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Sesamum indicum diet prevents hyperlipidemia in experimental rats

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ABSTRACT

Cardiovascular diseases and metabolic complications caused by hyperlipidemia are the leading cause of death globally. In this study, the hypolipidemic potency of *Sesamum indicum* (SI) seeds was investigated. Of the thirty-five (35) male rats used in the study, five (5) were randomly selected for baseline measurements and thirty (30) were fed high fat diet (HFD) for four (4) weeks before random assignment into three (3) groups. The experimental group was treated with 50% SI seed, the positive control group was given a hypolipidemic drug, atorvastatin (5 mg/kg/day) while the untreated group served as the negative control. With SI administration, the dyslipidemia induced by the HFD consumption in the plasma and the investigated body organs was reversed to a comparable degree with that of atorvastatin treatment. Taken together, this study demonstrates the hypolipidemic potency of SI in ameliorating hyperlipidemia and its associated complications, facilitated by the inhibition of HMG-CoA reductase activity.

1. Introduction

Hyperlipidemia is the major cause of cardiovascular diseases (CVDs) and co-morbidities, and account for major mortality around the world, as it involves abnormal levels of circulating plasma lipids (Shimada et al., 2004). High concentrations of serum cholesterol, especially LDL-cholesterol, have been implicated as a high-risk factor for cardiovascular diseases as the deposition of oxidized low density lipoproproteins (LDL) leads to plaque formation and thickening of the arteries, resulting in cardiovascular complications (Reena et al., 2011; Shimada et al., 2004). Serum cholesterol concentration requires rigorous control. Recently, reports correlating improvement in cardiovascular health with the administration of botanical dietary supplements have been on a continual increase (Hsu & Parthasarathy, 2017; Mahmood et al., 2010; Nwozo et al., 2017; Visavadiya & Narasimhacharya, 2011).

Dietary intervention is recognized as a key measure in patient therapy and in the maintenance of human health. Diets rich in antioxidants have been shown to play an essential role in the prevention of cardiovascular disease and cancer and compare favorably with drug treatments for hyperlipidemia and hypertension (Hsu & Parthasarathy, 2017; Kris-Etherton et al., 2002; Mahmood et al., 2010; Nwozo et al., 2017). Dietary fat is deemed to play an important role in modulating risk factors for cardiovascular diseases (Hunter et al., 2010). As reported previously, replacing saturated fat with polyunsaturated fat has been found to obviate coronary events in animals and humans (Hegsted et al., 1993; Oyinloye et al., 2016; Sirato-Yasumoto et al., 2001). However, excessive consumption of unsaturated fatty acids leads to higher peroxidation in lipoproteins (Hegsted et al., 1993).

Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; CD36, cluster of differentiation 36; CPT1, carnitinepalmitoyltransferase-1; CVD, cardiovascular disease; HDL, high density lipoprotein; HDL-C, high-density lipoprotein-cholesterol; HDL-PL, high-density lipoprotein-phospholipid; HDL-TG, high-density lipoprotein-triglyceride; HFD, high fat diet; HMG-CoA, 3-Hydroxy-3-methyl glutaryl-coenzyme A; LDL, low density lipoprotein; NCD, non-communicable disease; PPAR-α, peroxisome proliferator-activated receptor-α; SI, *Sesamum indicum*; SREBP1, sterol regulatory element binding protein-1; TC, total cholesterol; UCP2, uncoupling protein 2; VLDL, very low-density lipoprotein.

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Sesame seeds (*Sesamum indicum*) a member of the *Pedaliaceae* family is regarded as the oldest oil-yielding seed crop known to humanity. The oil seed is cultivated and obtained in high yields across the tropical and subtropical regions of Africa (Nigeria, Ethiopia, Burkina Faso, Somalia, Tanzania and Uganda), Asia (China, India, Myanmar, Korea, Russia and Turkey) and America (Mexico and South America) (Nzikou et al., 2009) due to its wide spectrum of pharmacological activities, therapeutic and nutritional importance which includes cholesterol-lowering effect and prevention of high blood pressure, attributable to the presence of two unique substances in the seed: sesamin and sesamolin (Aslam et al., 2020). In many parts of the world, sesame seed has been utilized in the cure/prevention of various illnesses due to its high level of mono- and polyunsaturated fatty acids (omega-3 and omega-6 fatty acids), vitamin E, phytosterols, fiber, and other nutraceutical components (Andargie et al., 2021; Asgary et al., 2013; Kumar et al., 2013). The lignan constituents have attracted significant attention due to their antiaging, anticancer, antidiabetic, anti-inflammatory and antioxidative properties (Afroz et al., 2019; Hsu & Parthasarathy, 2017; Kumar & Singh, 2015; Nwozo et al., 2017; Wu et al., 2019). Although a large body of research had been directed towards unravelling the nutritional and therapeutic relevance of *Sesamum indicum* (SI) oils, however, less attention is focused on the health-promoting effects of the seeds, hence the main thrust of the present study.

