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Methanol leaf extracts of *Chrysophyllum albidum* and *Irvingia gabonensis* protected against dyslipidaemia and oxidative stress induced by high-fat diet in Wistar rats

Osebahiemen Ibukun^{1*} and Ehimwenma S. Omoregie²

Abstract

Background: High-fat diet (HFD) has been linked to oxidative stress, dyslipidaemia, obesity and cardiovascular diseases. Studies have shown that medicinal plants have antioxidant properties and may have protective effects against oxidative stress and dyslipidaemia induced by high-fat diet. *Chrysophyllum albidum* (white star apple) and *Irvingia gabonensis* (African bush mango) are very useful medicinal plants common in the tropical and subtropical regions of the world. This study was aimed at investigating the protective effect of methanol leaf extracts of *Chrysophyllum albidum* and *Irvingia gabonensis* against dyslipidaemia and oxidative stress in Wistar rats promoted by the consumption of HFD as well as characterize active compounds in the extracts. Thirty-six male Wistar rats were assigned into six groups of six animals each and respective groups received normal fat diet (NFD), HFD, HFD + *Chrysophyllum albidum* (250 mg/kg/ 500 mg/kg), HFD + *Irvingia gabonensis* (250 mg/kg/ 500 mg/kg) for fifty six days. Dietary intake, body weight, lipid profile and indicators of oxidative stress were measured.

Results: Administration of plant extracts did not change the pattern of food intake of the animals. There was a significant inhibition ($p < 0.05$) of increase in the body weight of rats treated with plant extracts in comparison with those rats that consumed HFD only. There was significant increase ($p < 0.05$) in total cholesterol, triacylglycerol, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol and malondialdehyde concentrations in rats fed with HFD only when compared with NFD control and extract treated groups. However, HFD control produced significantly lower ($p < 0.05$) high-density lipoprotein cholesterol, reduced glutathione and glutathione peroxidase than normal control and extract treated groups. Gas chromatography flame ionization detector analysis of these extracts revealed the abundance of kaempferol, quercetin, luteolin, myricetin and naringenin and tannic acid.

Conclusions: The observed antioxidant and anti-dyslipidaemic properties of leaves of *Chrysophyllum albidum* and *Irvingia gabonensis* may be attributed to the presence of flavonoids and tannic acid.

Keywords: Flavonoids, *Chrysophyllum albidum*, *Irvingia gabonensis*, Oxidative stress, High-fat diet

Background

High-fat diet (HFD) is an important risk factor for several ailments such as obesity, dyslipidaemia, cardiovascular disease, type II diabetes, non-alcoholic fatty liver, non-alcoholic steatohepatitis and cancer (Vargas-Robles et al. 2015). Many reasons, such as high-fat, caloric-dense diets and sedentary lifestyles, are the contributing factors

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for the development of metabolic syndrome (McLaren 2007). The mechanisms for increased oxidative stress in metabolic syndrome include increased fatty acid oxidation, mitochondrial dysfunction and augmented NADPH oxidase activity (Lee 2013). HFD provoked dyslipidaemia is linked to oxidative stress, an accumulation of several transition metals as well as increased free radicals (Charadi et al. 2013).

Drugs used in the management of lipid disorders have been associated with adverse effects such as gastrointestinal, kidneys and heart problems (Rucker et al. 2007). Specifically, they have been known to cause abdominal pain, bloating, flatulence, diarrhoea, acute kidney injury, increase in blood pressure, increase in pulse rate and palpitation (Beyea et al. 2012; Kang and Park 2012). Therefore, there is a need to search for safer alternative treatments for these disorders. *Chrysophyllum albidum* (white star apple) and *Irvingia gabonensis* (African bush mango) have several medicinal properties. Reports have shown that their extracts have hepatoprotective, anti-bacterial, antioxidant and anti-hyperlipidaemic properties (Ainge and Brown 2001; Adewoye et al. 2010; Ibukun and Omoregie 2018). Olorunnisola et al. (2008) reported that the roots, bark and the leaf of *C. albidum* are used as natural remedy for sprain, bruise and wound in southern Nigeria and also for inhibition of microbial growth of wound contaminants. The high saponin content of *C. albidum* leaves and roots justifies the use of the extracts in control of cardiovascular diseases and reduction of blood cholesterol (Ogunleye et al. 2020). In addition, the bark of *C. albidum* has been used in treatment of yellow fever, fibroids and malaria, while the leaf is used as emollient and for the treatment of skin eruption, stomach ache and diarrhoea (Adewoye et al. 2010). Similarly, *Irvingia gabonensis* has several medicinal uses. The stem bark is used to treat hernias, yellow fever and dysentery (George and Zhao 2007). The antibiotic properties of the bark help heal scabby skin, and the boiled bark relieves tooth pain (Ainge and Brown 2001). Long-term anti-diabetic and anti-hyperlipidaemic effects of aqueous stem bark extract of *I. gabonensis* in streptozotocin-induced diabetic rats have been reported by Omonkhua et al. (2014). Emejulu et al. (2014) have also reported that the fruit juice of *I. gabonensis* possess hypolipidaemic effect on sodium fluoride induced dyslipidaemia in rats. Leaves of *I. gabonensis* are used locally to treat diarrhoea (Unaeze et al. 2017) and as antidote against poison (Hubert et al. 2010). Leaf extract of *I. gabonensis* has been found to be nephroprotective (Ewere et al. 2016) and attenuates cadmium-induced haematological derangements in rats (Ewere et al. 2017).

Most research on *C. albidum* and *I. gabonensis* has been focused on the fruits rather than leaves. Also, there

is paucity of information on the effect of leaves from these plants on dyslipidaemia and oxidative stress in rats, despite the fact that they are rich in several phytochemicals such as saponins, flavonoids, alkaloids, tannins and steroids (Ojemekele et al. 2017). These phytochemicals have been suggested to possess antioxidant and anti-dyslipidaemic properties (Krishnaiah et al. 2007; Mohamed et al. 2014). Therefore, this study was aimed at evaluating the protective effects of methanol leaf extracts of *C. albidum* and *I. gabonensis* on dyslipidaemia and oxidative stress induced by high-fat diet in Wistar rats.

Methods

Chemicals and reagents

1,1-diphenyl-2-picrylhydrazyl radical (DPPH), 2,4,6-tripyridyl-S-triazine (TPTZ), ferric chloride, methanol, hexane, dichloromethane, ethyl acetate, ferrous sulphate, sodium chloride, tannic acid, Folin–Denis reagent, 5,5'-dithiobis-2-nitrobenzoic acid (DTNB), sodium acetate, acetic acid, thiobarbituric acid, trichloroacetic acid, hydrochloric acid, sodium azide, reduced glutathione, sodium carbonate, aluminium chloride, ethanol, quercetin, gallic acid, Folin–Ciocalteu reagent, hydrogen peroxide, sodium dihydrogen phosphate and disodium hydrogen phosphate were obtained from Sigma-Aldrich (USA). Cholesterol, triacylglycerol and high-density lipoprotein cholesterol kits were obtained from Randox laboratory (UK), with catalogue number CH200, TR 210 and CH203, respectively. All chemicals and reagents used were of analytical grade.

Animals

Male Wistar albino rats weighing 130–150 g obtained from animal house of University of Benin, Edo state, Nigeria, were used for the study. The animals were allowed to acclimatize for 14 days before beginning the experiment. They were housed in polypropylene cages at a temperature of 25–30 °C, relative humidity of 35–45% and 12 h for both light and dark cycles. They had free access to the formulated diet and water. The animals were handled with great care so as to minimize pain, and all experiments were conducted in strict compliance with internationally accepted principles for laboratory animals' use and care (Olfert et al. 1993).

