Therapeutic effects of Baobab fruit pulp *(Adansonia digitata)* aqueous extract on liver and cardiovascular system of high-fat diet rat model

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Abstract

This study examined Baobab fruit pulp (BFP) therapeutic effects on liver and cardiovascular in high fat diet (HFD) rats. Sixty male rats classified into; negative control, HFD. BFP, HFD+LDBFP, HFD+HDBFP, and HFD+Statin. At end, rats sacrificed; liver, heart and coronary arteries examined histopathological and blood samples withdrawn for measurement of blood glucose; lipid profiles [total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), LDL-C, vLDL-C]; liver functions [aspartate aminotransaminase (AST), alkaline phosphatase (ALP), alanine aminotransaminase (ALT), albumin, total protein (TP)]; cardiac enzymes [creatinine kinase-MB (CK-MB), troponin]; oxidative stress [malondialdehyde (MDA), glutathione (GSH), superoxide dismutase (SOD)]. Blood glucose and TC, LDL-C, TG, and vLDL-C, AST, ALT, ALP, CK-MB, Troponin, MAD serum levels were higher; while HDL-C, total proteins, albumin, SOD, GSH were lowered in HFD versus other groups; they ameliorated with HDBFP and Statin. Biochemical changes confirmed histopathological observations. In conclusion, HDBFP slow hypercholesterolemia-induced oxidative stress via its antioxidant capacity.

Keywords: Baobab Fruit Pulp (*Adansonia digitata L.*), Cardiac enzymes, Hypercholesterolemia, Liver functions, Oxidative stress.

1. Introduction

Dyslipidemia is a crucial factor in atherosclerosis development, which is linked to majority of cardiovascular-related problems as stroke myocardial infarction, hypertension, hypercholesterolemia, and hyperglycemia renal injury, and hyperglycemia (Abo-Elmaaty et al., 2020). Dyslipidemia can be caused by hereditary disorders as polygenic hypercholesterolemia (familial combined hypercholesterolemia) and familial hypercholesterolemia (FH) or associated with other diseases as type two diabetes mellitus, cholestatic hepatic disorders, nephrotic syndrome, hypothyroidism, obesity and chronic kidney failure. Dyslipidemia could also be due to unhealthy eating habits, as consuming large fat amounts on a regular basis (Fan et al., 2018). Saudi Arabia's food consumption pattern and total daily energy expenditure have altered substantially, as evidenced by an increase in high fat diet (HFD) intake and a drop in total daily energy expenditure (Alkhaldy et al., 2020). Oxidative stress is the cause via which dyslipidemia, especially hypercholesterolemia, leads to tissue destruction or causes different clinical disorders (Liu et al., 2017). Because the liver and heart are considered to be the principal risk organs for hypercholesterolemia (Lajis and Ismail, 2020), oxidative stress in hypercholesterolemia may cause harm to these organs.

The practice of supplementing one's diet with antioxidants to avoid free radical damage is gaining popularity. The majority of antioxidants come from natural sources and used in foods. The Baobab tree (*Adansonia digitata L.*) is a deciduous tree of Bombacaceae family. It grows on African and Indian savannas and is high in micronutrients and phytochemicals (Ismail et al., 2020). The bark, leaves, fruit seeds, and other tree parts used to

treat ailments as malaria, diarrhea, fever, and inflammation (Althwab et al., 2019). Aromatic substances, organic acids, minerals, particularly ascorbic acid, amino acids as alanine, proline, lysine, glycine, arginine, serine, valine and methionine, vitamins as B2, B1, B3, beta carotene, and Triterpenoids as alpha-amyrin, beta-amyrin, ursolic acid AND beta-sitosterol are all rich in fruit pulp (Ismail et al., 2020). Baobab has antilipidemic, hypoglycaemic, anti-inflammatory, analgesic/antipyretic, antimicrobial, anti-obesity, cardioprotective and hepatoprotective effects (Hanafy et al., 2016). An experimental study reported that simulations feeding of hyperlipemic rats with HFD and aqueous extract of *Adansonia digitata L* led to suppress hyperlipidemic status (Sidi-Aliyu, 2006). Also, (Elamin et al., 2019) reported that adding of 4 and 8% of Baobab power into high lipid diets led to decreased in serum levels of triglyceride, total cholesterol and low density lipoprotein cholesterol in HFD versus control rats.

Statins are class of hypocholesteremic medicines that used to reduce cardiovascular- deaths and morbidity in individuals with and without coronary artery diseases and hypercholestermia. Statins have a variety of beneficial actions that didn't directly linked to their actions on lipid metabolism, as antithrombotic, antiangiogenic, anti-inflammatory, antihypertensive actions and immunosuppressive properties (Groner et al., 2021).

The aim of this experimental research was to study the therapeutic actions of oral administration of Baobab fruit pulp aqueous extract (BFP) at low and high doses (100 and 300 mg/kg/day) for 4 weeks on liver and cardiovascular system functions and structures in rat's model of HFD.

2. Materials and method

2.1. Diet and chemicals

Normal commercial rats' chow diet was obtained from Baghafar Company for Pharmaceutical and Chemical, Jeddah, Saudi Arabia. Pure BFP purchased from local market from Jeddah, Saudi Arabia. Twenty grams of pulp sample powder was weighed and dissolved into 100 ml of distilled water to prepare a concentration of 200 mg/ml of BFP. Aqueous BFP was freshly prepared daily and doses were taken orally through orogastric gavage according to animal weight. Cholesterol and bile salt were obtained from Acros Organics Company, Jeddah, Saudi Arabia. Statin (coated tablets, 40 mg) was obtained from local pharmacy, Jeddah, Saudi Arabia.

2.2. Animals

Sixty adult male Albino rats (130-170g) were purchased from King Fahad Medical Research Center (KFMRC), King Abdulaziz University (KAU), Jeddah, Saudi Arabia. The rats housed in well-aerated standard clean poly acrylate plastic cages with five rats per cage and allowed to acclimatize to laboratory environment for 1 week (12-h light/dark cycle), 40-45% humidity and room temperature (23±2◦C). Rats fed on regular commercial chow and had free access to water ad libitum. This experimental study was made at KFMRC, KAU, Jeddah, Saudi Arabia. The experimental made in accordance with ethical guidelines of Animal Care and Use Committee of KAU and with ARRIVE (Animals in Research: Reporting in vivo Experiments) reporting protocol.

2.3. Induction of hypercholesterolemia

Forty rats were fed on HFD. The HFD formula is composed of 2% cholesterol, 40% sucrose, 10% peanut oil, 1% cholic acid, and 47% ordinary laboratory diet (Sikarwar and Patil, 2012). The standard laboratory diet composed of 2.94% sesame oil, 2.93% dried whole milk powder, 23.5% maize flour, 5.87% dried meat, 0.01% sodium chloride and 11.75% wheat bran flour (abundant in fibres, minerals, vitamin E, thiamine, vitamin B6, folate, and phenolic) (Sikarwar and Patil, 2012). Blood samples were taken to determine total cholesterol (TC) levels. Hypercholesterolemic rats were described as those had blood TC level of ≥300 mg/dl (Kalsoom and Jafari, 2011).

2.4. Experimental design

After a period of adaption (1 week), rats randomly classified to six groups (10 rats each). Negative control: rats fed ordinary laboratory chow diet and ad libitum tap water for 12 weeks. HFD: rats fed on HFD and ad libitum tap water for 12 weeks. BFP: rats fed standard laboratory chow diet for 8 weeks and administered by oral gavage

100 mg/kg/day BFP (Gwarzo, 2013) during last 4 weeks. HFD + LDBFP: rats fed on HFD for 8 weeks then administered orally low dose 100 mg/kg/ day BFP during last 4 weeks (Gwarzo, 2013). HFD + HDBFP: Rats fed on HFD for 8 weeks then administered orally high dose 300 mg/kg/day BFP during last 4 weeks (Gwarzo, 2013). HFD + Statin: rats fed on HFD for 8 week then administered orally Statin (40 mg/kg/day) during the last 4 weeks (Alharbi and Sindi, 2020). During the experimental period, animal total body weights were recorded every week. At experimental end, rats fasted overnight, anesthetized with diethyl ether, bled and sacrificed. Blood samples obtained into plain tubes for further analysis of biochemical markers. Heart, coronaries and liver were removed, cleaned, and weighted. Liver, heart and coronary arteries were dissected for histopathological examinations.