3-Hydroxy-3-methyl glutaryl-CoA reductase or HMG-CoA reductase (EC 2.3.3.10) is a polytopic transmembrane protein and a rate-limiting enzyme in cholesterol biosynthesis catalyzing the reaction mediated by sterols and non-sterol metabolites derived from mevalonate, in which HMG-CoA is converted to mevalonate (Mukherjee et al., 2016). HMG-CoA reductase inhibitory activity has been the focus of numerous and extensive research to discover novel anticholesterolemic drugs based on cholesterol-synthesis-inhibiting mechanism. Among them, statins of synthetic origin have been shown to display hypolipidemic effect via a competitive inhibitory effect on HMG-CoA reductase via the mevalonate pathway. Though statins are well tolerated, they are sometimes reported to have side effects leading to muscle tissue wastage, renal failure and hepatotoxicity (Babu & Li, 2015; Bjornsson, 2017). It is therefore imperative to investigate alternative diet therapy with lipid-lowering effect with minimal or no side-effects, possibly to make way for alternate means of managing hyperlipidemia and its associated co-morbidities. In this regard, in the present study, we hypothesized that *Sesamum indicum* (SI) seeds could serve as an effective nutraceutical to ameliorate hyperlipidemia-associated morbidities with minimal side-effects as commonly encountered with the use of standard hypolipidemic drugs. Thus, we compared the effect of SI with the use of oral hypolipidemic drug 'atorvastatin' in managing hyperlipidemia in model Wistar strain rats and established its hypolipidemic potency in treating hyperlipidemia and associated complications.

2. Materials and methods

2.1. Materials

All the chemicals used in the study were of analytical grade. Glass-distilled water was used for all preparations. SI seeds, maize and palm oil were purchased from a local market at Sabo, Sagamu, Ogun State, Nigeria. The SI seeds were cleaned of stones, sand and other particles, washed, sun-dried and ground to fine powder. Groundnut cake was obtained from Enigbokan Mill, Ikenne-Remo, Ogun State, Nigeria while commercial rat chow was purchased from Ladokun Feeds, Mokola, Ibadan, Oyo State, Nigeria.

2.2. Animal management

Thirty-five (35) four-week old male Wistar rats were obtained from the Department of Physiology, University of Ibadan, Ibadan, Nigeria and housed in well-ventilated and spacious single cell cage at a controlled room temperature of 27 ± 3 °C, 12 h light and dark cycle, acclimatized for 2 weeks and fed *ad libitum*. The cages, water and feeding troughs as well as the animal house were cleaned on daily basis and maintained in good sanitary condition to enhance the well-being of the animals. The animals were weighed fortnightly and all experiments including animal handling were carried out using standard protocols in accordance with the guidelines of the Institutional Animal Care and Use Committee as approved by the Ethical Committee of Olabisi Onabanjo University, Ago-Iwoye, Ogun State, Nigeria.

Following the rats' acclimatization for two (2) weeks and maintenance on commercial rat chow and portable drinking water, five (5) rats were randomly selected for baseline measurement while the remaining thirty (30) rats were fed high-fat diet for four weeks. The composition of the commercial rat chow and high-fat diet are presented on Table 1. The animals were thereafter randomly assigned into three (3) groups namely: the experimental group (treated with 50% SI seed + 50% HFD), the positive control (treated orally with 5 mg/kg/day atorvastatin + HFD) and the negative control (untreated and maintained on HFD) groups. Each group was treated for four (4) weeks. Five (5) animals were randomly selected and sacrificed from each group fortnightly with the kidney, liver, heart and brain excised to investigate the lipid profile. The HMG-CoA reductase activity in the rats' plasma was also investigated in all the groups. None of the experimental animals was excluded during the whole experimental process.

2.3. Lipid extraction from rat organs and plasma

10% homogenate of each tissue was prepared in chloroform–methanol mixture (2:1, v/v) in an ice-cold environment and centrifuged at 4,000 rpm for 10 min. Lipids were extracted afterwards from the homogenate using the method of Folch et al. (1957), following the scheme reported by Banjoko et al. (2012).

2.4. Lipid profile determination

Total cholesterol and triglyceride concentrations of the plasma and extracted lipids from the rat organ homogenates were determined with commercial assay kits (Randox Laboratories, Antrim, United Kingdom). High density lipoprotein (HDL)-cholesterol and triglycerides content were determined with the same commercial kits used for total cholesterol and triglyceride concentration estimations after very low-density lipoproteins (VLDL) were precipitated with heparin-$MnCl_2$ solution as described by Gidez et al. (1982).

2.5. Determination of total phospholipids content in rat organs and plasma

Total phospholipids content in the organs were extracted with chloroform–methanol mixture (2:1 v/v) as described by Folch et al. (1957) after which phospholipids content was determined following the

Table 1
Composition of high fat diet and commercial rat chow used in the study.

Composition of high fat diet		Proximate composition of high fat diet and commercial rat chow		
Ingredient	g/kg	Component	High fat diet (%)	Commercial rat chow (%)
Maize	500	Carbohydrate	51.6	68.4
Full-cream powdered milk	300	Protein	19.4	21.0
Groundnut cake	200	Fat	16.1	3.5
Palm oil	50	Vitamins	2.72	2.0
Vitamin mix	20	Minerals	2.72	2.0
Mineral mix	20	Methionine	0.28	–
Methionine	3	Cholesterol	0.91	–
Cholesterol	10	Fibre	5.5	6.0

method of Stewart (1980).