Collection of plant materials and identification

Leaves of *Chrysophyllum albidum* and *Irvingia gabonensis* were collected from a private farm at Ewu, Edo State, Nigeria (6.8015°N, 6.2495°E). The fresh leaves were identified by Prof. M.E. Osawaru at the Department of Plant Biology and Biotechnology of the University of Benin, Benin City, Nigeria. Herbarium specimens with voucher numbers UBHc362 and UBHi153 for *Chrysophyllum*

albidum and *Irvingia gabonensis*, respectively, were deposited at the Herbarium.

Preparation of plant extracts

The leaves were rinsed properly with water and air-dried away from direct sunlight. They were then pulverized using hands, soaked in methanol for 72 h and filtered with a double-layered muslin cloth (100 µm). Each filtrate was separately concentrated using a rotary evaporator (RE-52A, Lanphan, China) at 40 °C and stored in air-tight sterile bottles.

Preparation of experimental diet

NFD and HFD were formulated using a slightly modified method of Cha and Jones (1998) as follows:

NFD Casein (15%), corn starch (60%), sucrose (10%), soya bean oil (4%), vitamins and minerals mix (4.5%), cellulose (6.5%).

HFD Casein (15%), corn starch (40%), sucrose (10%), soya bean oil (4%), beef tallow (20%) vitamins and minerals mix (4.5%), cellulose (6.5%).

Experimental design

Thirty-six male Wistar rats were randomly assigned into six groups consisting of six animals each. High-fat diet (20% w/w beef tallow) was used to induce dyslipidaemia and oxidative stress in the experimental rats in groups 2–6.

The groups were treated as follows:

Group 1 Represented the normal fat diet control. The animals were fed normal fat diet (NFD) and orally administered the vehicle (carboxymethyl cellulose 0.5% solution) once daily for eight weeks.

Group 2 Served as the high-fat diet control. The rats were fed with HFD and given the vehicle orally, once daily for eight weeks.

Group 3 The rats were orally treated (once daily) with the methanol extract of leaf of *Chrysophyllum albidum* (250 mg/kg) along with the HFD for eight weeks.

Group 4 The rats were orally treated (once daily) with the methanol leaf extract of *Chrysophyllum albidum* (500 mg/kg) along with HFD for eight weeks.

Group 5 The rats were orally treated (once daily) with the methanol leaf extract of *Irvingia gabonensis* (250 mg/kg) along with HFD for eight weeks.

Group 6 The rats were orally treated (once daily) with the methanol leaf extract of *Irvingia gabonensis* (500 mg/kg) along with HFD for eight weeks.

During the period of the study, body weight (g) of animals was recorded on a weekly basis and feed intake was recorded daily. At the end of the experiment (56 days), the rats were subjected to overnight fasting and then

killed by cervical dislocation. Blood samples were collected via cardiac puncture into sterile tubes and allowed to stand for 30 min at 20–25 °C. The clear serum was separated at 2500 g for 15 min using a centrifuge.

Liver and heart samples were harvested and placed in containers with normal saline and stored at 4 °C. A sample of liver tissue (1 g) was homogenized in 9 mL of cold normal saline (0.9%), while 0.5 g of heart was homogenized in 4.5 mL of ice cold normal saline. The homogenates were centrifuged at 1000 g for 15 min, and the supernatant was stored for subsequent analyses.

Estimation of serum lipid profile

Total cholesterol concentration Allain et al. (1974).

Triacylglycerol Concentration (Tietz 1990).

High-Density Lipoprotein Cholesterol (HDL-C) Concentration (Tietz 1990).

Low-Density Lipoprotein Cholesterol ((LDL-C) Concentration

The low-density lipoprotein (LDL) cholesterol concentration was estimated using the formula by Friedewald et al (1972)

Very Low-Density Lipoprotein Cholesterol (VLDL-C) Concentration

Very low-density lipoprotein (VLDL) cholesterol concentration was estimated using the formula by Friedewald et al (1972).

Estimation of indicators of oxidative stress

Glutathione peroxidase activity, malondialdehyde and reduced glutathione concentrations were measured in the liver and heart using established protocols as follows:

Glutathione peroxidase

In this procedure, the rate of oxidation of glutathione by hydrogen peroxide is used to measure glutathione peroxidase activity. Glutathione leftover in the solution at a given time is estimated by its reaction with DTNB (5,5'-dithiobis-(2-nitrobenzoic acid)) (Rotruck et al. 1973).

Malondialdehyde

This method depends on the formation of malondialdehyde (MDA) as an end product of lipid peroxidation which reacts with thiobarbituric acid (TBA) producing a pink chromagen which can be measured spectrophotometrically at 532 nm (Buege and Aust 1978).

Reduced glutathione

The reduced form of glutathione comprises in most instances the bulk of cellular non-protein sulfhydryl

groups. This method is based upon the development of a relatively stable (yellow) colour when 5,5'-dithio-bis-(2-nitrobenzoic acid) (Ellman's reagent) is added to sulfhydryl compounds. The chromophoric product resulting from the reaction of Ellman's reagent with the reduced glutathione, 2-nitro-5-thiobenzoic acid possesses a molar absorption at 412 nm (Ellman 1959).

Fractionation of the extracts and determination of the most active fraction

The crude methanol extract of leaves of *C. albidum* and *I. gabonensis* (10 g) was dissolved separately in a 100 mL mixture of methanol and water (4:1). Then, it was extracted successively with different organic solvents of increasing polarity: hexane, dichloromethane and ethyl acetate to obtain their respective fractions. They were concentrated by rotary evaporator (Hossain et al. 2014).

The various fractions obtained were subjected to phytochemical screening (qualitative and quantitative). Quantification of phytochemicals included total phenols (Cicco et al. 2009), total flavonoids (Miliauskas et al. 2004) and total tannins (Polshettiwar and Ganjiwale 2007), which was carried out to determine the phytochemicals present in the extracts that may also be responsible for their in vivo activities.

Evaluation of antioxidant potential of fractions

The various fractions (hexane, dichloromethane and ethyl acetate fractions from *C. albidum* and *I. gabonensis*) were evaluated in vitro for antioxidant property using the follow assays:

Ferric reducing antioxidant potential

This assay is based on electron transfer to reduce Fe^{3+} to Fe^{2+} using 2,4,6-tripyridyl-S-triazine (TPTZ), forming an intense blue iron two-ion TPTZ complex that is read at 593 nm.

Procedure

1.5 mL of freshly prepared FRAP solution (25 mL of 300 mM acetate buffer (pH 3.6), 2.5 mL of 10 mM 2,4,6-tripyridyl-S-triazine (TPTZ) in 40 mM HCl and 2.5 mL of 20 mM ferric chloride ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$) solution) was added to 1 mL of the sample (1 mg/mL). The reaction mixtures were incubated at 37 °C for 30 min, and the absorbance at 593 nm was measured. FeSO_4 was used for the calibration curve and ascorbic acid served as the positive control. FRAP values (expressed as mg Fe (II)/g of the extract) for the extracts were then extrapolated from the standard curve (Benzie and Strain 1996).

1,1-Diphenyl-2-picrylhydrazyl radical (DPPH) scavenging activity

The free radical scavenging capacity of the leaf extracts against 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical was determined by the method of Brand-Williams et al (1995).

The assay is based on the rate at which a compound donates electron or hydrogen atom to DPPH which results in change of colour from deep violet to golden yellow which can be read at 570 nm.

Procedure

Briefly, 0.5 mL of 0.3 mM DPPH solution in methanol was added to 2 mL of various concentrations (0.01 – 0.2 mg/mL) of the sample. The reaction tubes were shaken and incubated for 15 min at room temperature in the dark, absorbance read at 517 nm. All tests were performed in triplicates. Ascorbic acid was used as the standard control, with similar concentrations as the test samples prepared. A blank containing 0.5 mL of 0.3 mM DPPH and 2 mL of methanol was prepared and treated as the test samples. The radical scavenging activity was calculated using the following formula:

$$\text{DPPH radical scavenging activity (\%)} = [(A_0 - A_1) / (A_0)] \times 100.$$

Where:

A_0 = Absorbance of DPPH radical + methanol.