2.5. Biological evaluation

During experimental period, all rats body weights was recorded at regular intervals (every week) using an electronic scale balance (AE ADAM Equipment, Inc. UK). The biological values for different groups were evaluated by body weight gain percent determination by subtract final body weight from initial body weight then divided by initial body weight and multiply by 100. At end of experiment, the liver, coronary arteries and heart were dissected, washed with saline and organs were weighed utilizing an electronic scale balance. Relative organs weights were calculated by organ weight divided by final body weight multiple by 100.

2.6. Biochemical analysis

At experiment end, blood samples (3 ml) were gathered onto plain tubes from retro-orbital veins of eye. Blood samples left for 10 min and then centrifuged for 10 min at 4,000 rpm (Hermle LaborTechnik GmbH - Z 200 A Universal Compact Centrifuge, Wehingen, Germany) to get serum that kept at −20°C till analysis for estimation of serum triglycerides (TG) (Cat # MBS726298), TC (Cat # MBS722885) and high density lipoprotein cholesterol (HDL-C) (Cat # MBS267830) by auto analyzer (COBAS Roche Integra 400 Plus, Switzerland) based upon methods protocol. Low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (vLDL-C) (Cat # MBS706188) were calculated utilizing Friedewald equation (Zheng et al., 2015). Liver function tests were determined by measuring alanine amino transaminase (ALT) (Cat # MBS269614), aspartate amino transaminase (AST) (Cat # MBS264975), alkaline phosphatase- (ALP) (Cat # MBS011598), albumin (Cat # MBS2540439), and total protein (TP) (Cat # MBS2540455) according to manufacturer instructions. Cardiac enzymes [creatinine kinase-MB (CK-MB) (Cat # MBS705376) and troponin (Cat # MBS285870)] and oxidative stress markers as malondialdehyde (MDA) (Cat # MBS268427), superoxide dismutase (SOD) (Cat # MBS036924) and glutathione (GSH) (Cat # MBS265966) were estimated by Quantitative Sandwich ELISA kits for rats according to manufacturer instructions (My Biosource Company, via Mansour Scientific Foundation for Research and Development Company (MSFRDC), SA.

2.7. Histopathological examination

Dissected cardiac muscle, coronary arteries, and liver samples from rats fixed in 10% formal saline for one day before being rinsed with distilled water. For dehydration, increasing serial dilutions of ethyl alcohol were utilized. Samples were cleaned in xylene before being embedded in paraffin for 24 hours at 56°C in hot oven. The paraffin blocks made and cut to a thickness of 4–6 mm. For histological studies under a light microscope, sections were mounted on glass slides, deparaffinized, and stained with hematoxylin and eosin (H&E) (Olympus BX51-USA).

2.8. Statistical Analysis

The values analyzed utilizing IBM SPSS Statistics for Windows, version 23 (IBM SPSS, IBM Corp., Armonk, N.Y., USA). Shapiro – Wilk test was utilized to evaluate normal value distribution. Collected value presented as mean +/- standard deviation (SD). Statistical comparisons made by One-Way analysis of variance then Turkey's test to determined significance between groups. Significance were based on probability of $P < 0.05$.

3. Results

3.1. Body weights and Organs weights

Final body weights were significantly elevated in HFD group versus negative control and HFD + HDBFP (P <0.050 for both). Weight gain was significantly elevated in HFD and BFP groups versus negative control (P <0.001 and P <0.050) and was significantly lower in HFD + LDBFP and HFD + HDBFP versus HFD group (P <0.050 and P <0.010). Percentage changes in body weight was significantly elevated in HFD group versus negative control (P <0.001) but was significantly lower in BFP and HFD + HDBFP versus HFD (P <0.010 and P <0.050) (Table 1).
Absolute liver weight was significantly higher in HFD versus negative control and HFD + HDBFP (P <0.050 for both). Meanwhile, absolute heart weight was significantly elevated in HFD versus negative control, BFP, HFD + LDBFP, HFD + HDBFP and HFD + Statin (P <0.001 for all). Relative heart weight was significantly higher in HFD versus negative control and HFD + Statin (P <0.050 and P <0.001).

Table (1): Effects of Baobab Fruit Pulp Aqueous Extract (BFP) and Statin on total body weights and liver and heart weights in control and high fat diet (HFD) fed rats.

Groups	Negative control	HFD	BFP	HFD + LDBFP	HFD + HDBFP	HFD + Statin
Total body weights						
Initial body weight (grams)	149.40±12.04	140.00±18.71	151.90±4.56	147.00±11.98	141.60±17.65	148.30±8.37
Final body weight (grams)	305.50±6.77	350.50±27.9*	320.00±17.68	343.30±44.93	305.80±30.01$^{\#}$	339.00±32.48
Wight gain (grams)	156.10±12.68	210.50±27.13***	168.10±20.51$^{*,\#}$	196.30±36.46	164.20±23.07$^{\#\#}$	190.70±38.17
Percentage change in body weight (%)	51.09±3.95	59.98±4.91***	52.36±3.63$^{\#\#}$	56.84±3.70	53.61±4.30$^{\#}$	55.75±6.19
Percentage change in final weight versus negative control (%)	-	14.73%	4.75%	12.37%	0.1%	10.97%
Organs weights						
Absolute liver weight (grams)	7.55±0.59	9.19±1.38*	8.10±1.12	8.64±1.52	7.38±0.85$^{\#}$	8.76±1.22
Relative liver weight (%)	2.47±0.15	2.63±0.39	2.54±0.37	2.51±0.20	2.42±0.22	2.59±0.32
Absolute heart weight (grams)	0.90±0.01	1.11±0.10***	0.88±0.10$^{\#\#\#}$	0.99±0.11$^{\#\#\#}$	0.90±0.05$^{\#\#\#}$	0.89±0.05$^{\#\#\#}$
Relative heart weight (%)	0.30±0.01	0.32±0.04$^{\#}$	0.27±0.04	0.29±0.02	0.30±0.02	0.26±0.03$^{\#\#\#}$

Data were represented as mean +/- standard deviation (SD). *: Significance versus negative control group; $^{\#}$: significance versus HFD. HFD: high fat diet; BFP: Baobab Fruit Pulp. *: P <0.050; **: P <0.010; ***: P <0.001.

3.2. Levels of blood glucose and lipid profiles

Blood glucose, TG, TC, LDL-C values were significantly elevated in HFD and HFD + LDBFP groups versus negative control (P <0.001 for both), but was significantly lower in BFP, HFD + LDBFP and HFD + HDBFP versus HFD (P <0.001 for all). Serum values of vLDL-C were significantly higher in HFD group versus negative control (P <0.001), but was significantly lower in BFP, HFD + LDBFP, HFD + HDBFP and HFD + Statin groups versus HFD (P <0.001 for all) Meanwhile, serum values of HDL-C were significantly lower in HFD and HFD + LDBFP versus negative control (P <0.001 for both); but was significantly higher in BFP, HFD + LDBFP, HFD + HDBFP and HFD + Statin groups versus HFD group (P <0.001, P <0.050, P <0.001 and P <0.001, respectively). (Table 2).

Table (2): Effects of Baobab Fruit Pulp (BFP) and statin administration on blood glucose and lipid profile in control and high fat diet (HFD) fed rats.