2.6. HMG-CoA reductase activity assay in the plasma

The activity of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase was determined following the schemes of Rao and Ramakrishnan (1975) in which the ratio of the concentrations of HMG-CoA and mevalonate in the rat plasma serves as an index of the activity of HMG-CoA reductase required to convert HMG-CoA to mevalonate in the presence of NADPH indirectly indicating the inhibition or activation of cholesterogenesis. Increase in the ratio implies decrease in the activity of the enzyme/inhibition of cholesterogenesis in the plasma and vice versa.

2.7. Statistical analyses

Results were expressed as mean ± SEM and analyzed using Analysis of Variance (ANOVA) followed by Tukey's test for pairwise comparison between the various groups of animals to determine the influence of treatments, and $p < 0.05$ was considered significant. SPSS version 20 was employed in the analysis of the obtained data.

3. Results

3.1. Sesamum indicum administration led to weight changes in hyperlipidemic rats

The weight changes of the animals over the four-week duration of treatment is presented in Table 2. The weights of the animals in the *Sesamum indicum* (SI) and the drug-treated groups steadily increased from 62.40 ± 3.71 g to 180.00 ± 14.14 g and 63.00 ± 5.39 g to 136.00 ± 29.00 g respectively, while in the untreated group, the weights increased rapidly from 63.00 ± 3.74 g to 234.00 ± 31.30 g. The progressive increase in weight of the rats in all the groups through the course of the study could be attributed to the high-fat diet the rats were fed with, as there was a significant increase in the weights of all the rats obtained in the 4th week of treatment compared with that of the baseline weights. Notably, a significant reduction in the weights of animals in the experimental group (SI-treated animals) compared with that of the negative control group (untreated animals) was observed as shown in Table 2. This might be indicative of the hypolipidemic potency of SI as its administration on the hyperlipidemic rats in this study had a significant weight-reducing effect comparable to that obtained with atorvastatin treatment. The weight-reducing effect of SI on hyperlipidemic rats observed in this study is consistent with the reports of Nandakumaran et al. (2015) and Aslam et al. (2020) who observed a substantial decrease in rats' body weight after 30- and 42-days continuous administration of SI oil.

Table 2
The mean weights and weight changes of animals fed high fat diet (0–4 week) and treated over a 4-week period (4–8 week) with *Sesamum indicum* or atorvastatin.

Groups	*Baseline weight (g)	2nd week weights (g)	4th week weights (g)	6th week weights (g)	8th week Weights (g)
Untreated	63.00 ± 3.74[a]	62.60 ± 7.53[a]	110.42 ± 5.45[a]	138.00 ± 30.33[a,b]	234.00 ± 31.30[b,c]
Drug-treated		63.00 ± 5.39[a]	108.28 ± 4.81[a]	92.00 ± 08.37[a]	136.00 ± 29.00[a,b]
Sesamum indicum-treated		62.40 ± 3.71[a]	109.21 ± 6.50[a]	107.00 ± 21.09[a,b]	180.00 ± 14.14[a,c]

Values are expressed as mean ± SEM, n = 5. Values with different superscript letters down the columns and across rows are significantly different at $p < 0.05$.
*Animals in the groups were randomly selected after 2 weeks of acclimatization on commercial rat chow and water, sacrificed and weight at week 0 noted.

3.2. Ameliorative effect of Sesamum indicum administration on the lipid profile of hyperlipidemic rats

The estimated total cholesterol (TC) concentration in both the hepatic and extra-hepatic tissues as well as the plasma of the animals studied is depicted in Fig. 1a. It is noteworthy that the TC concentration was significantly lower in the SI-treated rats across all the investigated tissues in the study, with the anti-hypercholesterolemic effect of SI being more pronounced in the liver followed by the heart, and then the kidney, brain and plasma, as there was about 3-fold reduction in the cholesterol concentration compared with that of the untreated rats. As inferred from the study outcomes, the consumption of the hyperlipidemic diet resulted in hypercholesterogenesis as there was 10-, 8- and 6-fold respective increments in cholesterol concentrations in the liver, heart, kidney, brain and plasma of the untreated rats compared with the baseline data. However, the continued administration of SI reversed the cholesterogenesis to similar levels observed with atorvastatin treatment. These observations are consistent with that of El-Baz et al. (2015) who reported 196.3 and 206.15% lipid reduction in hypercholesterolemic rat models by administration of 5 and 10% prophylactic black sesame seed oil. This observation is implicative of the hypolipidemic potency of SI and its comparative effectiveness with the use of the lipid-scavenging drug, atorvastatin.

