bello University Zaria, Kaduna Nigeria. Between May, 2015 to October, 2016.
Methodology: Thirty (30) male rabbits (5-8 weeks of age) divided into six groups of (n=5) were

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used, Group I (Normal control) was treated with standard animal feed (SAF) throughout the experimental period, Group II-VI were treated with high fat diet (SAF = 69% + Cholesterol = 1% + Ground nut meal = 20% + ground nut oil = 10%) for 11 weeks to induced hyperglycemia and ascertain DAM for the study. Thereafter, DAM groups (Group II-VI) were treated for six weeks of experimental protocol; Group II was treated with SAF only, Group III = DAM treated on SAF + cholestran (0.26 g/kg), Group IV = DAM treated on SAF + clove buds (12.5%) supplements, Group V = DAM treated on SAF + fermented ginger (12.5%) supplements, and Group VI = DAM treated on SAF + clove buds (12.5%) + fermented ginger (12.5%). After treatment, animals were sacrifice and serum from blood samples was used for laboratory assessments of lipid profile (total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-c)), triiodothyronine (T_3), thyroxin (T_4) and thyroid stimulating hormone (TSH) using standard procedures, data obtained were statistically analyzed.

Results: A significantly (*P*=0.05) decrease in TC level in DAM group treated on fermented ginger (12.5%) supplement when compared to DAM treated on SAF. T_3 and T_4 levels significantly decrease in all supplement treated groups compared to DAM treated on SAF group.

Conclusion: Clove (12.5%), fermented ginger (12.5%) and clove (12.5%) + fermented ginger (12.5%) supplements reveal a pronounced decreasing effects on higher lipid indices and thyroid hormones levels in high fat diet induced insulin resistant rabbits. Hence, further work to validate their ameliorative effects on similar conditions for reliability and medicinal use is needed.

Keywords: Clove and fermented ginger supplements; lipid profile; thyroid hormones.

1. INTRODUCTION

Consumption of high Fat Diet (HFD) is a nutritional condition that accounts for the largest incidence of metabolic syndrome in the world [1]. Defective insulin secretion leads to various metabolic aberrations and T2DM. The impairments include hyperglycaemia due to defective insulin-stimulated glucose uptake, up-regulated hepatic glucose production and dyslipidaemia [2]. The excessive consumption of high fat diet has been associated with an increased incidence of enhanced formation of oxidative stress. consequently, leads to high levels of circulating free fatty acids (FFA) and glucose which are potent inducers of reactive oxygen species (ROS) in cells [3]. Lipotoxicity impairs cell function and viability due to chronic exposure to FFA, leading to the induction of β-cell endoplasmic reticulum stress, and glucose-induced β-cell dysfunction and apoptosis [4].

Hyperthyroidism have been proved to worsening of metabolic disorder such as diabetes. It was shown that surgical removal of parts of thyroid gland had an ameliorative effect on the restoration of glucose tolerance in hyperthyroid patients, suffering from co-existing diabetes [5]. There is a deep underlying relation between diabetes mellitus and thyroid dysfunction [6]. Thyroid hormones directly control insulin secretion. Hypothyroidism, result into a reduction in glucose-induced insulin secretion by beta cells, and the response of beta cells to glucose or catecholamine is increased in hyperthyroidism due to increase beta cells mass. Moreover, insulin clearance is increased in thyrotoxicosis [7]. Thyroid hormones are insulin antagonists, both insulin and thyroid hormones are involved in cellular metabolism. Excess or deficit of any among the hormones can result in functional derangement of the other [8]. In hypothyroidism, glucose-induced insulin secretion by the β-cell is reduced while in hyperthyroidism, β-cell response to glucose or catecholamine stimulation appears to be increased and is accompanied by an increased β-cell mass [9,10]. The rates of glucose oxidation and glycogen synthesis are decreased in hypothyroidism due to down-regulation of glucose transporter GLUT5 in humans and impaired GLUT4, GLUT2, and GLUT3 transporters in animal model [11]. Hyperthyroidism is associated with increased GLUT2 expression, as compared to the hypothyroid state [12]. Alterations in lipid metabolism further link thyroid hormone to insulin resistance [13]. Thyroid hormones-dependent fatty acid uptake is tissue specific and may be increased in both hyperthyroidism and hypothyroidism depending on the underline cause [14]. Thyroid hormone stimulates catecholamine action, which in turn increase lipolysis in adipose tissue, hence increasing circulating FFAs [15]. The excessive consumption of high fat diet has been associated with an increased incidence of diabetes mellitus, Through formation inducing oxidative stress by excessive generation of reactive oxygen species

