The 7th international- 21th Arabic conference for Home Economics "Home Economics and sustainable development2030" December -15th, 2020

Journal of Home Economics

http://homeEcon.menofia.edu.eg ISSN 1110-2578

Nutraceutical Effect of Diets Containing Graviola Fruit Parts on Hepatointoxicated Rats.

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Abstract:

This study aimed to investigate the effect of different Graviola (*Annona muricata*, L.) fruit parts including (Pulp), (Green Peel), (Black Seeds) and their blend on amelioration the hepatotoxicity in CCl_4 injected rats. Fifty (50) adult male albino rats, weighing (180±10g) were divided into ten groups, five rats each. Group 1 was fed on the basal diet and set as a negative control group (normal rats), meanwhile the nine other groups were injected by 0.2 mg/kg body weight by Carbon Tetrachloride (CCl_4) for two weeks to induce the liver impaired. Group 2 was left as a positive control group and fed on basal diet only, while other groups 3, 4, 5, 6, 7, 8, 9 and 10 were fed on supplemented diet with 5% and 7.5% powder of *Annona* pulp, *Annona* peels, *Annona* seeds and mixture of all, respectively. Body weight, feed intake, feed efficiency ratio, internal organs weight, serum glucose, liver functions, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) enzymes, total protein, total cholesterol, triglycerides, high-density lipoproteins cholesterol (HDLc), low-density lipoproteins cholesterol (LDLc) and very low-density lipoproteins cholesterol (VLDLc), kidney functions (urea, creatinine and uric acid), total bilirubin, direct bilirubin, indirect bilirubin, antioxidant enzymes (Catalase, Superoxide Dismutase, and Glutathione Peroxidase) assayed. Histopathological changes of liver and kidney have been evaluated. From the obtained results, it was revealed that feeding on Graviola fruit parts powders (G3, G4, G5, G6, G7, G8, G9 & G10) caused a significant ($P \leq 0.05$) increase in weight gain, feed intake, feed efficiency ratio, HDLc, total protein, albumin, globulin, CAT, SOD, GPx with a significant ($P \leq 0.05$) decreases in the rest of the analyses as compared with control (+ve) group, and enhanced the kidney and liver functions with the decrease of ALT, AST, ALP, total bilirubin, indirect bilirubin, albumin, globulin, which reflects the powerful nutraceutical therapeutic effect for feeding on Graviola fruit parts including (The Pulp), (Green Peel), (Black Seeds) and their blend to combat the hepatointoxication induced by CCl_4 in male albino rats. The best treatments were for *Annona* pulp 7.5%.

Key words: Carbon Tetrachloride (CCl_4)– Hepatointoxication– Graviola– *Annona* fruit parts- *Annona muricata*- Liver enzymes– Antioxidant enzymes.

Introduction:

Liver is necessary for survival and there is currently no way to compensate for the absence of liver functions in the long term, although new liver dialysis techniques can be used in the short term (**Uboh *et al.*, 2010**). The highly specialized tissues in the liver regulate a wide variety of high-volume biochemical reactions including the synthesis and breakdown of small and complex molecules, many of which are necessary for normal vital functions (**Nwogu *et al.*, 2010**). Liver is a target organ and primary site of detoxification and is generally the major site of intense metabolism and is therefore prone to various disorders as a consequence of exposure to the toxins of extrinsic as well as intrinsic forms. The liver plays important role in metabolism to maintain energy level and structural stability of body (**Guyton and Hall, 1996**). It is also site of biotransformation by which a toxic compound has been transformed in less harmful form to reduce toxicity (**Hodgson, 2004**). Liver is a major organ attacked by reactive oxygen species (ROS) (**Sanchez-Valle *et al.*, 2012**). Many natural agents possessing antioxidative properties have been reported to prevent and treat liver damages caused by free radicals induced by toxic substance (**Adefolaju *et al.*, 2009**).