Groups	Negative control	HFD	BFP	HFD + LDBFP	HFD + HDBFP	HFD + Statin
Blood glucose (mg/dl)	85.30±2.87	177.80±9.47***	93.80±5.37$^{\#\#\#}$	143.30±7.99$^{***,\#\#\#}$	94.80±10.75$^{\#\#\#}$	84.30±3.83$^{\#\#\#}$
Lipid profile						
TC (mg/dl)	128.50±3.14	273.00±45.48***	121.00±7.79$^{\#\#\#}$	190.40±9.37$^{***,\#\#\#}$	151.70±28.88$^{\#}$	114.00±8.11
TG (mg/dl)	72.50±1.78	133.50±14.25***	72.90±1.85 $^{\#\#\#}$	86.40±4.11$^{***,\#\#\#}$	79.40±7.56 $^{\#\#\#}$	69.40±3.34 $^{\#\#\#}$
LDL-C mg/dl)	85.30±1.25	239.10±49.41***	77.60±8.30$^{\#\#\#}$	158.50±4.67$^{***,\#\#\#}$	118.30±44.15$^{\#\#\#}$	67.90±8.80$^{\#\#\#}$
VLDL-C (mg/dl)	14.50±0.36	28.60±7.00***	14.58±0.37$^{\#\#\#}$	17.28±0.82$^{\#\#\#}$	16.28±1.15$^{\#\#\#}$	14.68±1.09$^{\#\#\#}$
HDL-C (mg/dl)	43.20±2.25	28.90±5.59***	43.40±1.71$^{\#\#\#}$	33.90±0.88$^{***,\#}$	37.80±4.76$^{*,\#\#\#}$	41.20±2.82 $^{\#\#\#}$

Data were represented as mean +/- standard deviation (SD). *: Significance versus Control negative group; $^{\#}$: significance versus HFD. HFD: high fat diet; BFP: Baobab Fruit Pulp. *: P <0.050; **: P <0.010; ***: P <0.001.

3.3. Liver functions and cardiac enzymes

The serum values of liver enzymes (AST, ALT and ALP) were significantly higher in HFD and HFD + LDBFP groups versus control (P <0.001 for all) but were significantly lower in BFP, HFD + LDBFP, HFD + HDBFP and HFD + Statin groups versus HFD (P <0.001 for all). Serum levels of total proteins were significantly lower in HFD, HFD + LDBFP and HFD + HDBFP groups versus control (P <0.001 for all) but were significantly elevated in BFP, HFD + HDBFP and HFD + Statin groups versus HFD (P <0.001 for all). Serum levels of albumin were significantly elevated in BFP, HFD + LDBFP, HFD + HDBFP and HFD + Statin groups versus HFD (P <0.001 for all). Indicating high affection of the liver by HFD that led to decrease of liver ability to form proteins. The serum values of cardiac enzymes (CK-MB and Troponin) were significantly elevated in HFD, HFD + LDBFP and HFD + Statin groups versus control (P <0.001, P <0.001 and P <0.050 and P <0.001, P <0.001 and P <0.050, respectively) but were significantly decreased in BFP, HFD + LDBFP, HFD + HDBFP and HFD + Statin versus HFD (P <0.001 for all) (Table 3).

Table (3): Effects of Baobab Fruit Pulp (BFP) and statin administration on liver function tests in control and high fat diet (HFD) fed rats.

Groups	Negative control	HFD	BFP	HFD + LDBFP	HFD + HDBFP	HFD + Statin
Liver functions						
AST (U/L)	17.40±0.97	116.90±20.05***	16.10±2.96$^{\#\#\#}$	37.40±5.74$^{***,\#\#\#}$	29.43±11.52$^{\#\#\#}$	28.59±5.80$^{\#\#\#}$
ALT (U/L)	20.80±1.32	91.80±24.11***	25.70±6.95$^{\#\#\#}$	45.50±5.46$^{***,\#\#\#}$	33.70±14.46$^{\#\#\#}$	21.81±3.36$^{\#\#\#}$
ALP (U/L)	46.40±3.20	129.80±7.04***	48.30±2.87$^{\#\#\#}$	75.50±5.93$^{***,\#\#\#}$	61.60±16.41$^{**,\#\#\#}$	53.20±6.78$^{\#\#\#}$
Total protein (g/dl)	8.02±0.39	3.66±0.46***	7.41±0.50$^{\#\#\#}$	6.66±0.87$^{***,\#\#\#}$	6.80±0.66$^{***,\#\#\#}$	7.22±0.33$^{*,\#\#\#}$
Albumin (g/dl)	4.17±0.29	2.32±0.38***	4.08±0.37$^{\#\#\#}$	3.81±0.19$^{\#\#\#}$	3.95±0.37$^{\#\#\#}$	3.91±0.28$^{\#\#\#}$
Cardiac enzymes						
CK-MB (U/L)	109.60±2.22	217.30±11.95***	111.50±1.78$^{\#\#\#}$	191.40±9.85$^{***,\#\#\#}$	112.20±8.64$^{\#\#\#}$	123.00±6.24$^{*,\#\#\#}$
Troponin (ng/ml)	0.26±0.04	0.76±0.10***	0.26±0.05$^{\#\#\#}$	0.61±0.04$^{***,\#\#\#}$	0.30±0.09$^{\#\#\#}$	0.35±0.03$^{*,\#\#\#}$

Data were represented as mean +/- standard deviation (SD). *: Significance versus Control negative group; $^{\#}$: significance versus HFD. HFD: high fat diet; BFP: Baobab Fruit Pulp; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: Alkaline phosphatase. *: P <0.050; **: P <0.010; ***: P <0.001.

3.4. Serum levels of oxidative stress markers

Administration of HFD led to increase in oxidative stress markers as malonaldehyde. The serum values of MDA were significantly elevated in HFD, HFD + LDBFP and HFD + HDBFP groups versus control (P <0.001 for both) but were significantly decreased in BFP, HFD + LDBFP, HFD + HDBFP and HFD + Statin versus HFD (P <0.001 for all). The serum values of SOD were significantly decreased in HFD, HFD + LDBFP, HFD + HDBFP and HFD + Statin groups compared with control (P <0.001 for all) but were significantly higher in BFP, HFD + LDBFP, HFD + HDBFP and HFD + Statin versus HFD (P <0.001, P <0.010, P <0.001, and P <0.010, respectively). The serum values of GSH were significantly declined in HFD, HFD + LDBFP, HFD + HDBFP groups versus control (P <0.001, P <0.050 and P <0.050) but were significantly raised in BFP, HFD + LDBFP, HFD + HDBFP and HFD + Statin versus HFD (P <0.001 for all) (Table 4).

Table (4): Effects of Baobab Fruit Pulp (BFP) and statin administration on oxidative stress in control and high fat diet (HFD) fed rats.

Groups	Negative control	HFD	BFP	HFD + LDBFP	HFD + HDBFP	HFD + Statin
MDA (nmol/ml)	0.31±0.05	1.34±0.26***	0.27±0.04$^{\#\#\#}$	1.00±0.09$^{***,\#\#\#}$	0.75±0.25$^{***,\#\#\#}$	0.49±0.05$^{\#\#\#}$
SOD (U/ml)	174.70±8.50	129.00±6.53***	181.80±4.80$^{\#\#\#}$	145.20±4.80$^{***,\#\#}$	156.90±17.79$^{***,\#\#\#}$	144.20±6.20$^{***,\#\#}$
GSH (ng/ml)	16.39±0.64	11.12±0.44***	17.69±0.61$^{*,\#\#\#}$	15.15±1.03$^{*,\#\#\#}$	15.69±1.29$^{\#\#\#}$	15.73±0.78$^{\#\#\#}$

Data were represented as mean +/- standard deviation (SD). *: Significance versus Control negative group; $^{\#}$: significance versus HFD. HFD: high fat diet; BFP: Baobab Fruit Pulp, MDA: malonaldehyde; SOD: super oxide dismutase; GSH: glutathione. *: P <0.050; **: P <0.010; ***: P <0.001.