A_1 = Absorbance of DPPH radical + sample or standard.

The 50% inhibitory concentration (IC_{50}) value was calculated as the effective concentration of the sample that is required to scavenge 50% of the DPPH free radicals. This was extrapolated from a straight line graph of percentage inhibition of DPPH against sample concentration (Brand-Williams et al. 1995).

The fraction that has the highest concentration of phytochemicals and antioxidant property was regarded as the most active fraction and was subjected to gas chromatography flame ionization detector (GC-FID) analysis.

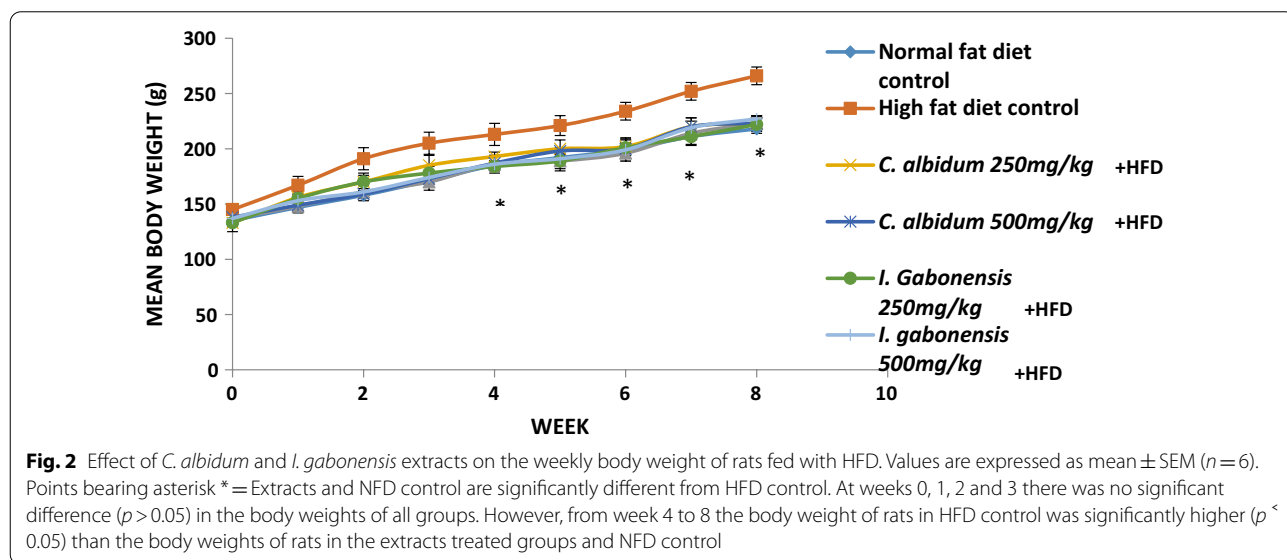
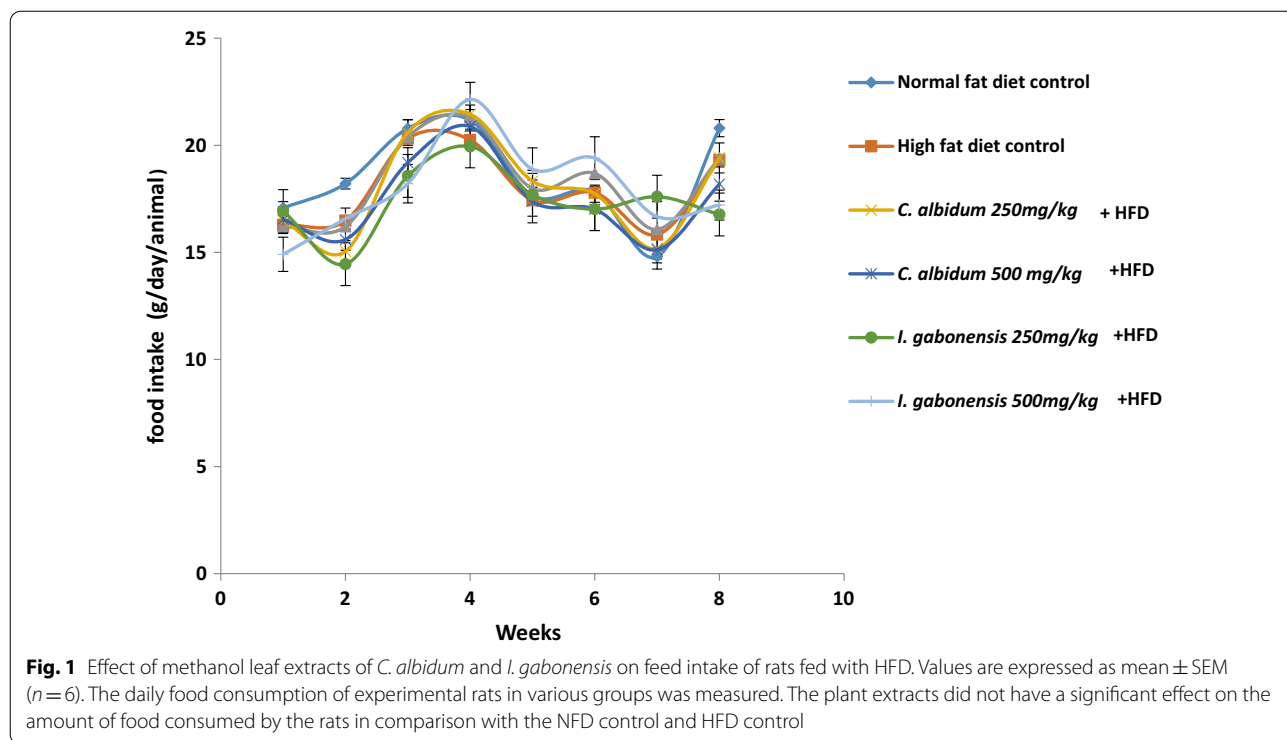
Statistical analysis

The results were analysed using the statistical package for social sciences (SPSS) version 23 for windows. One-way analysis of variance (ANOVA) was used to compare standard error of mean. Data were termed significant at $p < 0.05$. Inter-group comparisons were done by the Tukey's post hoc test.

Results

Feed consumption of rats

Figure 1 represents the effect of *C. albidum* and *I. gabonensis* extracts on feed intake by rats. There was no significant ($p > 0.05$) difference in the daily feed



consumption in rats treated with the extracts in comparison with the controls.

Body weight

Figure 2 shows the effect of *C. albidum* and *I. gabonensis* extracts on weekly body weight of rats fed with different diets. From week 4 to 8, the mean body weight of rats fed with high-fat diet alone was significantly higher ($p < 0.05$)

when compared to rats in the extracts treated groups and NFD control (Fig. 2).