From the data presented in Fig. 1b, the triglyceride (TG) constipation in the untreated rats induced by the consumption of the hyperlipidemic diet was reversed in the SI-treated rats in a comparable degree to that of the drug-treated rats across all tissues investigated in the study. The significant reduction in the TG concentration was more evident in all the studied organs compared with the plasma as there was about 8-fold reduction in the brain and 5-fold reduction in the liver, heart and kidney compared with only about 2-fold reduction in the plasma. The observed outcomes are consistent with the reduced levels of TC, TG and LDL-cholesterol levels associated with SI administration in cadmium-induced oxidative stress in Wistar strain rats reported by Oyinloye et al. (2016), and that of Sirato-Yasumoto et al. (2001) who reported that sesame rich in lignans profoundly affects hepatic fatty acid oxidation and lowered serum triacylglycerol levels. The observed decrease in TG concentration in the SI-treated rats compared with that of the untreated rats serves as an indicator of the hypolipidemic potency of SI, and thus has the potential of being preferred as sole usage or as an adjuvant therapeutic remedy for hyperlipidemia-related disorders compared with commonly employed hypolipidemic drugs.

Elevated phospholipid concentrations which may be indicative of phospholipidosis was observed in all the organs and plasma of the untreated hyperlipidemic rats compared with the baseline data, however only to significant levels in the liver and heart of the rats as presented in Fig. 2a. The ameliorative effect of SI in reducing the phospholipid levels in the SI-administered rats comparable to the drug-treated rats was demonstrated in all the studied tissues with the effect more evident in the kidney, liver and heart of the rats with about 2–3-fold reduced phospholipid levels. The mitigating effects of SI in assuaging the phospholipidosis induced by the high-fat diet fed to the rats demonstrate its hypolipidemic potency and comparative effectiveness to commonly employed hypolipidemic remedies.

The HDL-cholesterol (HDL-C) concentrations in the organs and plasma of the investigated rats are presented in Fig. 2b. The HDL-C concentrations of the investigated rat organs except that of the plasma in the untreated hyperlipidemic rats were significantly reduced ($p < 0.05$) compared with the baseline data, with about 73-, 28-, 44-, 34- and 2-fold respective reduced HDL-C concentrations in the kidney, liver, heart brain and plasma of the untreated rats. However, with the administration of SI in the experimental group rats, HDL-C concentrations were significantly improved in most of the investigated rat organs with about 31-, 7-, 19-, 15- and 2-fold improvement in the kidney, liver, heart, brain and plasma of the rats. Compared with the other investigated tissues in the study, the HDL-C concentrations in the rats' plasma

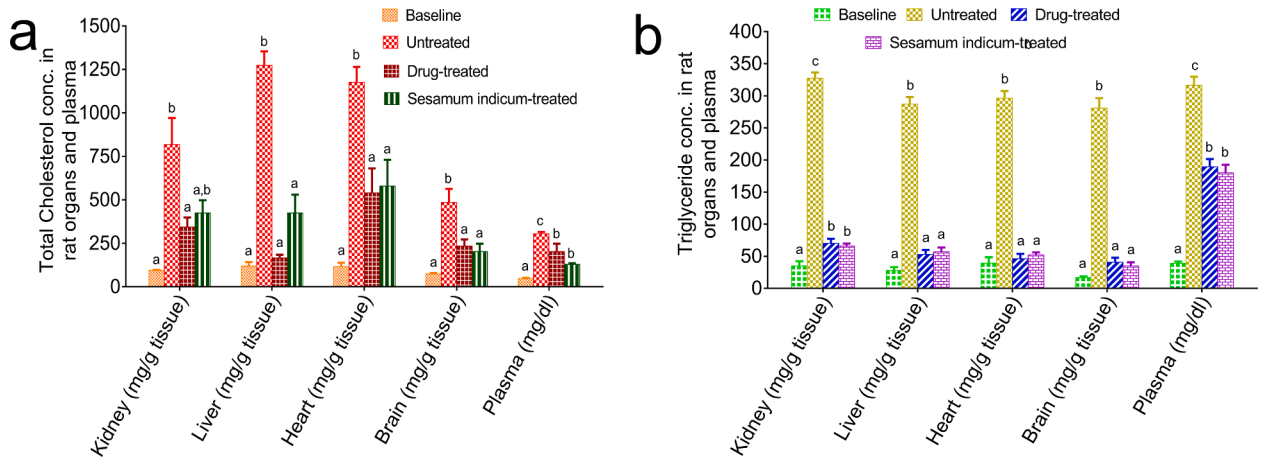

Fig. 1. Total cholesterol and triglyceride concentrations in rat organs and plasma. (a) Total cholesterol concentration in the kidney, liver, heart, brain and plasma of *Sesamum indicum*-treated, drug treated and untreated rats. (b) Total triglyceride concentration in the kidney, liver, heart, brain and plasma of *Sesamum indicum*-treated, drug treated and untreated rats. All values are expressed as mean ± SEM, n = 5. Bars belonging to the same assayed tissue with different letters are significantly different at $p < 0.05$.

