Anti-hyperlipidemic and Anti-hypercholesterolemic effect of aqueous extract of guava (*Pisidum guajava Linn*.) leaves on rats

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Abstract:

The aim of the present study is to investigate the ameliorative effect of aqueous guava leaf extract (AGLE) with different doses (200, 350, 500 & 650 mg/kg b.wt.) taken ***p.o*** in rats fed high fat high cholesterol (HFC) diet for 8 weeks. The four doses of AGLE cause a significant decrease in food intake, final body weight, gain in body weight, serum TAG, VLDL-C, risk ratio as well as liver TAG and malondialdehyde level. Also doses of AGLE (350,500 and 650 mg/kg b.wt.) cause a significant decrease in relative liver weight, serum AST and LDL-C but a significant increase in HDL-C and leptin hormone. While doses (500 & 650 mg/kg b.wt.) cause a significant decrease in serum TC. The highest dose causes a significant decrease in serum ALT and adiponectin hormone. Total liver cholesterol was decreased significantly in groups given (200 & 350 mg/kg b.wt.) but no significant decrease in doses (500 & 650 mg/kg b.wt.). As well as ghrelin hormone does not show significant decrease in the four treated groups fed HFC diet and given AGLE compared to rats fed HFC diet only.

Keywords: guava leaves; HFC diet; rats; adiponectin; leptin; ghrelin.

1. Introduction:

Hyperlipidemia relates to increased oxidative stress causing significant production of oxygen free radicals, which may lead to oxidative modifications in low-density lipoproteins, which present a significant function in the initiation and progression of atherosclerosis and associated cardiovascular diseases ***(Mishra et al., 2011).*** Dyslipidemia indicates disorders of lipoprotein metabolism, including lipoprotein overproduction or deficiency ***(Ahmed et al., 1998).***

Illnesses that may elevate cholesterol levels include polycystic ovary syndrome and kidney disease. The higher levels of female hormones like estrogen, have been noted to increase or change cholesterol levels. As well as, drugs like diuretics, beta-blockers and medicines used to treat depression have also been reported to raise cholesterol levels. Other modifying factors in the development and progression of hyperlipidemia are age and gender. It has been shown that cholesterol levels rise as the person gets older ***(Lipman et al., 2000).***

Low HDL cholesterol levels are typically accompanied by an increase in blood triacylglycerol levels. High lipid levels can speed up a process called atherosclerosis, or hardening of the arteries. Plaque is made of lipids and other materials circulating in the blood. As more plaque builds up, arteries can narrow and stiffen. Eventually, enough plaque may build up to reduce blood flow through arteries ***(Harikumar et al., 2013).***

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Leaves of the guava tree have been used as food and medicine with anti-inflammatory, antihypertensive and anti-diabetic properties. It was reported that oral administration of guava leaf extract had anti-obesity effects, reducing body weight gain, adipogenesis and improving insulin resistance ***(Yoshitomi et al., 2012b).***With no exhibition of acute or chronic toxicity ***(Deguchi and Miyazaki, 2010).***

On the other hand the main constituents of guava leaves are phenolic compounds, isoflavonoids, gallic acid, catechin, epicatechin, rutin, naringenin and kaempferol ***(Barbalho et al., 2012).***

Aqueous extracts from guava leaves have antioxidant or radical-scavenging activity. Most of the activity is associated with polyphenols, however, the guava extract also contain antioxidants such as ascorbic acid and carotenoids ***(Yamashiro et al., 2003).***

Guava leaf extract has analgesic, anti-inflammatory, antimicrobial, hepatoprotective and antioxidant activities. These effects are probably due to the presence of phenolic compounds ***(Ryu et al., 2011).***

Adiponectin, is the most abundantly secreted adipokine ***(Scherer et al., 1995)***. Adiponectin action on glucose metabolism may be mediated by enhanced 5´-AMP-activated protein kinase (AMPK) that in turn increases fatty acid oxidation and glucose uptake ***(Yamauchi et al., 2002)***.Also ***Tomas et al.(2002)*** showed that the adiponectin globular domain could enhance muscle fat oxidation and glucose transport via AMPK activation and acetyl-CoA carboxylase inhibition .

Leptin's biological action is mediated by the long form of the leptin receptor (LEPRb), which is expressed in many brain areas including the hypothalamus, the main leptin target. Arcuate nucleus (ARC) contains at least two principal populations of neurons that have opposing actions on energy balance, the orexigenic (appetite-stimulating) agouti-related protein (AgRP) neurons and the anorexigenic (appetite suppressing) proopiomelanocortin (POMC) neuron. Both neuronal populations contain LEPRb-expressing cells. Leptin exerts its anorexigenic effects by inhibiting AgRP neurons while activating POMC neurons (***Zhou and Rui, 2013).***

Ghrelin has various physiological functions other than growth hormone stimulation, for example, the stimulation of appetite (hyperphagia). Ghrelin is the only molecule to date that has been shown to exert a hyperphagic effect when administrated peripherally ***(Sugiishi et al., 2013).***

2. Materials and Methods:

2.1. Materials:

- Guava leaves *(Pisidium guajava linn.)* were purchased from the Ministry of Agriculture, Cairo,Egypt.
- Cholesterol and bile salts were purchased from Sigma Chemical Company, (St. Louis, MO, USA).