Effect of *C. albidum* and *I. gabonensis* extracts on lipid profile of rats

Total cholesterol, triacylglycerol, LDL-C and VLDL-C concentrations were significantly higher ($p < 0.05$) in HFD control than NFD control and extract treated

Table 1 Effect of *C. albidum* and *I. gabonensis* extracts on lipid profile of rats fed with HFD

| | Total cholesterol (mg/dL) | Triacylglycerol (mg/dL) | LDL-C (mg/dL) | HDL-C (mg/dL) | VLDL-C (mg/dL) |
|--------------------------------------|-----------------------------|----------------------------|----------------------------|----------------------------|---------------------------|
| NFD control | 147.78 ± 5.69 ^a | 96.13 ± 3.47 ^a | 30.01 ± 7.35 ^a | 98.55 ± 2.36 ^a | 19.16 ± 0.64 ^a |
| HFD control | 199.59 ± 8.53 ^b | 123.33 ± 4.23 ^b | 101.11 ± 2.13 ^b | 73.81 ± 3.29 ^b | 24.67 ± 0.85 ^b |
| HFD + <i>C. albidum</i> 250 mg/kg | 120.75 ± 18.13 ^a | 91.39 ± 8.55 ^a | 5.85 ± 1.84 ^c | 97.25 ± 2.65 ^a | 18.45 ± 1.62 ^a |
| HFD + <i>C. albidum</i> 500 mg/kg | 129.31 ± 11.47 ^a | 95.90 ± 2.67 ^a | 8.93 ± 1.41 ^c | 101.53 ± 4.11 ^a | 19.18 ± 0.53 ^a |
| HFD + <i>I. gabonensis</i> 250 mg/kg | 126.9 ± 13.01 ^a | 96.34 ± 4.86 ^a | 3.29 ± 0.72 ^c | 104.82 ± 3.09 ^a | 19.27 ± 0.97 ^a |
| HFD + <i>I. gabonensis</i> 500 mg/kg | 129.14 ± 3.58 ^a | 93.35 ± 2.90 ^a | 8.94 ± 1.78 ^c | 100.53 ± 2.75 ^a | 18.67 ± 0.58 ^a |

^{a, b, c} These lower case letters a, b and c are different levels of significance at $p < 0.05$. a is significantly different from b and c, and vice versa. b is also significantly different from c and vice versa. The use of such alphabets is to show the homogenous sets which would bear same alphabet so that the different sets can easily be identified

Data are expressed as mean ± SEM ($n = 6$). Values in the same column with different superscripts are significantly different ($p < 0.05$) from each other

Table 2 Effect of *C. albidum* and *I. gabonensis* extracts on GSH, MDA levels and glutathione GPx activities of rat liver and heart homogenates

| | GSH (µg/ml) | | GPx (mgGSH oxid./min/g tissue) | | MDA (mM/g tissue) | |
|--------------------------------------|---------------------------|---------------------------|--------------------------------|---------------------------|---------------------------|---------------------------|
| | Liver | Heart | Liver | Heart | Liver | Heart |
| NFD control | 83.20 ± 3.05 ^a | 28.88 ± 4.13 ^a | 20.88 ± 0.25 ^a | 18.69 ± 0.31 ^a | 1.10 ± 0.22 ^a | 0.74 ± 0.01 ^a |
| HFD control | 49.23 ± 3.98 ^b | 4.69 ± 1.19 ^b | 15.75 ± 0.25 ^b | 13.63 ± 0.25 ^b | 2.94 ± 0.06 ^b | 1.08 ± 0.02 ^b |
| HFD + <i>C. albidum</i> 250 mg/kg | 72.63 ± 2.63 ^a | 5.13 ± 0.63 ^b | 19.08 ± 0.45 ^a | 20.76 ± 0.63 ^a | 1.42 ± 0.09 ^{ac} | 0.75 ± 0.22 ^{ac} |
| HFD + <i>C. albidum</i> 500 mg/kg | 73.32 ± 5.19 ^a | 22.5 ± 2.75 ^a | 20.82 ± 0.57 ^a | 19.32 ± 0.63 ^a | 2.20 ± 0.14 ^d | 0.88 ± 0.04 ^c |
| HFD + <i>I. gabonensis</i> 250 mg/kg | 71.57 ± 3.69 ^a | 3.63 ± 0.13 ^b | 20.76 ± 0.88 ^a | 19.32 ± 0.94 ^a | 2.10 ± 0.10 ^d | 0.87 ± 0.08 ^c |
| HFD + <i>I. gabonensis</i> 500 mg/kg | 80.51 ± 1.74 ^a | 9.63 ± 1.13 ^b | 20.63 ± 0.50 ^a | 18.88 ± 0.50 ^a | 2.18 ± 0.11 ^d | 0.88 ± 0.03 ^c |

^{a, b, c, d} These lower case letters a, b, c and d are different levels of significance at $p < 0.05$. a is significantly different from b and c, and vice versa. b is also significantly different from c and vice versa. The use of such alphabets is to show the homogenous sets which would bear same alphabet so that the different sets can easily be identified

Data are expressed as mean ± SEM ($n = 6$). Values in the same column with different superscripts are significantly different ($p < 0.05$) from each other

groups. However, HDL-C concentration was significantly lower ($p < 0.05$) in HFD control than NFD control and extract treated groups (Table 1).

Effect of *C. albidum* and *I. gabonensis* extracts on antioxidant indices of rats

The concentration of GSH, MDA and activity of GPx in rats' liver and heart homogenates are depicted in Table 2. The concentration of GSH in the liver of extract treated groups was significantly higher ($p < 0.05$) than that of high-fat diet control. The GPx activity in the liver and heart of extract treated groups was significantly higher ($p < 0.05$) than that of high-fat diet control. The liver and heart MDA concentrations were significantly ($p < 0.05$) lower for the extract treated groups than the high-fat diet control.

Phytochemical constituents and in vitro antioxidant capacity of fractions from leaf extracts of *C. albidum* and *I. gabonensis*

The phytochemical screening (qualitative) results of n-hexane, dichloromethane, ethyl acetate and

hydromethanol fractions from leaf extracts of *C. albidum* and *I. gabonensis* are shown in Tables 3 and 4, respectively.

Quantitatively, the total phenols, total flavonoids and total tannins contents of the ethyl acetate fraction of both *C. albidum* and *I. gabonensis* were significantly higher ($p < 0.05$) than those of hexane, dichloromethane and hydromethanol fractions (Tables 5 and 6).

The results of the DPPH radical scavenging activities of the various fractions from *C. albidum* and *I. gabonensis* are shown in Figs. 3 and 4, while their corresponding IC₅₀ values are presented in Tables 7 and 8, respectively. The ethyl acetate fractions of both extracts had significantly lower ($p < 0.05$) IC₅₀ values and therefore better DPPH radical scavenging ability than the other fractions. Only the positive control, ascorbic acid had significantly lower ($p < 0.05$) IC₅₀ value than ethyl acetate fraction.

Figures 5 and 6 indicate the ferric reducing antioxidant potential (FRAP) of the fractions from leaf extracts of *C. albidum* and *I. gabonensis*, respectively. Also, the ethyl acetate fraction of both plant extracts had the highest FRAP values in comparison with the other fractions.

Table 3 Phytochemical constituents of fractions from leaf extracts of *C. albidum*

| | Hexane | Dichloromethane | Ethyl acetate | Hydromethanol |
|--------------------|--------|-----------------|---------------|---------------|
| Saponins | + | – | + | – |
| Alkaloids | – | – | – | – |
| Flavonoids | – | – | ++ | + |
| Tannins | + | – | ++ | – |
| Cardiac glycosides | – | – | – | – |
| Steroids | – | – | – | – |
| Terpenoids | – | – | – | – |
| Phenols | + | + | +++ | + |

– = absent, + = trace amounts, ++ = moderate amount, +++ = high amounts. $n = 3$

Table 4 Phytochemical constituents of fractions from leaf extract of *I. gabonensis*

| | Hexane | Dichloromethane | Ethyl acetate | Hydromethanol |
|--------------------|--------|-----------------|---------------|---------------|
| Saponins | – | + | + | – |
| Alkaloids | – | + | – | – |
| Flavonoids | – | – | ++ | ++ |
| Tannins | + | + | ++ | + |
| Cardiac glycosides | – | – | – | – |
| Steroids | – | – | – | – |
| Terpenoids | – | – | – | – |
| Phenols | + | + | +++ | ++ |

KEY: – = absent, + = trace amounts, ++ = moderate amount, +++ = high amounts. $n = 3$