3.5. Histological results

3.5.1. Histological results of liver

Light microscopic examination of liver tissue provided evidence of the effects of HFD on liver histology and effective role of low and high doses of BFP aqueous extract or Statin on HFD effects. Figure (1) showed H&E stained sections of liver tissue of different groups. It showed that compared to normal control hepatic tissue (NC), hepatocytes of HFD group (a. HFD) showed marked deposition of lipid droplets of various sizes that result in swollen cells (dotted arrows) and compression and absence of blood sinusoids in-between. Other hepatocytes showed small dark inactive nuclei (thick black arrow). Some samples (b. HFD) showed inflammatory cells near portal area (star). LDBFP produced partial decreased in lipid deposition in (HFD + LDBFP) and still cells showed degenerated nuclei. While, HDBFP resulted in marked absence of lipid deposition and normal hepatocytes in HFD + HDBFP. Stain in HFD + Statin group gave evident restoration of hepatocytes and sinusoid to its normal control structure and absence of lipid deposition within hepatocytes.

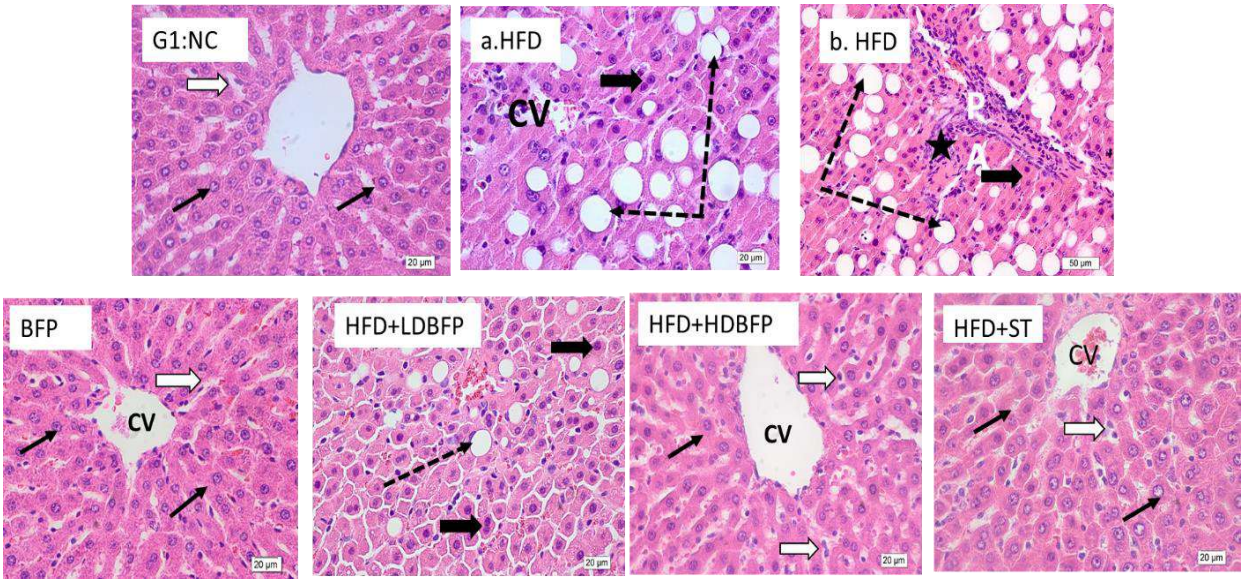


Figure (1): Sections from rat liver stained by H&E to show：
NC group: showed hepatocyte cords with central rounded nuclei (black arrows) and normal homogenous cytoplasm. Notice the thin blood sinusoids between the cell cords (white arrows). a. HFD group: showed swollen hepatocytes that compressing blood sinusoids, most were filled with lipid droplets of various sizes (dotted black arrows). Other cells showed dark inactive nuclei (thick black arrow). b. HFD group: section near portal area (PA) showed decrease in hepatocytes with lipid deposition (dotted arrow). Still many hepatocytes showed dark inactive nuclei (thick black arrows) of lipid deposition (dotted arrow) with an increase in inflammatory cells (star). BFP group: no alteration in normal hepatocytes structure (black arrows) could be observed. Blood sinusoids showed prominent nuclei of phagocytic Kupffer cells (white arrow). HFD + LDBFP group: showed potential decrease in hepatocytes with lipid deposition (dotted arrows). Some cells showed dark degenerated nucleic (black arrow) HFD + HDBFP group: showed complete absence of lipid deposition within hepatocytes which looked similar to control with active rounded nuclei (black arrows). Blood sinusoids looked normal but with prominent nuclei of phagocytic Kupffer cells (white arrow). HFD + Statin group: liver tissue looked similar to normal control group with absence of lipid deposition within hepatocytes. The cells showed rounded active vesicular nuclei (thin black arrows). Blood sinusoids looked also normal (black arrows).

3.5.2. Histological results of heart (cardiac muscle fibers)

Histological examination of left ventricle of rat heart showed that in NC group showed normal continuity of cardiac muscle fibers with their oval active central nuclei. Fibroblasts of connective tissue could be seen between the fibers. Their nuclei are flat and dark. Blood capillaries between fibers were thin and compressed. In HFD group focal damage of cardiac fibers was observed the muscles lost its continuity and their nuclei appeared smaller and dark. Mild dilation capillaries could be seen among affected muscles. No alteration in cardiac tissue could be observed in the group receiving BFP. Moderate protection was observed in the group receiving low dose BFP (HFD + LDBFP) where some degenerated dark stained muscles could be seen. On the other hand marked protection with only few hypertrophied muscles could be seen in the group receiving high dose BFP (HFD + HDBFP) which matches the result of statin medication (Figure 2).

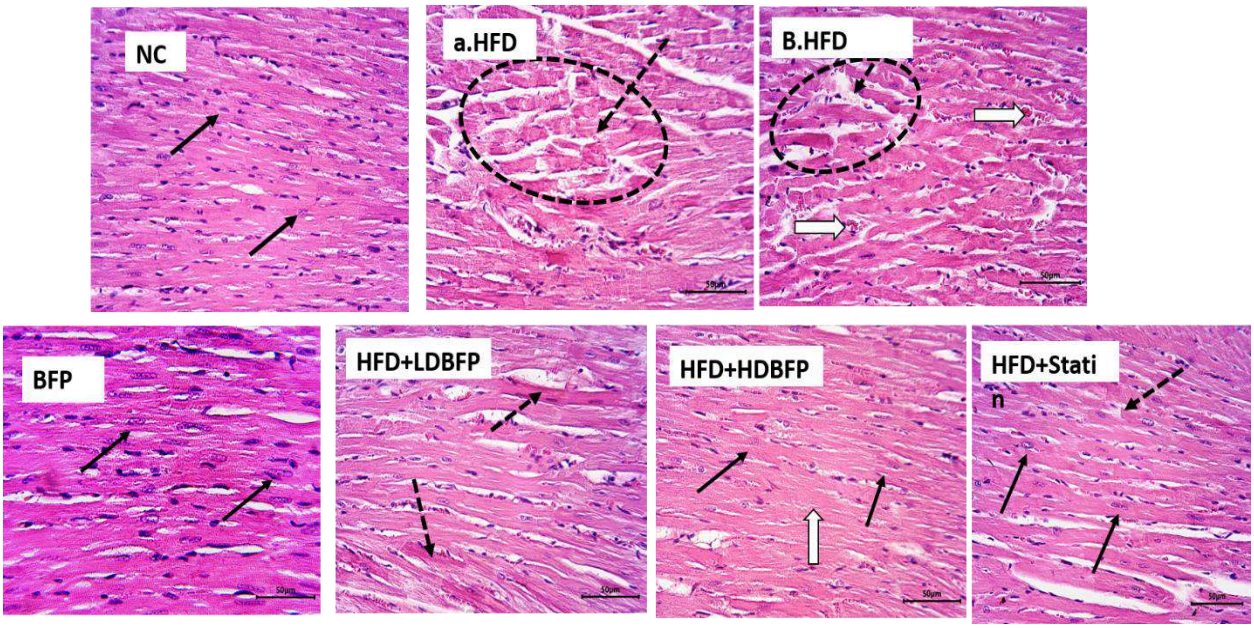
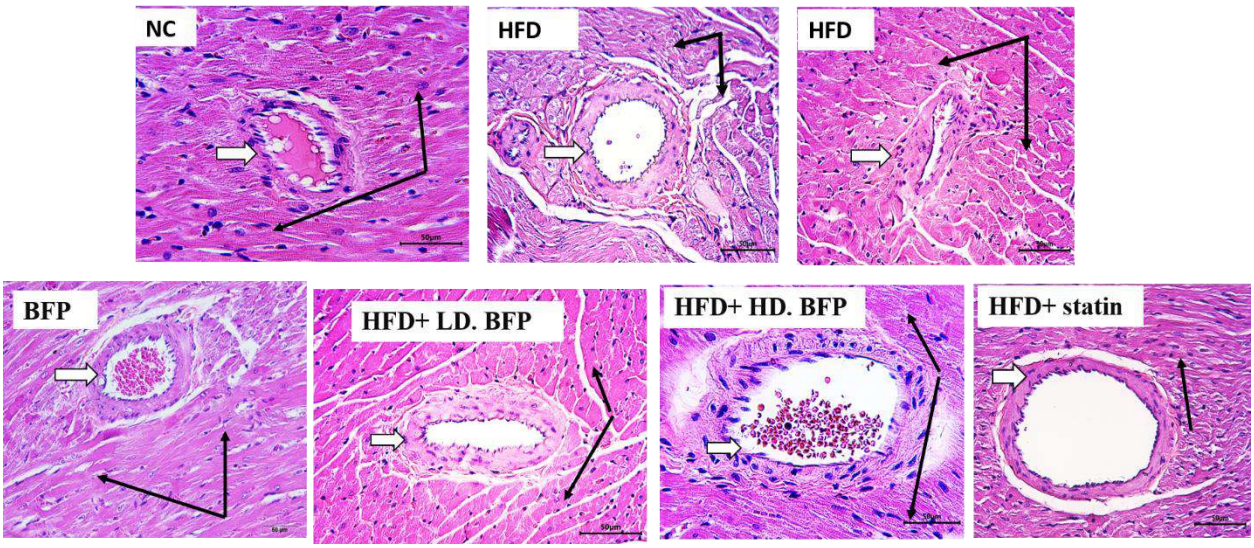