2.1.1. Preparation of aqueous extract of guava leaves:

The leaves were air-dried for 2 weeks and then ground into fine powder using an electric dry mill (Moulinex). A total of 200g of the ground powder was soaked in 1 L of distilled water for 48 hours at room temperature. The mixture was filtered into 500 ml conical flask with gauze. The filtrate was dried at a temperature of 50-55 ºC by using rotary evaporator to produce a gel-like extract, which weighed 20.5 g and stored in air-tight container in refrigerator until used. (***Uboh et al., 2010).***

2.1.2. Biological experiment:

2.1.3.1. Diet:

The balanced diet was prepared as described by ***Revees et al. (1993)*** and HFC diet was prepared as described by ***Lin-Lee et al. (1981).***

2.1.3.2. Animals:

Adult male Wistar albino rats weighing 100 g ± 5 g were used. These animals were obtained from Helwan Farm, Vaccine and Immunity Organization, Helwan, Egypt.

2.1.3.3. Experimental design:

In this study seventy two rats were subjected to experimentation for eight weeks. Rats were randomly divided into six groups with 12 rats in each with similar average weight. Rats were housed individually with constant environment in controlled stainless steel cages, temperature(25 °C± 5°C), humidity (50% ± 10%), and light cycle were held constant 12/12 hr. Food and water were provided *ad-libitum*. The animals were weighed weekly and accordingly the doses of aqueous guava leaves extract were adjusted. The oral doses were given using intragastric intubation per ose ***(p.o).***

The experimental groups illustrated as follows:

Group (1): Rats fed on balanced diet and given ***p.o*** distilled water and served as negative controls.

Group (2): Rats fed HFC diet and given ***p.o*** distilled water and served as positive controls.

Group (3): Rats fed HFC diet and given aqueous extract of guava leaves (200 mg / kg b.wt.) (3 times / week).

Group (4): Rats HFC diet and given aqueous extract of guava leaves (350 mg/ kg b.wt.) (3 times / week).

Group (5): Rats fed HFC diet and given aqueous extract of guava leaves (500 mg/ kg b.wt.) (3 times/ week) according to ***Roy and Das, (2011).***

Group (6): Rats fed HFC and given aqueous extract of guava leaves (650 mg/ kg b.wt.) (3 times/ week).

2.2. Methods:

2.2.1. Blood samples collection:

At the end of the experimental period, the animals were anesthetized with diethylether after 12 hours fasting, the whole blood samples were taken from the hepatic portal vein. About 4 ml was collected in tubes for separating serum by allowing blood samples left for 15 minutes at 37°C then serum was separated by centrifugation at 4000 rpm for 15 minutes. The serum was removed to be frozen in plastic vials at -20 °C for subsequent biochemical analysis.

2.2.2. Liver samples collection:

Liver was removed immediately and washed twice with saline solution (0.9% NaCl) then blotted between filter paper to dry. Liver tissue was stored at -20 °C for determination of total cholesterol, triacylglycerols, total antioxidant capacity and malondialdehyde level.

2.3. Biological assessment:

Determining of body weight, relative liver weight and food intake.

2.4. Biochemical analysis:

- Serum ALT and AST activities were estimated using kinetic method kits according to ***Bergmeyer et al. (1976)*** and using OLYMPUS analyzer (AU680).
- Serum total cholesterol, triacylglycerol and high density lipoprotein cholesterol (HDL-C) were estimated using enzymatic color test according to ***Allain et al. (1974), Shephard and Whiting, (1990) and Riesen, (1998)*** respectively using OLYMPUS analyzer (AU680).While low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C) and risk ratio were calculated according to ***Friedewald et al. (1972)*** and ***Wilson et al. (1980)*** respectively.
- Serum adiponectin, ghrelin, and leptin were determined using the enzyme linked immunosorbent assay (ELISA) method according to ***Zoccali et al. (2003), Volland et al. (1999)*** and ***Sainsburry et al. (1996)*** respectively.
- Total cholesterol, triacylglycerol, malondialdehyde and total antioxidant capacity were determined in liver according to ***Richmond, (1973), Fassati and Prencipe, (1982), Ohkawa et al. (1979) and koraccevic et al. (2001)*** respectively.