Table 5 Quantification of phytochemicals of fractions from leaf extracts of *C. albidum*

| Phytochemical | Hexane | Dichloromethane | Ethyl acetate | Hydromethanol |
|--|---------------------------|---------------------------|----------------------------|---------------------------|
| Total phenols(mg gallic acid equivalent/g extract) | 85.65 ± 1.5 ^a | 89.50 ± 2.00 ^a | 220.55 ± 8.00 ^b | 76.40 ± 4.50 ^a |
| Total flavonoids (mg quercetin equivalent/g extract) | 75.00 ± 2.50 ^a | 80.50 ± 1.50 ^a | 120.50 ± 4.50 ^b | 72.00 ± 2.50 ^a |
| Total tannins (mg tannic acid equivalent/g extract) | 38.75 ± 2.00 ^a | 34.50 ± 1.40 ^a | 65.60 ± 2.50 ^b | 24.50 ± 1.00 ^c |

^{a, b, c} These lower case letters a, b and c are different levels of significance at $p < 0.05$. a is significantly different from b and c, and vice versa. b is also significantly different from c and vice versa. The use of such alphabets is to show the homogenous sets which would bear same alphabet so that the different sets can easily be identified

Values are expressed as mean ± SEM ($n = 3$). Values in the same row with different superscripts are significantly different ($p < 0.05$) from each other

Table 6 Quantification of phytochemicals of fractions from leaf extracts of *I. gabonensis*

| Phytochemical | Hexane | Dichloromethane | Ethyl acetate | Hydromethanol |
|--|---------------------------|---------------------------|-----------------------------|---------------------------|
| Total phenols (mg gallic acid equivalent/g extract) | 88.65 ± 2.5 ^a | 95.50 ± 4.00 ^a | 380.55 ± 12.00 ^b | 89.40 ± 2.50 ^a |
| Total flavonoids (mg quercetin equivalent/g extract) | 85.00 ± 1.50 ^a | 85.50 ± 2.00 ^a | 240.50 ± 5.00 ^b | 82.00 ± 1.50 ^a |
| Total tannins (mg tannic acid equivalent/g extract) | 47.55 ± 3.00 ^a | 42.50 ± 3.50 ^a | 85.50 ± 3.50 ^b | 44.50 ± 2.00 ^a |

^{a, b} are different levels of significance at $p < 0.05$. a is significantly different from b and vice versa. The use of such alphabets is to show the homogenous sets which would bear same alphabet so that the different sets can easily be identified

Values are expressed as mean ± SEM ($n = 3$). Values in the same row with different superscripts are significantly different ($p < 0.05$) from each other

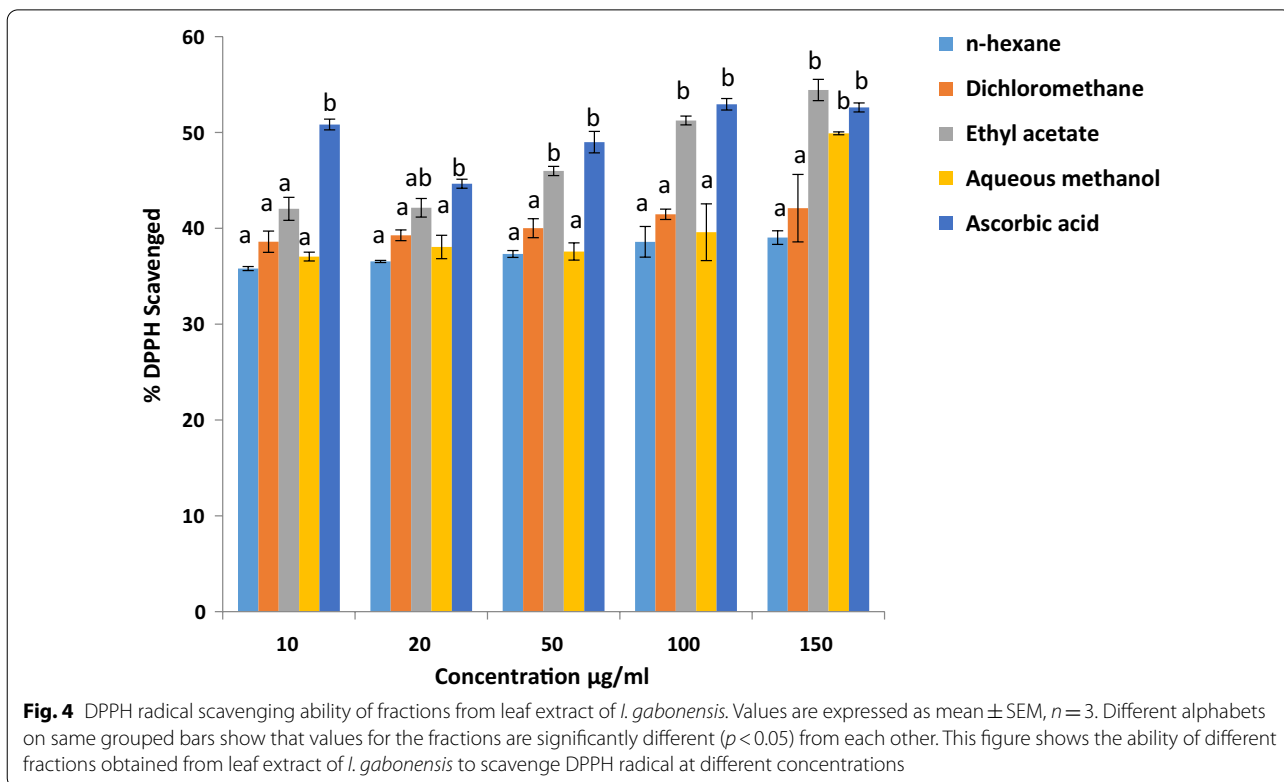
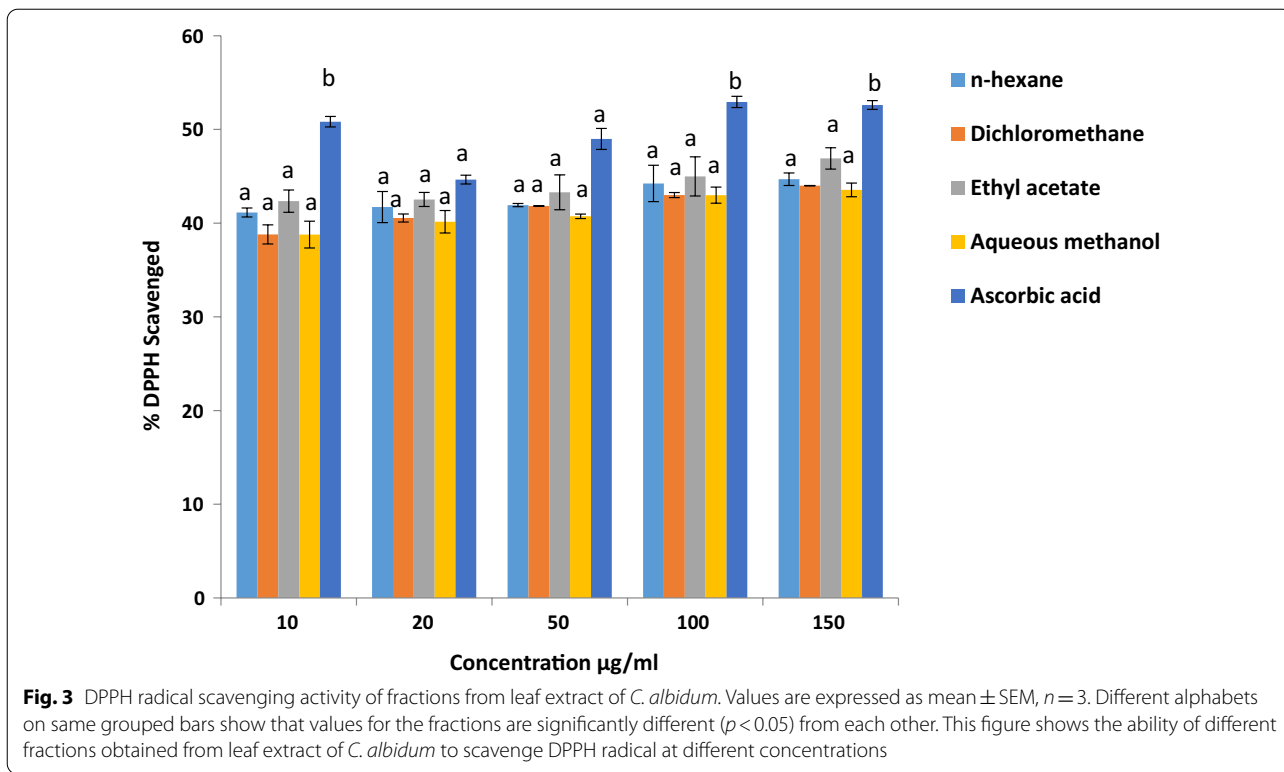