Figure (2): Sections from rat left ventricle stained by H&E showed:
Negative control group: showed that cardiac muscle fibers run longitudinally with central oval nuclei (Black arrows). Notice the intact fibers with fibroblast nuclei running between them.
HFD group (a&b): There is focal destruction and discontinuity of cardiac muscle which looked more stained than NC (dotted circles and arrows)/ blood capillaries were slightly dilated (white arrows).
BFP group: No alteration was observed in cardiac muscle (black arrow) compared with NC.
HFD + LDBFP group: showed moderate improvement of cardiac muscles except of few scattered fibers still showed shrinkage and dark staining (dotted arrows).
HFD + HDBFP group: showed marked protection of cardiac fibers with only few hypertrophied fibers (white arrow).
HFD + Statin group: showing marked protection of muscle fibers which looked similar to control (black arrows (HFD + Statin).

3.5.3. Histological results of coronary arteries

Coronary arteries are the name given to vessels supplying heart wall and cardiac muscles. They are the common vessels affected by HFD. Figure (3) showed that in HFD group the walls of the arteries are thickened and looked unhealthy compared to NC group. No alteration was observed in group receiving BFP alone. Administration of LDBFP did not improve wall thickening of coronaries but the lumen is wide and patent. HDBFP (HFD + HDBFP) showed patent wide lumen and less thick wall compared to HFD group with healthy nearby muscles. Statin medication provided superior effect (Figure 3).



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Negative control group: showed that cardiac muscle fibers run longitudinally with central oval nuclei (Black arrows). Notice the intact fibers with fibroblast nuclei running between them.
HFD group (a&b): There is focal destruction and discontinuity of cardiac muscle which looked more stained than NC (dotted circles and arrows)/ blood capillaries were slightly dilated (white arrows).
BFP group: No alteration was observed in cardiac muscle (black arrow) compared with NC.
HFD + LDBFP group: showed moderate improvement of cardiac muscles except of few scattered fibers still showed shrinkage and dark staining (dotted arrows).
HFD + HDBFP group: showed marked protection of cardiac fibers with only few hypertrophied fibers (white arrow).
HFD + Statin group: showing marked protection of muscle fibers which looked similar to control (black arrows (HFD + Statin).

4. Discussion

Dietary fat intake is the primary factor for obesity development. HFD increase incidence of diabetes mellitus, hypertension and other degenerative disorders. Patients with cardiovascular and cerebrovascular diseases consume diets rich in fat than general population (Harastani et al., 2020). Adverse effects of synthetic hypolipidemic drugs were reported (Wang et al., 2021). Due to that, interests of scientists shifted towards alternative therapeutic approach.

The results of this study showed a significant elevated in rat's final body weight in group that received HFD for 12 weeks versus negative control and HFD rats received Baobab fruit aqueous extract groups for 4 weeks. Weight gain and percentage changes in body weight were significantly higher in HFD group versus negative control and BFP and HFD rats received high dose BFP groups. Percentage changes in final weights versus negative control group were in HFD (14.73%), in BFP (4.75%), HFD + LDBFP (12.37%), HFD + HDBFP (0.10%), and HFD + Statin (10.97%) with most percentage decrease in HFD + HDBFP group. In this respect, Abbas and Sakr (2013) revealed that HFD administration to rats for 15 weeks significantly increased final body weight but insignificant change body weight gain. Althwab et al. (2019) reported that feeding HFD for 9 weeks resulted in elevation in body weight of rats and body weight gain was 93% in HFD group that didn't received Baobab fruit aqueous extract. Meanwhile, there was decline in body weight gain in all rats that received different concentrations of BFP (2.5%, 5.0% and 10.0%). Suliman et al. (Suliman et al., 2020) reported significant weight loss of 4.0%, 8.7 % and 11.0% after oral intake of 200, 400, and 800 mg/kg/day of BFP in HFD groups. Mechanism by which HFD increased rodent's body weight linked to disturbed β-oxidation, liver steatosis, and oxidants formations (Cho et al., 2017).

Results of this research revealed that absolute liver weight was significantly higher in HFD versus negative control and HFD + HDBFP. Meanwhile, absolute heart weight was significantly elevated in HFD versus negative control, BFP, HFD + LDBFP, HFD + HDBFP and HFD + Statin groups. However, relative heart weights were significantly

higher in HFD versus negative control and HFD + Statin groups. Abbas and Sak (2013) reported significant elevation of relative liver and heart weight to body weight ratio in HFD group versus negative control and explained that by fat accumulation in the hepatic and myocardium cells. Histopathological analysis of HFD group's liver revealed fatty alterations in hepatocytes and granularity in sarcoplasm, and increased intracellular lipids in localized cardiac myocytes. Matos et al. (Matos et al., 2005) and Amr and Abeer (2011) claimed raised in liver weight in HFD groups due to their higher fat contents. Normal liver contains some fats (about 5% of total liver weight). Matos et al. (2005) and Amr and Abeer (Amr and Abeer, 2011) reported intracellular lipid accumulation in cardiomyocytes in HFD groups. Suliman et al. (2020) reported raised liver weights were significantly decline from two to one fold by normal resolution and showed more decline to <1 fold after Baobab treatment. Meanwhile, Chess et al. (2008) reported insignificant changes in heart mass between standard chow diet and HFD-treated mice.