or via defective insulin signaling pathway [16, 17,18]. Diabetes mellitus is now a common, growing, serious and costly, but potentially preventable disease appearing across populations globally [19]. Continuous consumption of calories-rich meals, junk food and sedentary lifestyle has culminated into an epidemic of diabetes worldwide. The existing management of diabetes is indeed costly and associated with many side effects ranging from flatulence, constipation and hypoglycemia, hence, the need for an effective alternative approach with fewer or non-side effects is needed for diabetes mellitus. Syzygium aromaticum (clove) and Zingiber officinale (ginger) are important spices used in the preparation of several delicacies and in folklore for diabetes management (Adefegha et al. 2014), the effects of their extracts has been studied in animal model with paucity in the results. Hence, this study is aimed to determine the specific effect of clove and fermented ginger supplements on lipid profile and thyroid hormones in high fat diet induced hyperglycemia in rabbits.

2. MATERIALS AND METHODS

2.1 Materials

Digital glucometer (Accu-Chek Advantage, Roche Diagnostic, Germany). Glucose- test strips for assessment of plasma glucose levels, manufacture by accu-check Advantage II, Roche Diagnostics GmbH Germany. Animal feed (pelletised growers feed, of vital feed, km 17, Zawan Roundabout P.O. box 13462, jos, Plateu state Nigeria.), (Crude protein 13%, fat 8%, crude fibre 15%, calcium 0.9%,). Clove buds and fresh Ginger rhizome, Dissecting kits, Digital weighing scale, Test tubes/rack, syringe and needle, Microplate reader RT-2100C, Rayto, 800D Table Toplow Speed centrifuge, and Micropipette automated and graded

2.2 Drugs and Reagents

All chemicals used were of analytical grades; these included:

i. Cholesterol (powder) was purchased from KEM LIGHT Laboratory PVT. LTD, Mumbai India. (CAS: 57-88-5, m.w: 386.67, lot no.: 100814).
ii. Cholestran powder (made in Egypt PHARCO pharmaceuticals Alexandria) was purchased from Amira Pharmacy, tudunwada zaria.
iii. Methylated spirit, cotton wool,
iv. Rabbit T_3, T_4 and TSH ELISA Kits, (GenAsia Biotech Co., Ltd., 7thfloor,Wujiaochang Technology Building, No. 1675, Huangxing Road, Yangpu District, Shanghai, China).

2.3 Animals

A total of thirty (30) male rabbits aged 5-8 weeks were used for the study, animals were housed in the animal house of Department of Human Physiology, Faculty of Medicine Ahmadu Bello University Zaria, under standard laboratory conditions and had access to feed (Pelletised Growers feed) and water ad libitum. Animal care and use was in accordance with the guide for the care and use of laboratory animals, institute for laboratory animal research, national institute of health (NIH Publication No.80-23; 1996).

2.4 Methods

2.4.1 Authentication of supplements

Clove (*Sygizium aromaticum*) buds and ginger (*Zingiber officinale*) rhizome after purchased were presented to the herbarium unit of the department of biological sciences, faculty of science, Ahmadu Bello University, Zaria, where they were identified and authenticated with a deposited voucher number of 900127 and 2261 respectively.