2.5. Statistical analysis:

The data were presented as mean ± SE. One-way analysis of variance (ANOVA) followed by post hoc-least significant difference analysis (LSD) was performed using the statistical package for social science (SPSS) version 16 to compare all the treated groups. The value of $p \leq 0.05$ was considered statistically significant and $p \leq 0.001$ was considered statistically very highly significant (***Daniel, 2005).***

3. Results and Discussion:

3.1 Results:

The results showed no significant difference in initial body weight between the six studied groups. Also table (1) showed a significant decrease in food intake ($p \leq 0.001$) in group (2) fed high fat high cholesterol diet (HFC) compared to group (1) fed basal diet. All groups treated per orally (*p.o)* with aqueous guava leaf extract (AGLE), with the four different doses, showed significant decrease in food intake ($p \leq 0.001$) compared to group (2). Also a significant decrease in food intake ($p \leq 0.05$) was found in group (5) compared to group (3) and group (4).

The relative weight was higher in group (2) than in group (1) ($p \leq 0.001$) .There was a significant decrease in relative liver weight ($p \leq 0.05$) in groups (4, 5 & 6) compared to group (2).

On the other hand there was a significant decrease in final body weight and gain in body weight ($p \leq 0.05$) in group (3) and in groups (4, 5 &6) $p \leq 0.001$ compared group (2).

Final body weight was decreased in groups (4 & 5) ($p \leq 0.05$) compared to group (3), also a significant decrease in final body weight ($p \leq 0.001$) and gain in body weight ($p \leq 0.05$) was found in group (6) compared to group (3).

Table (1): Initial body weight, final body weight, gain in body weight (g), food intake (g/day) and relative liver weight in different experimental groups.

Parameter / Rat groups	Initial body weight (g)	Final body weight (g)	Gain in body weight (g)	Food intake (g/day)	Relative liver weight
Group 1	97.09±4.90	229.6±3.09	132.6±7.55	17.31±0.08	2.63±0.13
Group 2	92.18±3.67	224.6±3.30	132.5±5.74	1 15.64±0.12	1 4.43±0.16
Group 3	98.00±4.45	a,b 208.8±3.47	a,b 110.8±6.52	1,2 13.23±0.15	1 4.07±0.17
Group 4	99.00±4.70	1,2,c 190.8±6.50	1,2 91.82±8.93	1,2 12.77±0.39	1,b 3.78±0.10
Group 5	95.00±4.02	1,2,c 191.6±6.76	1,2 96.64±5.78	1,2,c,d 11.95±0.46	1,b 3.78±0.12
Group 6	92.45±4.55	1,2,3 180.1±5.57	1,2,c 87.64±6.73	1,2 12.57±0.26	1,b 3.79±0.17

Group 1: basal diet (-ve control) Group 2 : HFC diet (+ve control) Group 3 : HFC diet +200 mg/kg b.wt. (AGLE) Group 4: HFC diet +350 mg/kg b.wt. (AGLE) Group 5: HFC diet +500 mg/kg b.wt. (AGLE) Group 6: HFC diet +650 mg/kg b.wt. (AGLE). Significant difference ($p \leq 0.05$): compared to: (a): to group (1), (b): to group (2), (c) to group (3), (d) to group (4), (e) to group (5), (f) to group (6). Significant difference ($p \leq 0.001$): compared to: (1): to group (1), (2): to group (2), (3) to group (3), (4) to group (4), (5) to group (5), (6) to group (6).

HFC: High fat high cholesterol diet. AGLE: Aqueous guava leaf extract.

Tables (2&3) illustrated a significant increase in serum total cholesterol, LDL-C and risk ratio but a significant decrease in serum HDL-C in rats fed HFC diet compared to negative control group.

The results showed a significant decrease ($p \leq 0.05$) in serum total cholesterol in group (5) compared to group (2) and group (3). While group (6) in which rats given the highest dose of the extract showed a significant decrease ($p \leq 0.001$) in total cholesterol compared to group (2), group (3), and group (4) and ($p \leq 0.05$) compared to group (5). The mean value in group (6) returned to normal levels as in group (1) (negative control).

On the other hand a significant decrease ($p \leq 0.001$) in triacylglycerol and VLDL-C in groups (4, 5 & 6) but ($p \leq 0.05$) in group (3) compared to group (2). While a significant decrease ($p \leq 0.05$) in groups (4 & 6) compared to group (3).

There was a significant increase in ($p \leq 0.05$) HDL-C in groups (4, 5 & 6) given different doses of AGLE (350, 500 & 650 mg/kg b.wt. respectively) compared to rats fed HFC. At the same time LDL-C significantly decreased ($p \leq 0.05$) in both groups (4&5) compared to group (2) and group (3) respectively. But in group (6) the highest dose of AGLE (650mg/kg b.wt.) showed a significant decrease ($p \leq 0.001$) in LDL-C compared to groups (2, 3, 4 & 5) respectively.

Risk ratio was significantly decreased in group (3), ($p \leq 0.05$) and also in groups (4, 5 & 6), ($p \leq 0.001$) compared to group (2). Also, group (5) showed a significant decrease in risk ratio ($p \leq 0.05$) compared to group (3), while the decrease in group (6) was significantly compared to group (3 &4), ($p \leq 0.001$), and (5), ($p \leq 0.05$).