In this study, serum levels of blood glucose, TC, TG, LDL-C and vLDL-C were significantly higher; while HDL-C values were significantly lower in HFD versus negative control. These changes in blood glucose and lipid profile ameliorate after administration of Baobab fruit watery extract especially high dose (300 mg/kg/ day) and Statin. These results were similar with previous researches investigating HFD actions on lipid profile (Abbas and Sakr, 2013). Cholic acid present in HFD improves cholesterol absorption due to its emulsifying property and inhibitory effect on hepatic cholesterol 7-α hydroxylase action lead to hypercholestermia (Fan et al., 2015). Bako et al. (Bako et al., 2014) found that methanolic extract of fruit pulp of Baobab not only decreased blood glucose, TG, TC, LDL-C but also enhanced HDL-C. Althwab et al. (Althwab et al., 2019) found an increase in circulating TC, LDL-C, TG values, and a decrease in HDL-C level of animals fed HFD and amelioration of these changes by administration of Baobab fruit pulp extract with concentrations (2.5%, 5.0% and 10.0%) with best results obtained with 10.0%. Suliman et al. (2020) studied protective and therapeutic potential of Baobab fruit extract on high sugar/high fat diet-simulated metabolic syndrome in Wistar male rats. They reported that oral intake of 200, 400, and 800 mg/kg/day BFP led to significant dose dependent decline in TG, TC, and LDL-C with elevation in HDL-C followed one week of therapy. The fruit could enhance LDL-C reuptake by the liver, enhance fatty acid consumption by hepatocytes and elevate plasma TG catabolism by increasing formation of hepatic enzyme carnitine synthase that formed from methionine and lysine in presence of vitamin C (Aledo et al., 2017). HDL-C fosters TC removal from peripheral tissue to liver for catabolism and excretion and competes with LDL-C receptor sites on arterial smooth muscle cells and thus partially suppresses uptake and destruction of LDL-C. Suliman et al. (Suliman et al., 2020) reported that Baobab fruit led to significant elevation in HDL-C that indicate its synergistic action due to vitamin C. Abdelgadir et al. (2019) evaluate hypolipidemic actions of 96% maceration and Soxhlet ethanolic extracts of Baobab fruit pulp on hyperlipidemic Wister Albino male rats that orally intake maceration and Soxhlet extracts once daily for 28 days by two doses (200 and 400 mg/kg/day). Both extracts significantly lowered serum TC, TG, and LDL-C depends more on concentration and treatment continuation, but not affecting HDL-C levels. Flavonoids, terpenes and other phytochemicals in fruit pulp enhance insulin secretion from pancreatic β cells, leading to decline of blood glucose and plasma levels of free fatty acids, consequently suppress formation of TC and TG (Bako et al., 2014). Hypolipidemia of fruit pulp extract may also be due to saponins that had hypolipidemic and anti-obese action, relating to their ability to suppress pancreatic lipase enzyme in addition to their antioxidant action (Hu et al., 2012) and to presence of nicotinic acid that can increase HDL-C, decline lipoprotein Lp (a) and TG (Bako et al., 2014). Statin was commonly used with controlled diet regimen to decrease TG and LDL-C in hypercholesteremic or hyperlipidemic patients. As it reduced cholesterol biosynthesis through inhibiting the 3-hydroxy-3-methylglutarylcoenzyme A reductase A enzymes (HMG-CoAR) (Hyun et al., 2020). Hypercholesterolemia and hypertriglyceridemia are independent risk factors that fastened coronary artery diseases development and progression to atherosclerosis (Beheshti et al., 2020)

The results of this research revealed that HDBFP and Statin attenuated cardiac and hepatic disorders, resulting from dyslipidemia. The serum values of liver enzymes (AST, ALT and ALP) were significantly elevated while, total proteins and albumin were significantly decline in HFD groups versus negative control. These changes in liver function tests were improved by administration of low and high doses of BFP and Statin for 4 weeks, especially with HDBFP and Statin. The elevation of serum liver enzymes levels due to their leakage into serum as from damaged liver cells (Xu et al., 2021). Al-Qarawi et al. (2003) reported that Baobab fruit extract had both protection and restoration actions of liver destruction in rats due to presence of triterpenoids, β-sitosterol, β-amyrin palmitate, terpenoids and ursolic acid in fruit. Also, other bioactivities of Baobab fruit including analgesic, anti-inflammatory and antimicrobial activities could have hepatoprotective activity (Al-Qarawi et al., 2003). Suliman et al. (2020) reported that ALT, AST and ALP, total protein and albumin were significantly normalized by Baobab fruit oral administration (200, 400, and 800 mg/kg/day). Feeding rats on HFD was found to result in marked deposition of lipid

droplets within hepatocytes result in their swelling and comprising blood sinusoids, other cells showed degenerated inactive nuclei and ill-defined outlines indicating necrosis and this could explained release of its contents to nearby circulation and elevation of liver enzymes. Such changes were also observed by other researchers either in human liver biopsy of hypercholesteremic hyperlipidemic patients (Choudhary et al., 2021) or in experimental HFD animal models (Benjamin et al., 2021). Meanwhile, administration of Baobab fruit oral extract in low dose produced partial decreased in lipid deposition; while high dose of Baobab and Statin led to restoration of hepatocytes and sinusoid to its normal control structure. These effects could be linked to its antioxidative activity proved by increased antioxidant markers (SOD and GSH) and decreed MDA levels and keep hepatocytes cellular integrity (Abbas and Sakr, 2013). Suliman et al. (2020) reported that examination of hepatic tissue in high sugar/high fat diet-simulated metabolic syndrome showed a dose dependent partial decreased in hepatic damage severity and elimination of inflammatory infiltration especially in simultaneously treated group administered. Statin medication in this study markedly decrease lipid deposition within hepatocytes which explained biochemical results reported in this paper (Hyun et al., 2020).

The result of this research revealed that serum levels of cardiac enzymes (CK-MB and Troponin) were significantly elevated in HFD groups and these enzymes were decline after administration of low and high doses of BFP and Statin but still high than negative control. Histological examination of left ventricle of rat heart showed that in HFD group focal damage of myocardium, loss of muscles continuity, mild capillaries dilation was among affected myocardium with thickened of coronary arteries walls. Administration of LDBFP led to moderate protection of myocardium, didn't improve coronaries wall thickening but lumen is wide and patent. On the other hand in groups receiving high dose Baobab and Statin marked protection with only few hypertrophied myocardium was found and coronary arteries showed patent wide lumen and less thick wall with healthy nearby muscles. Statin medication provided superior effect on coronary. Abbas and Sakr (2013) reported occurrence of oxidative damage in heart of rats on HFD for 15 weeks that was confirmed by changes in oxidative stress markers in cardiac homogenate (significant elevation in Thiobarbituric acid reactive substances (TBARS) and decrease in antioxidants) as well as by histopathological examination that showed myocardial cell destruction. Suliman et al. (2020) reported that examination of cardiac tissue revealed a dose dependent reversal to almost normal morphology in heart after administration of different concentrations of Baobab. The antioxidative, and antinitrosive activities of Baobab could be via L arginine/ Nitric oxide pathway (Tripathi and Pandey, 2013), lysine and proline that mediate endothelial repair in vitamin C presence of (Barteková et al., 2021). Statins reduce free radicals formation in arterial wall (Wagner et al., 2000) and myocardium during ischemia–reperfusion injury by suppressing oxygen-derived free radicals formed during reperfusion (Maack et al., 2003).