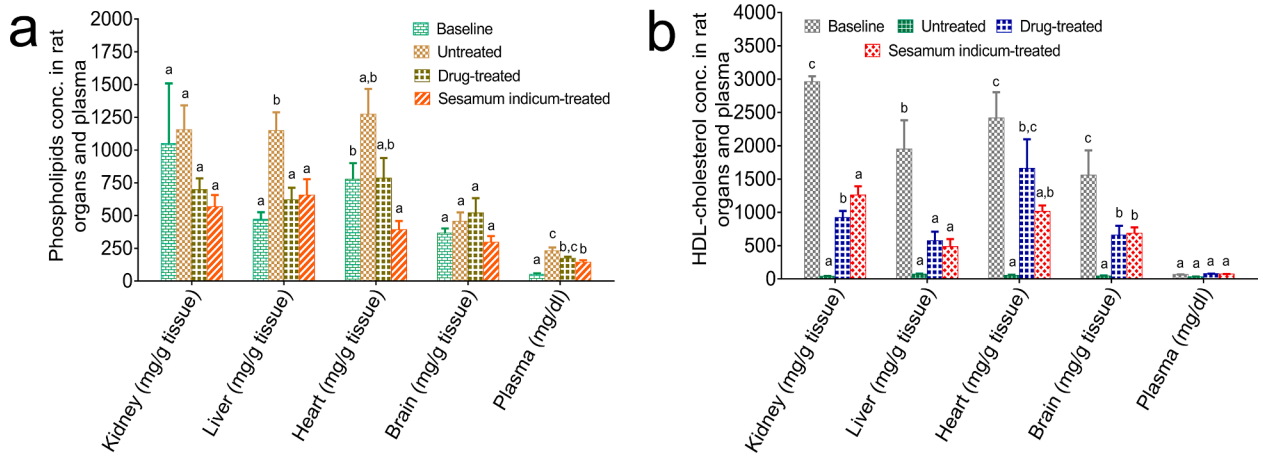

Fig. 2. Phospholipid and HDL-cholesterol concentrations in rat organs and plasma. (a) Phospholipid concentration in the kidney, liver, heart, brain and plasma of *Sesamum indicum*-treated, drug treated and untreated rats. (b) HDL-cholesterol concentration in the kidney, liver, heart, brain and plasma of *Sesamum indicum*-treated, drug treated and untreated rats. All values are expressed as mean ± SEM, n = 5. Bars belonging to the same assayed tissue with different letters are significantly different at $p < 0.05$.

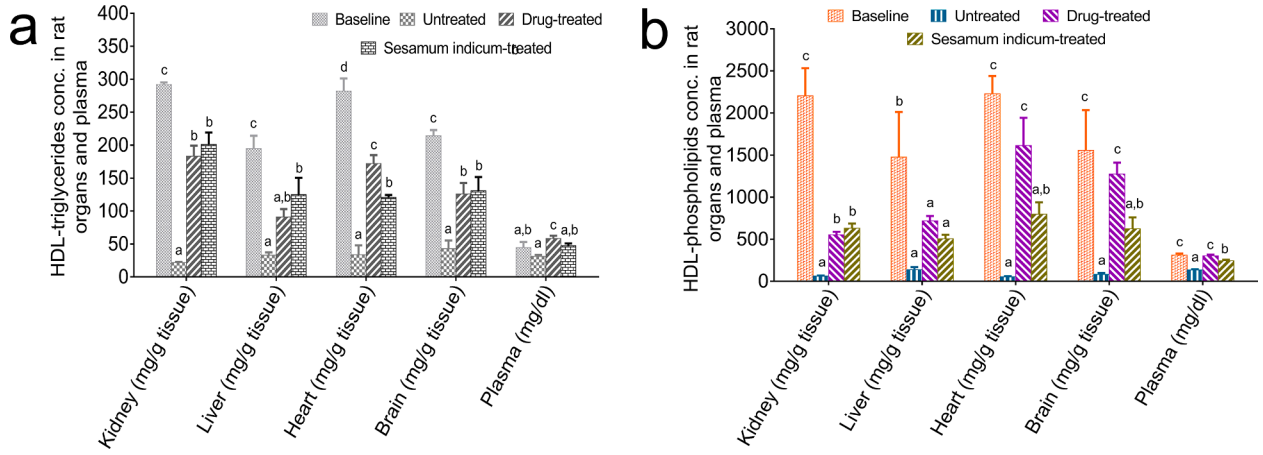

Fig. 3. HDL-triglyceride and HDL-phospholipid concentrations in rat organs and plasma. (a) HDL-triglyceride concentration in the kidney, liver, heart, brain and plasma of *Sesamum indicum*-treated, drug treated and untreated rats. (b) HDL-phospholipid concentration in the kidney, liver, heart, brain and plasma of *Sesamum indicum*-treated, drug treated and untreated rats. All values are expressed as mean ± SEM, n = 5. Bars belonging to the same assayed tissue with different letters are significantly different at $p < 0.05$.

were quite very low. The enhanced HDL-C concentrations in the SI-treated rats across all tissues examined in the study compared with that from the tissues of untreated rats is implicative of the hypolipidemic potency of SI as HDL-C is inversely correlated with hyperlipidemia-associated morbidities. These observations are consistent with that of Oyinloye et al. (2016) who reported reduced serum TC, TG and LDL-cholesterol levels and enhanced HDL-C levels as a result of the administration of 200 or 400 mg/kg body weight SI to rats with cadmium-induced oxidative stress.