Annona muricata, Linn. is an evergreen plant which distributed in tropical and subtropical regions. *A.muricata* fruit belongs to the family of *Annonaceae* is also commonly known as sirsak, graviola, soursop and gunbanana (**Desmiaty *et al.*, 2017 & Patel and Patel, 2016)**. Traditionally, all parts of the Graviola tree are used in natural medicine in many countries for the treatment of number of diseases, including the bark, leaves, roots, fruit, and fruit seeds (**Onyechi *et al.*, 2012**). It is used as a strong diuretic for swollen feet (edema) and as a tonic used for dysentery, mouth sores, fever, liver problems, for an anthelmintic and antirheumatic, for neuralgia, rheumatism, arthritis pain and as an antiparasitic, intestinal colic, antidiabetic, high blood pressure and diarrhea hypertension and parasites (**Kedari and Khan, 2014**). Furthermore, pharmacological studies showed that *A. muricata* has been showed to have biological and pharmacological activities such as antifungal, antibacterial, antioxidant and anticancer properties on multidrug resistant cancer cell line (**Vieira et al., 2010**). Intensive chemical investigations of the leaves, fruit pulp, and seeds of different species of Graviola have resulted in the isolation of a great number of acetogenins (AGEs); bulatacin, asimisin, and squamosin (**Anuragi *et al.*, 2016**). **Adewole and Ojewole, (2010)** observed hepatic benefits after administration of an aqueous leaf extract of Graviola to streptozotocin-induced diabetic rats. The described benefits in liver consisted mainly of increases in antioxidant enzymes (Catalase, Superoxide Dismutase, and Glutathione Peroxidase) and levels of glutathione to reduce oxidative stress in this tissue. However, other positive effects of this treatment included improvements in blood lipid levels, specifically a decline in diabetes-induced levels of LDL, total cholesterol, and triglycerides and an increase in HDL.

The previous studies showed that different plant parts could be used successfully in treatment/prevention of different diseases. Thereupon, the experiment was conducted to study the effect of Graviola fruit parts including (Pulp), (Green Peel), (Black Seeds) and their blend on amelioration the hepatotoxicity in CCl_4 injected rats by studying body weight gain, feed intake, feed efficiency ratio, liver functions, kidney functions, blood glucose and lipid profile.

Material and Methods

Materials:

Plants: The tested plant in this investigation was Graviola (*Annona muricata*, L.) fruit parts including (Pulp), (Green Peel), (Black Seeds) and their blend collected from Horticulture Research Institute, Agricultural Research Center, Ministry of Agriculture, Giza, Egypt.

Chemicals: Carbon tetra chloride (CCl_4) was purchased from El-Gomhoria Company for Drugs and Medical Equipments, Cairo, Egypt, as 10% liquid solution.

Diets: Diet consists of casein, sucrose, corn oil, choline chloride, vitamins mixture, mineral mixture, cellulose, and corn starch were purchased from El-Gomhoria Company for Drugs and Medical Equipments, Cairo, Egypt.

Experimental design:

Fifty (50) adult male albino rats were fed on basal diet for 7 days for acclimatization. Then, rats were randomly distributed into 10 equal groups, 5 rats each. Group 1(healthy rats) was fed on the basal diet and set as a negative control group (normal rats). The other 9 groups were injected by carbon tetrachloride (CCl_4) in olive oil 50% v/v (2ml/kg b.wt) twice a week for 14 days to induce chronic damage of the liver according to the method described by **Jayasekhar *et al.*, (1997).** All groups were fed for 4 weeks according to the following groups:

Group (1) :control negative (-ve), in which normal rats (n=5) were fed on basal diet only for 28 days.

Group (2) :control positive (+ve) in which hepatotoxic rats (n=5) were injected by CCl_4 were fed on basal diet only for 28 days.

Group (3) :CCl_4 hepatotoxicity rats (n=5) were fed on basal diet containing 5% pulp of Graviola powder for 28 days.

Group (4) :CCl_4 hepatotoxicity rats (n=5) were fed on basal diet containing 7.5% pulp of Graviola powder for 28 days.

Group (5) :CCl_4 hepatotoxicity rats (n=5) were fed on basal diet containing 5% seeds of Graviola powder for 28 days.

Group (6) :CCl_4 hepatotoxicity rats (n=5) were fed on basal diet containing 7.5% seeds of Graviola powder for 28 days.

Group (7) :CCl_4 hepatotoxicity rats (n=5) were fed on basal diet containing 5% green peel of Graviola powder for 28 days.

Group (8) :CCl_4 hepatotoxicity rats (n=5) were fed on basal diet containing 7.5% green peel of Graviola powder for 28 days.

Group (9) :CCl_4 hepatotoxicity rats (n=5) were fed on basal diet containing 5% mixture of them with equal ratio (1:1:1 W/W) for 28 days.