Administration of HFD led to increase in oxidative stress markers. The results of this research revealed that serum levels of MDA were significantly elevated but SOD and GSH were significantly decline in HFD treated groups versus negative control. These effects were partially improved after oral administration of Baobab fruit aqueous extract especially with high dose administration (300 mg/kg/day). The Baobab fruit contains α/β-amyrin, β-sitosterol, vitamin C, and uroslic acids (Kabore et al., 2011). Vitamin C and these three pentacyclic triterpenoids mediate antioxidant, anti-inflammatory, and antidiabetic actions by improving insulin sensitivity, antilipidemic, lipoprotein expression, and liver protection (Santos et al., 2012). As a rich methionine source –a sulphur containing amino-acid–it could suppress lipid peroxidation as a strong antioxidant (Aledo et al., 2017). Althwab et al. (2019) reported that lipid peroxidation is the main cause of ill effects accompanying feeding HFD. There was a significant elevation in MDA levels and a significant reduction in GSH and serum total antioxidant capacity. The reduction in GSH levels indicate high consumption of GSH in neutralization of free radicals generated following HFD consumption. These changes were accompanied by reduced antioxidant enzymes activities (SOD, catalase and glutathione peroxidase) that act as free radical scavenging system. The observed elevation in cardiac and hepatic homogenate TBARS in rats fed with HFD reported in previous researches investigating HFD actions on cardiac and hepatic TBARS (Kucukgergin et al., 2010, Olorunnisola et al., 2012, Abbas and Sakr, 2013). This raised in cardiac TBARS could be due to elevation in reactive oxygen species (ROS) production and decline in antioxidants. Hypercholesterolemia elevates ROS values via different mechanisms. A high-cholesterol diet elevates cardiac superoxide anion generation and NADPH oxidase expression (Csont et al., 2007) that utilizes antioxidant capacity of heart and liver (Olorunnisola et al., 2012). Althwab et al. (2019) reported that increasing Baobab concentration would increase antioxidative activity. The phenolic groups in polyphenols accept an electron to form relatively stable phenoxyl radicals, thereby disrupting chain oxidation reactions in cellular components. Polyphenols are potent inhibitors of LDL-C oxidation and this oxidation type is considered to be mechanism in atherosclerosis occurrence. Vitamin C antioxidant activity develops

in two ways: (a) directly, by scavenging oxygen free radicals and (b) indirectly, by regenerating other antioxidant systems (Abbasi et al., 2018)

5. Conclusions

Baobab fruit pulp especially high dose and Statin showed antilipidemic activities, hepatic and cardiac tissue protection which was reflected by improvement of lipid profile, liver function tests and cardiac enzymes activities. It's important to connect the diverse/ wide spectrum of pharmacological, protective, and therapeutic properties of Baobab fruit pulp, which are mediated synergistically by multi-active chemicals via multi-biological targets. Potent antioxidant/anti-inflammatory actions might be the chief mechanism that drives therapeutic actions. Baobab fruit could be proposed for HFD management and other complex diseases linked to oxidative stress. Additional researches are highly recommended and clinical trials are essential. Hence, Baobab fruit pulp could be used as functional food for natural therapy and prevention hyperlipidemia associated health disorders.

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References

Abbas, A. M. and Sakr, H. F. (2013) Simvastatin and vitamin E effects on cardiac and hepatic oxidative stress in rats fed on high fat diet. *Journal of physiology and biochemistry* 69**:** 737-750.

Abbasi, I. H. R.; Abbasi, F.; Wang, L.; Abd El Hack, M. E.; Swelum, A. A.; Hao, R.; Yao, J. and Cao, Y. (2018) Folate promotes S-adenosyl methionine reactions and the microbial methylation cycle and boosts ruminants production and reproduction. *Amb Express* 8**:** 1-10.

Abdelgadir, N. A.; Salih, A. M. and Ayoub, S. M. (2019) Hypolipidemic effect of ethanolic extracts of Adansonia digitata fruit pulp on hyperlipidemic albino rats. *The Journal of Phytopharmacology* 8**:** 279-281.

Abo-Elmaaty, A. M.; Behairy, A.; El-Naseery, N. I. and Abdel-Daim, M. M. (2020) The protective efficacy of vitamin E and cod liver oil against cisplatin-induced acute kidney injury in rats. *Environmental Science and Pollution Research* 27**:** 44412-44426.

Al-Qarawi, A.; Al-Damegh, M. and El-Mougy, S. (2003) Hepatoprotective influence of Adansonia digitata pulp. *Journal of herbs, spices & medicinal plants* 10**:** 1-6.

Aledo, J. C.; Cantón, F. R. and Veredas, F. J. (2017) A machine learning approach for predicting methionine oxidation sites. *Bmc Bioinformatics* 18**:** 1-14.

Alharbi, N. G. and Sindi, H. A. (2020) Effect of Doum (Hyphaene Thebaica) Fruit Water Extract on hypercholesteremic Rats. *Life Science Journal* 17: 16-27.

Alkhaldy, A. A.; Taha, D. S.; Alsahafi, S. E.; Naaman, R. K. and Alkhalaf, M. M. (2020) Response of the public and restaurant owners to the mandatory menu energy-labelling implementation in restaurants in Saudi Arabia. *Public Health Nutrition* 23: 3435-3447.

Althwab, S. A.; Alsattame, S. M.; Al-Mundarij, T. I.; Hamad, E. M. and Mousa, H. M. (2019) Protective effect of baobab fruit pulp (Adansonia digitata L.) from oxidative stress induced in rats by high-fat diet. *Life Sci J* 16**:** 63-71.

Amr, A. R. and Abeer, E. (2011) Hypolipideimic and hypocholestermic effect of pine nuts in rats fed high fat, cholesterol-diet. *World Applied Sciences Journal* 15**:** 1667-1677.

Bako, H.; Mohammad, J.; Wazir, P.; Bulus, T.; Gwarzo, M. Y. and Zubairu, M. (2014) Lipid profile of alloxan-induced diabetic wistar rats treated with methanolic extract of adansonia digitata fruit pulp. *Science World Journal* 9**:** 19-24.

Barteková, M.; Adameová, A.; Görbe, A.; Ferenczyová, K.; Pecháňová, O.; Lazou, A.; Dhalla, N. S.; Ferdinandy, P. and Giricz, Z. (2021) Natural and synthetic antioxidants targeting cardiac oxidative stress and redox signaling in cardiometabolic diseases. *Free Radical Biology and Medicine* 169**:** 446-477.

Beheshti, S. O.; Madsen, C. M.; Varbo, A. and Nordestgaard, B. G. (2020) Worldwide prevalence of familial hypercholesterolemia: meta-analyses of 11 million subjects. *Journal of the American College of Cardiology* 75**:** 2553-2566.

Benjamin, K. B.; Alfonso, P. G. I.; De Dios, M. B. C. R.; Agapito, J. D. and Cena, R. B. (2021) Effects of Peperomia pellucida (L.) methanolic extract on total cholesterol levels and liver histology of diet-induced hypercholesterolemic rats. *Philippine Journal of Health Research and Development* 25**:** 49-59.

Chess, D. J.; Lei, B.; Hoit, B. D.; Azimzadeh, A. M. and Stanley, W. C. (2008) Effects of a high saturated fat diet on cardiac hypertrophy and dysfunction in response to pressure overload. *Journal of cardiac failure* 14**:** 82-88.

Cho, Y.-E.; Im, E.-J.; Moon, P.-G.; Mezey, E.; Song, B.-J. and Baek, M.-C. (2017) Increased liver-specific proteins in circulating extracellular vesicles as potential biomarkers for drug-and alcohol-induced liver injury. *PloS one* 12**:** e0172463.

Choudhary, N. S.; Saraf, N.; Saigal, S.; Duseja, A.; Gautam, D.; Rastogi, A.; Bhangui, P.; Thiagrajan, S. and Soin, A. S. (2021) Nonalcoholic Fatty Liver in Lean Individuals: Clinicobiochemical Correlates of Histopathology in 157 Liver Biopsies from Healthy Liver Donors. *Journal of Clinical and Experimental Hepatology*. https://doi.org/10.1016/j.jceh.2021.01.004

Csont, T.; Bereczki, E.; Bencsik, P.; Fodor, G.; Görbe, A.; Zvara, Á.; Csonka, C.; Puskás, L. G.; Sántha, M. and Ferdinandy, P. (2007) Hypercholesterolemia increases myocardial oxidative and nitrosative stress thereby leading to cardiac dysfunction in apoB-100 transgenic mice. *Cardiovascular research* 76**:** 100-109.