Fig. 3a illustrates the concentration of high-density lipoprotein-triglyceride (HDL-TG) in rat organs and plasma. As observed in the study outcomes, there was a significant reduction in the HDL-TG concentration in the tissues of the untreated rats compared with the baseline measurements, while a significant increase was observed in the HDL-TG concentrations across all the investigated rat tissues except that of the plasma in both the drug-treated rats and SI-treated rats compared with that of the untreated rats. The increased HDL-TG concentrations observed in both the drug-treated rats and SI-treated rats' tissues may have negative health implications as previous studies identified HDL-TG as a cardiovascular risk marker, as its high concentration is associated with hypertriglyceridemia and several cardiovascular diseases due to its altered structure and function, opposite to that of HDL-C (Girona et al., 2019; Ito & Ito, 2020). A possible underlying reason for the elevated HDL-TG concentration in both the plasma and the investigated rat organs in the SI-treated rats might be the high saturated fatty acid content of sesame seeds which could have influenced the HDL-TG levels in the SI-supplemented rats as saturated fatty acids are known substrates for TG synthesis.

The concentrations of high-density lipoprotein-phospholipids (HDL-PL) is shown in Fig. 3b. The significantly reduced HDL-PL concentrations observed across all the investigated tissues of the untreated rats compared with the baseline values was improved by the administration of SI and atorvastatin in the experimental and drug-treated rats, respectively. As depicted in Fig. 3b, the HDL-PL concentrations were about 35-, 11-, 41-, 31- and 2-fold lower than the baseline data in the kidney, liver, heart, brain and plasma of the untreated rats. However, treatment with SI led to about 10-, 4- and 20-fold respective improvements in the HDL-PL concentrations in the kidney, liver and brain tissues, while only about 2-fold improvement was observed in the heart and plasma of the rats belonging to the experimental group, compared with those of the untreated rats. Previously, a direct correlation between increased HDL-PL concentrations and reduced incidence of cardiovascular diseases as it facilitates regression of atherosclerotic plaques by promoting the efflux of cholesterol from cells had been reported (Fournier et al., 2001). The elevated HDL-PL concentrations observed across the investigated tissues of the SI-treated rats is indicative of the hypolipidemic potential of sesame seed and its suitability as a therapeutic remedy for hyperlipidemic-related morbidities.

To ascertain the respective impacts of SI and atorvastatin on HMG-CoA reductase, the rate-limiting enzyme of the cholesterol biosynthetic pathway, catalyzing the reduction of HMG-CoA to mevalonate, the ratio of HMG-CoA to mevalonate which serves as the index of the activity of HMG-CoA reductase was determined in the plasma of the rats from both the treated and untreated groups. As evident from Fig. 4, there was a significant increase in the HMG-CoA/mevalonate ratio in both the SI-treated rats as well as the drug-treated rats compared with that of the untreated rats, implying the inhibition of HMG-CoA reductase activity in the treated rats. Moreover, previous studies had identified the inhibition of NADPH-dependent HMG-CoA reductase as the principal strategy for lowering blood lipid levels (Rai et al., 2009; Tuansulong et al., 2011). The observed inhibition of HMG-CoA reductase in the SI-treated rats which might be responsible for the reduced concentration of the major lipids (cholesterol, triglycerides and phospholipids) establishes the hypolipidemic potential of SI and its suitability as dietary therapy in the treatment of atherosclerosis and other hyperlipidemia-related disorders.

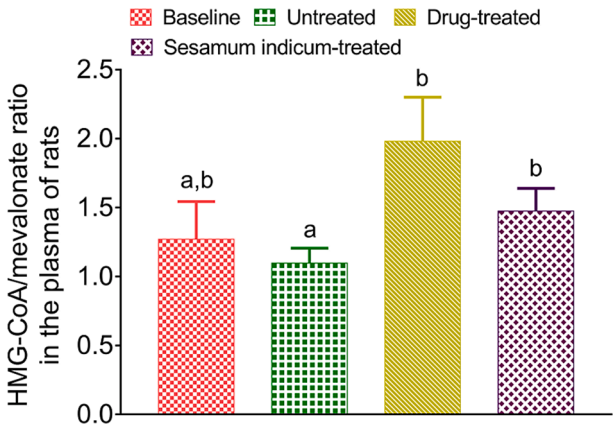

Fig. 4. HMG-CoA/mevalonate ratio as an index for the activity of HMG-CoA reductase in the plasma of *Sesamum indicum*-treated, drug-treated and untreated rats with the baseline measurements. All values are expressed as mean ± SEM, n = 5. Bars with different letters are significantly different at $p < 0.05$.