Group (10) :CCl_4 hepatotoxicity rats (n=5) were fed on basal diet containing 7.5% mixture of them with equal ratio (1:1:1 W/W) for 28 days.

Biological Evaluation:

During the experimental period (28days), the consumed diet was daily recorded (feed intake), biological evaluation of the different diets was carried out by determination of body weight gain (BWG) and feed efficiency ratio (FER) according to **Chapman *et al*., (1959).**

Blood Sampling:

At the end of the experiment, rats were fasted overnight and anesthetized with diethyl ether. Blood samples were collected in clean dry centrifuge tubes from hepatic portal vein; serum obtained by centrifugation was carefully aspirated, transferred into clean cuvette tubes and stored frozen at -20°C for analysis **(Malhotra, 2003).**

Serum samples were analyzed for determination the following Parameters:

Serum glutamate oxaloacetate transaminase S.GOT or (AST) was determined as Unit/L according to **Yound (1975),** S.GPT or (ALT) was determined as Unit/L according to **Yound (1975),** serum alkaline phosphatase (ALP) was determined U/L according to **IFCC** (**1983),** Serum total protein (TP) assessed according to **Henry (1974),** serum albumin (Alb) according to **Doumas *et al*., (1971),** serum globulin (G) according to **Chary and Sharma (2004),** serum albumin/globulin ratio according to **Srivastava *et al.*, (2002),** serum total bilirubin (T.Bil) according to **Doumas *et al.*, (1973),** serum direct bilirubin (D.Bil) & serum indirect bilirubin (Ind.Bil) according to **Chary and Sharma (2004),** total cholesterol was determined according to **Allain (1974),** enzymatic colorimetric determination of triglycerides was carried out according to **Fossati and Prencipe (1982)**, determination of HDL was carried out according to the method of **Lopez (1977),** determination of LDL and VLDL was carried out according to the method of **Lee and**

Nieman (1996), atherognic index (AI) was calculated as the VLDL + LDL cholesterol / HDL ratio according to the formula described by **Nakabayashi *et al.*, (1995),** urea determination was according to the enzymatic method of **Malhotra (2003),** uric acid was determined according to the method described by **Fossati *et al.*, (1980),** creatinine was determined according to the method described by **Bohmer (1971),** serum glucose according to **Yound (1975) and Tietz (1976)**, superoxide dismutase (SOD) was assayed according to the method of **Sun *et al.*, (1988),** Glutathione peroxidase (GPX) was carried out according to the method of **Zhao *et al.*, (2002)** and Catalase (CAT) activity was assayed following the method of **Diego (2011).**

Statistical Analysis:

The data were statistically analyzed using a computerized program by one way ANOVA .The results are presented as mean ± SD. Differences between treatments at $p \leq 0.05$ were considered significant.

Results and discussion:

A - Biological changes:

Results of body weight gain (BWG), feed intake (FI) and feed efficiency ratio (FER) of experimental rats are presented in table (1). BWG, FI and FER of CCl_4-intoxicated rats (positive control group) were decreased significantly, as compared with those of the normal rats. On the other hand, all tested plants increased BWG. Best treatment for BWG recorded for G4 (*Annona* pulp 7.5%). All tested fruit parts have significant increase FI compared to control (+). Best treatment for BWG, FI & FER recorded for G4 (*Annona* pulp 7.5%). FER was highest in case of G4 (*Annona* pulp 7.5%).These results agree with **Nwogu *et al.*, (2010)** who observed that there was significant increase in body weights of hepatointoxicated rats treated with aqueous extract of *Annona muricata,* this encouraged body weight gain and **Offor *et al.*, (2015)** who reported that FI, FER and BWG of hepatointoxicated rats (positive control group) were decreased significantly, as compared with those of the normal rats. **Alzergy *et al.*, (2018)** agreed with results of present work in that *Annona muricata* pulp group improved body weight gain (BWG) in hepatointoxicated mice.