Table (2): Serum total cholesterol, triacylglycerol, and HDL-C (mg/dl) in different experimental groups.

Parameters / Rat groups	Cholesterol (mg/dl)	Triacylglycerol (mg/dl)	HDL-C (mg/dl)
Group 1	101.0± 4.47	39.64± 0.96	67.82±3.02
Group 2	1 170.8± 10.22	41.82± 2.25	1 31.18±1.75
Group 3	1 171.2± 10.06	b 36.73± 1.27	1 38.00±0.43
Group 4	1 148.2 ±10.22	1,2,c 31.91± 2.31	1,b 41.36±4.56
Group 5	a,b,c 140.2± 11.87	a,2 33.27± 0.79	1,b 41.18± 3.81
Group 6	2,3,4,e 102.2± 6.98	1,2,c 30.45± 1.00	1,b 47.27± 4.09

Group 1: basal diet (-ve control) Group 2 : HFC diet (+ve control) Group 3 : HFC diet +200 mg/kg b.wt. (AGLE) Group 4: HFC diet +350 mg/kg b.wt. (AGLE) Group 5: HFC diet +500 mg/kg b.wt. (AGLE) Group 6 : HFC diet +650 mg/kg b.wt. (AGLE). Significant difference ($p \leq 0.05$): compared to: (a): to group (1), (b): to group (2) , (c) to group (3), (d) to group (4), (e) to group (5), (f) to group (6).
Significant difference ($p \leq 0.001$): compared to: (1): to group (1), (2): to group (2) , (3) to group (3), (4) to group (4), (5) to group (5), (6) to group (6).
HFC: High fat high cholesterol diet. AGLE: Aqueous guava leaf extract.

Table (3): LDL-C, VLDL-C, (mg/dl) and risk ratio in different experimental groups.

Parameters / Rat groups	LDL-C (mg/dl)	VLDL- C (mg/dl)	Risk ratio
Group 1	26.09± 1.76	7.92± 0.19	1.49±0.02
Group 2	1 131.3±10.86	8.36± 0.45	1 5.73±0.59
Group 3	1 126.0±8.74	b 7.35±0 .25	1,b 4.62±0.28
Group 4	1,b,c 100.5±10.06	1,2,c 6.38± 0.46	1,2 3.85±0.36
Group 5	1,b,c 92.55±10.05	a,2 6.65±0 .16	1,2,c 3.53±0.28
Group 6	2,3,4,5 48.91±4.48	1,2,c 6.09± 0.20	2,3,4,e 2.20±0.11

Group 1: basal diet (-ve control) Group 2 : HFC diet (+ve control) Group 3 : HFC diet +200 mg/kg b.wt. (AGLE) Group 4: HFC diet +350 mg/kg b.wt. (AGLE) Group 5: HFC diet +500 mg/kg b.wt. (AGLE) Group 6 : HFC diet +650 mg/kg b.wt. (AGLE). Significant difference ($p \leq 0.05$): compared to: (a): to group (1), (b): to group (2) , (c) to group (3), (d) to group (4), (e) to group (5), (f) to group (6).
Significant difference ($p \leq 0.001$): compared to: (1): to group (1), (2): to group (2) , (3) to group (3), (4) to group (4), (5) to group (5), (6) to group (6).
HFC: High fat high cholesterol diet. AGLE: Aqueous guava leaf extract.

Table (4) in which rats fed HFC diet showed a significant increase in some liver function tests as serum ALT, AST and in hormones as adiponectin but a significant decrease in leptin compared to rats fed basal diet.

Results indicated that group (6) had a significant decrease in serum ALT activity compared to groups (2), ($p \leq 0.001$), (3) and (4), ($p \leq 0.05$). Also, group (6) showed a significant decrease in serum AST activity compared to groups (2), (3), ($p \leq 0.001$), and (4), ($p \leq 0.05$).Both of group (4) & group (5) had a significant decrease in serum AST ($p \leq 0.05$) compared to group (2).

On the other hand results of adiponectin hormone indicated a significant decrease in group (6) ($p \leq 0.05$) compared to group (2) & group (3) respectively. Leptin hormone was increased in group (4) & group (5) ($p \leq 0.05$) and also in group (6) ($p \leq 0.001$) when all compared to group (3).

The three groups (4, 5 & 6) which were given three different doses of AGLE (350, 500 & 650 mg/kg b.wt. respectively) had a significant increase in serum leptin in groups (5 & 6) ($p \leq 0.001$) and group (4) ($p \leq 0.05$) when all compared to group (2).
Gherlin hormone showed no significant difference between the six studied groups.