3.3. Discussion

Generally, a high-fat diet is a risk factor leading to whole body fat accumulation and distribution, particularly the accumulation of visceral adipose tissue. Although many synthetic hypolipidemic drugs exist and are the first choice in lowering blood cholesterol levels in patients with or at risk of cardiovascular diseases due to their health benefits, however their inherent adverse side-effects such as hepatotoxicity in various clinical settings calls for natural remedies with minimal or no detrimental secondary effects (Bjornsson, 2017; Kumar et al., 2011). The SI seed supplementation at 50% used in this study was chosen since earlier results reported by Asgary et al (2013) indicated that 10 % SI supplementation did not yield any significant alteration in lipid profile parameters. The observed ameliorative effect of the SI seeds on HFD-induced abnormal lipid profile of experimental rats in this study made us conclude that SI seeds are suitable as sole or adjuvant curative remedy for hyperlipidemia and associated complications, in place of the commonly administered synthetic hypolipidemic drugs. Statins have been employed as choice drug in the management of hyperlipidemia and other pathologies associated with elevated lipid levels. The atorvastatin dose of 5 mg/kg/day employed in this study was chosen in line with the previous work of Seo et al. (2020). The observed increase in weight of the rats (Table 2) over the duration of the study serves as an indicator of the hyperlipidemic effect of the compounded high fat diet on the study animals. The fall in body weight gain in the SI-treated rats suggests that SI may have exerted inhibitory effects on gastrointestinal tract motility consequentially resulting in the decline in the quantity of food intake and ultimately reduced body weight. This observation is consistent with previous reports in which a significant reduction in feed intake occurred as a result of inclusion of sesame oil in the diet of animal models, with concomitant reduction in weight (Aslam et al., 2020; Biswas et al., 2010).

Lipoproteins mainly function in maintaining lipid homeostasis by transporting lipids (including cholesterol and TGs) through the vascular and extravascular fluids in the body. Generally, increased levels of HDL–C and a concomitant reduction in TG, TC, phospholipids and LDL-cholesterol levels are correlated with reduced vulnerability to atherosclerosis and other degenerative cardiovascular diseases (Reena et al., 2011; Shimada et al., 2004). As observed in our findings, the administration of SI significantly reduced ($p < 0.05$) the elevated TC, TG and phospholipid concentrations observed in the tissues of the untreated rats, while elevating the HDL-C concentrations, thereby demonstrating the potency of SI in reversing the dyslipidemia induced by the hyperlipidemic diet predisposing the untreated rats to cardiovascular diseases and co-morbidities. These observations are congruent with the findings

of Asgary et al (2013) in which decreased plasma concentration of lipids in rabbits fed with 5% SI oil-supplemented diet was reported. A possible explanation for the hypolipidemic effect of SI may be attributed to the seed's rich content in monounsaturated and polyunsaturated fatty acids, or the presence of bioactive substances possessing HMG-CoA reductase inhibitory properties. Moreover, as reported previously, sesame lignans reduce serum and liver cholesterol concentrations by inhibiting the intestinal absorption of cholesterol and reducing the activity of acyl-CoA cholesterol acyl transferase and 3-hydroxy-3-methyl glutaryl CoA reductase (Afroz et al., 2019; Andargie et al., 2021; Kumar & Singh, 2015; Wu et al., 2019). Furthermore, the observed hypotriglyceridemic effect of SI seed supplementation could be attributed to the presence of sesamol, one of the bioactive constituents that has been previously reported to inhibit the intestinal absorption of triglycerides and promote cholesterol efflux from the blood when administered at a dosage of 50 mg/kg and 100 mg/kg on hyperlipidemia model mice, thus attenuating hypercholesterolemia and associated disorders (Kumar et al., 2013; Sirato-Yasumoto et al., 2001). Another plausible mechanism for the observed lipid-lowering effect of SI may be due to the suppression of the expression of the lipogenesis-related gene - sterol regulatory element-binding protein-1 (SREBP1) (a key transcription factor involved in the biosynthesis of cholesterol and fatty acids) at the mRNA level or by the upregulation of the low density lipoprotein (LDL) receptor and the expression of cholesterol-7α-hydroxylase gene, the rate-limiting enzyme in the conversion of cholesterol to bile acids for excretion. Furthermore, the up-regulation of the expression of lipolysis-associated peroxisome proliferator-activated receptor-α (PPAR-α) and cluster of differentiation 36 (CD36), energy expenditure-associated uncoupling protein 2 (UCP2) and carnitinepalmitoyltransferase-1 (CPT1) at the mRNA level, and increased fatty acid oxidation via adenosine monophosphate-activated protein kinase (AMPK) activation in adipose tissues might contribute to facilitating the lipid-lowering effect of SI administration in the hyperlipidemic rats (Yuan et al., 2016). In a previous report, the supplementation of sesame seeds at 200 g/kg in rats' experimental diet was reported to increase the activity of both hepatic mitochondrial and peroxisomal fatty acid oxidation enzymes such as acyl-CoA oxidase, carnitine palmitoyltransferase, 3-hydroxyacyl-CoA dehydrogenase, and 3-ketoacyl-CoA thiolase, while enzymes involved in fatty acid synthesis including fatty acid synthase, glucose-6-phosphate dehydrogenase, ATP-citrate lyase, and pyruvate kinase were down-regulated (Sirato-Yasumoto et al., 2001). Moreover, the change in the rate of fatty acid synthesis and oxidation in the liver might be responsible for alterations in lipid concentrations in the plasma and extra-hepatic tissues as they depend on the liver for their lipid supply (Nwozo et al., 2017; Banjoko et al., 2012). The mechanisms by which SI administration modulates the expression and activity of these enzymes deserves attention in future studies.