Table (1): Body weight gain (BWG), feed intake (FI) and feed efficiency ratio (FER) of normal and hepatointoxicated rats (n=5 rats/groups)

Parameters / Groups	**BWG (g/day) Mean ± SD**	**FI (g/day) Mean ± SD**	**FER Mean ± SD**
G1: Control –ve	0.71^{a}± 0.009	13.34^{b}± 0.059	0.0523^{a}±0.0009
G2: Control +ve	0.10^{g}± 0.001	10.26^{j}± 0.009	0.0098^{g}±0.0003
G3: Annona pulp 5%	0.68^{a}± 0.008	13.20^{c}± 0.003	0.0515^{bc}±0.0001
G4: Annona pulp 7.5%	0.70^{a}± 0.002	13.38^{a}± 0.008	0.0523^{ab}±0.0006
G5: Annona peels 5%	0.60^{c}± 0.005	12^{f}± 0.002	0.0500^{c}±0.0008
G6: Annona peels 7.5%	0.64^{b}± 0.006	12.53^{d}± 0.006	0.0511^{bc}±0.0002
G7: Annona seeds 5%	0.53^{e}±0.025	11.78^{g}±0.004	0.0450^{e}±0.0007
G8: Annona seeds 7.5%	0.57^{d}±0.011	12.23^{e}±0.007	0.0466^{d}±0.0004
G9: Mixture of all 5%	0.47^{f}±0.004	11.30^{h}±0.005	0.0416^{f}±0.0003
G10: Mixture of all 7.5%	0.49^{f}±0.036	11^{i}±0.016	0.0445^{e}±0.0018
LSD	0.026	0.034	0.0013

Values with different letters indicate significant differences Between the groups (P≤0.05), and vice versa. LSD: least significant Differences (P≤0.05).

B- Relative organs weights:

Data presented in table (2), show the relative organ weight (liver, heart, kidneys, spleen and lungs). These results denoted that there was a significant increase in relative liver, kidneys, spleen, heart and lungs weights of hepatointoxicated rats control (+) group compared to normal rats control (-) group. All fruit parts diets G3, G4, G5, G6, G7, G8,G9 & G10 had significant decrease in liver, heart, kidney, spleen and lungs weight (g). The highest limit decrease obtained for G4 (*Annona* pulp 7.5%) in liver, kidneys and heart weights(g) & G3 (*Annona* pulp 5%) in lungs and spleen weights (g).

Table (2): Relative organs weights of normal rats and hepatointoxicated rats (n=5 rats/groups)

Parameters / Groups	**Liver (g) Mean ±SD**	**Heart (g) Mean ± SD**	**Lungs (g) Mean ± SD**	**Spleen (g) Mean ± SD**	**Kidneys (g) Mean ± SD**
G1: Control –ve	2.65^{c}±0.009	0.54^{i}±0.017	1.6^{c}±0.001	0.29^{h}±0.002	0.8^{h}±0.004
G2: Control +ve	4^{a}±0.01	0.86^{a}±0.024	2.41^{a}±0.008	0.57^{a}±0.008	2.11^{a}±0.035
G3: Annona pulp 5%	2.6^{c}±0.025	0.62^{g}±0.009	1.621^{c}±0.009	0.3^{h}±0.001	0.85^{g}±0.008
G4: Annona pulp 7.5%	2.55^{c}±0.007	0.53^{i}±0.001	1.66^{c}±0.005	0.33^{g}±0.009	0.82^{h}±0.005
G5: Annona peels 5%	2.68^{c}±0.002	0.68^{e}±0.007	1.68^{c}±0.004	0.35^{f}±0.005	0.9^{f}±0.003
G6: Annona peels 7.5%	2.63^{c}±0.006	0.57^{h}±0.004	2^{b}±0.28	0.38^{e}±0.003	0.86^{g}±0.002
G7: Annona seeds 5%	2.71^{c}±0.005	0.72^{c}±0.008	2.15^{b}±0.015	0.4^{d}±0.007	1.13^{d}±0.006

G8: Annona seeds 7.5%	2.69^{c}±0.018	0.65^{f}±0.004	2.08^{b}±0.006	0.38^{e}±0.006	0.95^{e}±0.001
G9: Mixture of all 5%	3^{b}±0.34	0.74^{b}±0.011	2.16^{b}±0.015	0.42^{c}±0.004	1.4^{b}±0.007
G10: Mixture of all 7.5%	2.82^{bc}±0.004	0.7^{d}±0.005	2.1^{b}±0.037	0.45^{b}±0.011	1.31^{c}±0.009
LSD	0.18	0.019	0.153	0.011	0.021

Values with different letters indicate significant differences Between the groups (P<0.05), and vice versa. LSD: least significant Differences (P≤0.05).