2.4.2 Preparation of high fat diet

The high fat diet was constituted in the Animal house of the Human Physiology Department as follows;

- 32% (8 kg) per weight out of 25 kg of standard animal feed, was removed,

Cholesterol powder weighing 0.25 kg, Groundnut mill 5kg, and ground nut oil 2.25 kg were accordingly added into the feed in a large bowl each at a time and mix thoroughly,

The final constituted diet composed of: about 40% fat, Crude protein 14%, crude fibre 15%, calcium 0.9%, metabolised energy 2550 Kcal/Kg min.

2.4.3 Preparation of supplement composed diets

The supplements containing diet were reconstituted in the Animal house of the Human Physiology Department, ABU, Zaria.

2.4.4 Fermented ginger supplemented diet

Raw fresh ginger rhizome were slice and air dried, then macerated in water for 48 hrs and then air dried again, This was then reduced using grinding engine to a powder state. 3.125 kg of the fermented ginger powder was then weight to give 12.5% of 25 kg bag of normal feed and then, 3.125 kg was weight and removed out of 25kg bag of standard feed. The fermented ginger powder was then added into the feed in a big bowl and mixed thoroughly (fermented ginger 12.5% supplemented diet).

2.4.5 Clove supplemented diet

Clove was reduced using grinding engine to a powder state, 3.125 kg of the powder was then weight to give 12.5% of the total weight (25 kg) of standard feed and the same quantity of the feed was removed and then the clove powder was then added in a big bowl and mixed thoroughly (clove 12.5% supplemented diet).

2.4.6 Fermented ginger and clove supplemented diet

Out of a bag weighing 25 kg of standard feed, 6.25 kg was removed, then 3.125 kg powder of fermented ginger and clove each was measured and added at a time into the feed in a big bowl and mix thoroughly to give a mixture of supplemented diet (fermented ginger 12.5% plus clove 12.5% supplemented diet).

2.4.7 Induction of hyperglycemia

Hyperglycemia was induced by feeding rabbits with high fat diet for about eleven (11) weeks, after which each animal was bled from marginal vein on the ear lobe, with a drop of blood, using strip and a digital glucometer, glycemic level were measured and recorded for each animal. Rabbits having glucose levels greater than 140 mg/dl were considered Hyperglycemic (diabetic model for the study), [20].

2.5 Experimental Design

Group I comprises normal rabbits (normal control), while group ii - group vi comprises of rabbits with glucose level of 140 mg/dl and above (considered diabetic model and randomly grouped) (n=5), placed on the following treatments;

Group i: Normal rabbits fed on animal standard feed

Group ii: Diabetic rabbits fed on standard feed for six weeks

Group iii: Diabetic rabbits fed on standard feed and administered cholestran (0.26g/kg body weight) for six weeks.

Group iv: Diabetic rabbits fed on 12.5% clove supplement for six weeks.

Group v: Diabetic rabbits fed on 12.5% fermented ginger supplement for six weeks.

Group vi: Diabetic rabbits fed on 12.5% clove and fermented ginger 12.5% supplements co-administered for six weeks [21].

2.6 Determination of Blood Glucose Levels

During the experimental period blood glucose levels were determined at weekly intervals, with a digital glucometer Using the glucose oxidase principle [22] (Accu-Chek Advantage, Roche Diagnostic, Germany), Rabbit were bled through marginal vein of the ear lobe by the use of disposable needle, the result were recorded in mg/dl [23].