Elamin, O.; Abdel Atti, K. & Dalia, A. (2019). Effect of baobab (Adansonia digitata) pulp powder on serum lipid profile of rats fed high lipid diets. *Pak J Nutr,* 18**,** 1053-1057**.**

Fan, J.; Chen, Y.; Yan, H.; Niimi, M.; Wang, Y. and Liang, J. (2018) Principles and applications of rabbit models for atherosclerosis research. *Journal of atherosclerosis and thrombosis* 25**:** 213-220.

Fan, J.; Kitajima, S.; Watanabe, T.; Xu, J.; Zhang, J.; Liu, E. and Chen, Y. E. (2015) Rabbit models for the study of human atherosclerosis: from pathophysiological mechanisms to translational medicine. *Pharmacology & therapeutics* 146**:** 104-119.

Groner, J.; Göpferich, A. and Breunig, M. (2021) Atherosclerosis: Conventional intake of cardiovascular drugs versus delivery using nanotechnology–A new chance for causative therapy? *Journal of Controlled Release* 333**:** 536-559.

Gwarzo, M. Y. (2013) Hypoglycemic Activity of Methanolic Fruit Pulp Extract of" Adansonia digitata" on Blood Glucose Levels of Alloxan Induced Diabetic Rats. *International Journal of Animal and Veterinary Advances* 5**:** 108-113.

Hanafy, A.; Aldawsari, H. M.; Badr, J. M.; Ibrahim, A. K. and Abdel-Hady, S. E.-S. (2016) Evaluation of hepatoprotective activity of Adansonia digitata extract on acetaminophen-induced hepatotoxicity in rats. *Evidence-Based complementary and Alternative medicine* 2016. https://doi.org/10.1155/2016/4579149

Harastani, R.; James, L. J.; Walton, J. and Woolley, E. (2020) Tackling obesity: A knowledge-base to enable industrial food reformulation. *Innovative Food Science & Emerging Technologies* 64**:** 102433.

Hu, X.-Q.; Xu, J.; Xue, Y.; Li, Z.-J.; Wang, J.-F.; Wang, J.-H.; Xue, C.-H. and Wang, Y.-M. (2012) Effects of bioactive components of sea cucumber on the serum, liver lipid profile and lipid absorption. *Bioscience, biotechnology, and biochemistry* 76**:** 2214-2218.

Hyun, M. H.; Jang, J. W.; Choi, B. G.; Na, J. O.; Choi, C. U.; Kim, J. W.; Kim, E. J.; Rha, S. W.; Park, C. G. and Lee, E. (2020) Risk of insulin resistance with statin therapy in individuals without dyslipidemia: A propensity-matched analysis in a registry population. *Clinical and Experimental Pharmacology and Physiology* 47**:** 947-954.

Ismail, B. B.; Yusuf, H. L.; Pu, Y.; Zhao, H.; Guo, M. and Liu, D. (2020) Ultrasound-assisted adsorption/desorption for the enrichment and purification of flavonoids from baobab (Adansonia digitata) fruit pulp. *Ultrasonics sonochemistry* 65**:** 104980.

Kabore, D.; Sawadogo-Lingani, H.; Diawara, B.; Compaoré, C. S.; Dicko, M. H. and Jakobsen, M. (2011) A review of baobab (Adansonia digitata) products: effect of processing techniques, medicinal properties and uses. *African Journal of Food Science* 5**:** 833-844.

Kalsoom, M. and Jafari, S. (2011) Effect of punica granatum flowers extract on hypercholesterolemic and alloxan induced diabetic rats. *Glob J Biotecnol Biochem* 6**:** 83-86.

Küçükgergin, C.; Aydın, A. F.; Özdemirler-Erata, G.; Mehmetçik, G.; Koçak-Toker, N. and Uysal, M. (2010) Effect of artichoke leaf extract on hepatic and cardiac oxidative stress in rats fed on high cholesterol diet. *Biological trace element research* 135**:** 264-274.

Lajis, A. F. B. and Ismail, N. H. (2020) Therapeutic application of herbal essential oil and its bioactive compounds as complementary and alternative medicine in cardiovascular-associated diseases. *Insights Depress Anxiety* 4: 025-036.

Liu, P.; Zhao, H. and Luo, Y. (2017) Anti-aging implications of Astragalus membranaceus (Huangqi): a well-known Chinese tonic. *Aging and disease* 8**:** 868.

Maack, C.; Kartes, T.; Kilter, H.; SchäFers, H.-J.; Nickenig, G.; BöHm, M. and Laufs, U. (2003) Oxygen free radical release in human failing myocardium is associated with increased activity of rac1-GTPase and represents a target for statin treatment. *Circulation* 108**:** 1567-1574.

Matos, S. L.; Paula, H. D.; Pedrosa, M. L.; Santos, R. C. D.; Oliveira, E. L. D.; Chianca Júnior, D. A. and Silva, M. E. (2005) Dietary models for inducing hypercholesterolemia in rats. *Brazilian archives of biology and technology* 48**:** 203-209.

Olorunnisola, O. S.; Bradley, G. and Afolayan, A. J. (2012) Protective effect of T. violacea rhizome extract against hypercholesterolemia-induced oxidative stress in Wistar rats. *Molecules* 17**:** 6033-6045.

Santos, F. A.; Frota, J. T.; Arruda, B. R.; De Melo, T. S.; De Castro Brito, G. A.; Chaves, M. H. and Rao, V. S. (2012) Antihyperglycemic and hypolipidemic effects of α, β-amyrin, a triterpenoid mixture from Protium heptaphyllum in mice. *Lipids in health and disease* 11**:** 1-8.

Sidi-Aliyu, B. (2006). Common Ethnomedicinal Plants of the Semiarid Regions of West Africa: Their Description and Phytochemicals, Triumph publishing company.

Sikarwar, M. S. and Patil, M. (2012) Antihyperlipidemic activity of Salacia chinensis root extracts in triton-induced and atherogenic diet-induced hyperlipidemic rats. *Indian journal of pharmacology* 44**:** 88.

Suliman, H. M.; Osman, B.; Abdoon, I. H.; Saad, A. M. and Khalid, H. (2020) Ameliorative activity of Adansonia digitata fruit on high sugar/high fat diet-simulated Metabolic Syndrome model in male Wistar rats. *Biomedicine & Pharmacotherapy* 125**:** 109968.

Tripathi, P. and Pandey, S. (2013) L-arginine attenuates oxidative stress condition during cardiomyopathy. *Indian Journal of Biochemistry & Biophysics***:** 99-104.

Wagner, A. H.; KöHler, T.; RüCkschloss, U.; Just, I. and Hecker, M. (2000) Improvement of nitric oxide–dependent vasodilatation by HMG-CoA reductase inhibitors through attenuation of endothelial superoxide anion formation. *Arteriosclerosis, thrombosis, and vascular biology* 20**:** 61-69.

Wang, X.-Y.; Song, X.-L.; Zhang, Y.; Luo, G.; Tai, H.-C.; Lin, Z.-H.; Zhu, P.-L.; Sun, N.; Chu, Z.-S. and Yu, Z.-L. (2021) Evaluation of Beneficial and Adverse Effects of a Diet Supplemented with Schisandrae Fructus Seed Ethanol Extract on Lipid and Glucose Metabolism in Normal and Hypercholesterolemic/Hyperglycemic Mice. *Evidence-Based Complementary and Alternative Medicine* 2021. https://doi.org/10.1155/2021/8858962

Xu, L.; Huang, Q.; Tan, X.; Zhao, Q.; Wu, J.; Liao, H.; Ai, W.; Liu, Y.; Lai, Z. and Fu, L. (2021) Patchouli alcohol ameliorates acute liver injury via inhibiting oxidative stress and gut-origin LPS leakage in rats. *International Immunopharmacology* 98**:** 107897.

Zheng, D.; Liang, Q.; Zeng, F.; Mai, Z.; Cai, A.; Qiu, R.; Xu, R.; Li, D. and Mai, W. (2015) Atorvastatin protects endothelium by decreasing asymmetric dimethylarginine in dyslipidemia rats. *Lipids in health and disease* 14**:** 1-6.