Table 7 IC₅₀ values for DPPH scavenging activity of fractions from leaf extract of *C. albidum*

| Fraction | IC ₅₀ (µg/mL) |
|------------------|-----------------------------|
| n-hexane | 307.06 ± 8.57 ^a |
| Dichloromethane | 329.44 ± 4.06 ^a |
| Ethyl acetate | 260.12 ± 10.12 ^b |
| Aqueous methanol | 342.72 ± 9.22 ^a |
| Ascorbic acid | 77.80 ± 2.21 ^c |

^{a, b, c} These lower case letters a, b and c are different levels of significance at $p < 0.05$. a is significantly different from b and c, and vice versa. b is also significantly different from c and vice versa. The use of such alphabets is to show the homogenous sets which would bear same alphabet so that the different sets can easily be identified

Values are expressed as mean ± SEM, $n = 3$. Values with different superscripts are significantly different ($p < 0.05$) from each other

Table 8 IC₅₀ values for DPPH scavenging activity of fractions from leaf extract of *I. gabonensis*

| Fraction | IC ₅₀ (µg/mL) |
|------------------|-----------------------------|
| n-hexane | 355.98 ± 12.35 ^a |
| Dichloromethane | 255.42 ± 12.77 ^b |
| Ethyl acetate | 96.31 ± 2.81 ^c |
| Aqueous methanol | 169.25 ± 1.81 ^d |
| Ascorbic acid | 77.80 ± 2.21 ^e |

^{a, b, c, d, e} These lower case letters a, b, c, d and e are different levels of significance at $p < 0.05$. a is significantly different from b and c, and vice versa. b is also significantly different from c and vice versa. The use of such alphabets is to show the homogenous sets which would bear same alphabet so that the different sets can easily be identified

Values are expressed as mean ± SEM, $n = 3$. Values with different superscripts are significantly different ($p < 0.05$) from each other

Phytochemical components in the ethyl acetate fraction of methanol leaf extracts of *C. albidum* and *I. gabonensis* identified by GC-FID

Based on result of quantitative phytochemical screening and in vitro antioxidant property, the ethyl acetate fraction was considered the most active fraction as it had higher amount of phytochemicals and antioxidant property than all the other fractions. Therefore, the ethyl acetate fractions of *C. albidum* and *I. gabonensis* extracts subjected to gas chromatography flame ionization detector (GC-FID) analysis revealed the phytochemical components shown in Tables 9 and 10, respectively.

The analysis showed the presence of various flavonoids. The most abundant flavonoids present in the ethyl acetate fraction of both *C. albidum* and *I. gabonensis* were kaempferol, quercetin, luteolin, myricetin and naringenin as highlighted in Tables 9 and 10, respectively.

Discussion

This present study evaluated the impact of leaf extracts of *Chrysophyllum albidum* and *Irvingia gabonensis* on dyslipidaemia and oxidative stress induced by HFD in Wistar rats. A link between HFD, lipid abnormalities and oxidative stress has been recognized for long, and HFD is considered to be a reliable method in induction of lipid abnormalities in experimental rats (Bais et al., 2014). Long-term feeding with HFD which has a high content of saturated fatty acids may lead to a decrease in the levels of polyunsaturated fatty acids (PUFAs) in hepatocyte cells, causing oxidative stress and inflammatory conditions. These conditions cause sterol regulatory element-binding protein (SREBP-1c) activation (Wali et al. 2020). This is a transcription factor that regulates genes that play a function in the synthesis of free fatty acids (FFAs) and increases the absorption of FFAs, cholesterol and triglycerides by stimulating the expression of fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC) (Ruiz et al. 2014). It has been suggested that the administration of HFD can increase the expression of FAS and ACC proteins. ACC protein plays a role in inhibiting fatty acid transport to the mitochondria, and thereby, fatty acids will be esterified into a large proportion of triglycerides and stimulate de novo lipogenesis. Furthermore, triglycerides are converted into VLDL. VLDL will then become LDL, resulting in an increase in LDL concentration followed by a decrease in HDL concentration (Zhang et al. 2020).

Research has also shown that prolonged consumption of a high-saturated fat diet induces oxidative stress, because it attenuates the hepatic antioxidant enzyme system and raises the concentration of lipid peroxidation products in the liver and plasma (Oliveros et al. 2004). Plant-derived polyphenols and polyphenol metabolites have long been recognized for their prominent antioxidative benefits, with minimal adverse effects. Antioxidant therapy with phytochemicals has been said to be effective in suppressing multiple oxidative stress pathways (Rodrigo and Gil-Becerra 2014).

Dyslipidaemia has been characterized as a major risk factor for cardiovascular risk, including atherosclerosis (Martins and Redgrave 2004). In this study, administration of *C. albidum* and *I. gabonensis* leaf extracts to rats at doses of 250 mg/kg and 500 mg/kg with HFD significantly lowered ($p < 0.05$) the levels of total cholesterol, VLDL-C, triacylglycerol, LDL-C and increased the level of HDL-C in comparison with HFD control. Similar results were obtained by Ghasi et al (2000), where treatment of rats with HFD and crude extract of a medicinal plant led to an increased serum HDL-C and decreased levels of total cholesterol, LDL-C, VLDL-C and triacylglycerol.