Table (4): Serum alanine aminotranseferase, aspartate aminotranseferase (U/L), adiponectin (ng/dl), leptin (Ug/L) and gherlin (pg/ml) in different experimental groups.

parameters / Rat groups	ALT (U/L)	AST (U/L)	Adiponectin (ng/dl)	Leptin (Ug/L)	Gherlin (pg/ml)
Group 1	46.36 ± 1.86	183.2 ± 3.95	57.36 ± 2.86	0.66±0.08	33.57 ± 4.59
Group 2	1 92.73 ± 8.59	1 330.2 ± 21.37	1 108.4 ± 5.89	1 0.39 ± 0.03	40.71 ± 3.52
Group 3	1 88.64 ± 9.59	1 318.1 ± 12.86	1 103.6 ± 4.81	a 0.42 ± 0.04	31.86 ± 4.69
Group 4	1 82.45 ± 6.92	1,b 288.5 ± 14.53	1 95.73 ± 4.83	b,c 0.60 ± 0.05	38.57 ± 3.89
Group 5	1 77.91 ± 3.72	1,b 284.3 ± 17.72	1 97.27 ± 4.59	2,c 0.65 ± 0.05	37.14 ± 3.60
Group 6	2,c,d 62.09 ± 1.66	a,2,3,d 245.5 ± 8.74	1,b,c 87.18 ± 3.55	2,3 0.72 ± 0.07	39.29 ±3.52

Group 1: basal diet (-ve control) Group 2: HFC diet (+ve control) Group 3 : HFC diet +200 mg/kg b.wt. (AGLE) Group 4: HFC diet +350 mg/kg b.wt. (AGLE) Group 5: HFC diet +500 mg/kg b.wt. (AGLE) Group 6 : HFC diet +650 mg/kg b.wt. (AGLE).

Significant difference ($p \leq 0.05$): compared to: (a): to group (1), (b): to group (2), (c) to group (3), (d) to group (4), (e) to group (5), (f) to group (6).

Significant difference ($p \leq 0.001$): compared to: (1): to group (1), (2): to group (2), (3) to group (3), (4) to group (4), (5) to group (5), (6) to group (6). HFC: High fat high cholesterol diet. AGLE: Aqueous guava leaf extract.

As shown in table (5) liver cholesterol & triacylglycerol were increased significantly in group (2) compared with group (1), also a significant increase in malondialdehyde level was found.

On determining the level of cholesterol in liver of the rats it was found that its level decreased significantly in group (3) and group (4) ($p \leq 0.05$) compared to group (2).

The level of triacylglycerol in liver was significantly decreased in groups (4, 5 & 6) compared to group (2).

Liver total antioxidant capacity was increased significantly in the two groups provided with the highest doses of AGLE (group 5 & group 6) in which group (5) ($p \leq 0.001$) & group (6) ($p \leq 0.05$) compared to group (4).

Finally liver malondialdehyde was decreased significantly in the four groups given orally AGLE (200, 350, 500 & 650 mg/kg b.wt.) compared to group (2) ($p \leq 0.001$) .While group (6) showed a significant decrease ($p \leq 0.05$) compared to groups (3), (4) and (5) ($p \leq 0.001$).

Table (5): Total cholesterol, triacylglycerol (mg/g), total antioxidant capacity (mmol/g) and malondialdehyde (nmol/g) in liver of different experimental groups.

Parameters / Rat groups	Liver cholesterol (mg/g)	Liver triacylglycerol (mg/g)	Liver total antioxidant capacity (mmol/g)	liver malondialdehyde (nmol/g)
Group 1	32.91±3.26	72.70±3.32	2.70±0.02	3.73 ±0.26
Group 2	1 106.2±9.24	1 101.3±4.10	2.68±0.03	1 6.65 ±0.53
Group 3	a,b 70.29±8.39	a 87.70±4.69	2.67±0.01	a,2 5.06 ±0.30
Group 4	a,b 71.61±11.88	b 85.71±8.09	a 2.63±0.02	2 4.54 ±0.13
Group 5	1,c,d 104.0±12.30	b 82.86±4.50	4 2.72±0.01	a,2 5.11 ±0.11
Group 6	1 83.40±9.41	2 73.10±5.30	d 2.69±0.02	2,c,d,5 3.67 ±0.14

Group 1: basal diet (-ve control) Group 2: HFC diet (+ve control) Group 3: HFC diet +200 mg/kg b.wt. (AGLE) Group 4: HFC diet +350 mg/kg b.wt. (AGLE)

Group 5: HFC diet +500 mg/kg b.wt. (AGLE) Group 6: HFC diet +650 mg/kg b.wt.

(AGLE).significant difference ($p \leq 0.05$): compared to: (a): to group (1), (b): to group (2), (c) to group (3), (d) to group (4), (e) to group (5), (f) to group (6).

Significant difference ($p \leq 0.001$): compared to: (1): to group (1), (2): to group (2), (3) to group (3), (4) to group (4), (5) to group (5), (6) to group (6).
HFC: High fat high cholesterol diet. AGLE: Aqueous guava leaf extract.