2.7 Termination of the Study

Animals were sacrifice at the end of six weeks treatment period by light anesthesia using chloroform vapour in an air-tight chamber, blood samples were collected via cardiac puncture using syringe and released into blood tubes (Plain tubes). Blood sample collected were centrifuge at 2000 g for 5- 10 min using a bench centrifuge to get serum for laboratory analysis and assay, which include;

2.8 Determination of Lipid Profile

Total serum cholesterol level was estimated by the enzymatic method [24]. Determination of High density lipoprotein cholesterol (HDL-C). and Serum high density lipoprotein cholesterol (HDL-

C) was estimated by the method reported by [25], Serum triglycerol (TAG) was estimated by the method of [26].While serum low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL-C) were calculated according to the Friedewald's formula:

- LDL-C = TC – (HDL-C+TAG/5)
- and VLDL-C=TAG/5 [27]
- LDL-C = Low density lipoprotein cholesterol
- VLDL-C = very low density lipoprotein cholesterol
- HDL-C = high density lipoprotein cholesterol.
- TC = total cholesterol
- TAG = serum triglycerol

Estimation of Thyroid hormones (T_3, T_4), and thyroid stimulating hormone (TSH).

Thyroid profile was estimated by using the enzyme-linked immunosorbent assay (ELISA) kits, using rabbit T_3, T_4 and TSH ELISA kits from Gen Asia Biotech Co., Ltd., Shanghai, China) in accordance to the manufacturers guide.

2.9 Ethical Approval

The rabbits were handled in accordance with the principles guiding the use and handling of experimental animals Ahmadu Bello University, Zaria, Nigeria, the study was approved after a scientific departmental proposal presentation session at the Department of Human physiology Faculty of Medicine, Ahmadu Bello University, Zaria, Nigeria. The use of animals and handling was approved to concurred with the guide for animal care and use of laboratory animals (NIH Publication No.80-23; 1996) with slight modification of limited number of animal to be use.

2.10 Statistical Analysis

Blood glucose levels were expressed as mean ± SEM. The data were analyzed using ANOVA followed by Tukey's post-hoc test to show multiple comparisons across experimental groups. Values of P =0.05 were considered as significant [27].

3. RESULTS

The results of the study after data analysis are presented in Table 1 and 2 below.

Table 1, display the results on lipid profile indices, while Table 2, presents the results of thyroid hormones (T3 and T4) and that of thyroid stimulating hormone (TSH).

Table 1, shows the results of lipid profile in control, and high fat diet induced-insulin resistance rabbits treated with clove, fermented ginger and a mix of clove and fermented ginger supplemented diet. Total cholesterol and high density lipoprotein cholesterol level were seen to be significantly lower in group 5 than that of group 2, triglyceride levels were seen to be significantly lower also in group 5 and 6, when compared to group 2 (diabetic rabbits fed on standard feed group).

Table 2, shows the results of serum thyroid hormones and thyroid stimulating hormone levels in control, and high fat diet induced insulin resistance rabbits treated with clove, fermented ginger and a mix of clove and fermented ginger supplemented diet. The results reveal a statistically significant decrease in serum T3 in

Table 1. Lipid profile of high fat diet induced-insulin resistance rabbits treated for six Weeks with clove 12.5%, fermented ginger 12.5% and co-administered clove12.5 + fermented ginger 12.5%, and in control groups

Groups	TC (mg/dL)	TG(mg/dL)	HDL(mg/dL)	LDL(mg/dL)
Group 1 (NC)	144.4±3.63	88.6±11.5	20.33±2.70	39.4±14.25
Group 2 (DC)	180.7±14.74	111.8±7.1	26.90±2.72	47.31±9.81
Group3(D+Chl 0.26g/kg)	184.3±11.32	79.8±10.9	23.11±2.10	18.6±7.52
Group 4 (D+CLV 12.5%)	180.15±15.17	117.5±16.24	20.81±1.4*	61.37±13.07
Group 5 (D+Fgg 12.5%)	143.06±23.47*	80.45±5.8*	17.20±3.72*	39.5±6.02
Group 6 (D+CLV 12.5% and Fgg 12.5%)	178.80±28.10	125.91±21.42	14.95±1.06*	69.71±10.55