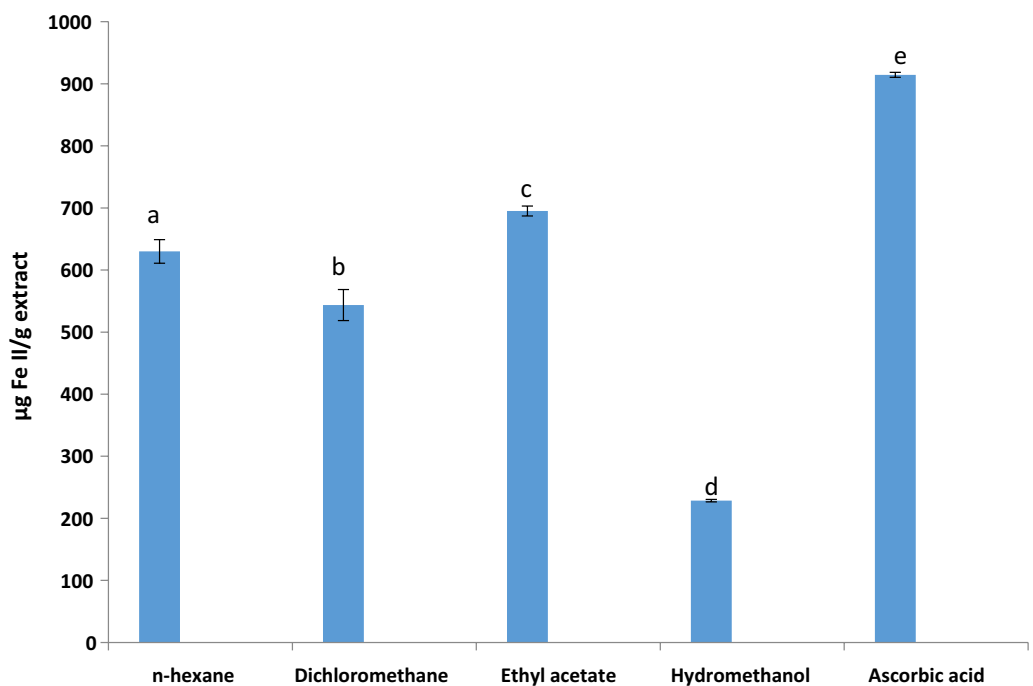


Fig. 5 Ferric reducing antioxidant potential (FRAP) of fractions from leaf extract of *C. albidum*. Values are expressed as mean ± SEM, $n = 3$. Different alphabets on bars show that values for the fractions are significantly different ($p < 0.05$) from each other. The ethyl acetate fraction from leaf extract of *C. albidum* had significantly higher ($p < 0.05$) FRAP value in comparison with the other fractions. However, ascorbic acid standard had significantly higher ($p < 0.05$) FRAP value than ethyl acetate fraction

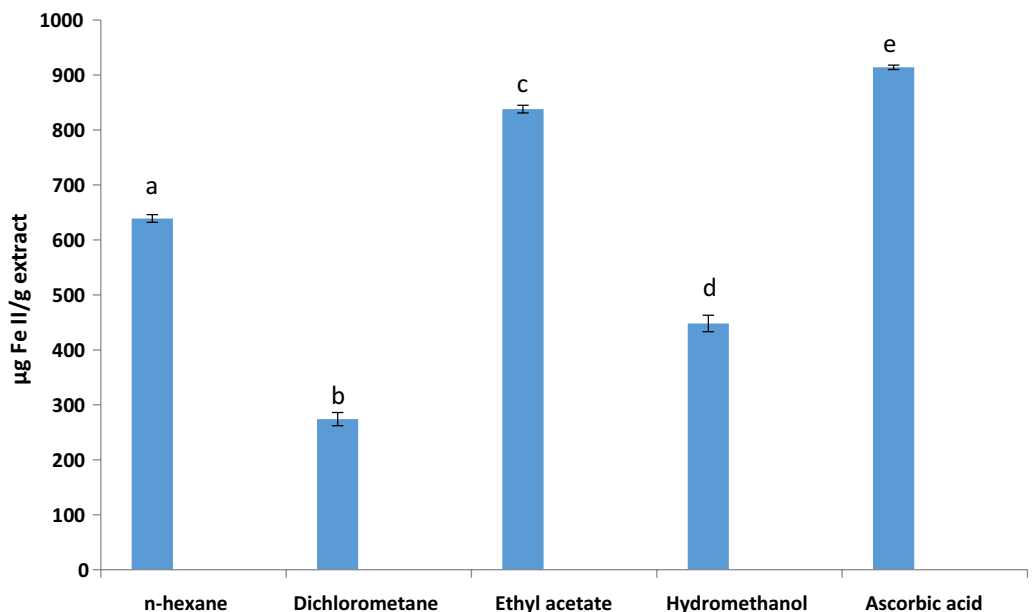


Fig. 6 Ferric reducing antioxidant potential (FRAP) of fractions from leaf extract of *I. gabonensis*. Values are expressed as mean ± SEM, $n = 3$. Different alphabets on bars show that values for the fractions are significantly different ($p < 0.05$) from each other. The ethyl acetate fraction from leaf extract of *I. gabonensis* had significantly higher ($p < 0.05$) FRAP value in comparison with the other fractions. However, ascorbic acid standard had significantly higher ($p < 0.05$) FRAP value than ethyl acetate fraction

Table 9 Phytochemical components identified by GC-FID in the most active (ethyl acetate) fraction from leaf extract of *C. albidum*

| Phytoconstituent | Retention time (min) | Peak area | Concentration (mg/100 g) |
|---------------------------------------|----------------------|----------------|--------------------------|
| (+)- Catechin | 13.740 | 94.285 | 0.921 |
| Resveratrol | 15.035 | 72.278 | 0.000010 |
| Genistein | 15.501 | 62.213 | 0.0000097 |
| Daidzein | 15.618 | 69.084 | 0.000011 |
| Apigenin | 15.895 | 139.552 | 0.303 |
| Diadzin | 16.453 | 231.071 | 0.000036 |
| Butein | 16.672 | 123.607 | 0.000019 |
| Biochanin | 17.092 | 217.931 | 0.000035 |
| Naringenin | 17.361 | 102.200 | 2.792 |
| Luteolin | 17.770 | 206.826 | 6.298 |
| Kaempferol | 18.052 | 198.042 | 22.066 |
| (-)- Epicatechin | 19.518 | 185.221 | 0.0030 |
| (-)- Epigallocatechin | 20.467 | 380.870 | 0.0044 |
| Gallocatechin | 21.820 | 149.096 | 0.000072 |
| Quercetin | 22.599 | 240.449 | 28.789 |
| (-)- Epicatechin-3-gallate | 22.854 | 91.096 | 0.00037 |
| (-)- Epigallocatechin-3-gallate23.470 | 23.470 | 157.250 | 0.00045 |
| Isorhamnetin | 23.966 | 107.663 | 0.0000054 |
| Robinetin | 24.185 | 129.949 | 0.000021 |
| Myricetin | 24.721 | 74.576 | 6.038 |
| Baicalin | 25.103 | 85.099 | 0.000013 |
| Nobiletin | 25.481 | 47.8126 | 0.0000074 |
| Baicalin | 25.865 | 32.861 | 0.0000051 |
| Isoquercetin | 25.953 | 126.919 | 0.076 |
| Tangeretin | 26.496 | 42.817 | 0.0000067 |
| Artemetin | 26.829 | 28.015 | 0.0000043 |
| Silymarin | 26.949 | 32.214 | 0.0000050 |
| Hesperidin | 28.524 | 14.985 | 0.000010 |
| Tannic acid | 19.516 | 121.563 | 66.355 |

Bold values denotes the ones in high concentrations in the extracts

In this study, the capacity of the extracts in ameliorating oxidative stress in rats was determined using measurement of MDA, GSH concentration and activity of GPx in the liver and heart. GSH is a tripeptide, non-enzymatic biological antioxidant present in the liver which protects cellular proteins against reactive oxygen species produced from a number of processes (Arivazhagan et al. 2000). Decreased level of GSH is associated with increased lipid peroxidation (Arivazhagan et al. 2000). GPx also functions in detoxifying hydroperoxides. It catalyses the reaction of hydroperoxides with reduced glutathione to form glutathione disulphide (GSSG) and the reduction product of hydroperoxide (Alam et al. 2012). MDA is a by-product of lipid peroxidation. Increased levels of lipid peroxidation determined by measurement of MDA