3.2. Discussion:

This work showed a significant decrease in food intake but a significant increase in relative liver weight in group (2) fed high fat high cholesterol diet (HFC) compared to group (1) fed basal diet .This is due to high fat cholesterol diet causes an increase in liver fat mass. But the results of the present study indicated that there was a decrease in the eating behavior of the rats fed with HFC diet as the presence of fat in the diet decrease food intake and increase satiety. Also the decrease in the physical activity may be due to the presence of high fat in the diet and that increased the prevalence of obesity.

All the groups which treated *(p.o)* with aqueous guava leaf extract (AGLE) with the four different doses showed significant decrease in food intake, final body weight and gain in body weight compared to group (2) fed HFC diet. As well as there was a significant decrease in relative liver weight in group (4), group (5) and group (6) compared to group (2). As guava leaf extract may activate AMP-activated protein kinase (AMPK) to increase fat oxidation, decrease hepatic gluconeogenesis and increase transport of glucose into the muscles. Agreeing with ***Yoshitomi et al.(2012a)*** who illustrated that body weight gain was about 20% lower in the SHRSP.Z-Leprfa/IzmDmcr (SHRSP/ZF) rats group that were given guava leaf extract than in SHRSP/ZF rats group as well as cause a significant decrease in adipose weight, body weight, liver weight and fat weight after 6-week treatment.

This study illustrated a significant increase in serum total cholesterol, LDL-C and risk ratio but a significant decrease in serum HDL-C in rats fed HFC diet compared to negative control group. While triacylglycerol and VLDL-C slightly changed but not significantly.

The elevated lipid level, especially hypercholesterolemia, results due to its increased absorption in the gut or endogenous synthesis and that agreed with ***Hirunpanich et al. (2006)*** who found that high cholesterol diet causes marked hypercholesterolemia i.e. increased level total cholesterol and LDL-C.

In this study there was no significant difference in triacylglycerol level between group (2) fed HFC and group (1) agreeing with ***Eisinger et al. (2014)***. All rats given AGLE orally had a significant decrease in the level of triacylglycerol, VLDL-C and risk ratio compared to group (2), and a significant decrease in total cholesterol in groups (5&6) compared to group (2).While LDL-C decreased in groups (4, 5 & 6) significantly but HDL-C increased significantly in the same groups compared to rats fed HFC diet. This may be due to the presence of flavonoids in AGLE that inhibit 3hydroxy-3methylglutaryl coenzyme A reductase (HMG CoA reductase), the enzyme crucial for cholesterol biosynthesis agreeing with ***Sung et al. (2004).*** Where flavonoids have anti-hypercholesterolemic activity ***(Wang et al., 2009).***

There are two main mechanisms proposed to explain the lowering of serum cholesterol by saponins present in AGLE. The first mechanism implies that saponins form insoluble complexes with cholesterol, thus inhibiting its intestinal absorption which increases the fecal cholesterol output. The second mechanism suggests that saponins form large aggregates with bile salts (BS) in the intestine and thus inhibit ileal BS reabsorption. The latter effect triggers an increased synthesis of BS from cholesterol in the liver, which leads to depletion of serum cholesterol and that agreed with ***Vinarova et al. (2015).***

The reduction in the serum total cholesterol levels following the administration of the extract may be attributed to reduction in the concentration of acetyl CoA resulting from decreased β-oxidation of fatty acids since acetyl CoA is a key substrate in the biosynthesis of cholesterol as indicated by ***Nwangwa and Ekhoye, (2013).***

The reduction observed in the serum triacylglycerols level can be due to inhibition of lipolysis. Also it can be attributed to the antioxidant activities of saponins which might have interfered with the oxidation of fatty acid agreeing with ***Owoyele et al. (2005)*** and ***(Nwangwa and Ekhoye, 2013).***

The increase in high density lipoprotein following the administration of aqueous extract of guava leaves can be clinically beneficial. It has been demonstrated that an increase in the concentration of HDL correlates inversely with coronary heart disease ***(Philip, 1995).***This is because HDL removes cellular cholesterol and transports it to the liver where it is converted to bile acids and eventually excreted from the body ***(Mayes, 1996)***, and as such will reduce the risk of coronary artery disease.

The study revealed that feeding HFC diet as in group (2) caused a significant increase in serum ALT and AST activities when compared to normal control group. Indicating a severe injury of the liver leading to liberation of the enzymes in the blood stream as hepatic parenchymal cells are damaged which may be due to the effect of HFC diet and the beginning of inflammation and oxidative stress agreeing with ***El-Kirsh et al. (2011).***

Also it was indicated a significant increase in adiponectin hormone but a significant decrease in leptin hormone in HFC diet fed rats. This increase in adiponectin may be due to accumulation of excessive amounts of storage lipids into adipose tissue causing adipocyte hypertrophy with the development of obesity. Subsequently resulting in secretion abnormalities of free fatty acids and adipocytokines as adiponectin which derived from adipocytes agreeing with ***Kamei et al. (2006).***