*Significant at P= 0.05 value: n=5 ; *=significant difference compared to diabetic control group (group 2). (NC= normal control): (DC= diabetic control); (Chl.=cholestran); (Fgg= Fermented ginger supplemented diet): (CLV= clove supplements).*

Table 2. Serum thyroids hormones and TSH level in controls, and in high fat diet induced-Insulin resistance rabbits treated for six weeks with clove 12.5%, fermented ginger 12.5% and co-administered clove12.5 + fermented ginger 12.5%

Groups	T3 (ng/ml)	T4 (ng/ml)	TSH (ng/ml)
Group 1	1.8±0.12	74.33±3.5	1.3±0.12
Group 2	2.1±0.071	79.4±1.5	0.8±0.093
Group 3	1.84±0.93	61.2±0.6	1.00±0.071
Group 4	1.72±0.06	47.4±1.36*	0.94±0.07
Group 5	1.6±0.14*	49.8±2.9*	1.64±0.093*
Group 6	1.5±0.93	58.00±2.02*	1.1±0.071

*Significant at P= 0.05 value: n=5; *=statistically significant difference when compared to diabetic control group (group 2)*

groups 4 and 5 levels, when compared to that of diabetic group on normal feed (group 2). T4 levels level were seen to be statistically significantly lowered in all supplemented diet treated groups (clove 12.5%, ginger 12.5% and combined clove 12.5% + ginger 12.5%), groups 4, 5, and 6, when compared to that of the diabetic rabbits group on normal feed (group 2). while the results on serum TSH shows a statistically significant increase in groups 5 and 6, when compared to diabetic rabbits on normal feed (group 2).

4. DISCUSSION

4.1 Effect of Clove and Fermented Ginger on Lipid Profile

In the present study, the results of lipid profile shows significant decrease in total cholesterol level in diabetic rabbits fed on 12.5% fermented ginger supplement diet (group 5) when compared to that of group 2 (diabetic rabbits fed on standard feed), the level of cholesterol in group 5 was noted to have no significant difference with that of normal control group rabbits, furthermore other diabetic treated groups (group 2, 3, 4, and 6) were seen to have a significant increase in total cholesterol level. These results is attributed to the effects of high fat diet in the experimental animals. triglycerides shows a decrease in value that is statistically significant different in diabetic rabbits fed on 12.5% fermented ginger supplement diet (group 5) when compared to that of group 2 (diabetic rabbits fed on standard feed). Results of high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol shows a statistically significant decrease in the group treated with fermented ginger, this result is in accordance with the work of [28] and. Both work shows the significant decrease effect of clove and ginger peel in total serum cholesterol, triglycerides, and low density lipoprotein. It has been established that chronic intake of high fat diet leads excessive adipose tissue fat accumulation, excessive fat is an attributing factor to insulin resistance, therefore the abnormalities seen in this study on lipid profile of high fat diet induced insulin resistance rabbits on normal feed may be as a result of the effects of overloaded high fat diet on the hepatic handling and clearance metabolic activity over time that leads to excess/higher levels of lipid in circulation and finally via several mechanisms results to hyperglycemia in the animals or insulin resistance [29], while in groups 5 treatment with 12.5% fermented ginger supplement indicate an improvement in lipid profile when compared to that of group 2 (diabetic rabbits on normal feed) this effects may be due to certain bioactive substance found in the supplement that are associated with decreasing the rate of lipid absorption from the GI tract through inhibition of necessary enzymes for lipid uptake, or enhancing hepatic clearance rate via up regulation of associated enzymes such as hepatic lipases.

Based on clinically recommendations, Lipid profile associated changes characterized by high plasma triglyceride concentration, low HDL cholesterol concentration and increased LDL-cholesterol particles concentrations is attributed to increased free fatty acid flux (lipogenesis) which leads to insulin deficiency or insulin resistance, hyperlipidemia or elevated lipid levels that leads to beta-cells failure and contributes to insulin dysfunction as seen to occur in diabetic dyslipidemia. Distorted lipid profile is related to increased risk of cardiovascular related diseases (CVDs) and high mortality rate associated with CVDs in diabetes mellitus.