Previous studies have shown that HDL functionality is a better determinant of HDL-mediated cardiovascular protection than HDL-cholesterol. In contrast to HDL-cholesterol, HDL–TG has been reported to be directly associated with metabolism and arteriosclerotic vascular alterations and serves as a biomarker for metabolic and cardiovascular risk (Girona et al., 2019; Ito & Ito, 2020; Srivastava, 2018). In our study, we observed an unexpected significant increase ($p < 0.05$) in the HDL-TG concentration in the tissues of the SI-administered rats and drug-treated rats compared with the untreated hyperlipidemic rats. In actual fact, the obtained baseline data shows high HDL-TG levels. As high HDL-TG levels are correlated with predisposition to arterial plaques due to their cholesterol-rich content, the enhanced HDL-TG concentrations observed both in the SI-treated rats as well as the drug-treated rats contradicts their suitability as hypolipidemic therapies. The underlying reason for this observed trend demands further investigations.

HDL-PL is a very important parameter in regulating the efficiency of cells in stimulating cholesterol efflux as enrichment of lipoproteins with phospholipids has been found to significantly enhance cellular cholesterol efflux since they regulate the size and composition of plasma HDL levels (Fournier et al., 2001). Moreover, lower HDL-cholesterol and particularly HDL-phospholipids but elevated HDL-triglycerides have been correlated with incidence of coronary artery disease (Fournier et al., 2001; Piperi et al., 2004; Srivastava, 2018). As noted in our study, dietary supplementation with *Sesamum indicum* in the experimental rats as well as the treatment of the rats in the drug-treatment group with atorvastatin markedly enhanced the HDL-phospholipid content in the investigated tissues, thus confirming the hypolipidemic potential of SI and its eligibility as an adjuvant lipid-lowering therapeutic agent.

The Inhibition of NADPH-dependent HMG-CoA reductase catalyzing the reduction of HMG-CoA to mevalonate, the significant rate-limiting regulatory step in cholesterol biosynthetic pathway has been identified as the main strategy utilized by commonly employed drugs for lowering blood cholesterol levels or reducing the risk of cardiovascular diseases (Mukherjee et al., 2016; Rai et al., 2009; Tuansulong et al., 2011). In our study, we observed a significant increase in the HMG-CoA/mevalonate ratio in the plasma of both SI-treated rats as well as that of the drug-treated rats compared with that of the untreated hyperlipidemic rats, implying the inhibition of HMG-CoA reductase activity as a result of the supplementation of SI in the diet of the experimental rats, thus reducing the amount of cholesterol synthesized in the tissues. Consistent with this observation is the reduced TC content of the liver and extra-hepatic tissues of both the SI-treated rats and the atorvastatin-treated rats observed in this study. This finding agrees with the report of Tuansulong et al. (2011) in which the hypocholesterolemic effect of morelloflavone derived from *Garcinia dulcis* in experimental animals was attributed to its inhibition of HMG-CoA reductase leading to a decrease in *de novo* cholesterol synthesis. Moreover, as reported previously, sesamin, one of the most important lignan components of sesame seeds exhibited hypocholesterolemic effect via the downregulation of HMG-CoA reductase activity (Hirose et al., 1991).

It is worthy to note a number of limitations of this study. In the first instance, we did not investigate the parameters related to oxidative stress and inflammation. Secondly, the histopathological studies of the organs were also not reported. We acknowledge further studies in these areas to demonstrate whether the induced hyperlipidemia is accompanied by inflammation and oxidative stress; and the possible ameliorative effects of the seed on these parameters compared with the use of atorvastatin.

3.4. Conclusion

In summary, in the present study we show that dietary supplementation with SI could favorably modulate dyslipidemia and atherogenicity of lipid profiles with its associated complications in rats fed high fat diet. The mechanism by which SI exhibits its hypolipidemic effect is attributed to the inhibition of the NADPH-dependent HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthetic pathway, mediated by its constituent phytochemicals. The hypolipidemic modulatory effects of *Sesamum indicum* observed in this study potentiates its suitability as adjuvant therapeutic agent for treating hyperlipidemia and associated morbidities, while obviating the detrimental hepatotoxic side–effects associated with the use of commonly employed blood lipid-lowering drugs.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Declarations

Conflict of interest: The authors declare that they have no competing interests.

Ethical approval: Approval for the handling of animals and testing in this study was obtained from the Institutional Animal Care and Use Committee, Olabisi Onabanjo University, Ago-Iwoye, Ogun State, Nigeria with ethical clearance number – OOU/SCIENG/EC/0001/230921.

Authors' contributions: MMA conceived the study. MMA, IAS, SOO, TAD and KMA carried out data analyses and interpreted the results. MMA, TAD and SOO drafted the manuscript. TAD, SOA and SOO proof-read the manuscript. MMA and other authors conducted the study and participated in sample assays. All authors read and approved the final draft of the manuscript.

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