The results of the present study seems to be in line with ***Cano et al. (2009)*** who indicated an increase in mean levels of adiponectin in high fat fed rats as well as a significant modification in its daily pattern in circulation. Although in dietary obese rats, a decrease in adiponectin mRNA levels were reported and does not translate to a parallel decrease in plasma adiponectin concentration ***(Barnea et al., 2006).***

The results of the present study indicated a significant increase in adiponectin hormone in rats fed HFC diet suggesting alteration of adiponectin secretion and/or turnover. This increase may be due to a marked decrease in adiponectin mRNA and total protein levels in epididymal adipose tissue and defects of adiponectin receptor expression and AMPK activity. But the decreased adiponectin expression does not translate to a parallel decrease in plasma adiponectin concentration, suggesting the possibility of post-transcriptional control mechanism(s). This explanation was in agreeing with ***Bonnard et al. (2008).***

Rats with high fat feeding deposited with excessive fats in their adipose tissue and also, they developed leptin resistance, which is crucial in the regulation of body weight by controlling fat deposition in adipose tissues. Obesity is correlated with the production of leptin as the adipocytes increases in onset obesity either in number or size and disturb the level of leptin. Although leptin regulates the appetite but in obese individuals signaling of leptin is attenuated and they exhibit leptin resistance ***(Myers et al., 2008).***

Ainslie et al. (2000) found that on short term, high fat diets lower circulating leptin concentrations in rats. Where after 4 weeks, plasma leptin concentrations were 24% lower in the animals fed the high fat diet than in those fed the control diet. Also at 14 weeks, there was still less leptin secreted per unit abdominal white adipose tissue (WAT) mass in the rats fed the high-fat diet than in those fed the control diet. The study showed that short-term, high-fat diets are associated with reduced leptin secretion.

Sugiishi et al. (2013) showed that ghrelin levels were not decreased in the rats fed a high fat diet (HFD) but were in rats fed a control diet, which suggested that ghrelin induced hyperphagia cannot be effectively inhibited after a meal following long term consumption of a HFD, even when serum glucose levels are elevated. It appeared that negative feedback of ghrelin secretion after glucose intake did not function in this long term HFD model. This finding suggested that appetite would not be suppressed to the normal extent even after a meal when chronically consuming a HFD.

In this study, it was observed a significant decrease in serum ALT, AST and adiponectin hormone in group (6) which treated with highest dose of aqueous extract of guava leaves and that may be due to its protective effect. Also dose dependent relationship between AGLE and protection.

Both of group (4) & group (5) had a significant decrease in serum AST compared to group (2). But the three groups (4, 5 & 6) which were given three different doses of AGLE (350, 500 & 650 mg/kg b.wt. respectively) had a significant increase in serum leptin when all compared to group (2). Gherlin hormone showed no significant difference between the six studied groups.

The decrease of serum ALT and AST activities in the present study by AGLE accounts for less fat infiltration of hepatocytes. Agreeing with ***Roy et al. (2011)*** who reported that the aqueous extract of *pisidium guajava* leaves showed good hepatoprotective activity when administrated at doses of 250 mg/kg and 500 mg/kg orally when compared with group given chemicals which induce liver toxicity.

Serum ALT and AST activities were decreased due to quercetin, a major bioflavonoid found in AGLE, which has been reported to reduce hepatic fat accumulation in mice fed a high-fat diet ***(Jung et al., 2013).***

It was expected that AGLE improved the deteriorative effect of serum adiponectin caused by HFC diet increased the expression of adiponectin receptor 1 and 2, with the activity of AMPK and mRNA expression of PPARα, which is a downstream adiponectin receptor. These results might suggest that GLE has an insulin resistance-improving effect by improving fatty liver and reduced adipose tissue due to a decreased adipocytokines. That was in line with ***Yoshitomi et al. (2012a).***

Aqueous guava leaf extract in the four treated groups showed no significant decrease in the level of ghrelin hormone which indicate that AGLE has no protective value on ghrelin hormone. On the other side this may be due to leptin which has an influence on circulating ghrelin levels. It has been hypothesized that the satiety-inducing effects of leptin include the suppression of ghrelin secretion ***(Yildiz et al., 2004).***

In table (5) liver cholesterol, triacylglycerol and malondialdehyde level were increased significantly when comparing group (2) with group (1).That was due to deposition of lipids and triacylglycerols in liver of experimental animals which was reported following high cholesterol diet supplementation agreeing with ***Lee et al.(2007).*** Also the concentration of malondialdehyde (MDA), a lipid peroxidation product, is the most frequently used biomarker for assessing oxidative stress in human subjects ***(Nielsen et al., 1997).***

Level of cholesterol in liver of the rats in group (3) and group (4) fed HFC and given AGLE was decreased significantly compared to rats fed HFC diet only. But liver total antioxidant capacity was increased significantly in the two groups provided with the highest doses of AGLE (group 5 & group 6). The level of triacylglycerol in liver was significantly decreased in groups (4, 5 & 6) compared to group (2) respectively. Finally liver malondialdehyde was decreased significantly in the four groups given orally AGLE (200, 350, 500 & 650 mg/kg b.wt.) compared to group (2).