The results of the present study shows an improvement in lipid profile especially in the

diabetic rabbits group fed on 12.5% fermented ginger when compared with lipid profile of diabetic rabbits fed on standard feed, this result agree with the work of [30], and is in line with a related study aimed to investigate the potential effect of fresh ginger extracts Zingiberofficinale roscoe (Family: Zingebiraceae) on serum lipid profile in alloxan-induced diabetes and propylthiouracil-induced hypothyroidism in rats, and revealed a decrease in the levels of total cholesterol (TC), and low density lipoprotein (LDL) in the serum of rats that were treated by ginger extracts, compared with the control groups [30]. The activity of fermented ginger supplement observed in the present study may be attributed to it active constituents especially the secondary metabolites of gingerols or shogaol of phenolic compounds origin, which have pronounced medicinal values, fermentation process enhences bioactive ingredients and their bioavailability for absorption, this may have aid in the effects observed. Ginger contain certain bioactive components that could facilitates liver clearance and metabolism of cholesterol via it vital role in the suppression/inhibition in synthesis of pro-inflammatory cytokines such as IL-1, TNF-α, and IL-8. Furthermore, ginger play a key role in the inhibition of COX and 5-lipoxygenase, essential for arachidonate metabolism, and down-regulating the induction of inflammatory genes, therefore it have potent antilipidemic activity [31].

4.2 Effect of Clove and Ginger on Serum Thyroid Stimulating Hormone, T_3, and T_4

Diabetes and thyroid disorders have been shown to mutually influence each other and associations between both conditions have long been reported [32,33]. Thyroid hormones contribute to the regulation of carbohydrate metabolism and pancreatic function, and on the other hand, diabetes affects thyroid function tests to variable extents. The result of this study reveal a statistically significant increase in serum T_3, and T_4 levels in diabetic rabbits group on normal feed, when compared to that in supplement treated groups (clove 12.5%, fermented ginger 12.5% and combined clove 12.5% + fermented ginger 12.5%).

Distort lipid profile observe in the group of diabetic animals on normal feed could be due to the fact that abnormal insulin signaling pathway also affects lipid metabolism and results in dyslipidemia, since chronic consumption of high fat diet leads to insulin resistance, existence of hyperglycemia in this animal model also could leads up-regulation of metabolic influence hormones including thyroid hormones, increased lipolysis is observed in higher levels of thyroid hormones resulting in an increase in FFA that stimulates hepatic gluconeogenesis. The increased release of FFAs could partially be explained by an enhanced catecholamine-stimulated lipolysis induced by the excess thyroid hormones [34], It is well known that diabetic subjects with Higher levels of thyroid hormones experience worsening of their glycemic control, and hyperthyroidism has been shown to precipitate diabetic ketoacidosis in subjects with diabetes [35,36]. Treatment with supplementations in the present study revealed a down regulatory effects of the clove and fermented ginger supplements on thyroids hormone, this observed effect could be attributed to secondary metabolites of medicinally active ingredients of clove (eugenol) and ginger(gingerol /shogaol) respectively, the revealed effects may be beneficial to diabetic condition, since higher levels of these hormones worsen metabolic syndromes signs, especially plasma levels of nutrients that include blood glucose and lipids levels [37].

5. CONCLUSION

Feeding rabbits for eleven weeks with high fat diet induces insulin resistance, dyslipidemia and higher levels of thyroid hormones in rabbits, treatment with 12.5% fermented ginger supplemented diet leads to an observe lowering effect on total cholesterol and triglycerides. Also high fat diet was seen to induced pronounce higher levels of thyroid hormones in the untreated group, while supplements of Clove, fermented ginger and their combined supplementation restored thyroid hormones levels in the treated animals almost to that of normal control.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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