Table 10 Phytochemical components identified in the most active (ethyl acetate) fraction of methanol extract of *I. gabonensis* leaf by GC-FID

| Phytoconstituent | Retention time (min) | Peak area | Concentration (mg/100 g) |
|---------------------------------------|----------------------|----------------|--------------------------|
| (+)- Catechin | 13.740 | 91.385 | 0.892 |
| Resveratrol | 15.037 | 64.715 | 0.0000091 |
| Genistein | 15.500 | 56.013 | 0.0000087 |
| Daidzein | 15.618 | 60.347 | 0.0000094 |
| Apigenin | 15.812 | 65.431 | 0.142 |
| Diadzin | 16.369 | 105.857 | 0.000016 |
| Butein | 16.669 | 97.409 | 0.000015 |
| Biochanin | 17.090 | 177.603 | 0.000029 |
| Naringenin | 17.358 | 81.794 | 2.234 |
| Luteolin | 17.767 | 191.769 | 5.840 |
| Kaempferol | 18.049 | 151.628 | 21.739 |
| (-)- Epicatechin | 19.515 | 132.593 | 0.0022 |
| (-)- Epigallocatechin | 20.461 | 271.438 | 0.0032 |
| Gallocatechin | 21.817 | 153.273 | 0.000074 |
| Quercetin | 22.595 | 139.002 | 16.643 |
| (-)- Epicatechin-3-gallate | 22.781 | 90.668 | 0.00037 |
| (-)- Epigallocatechin-3-gallate23.468 | 23.468 | 0.00021 | |
| Isorhamnetin | 23.964 | 56.447 | 0.0000029 |
| Robinetin | 24.182 | 74.907 | 0.000012 |
| Myricetin | 24.721 | 64.425 | 5.216 |
| Baicalin | 25.099 | 46.428 | 0.0000072 |
| Nobiletin | 25.479 | 23.593 | 0.0000036 |
| Baicalin | 25.860 | 13.446 | 0.0000021 |
| Isoquercetin | 25.953 | 54.831 | 0.033 |
| Tangeretin | 26.633 | 9.796 | 0.0000015 |
| Artemetin | 26.832 | 11.017 | 0.0000017 |
| Silymarin | 26.948 | 12.888 | 0.0000020 |
| Hesperidin | 28.524 | 5.043 | 0.0000035 |
| Tannic acid | 19.522 | 272.295 | 74.9712 |

Bold values denotes the ones in high concentrations in the extracts

have been associated with various disease conditions and pathological states (Wang et al. 2004).

The results from the study revealed significantly higher ($p < 0.05$) concentration of liver GSH in the extracts treated groups when compared to the rats in the HFD control. The results also showed significantly higher ($p < 0.05$) liver and heart GPx activities in the extracts treated groups when compared to the HFD control. The liver and heart MDA levels in the extract treated groups were significantly lower ($p < 0.05$) than that of the rats exposed to the high-fat diet without treatment. The relative decrease in the activity of GPx and GSH concentration in the rats induced with HFD could be attributed to their excessive utilization in mopping up the free radicals generated due to the HFD (Ma et al. 2011). In addition,

the high MDA concentration in the HFD control indicates evidence of lipid peroxidation as a result of the HFD.

The observed ameliorative effect of methanol leaf extracts of *C. albidum* and *I. gabonensis* against the aforementioned oxidative stress indices supports the work of Olorunnisola et al (2012), who also reported that oxidative stress induced by high-fat diet was ameliorated by a plant extract (*T. violacea*). In their study, administration of crude extracts of *T. violacea* rhizomes to rats fed with HFD protected against HFD induced reduction in GSH, reduction in GPx activity and increase in MDA in liver, heart and aorta. Also in this present study, leaf extracts of *C. albidum* and *I. gabonensis* inhibited HFD induced lowering of GSH, lowering of GPx and rise in MDA in liver and heart of rats fed.

In this study, the findings on weight gain in HFD fed rats suggest that the extracts significantly inhibited weight gain. In a previous study, Bias et al. (2014) speculated that treatment of HFD fed rats with methanol leaf extract of *Moringa oleifera* for 49 days resulted in a significant reduction in body weight compared to the HFD control. They therefore suggested that leaf extracts of *Moringa oleifera* have weight-reducing potential. These findings from this research are in line with the report by Bias et al. (2014). In our study, the extracts probably acted to inhibit weight gain by lowering fat accumulation in the body. This can be seen from the significant reduction in the serum concentration of triacylglycerol in rats treated with the extracts in comparison with the HFD control.

To ascertain the effect of the plant extracts on appetite of rats, food consumption was measured daily. It was observed that administration of *C. albidum* and *I. gabonensis* extracts did not affect feed consumption. This indicates that the extracts produced antioxidant and anti-obesity effects, in HFD rat model, without affecting appetite.

In a recent study by Zalar et al. (2022), HFD was used to induce dyslipidaemia in rats. However, treatment of the rats with an alkaloid extract from *Colchicum autumnale* L. significantly reduced plasma levels of total cholesterol, LDL-C and triacylglycerol while increasing HDL-C level in comparison with the HFD control. Also, they reported that HFD lowered GSH concentration and increased MDA concentration, signifying induction of oxidative stress. However, administration of extract reduced oxidative stress in the rats. Similarly, in another recent research by Labban et al. (2021), *Garcinia mangostana* and *Curcuma longa* ameliorated oxidative stress and dyslipidaemia in rats fed with HFD. Reports from these studies are also consistent with our findings in this present study.

Upon analysis of the various fractions resulting from the extracts using solvents with increasing polarities (hexane < dichloromethane < ethyl acetate), ethyl acetate fractions of both extracts had higher amounts of phytochemicals (phenols, flavonoids and tannins) than the other fractions. The ethyl acetate fractions also showed significantly higher ($p < 0.05$) antioxidant property than the other fractions and were therefore suggested to be the most active fraction. The higher antioxidant property of ethyl acetate fractions may be due to the presence of higher amount of phytochemicals in comparison with the other fractions.

GC-FID analysis of the ethyl acetate fraction from crude extract of *C. albidum* and *I. gabonensis* revealed the presence of twenty-eight known flavonoids, which consisted of high concentrations of kaempferol, quercetin, luteolin, myricetin and naringenin. The remaining flavonoids were less than 1 mg/100 g in the extracts. Tannic acid was also detected in abundant amounts in the extracts. Kaempferol, quercetin, luteolin, myricetin and naringenin are flavonoids present in different plant species (especially vegetables and fruits). Tannic acid is a polyphenol which is water soluble and has the ability to complex macromolecules and metal ions (Leal et al. 2015). These phytochemicals have several properties including strong antioxidant properties and anti-dyslipidaemic properties (Brusselmans et al. 2005; Fang et al. 2008; Ilhami et al. 2010). Specifically, flavonoids have been reported to lower lipid levels by inhibiting lipid absorption, lipogenesis and stimulating lipolysis (Al Shukor et al. 2016). Therefore, these phytochemicals may be responsible for the protective effects of the plant extracts against dyslipidaemia and oxidative stress induced by HFD as observed in this study.

Conclusions

The study has shown that methanol leaf extracts of *C. albidum* and *I. gabonensis* have significant weight gain inhibitory activity in rats without affecting feed consumption. The extracts also exhibited protective effect against dyslipidaemia and oxidative stress induced by high-fat diet in rats. These desirable properties may be due to the presence of several bioactive compounds in the extracts. However, there is need for further preclinical trials and thorough investigation of their mode of action, bioavailability and pharmacokinetics.

Abbreviations

HFD: High-fat diet; NFD: Normal fat diet; GC-FID: Gas chromatography flame ionization detector; FRAP: Ferric reducing antioxidant power; DPPH: 1,1-Diphenyl-2-picrylhydrazyl; GPx: Glutathione peroxidase; GSH: Reduced glutathione; MDA: Malondialdehyde.

Acknowledgements

The authors are grateful to members of malaria research, molecular biology and toxicology unit, Department of Biochemistry, Faculty of Life Sciences, University of Benin for their support.

Author contributions

OI contributed to methodology, data analysis and drafting of the manuscript. ESO contributed to investigation, methodology, supervision and editing of the drafted manuscript. All authors read and approved the final manuscript.

Funding

The authors declare that there is no funding in the manuscript.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate

All procedures using animals obtained the approval of Life Sciences Institutional Animal Ethical Committee, University of Benin with LS19225 ethical number.

Consent for publication

Not applicable.

Competing interests

No competing interests were declared by the authors.

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Received: 24 March 2022 Accepted: 25 June 2022

Published online: 13 July 2022

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