This can be explained by fatty acid β-oxidation which takes place in two cellular organelles, mitochondria and peroxisomes ***(Rao & Reddy, 2001).*** In liver cells, it is proposed that mitochondrial oxidation might have the largest impact on total β-oxidation agreeing with ***Reddy & Hashimoto, (2001)***.

Activation of AMPK leads to a decrease in intracellular malonyl-CoA, which is a precursor of the biogenesis of fatty acid and a potent inhibitor of carnitinepalmitoyltransferase (CPT) ***(Towler & Hardie, 2007).*** CPT is a rate-limiting enzyme of mitochondrial β-oxidation and plays an important role in the transport of fatty acid to inside the mitochondria. On the other hand, peroxisome proliferator activated receptor alpha (PPARα) controls the transcription of many genes involved in lipid catabolism, such as medium-chain acyl-CoA dehydrogenase (MCAD), acyl-CoA oxidase (ACO) and also CPT. It was demonstrated that CPT activity in the SHRSP/ZF group and given guava leaf extract increased compared with the SHRSP/ZF control group. In addition, it was evaluated mRNA expression, MCAD as a marker of enzyme mitochondrial β-oxidation, and ACO as a marker of point to control peroxisomal one ***(Reddy & Hashimoto, 2001)***. So GLE treatment increases energy expenditure by increasing fatty acid β-oxidation in liver cells.

Agreeing with ***Uboh et al. (2010)*** AGLE contains flavonoids which are powerful antioxidant polyphenolic compounds as well as ***Faure et al. (1991)*** have shown that flavonoids inhibit peroxidation of polyunsaturated fatty acids in cell membranes.

Malondialdehyde level was reduced due to the presence of quercetin in AGLE which was reported to be a strong antioxidant by increasing endogenous antioxidant activities and by directly scavenging free radicals ***(Annapurna et al., 2009).***

4. Conclusion

The most effective AGLE dose in the present study is 650 mg/kg b.wt. which had antihyperlipidemic and antihypercholesterolemic effect.

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الملخص باللغة العربية

التاثير المخفض للدهون و الكوليستيرول للمستخلص المائى لورق الجوافة على الجرذان

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الهدف من هذا البحث هو دراسة التاثير المحسن للمستخلص المائى لورق الجوافة المعطى عن طريق الفم بجرعات مختلفة (200، 350، 500، 650 مجم/كجم من وزن الجسم) فى الجرذان المغذاه على وجبة عالية من الدهون و الكوليسترول لمدة ثمانى اسابيع. لقد اظهرت النتائج ان الجرعات الاربعة تسببت فى حدوث انخفاض ذو دلالة احصائية فى كمية الطعام المتناولة و الوزن النهائى و الوزن المكتسب و الدهون الثلاثية و كوليستيرول الليبوبروتينات منخفضة الكثافة جدا بالمصل و نسبة الخطورة . و كذلك الدهون الثلاثية و المالون داى الدهايد بالكبد. كما ان الجرعات (350، 500، 650 مجم/كجم من وزن الجسم) تسببت فى انخفاض ذو دلالة احصائية فى الوزن النسبى للكبد و انزيم اسبارتات ا ميزو ترانسفيراز و كوليستيرول الليبوبروتينات منخفضة الكثافة بالمصل. ولكن حدوث زيادة ذات دلالة احصائية فى كوليستيرول الليبوبروتينات عالية الكثافة و هرمون الليبتين بالمصل. بينما تسببت الجرعات(500 و 650 مجم/كجم من وزن الجسم) فى انخفاض ذو دلالة احصائية فى الكوليستيرول الكلى بالمصل. اما بالنسبة للجرعه الاعلى تركيزا احدثت انخفاض ذو دلالة احصائية فى انزيم الانين ام يزو ترانسفيراز و انزيم اسبارتات ام يزو ترانسفيراز و هرمون الاديبونكتين بالمصل. المجموعات التى تناولت جرعات (200، 350 مجم/كجم من وزن الجسم) حدث بها انخفاض ذو دلاله احصائية فى كمية الكوليستيرول الكلى بالكبد ولكن لم يحدث انخفاض ذو دلالة احصائية فى الجرعات (500، 650 مجم/كجم من وزن الجسم). و بالنسبة لهرمون الجريلين لم ينخفض بدلاله احصائية فى المجاميع الاربعة وهذا عند مقارنة الجرذان المغذاه على وجبة عالية من الدهون و الكوليسترول و معطاة المستخلص المائى لورق الجوافة بالجرذان المغذاه على وجبة عالية من الدهون و الكوليسترول فقط.