C- Biochemical data changes:

1-Liver enzymes activities:

Data presented in table (3) show the effect of feeding by tested Graviola fruit parts (The Pulp), (Green Peel), (Black Seeds) and their blend for hepatointoxicated rats on liver enzymes (AST, ALT& ALP) and AST/ALT ratio. Results in table (3) showed significant elevations in serum activity of AST, ALT and ALP enzymes compared with those of the normal rats. All Graviola fruit parts diets G3, G4, G5, G6, G7, G8, G9 & G10 had significant ameliorations in serum activity of AST, ALT and ALP enzymes as well as AST/ALT ratio as compared with those of the positive control rats. The highest decreased limit of ALP obtained for G4 (*Annona* pulp 7.5%) with significant difference with control (-) group. These results are in agreement with **Nwogu *et al.*, (2010)** who reported that *Annona muricata* leaf-extracts significantly reduced the elevated serum levels of ALP in acute liver damage induced by different hepato-toxins, and reduced the elevated serum levels of AST, signifying the modulatory effect of the extract on the hepatic biomarkers and its hepato-protective potentials. The best formula showing maximum numerical reductions of AST activity was observed for G4 (*Annona* pulp 7.5%). The highest decreased limit in ALT (U/L) obtained for G4 (*Annona* pulp 7.5%). **Owolabi *et al.*, (2013)** recorded that treatment of albino rats with *Annona muricata* aqueous leaf-extracts significantly reduced the elevated activities of the alanine aminotransferase (ALT). **Shrivastava and Gilhotra, (2017)** revealed that, CCl_4 administration showed significant elevation in ALP activity which was significantly (P<0.5) reduced by treatment with *Annona squamosa* extract.

Table (3): Serum activity of AST, ALT & ALP and AST/ALT ratio in normal and hepatointoxicated rats (n=5 rats/groups)

Parameters / Groups	AST (U/L) Mean ±SD	ALT (U/L) Mean ± SD	AST/ALT (U/L) Mean ± SD	ALP (U/L) Mean ± SD
G1: Control –ve	21^{g}± 1.81	13^{g}± 1.91	1.62^{b}±0.001	94^{h}±1.89
G2: Control +ve	68^{a}± 1.75	49^{a}± 1.83	1.39^{d}±0.022	278^{a}±1.75
G3: Annona pulp 5%	29^{f}± 1.62	18^{f}± 1.71	1.61^{b}±0.009	89^{i}±1.61
G4: Annona pulp 7.5%	27^{f}± 1.36	16^{f}± 1.39	1.69^{a}±0.005	85^{j}±1.52
G5: Annona peels 5%	48^{b}± 1.54	37^{b}± 1.52	1.30^{e}±0.002	167^{b}±1.44
G6: Annona peels 7.5%	41^{d}± 1.21	30^{c}± 1.28	1.37^{d}±0.003	160^{c}±1.33
G7: Annona seeds 5%	45^{c}±1.09	29^{c}±1.02	1.55^{c}±0.038	155^{d}±1.28
G8: Annona seeds 7.5%	42^{d}±2.48	27^{cd}±1.44	1.56^{c}±0.006	142^{e}±1.11
G9: Mixture of all 5%	39^{d}±1.14	25^{d}±1.12	1.56^{c}±0.014	137^{f}±1.05
G10: Mixture of all 7.5%	36^{e}±1.52	22^{e}±1.66	1.04^{f}±0.008	130^{g}±1.45
LSD	2.72	2.78	0.026	2.49

Values with different letters indicate significant differences between the groups (P≤0.05), and vice versa. LSD: least significant Differences (P≤0.05).

2-Lipids fraction of serum:

Data presented in table (4), show the effect of feeding by Graviola fruit parts diets on serum lipids fractions. It could be observed that hepatointoxication accompanied by the rise of TC, TG, VLDL, LDL, AI ratio. All hepatointoxicated rats fed on all tested fruit parts diets (G3, G4, G5, G6, G7, G8, G9 & G10) had significant decreases in serum total cholesterol (TC) (mg/dl) ranging from -50.19% to -63.60% compared to control (+) group. The highest decreased limit obtained for G4 (*Annona* pulp 7.5%). **Maarof *et al.*, (2015)** showed that the total cholesterol level was significantly reduced (P≤0.05) in soursop at medium and high dosage compared to control group.

All Experimental diets (G3, G4, G5, G6, G7, G8, G9 & G10) presented a significant decrease in serum triglycerides (TG) (mg/dl) ranging from -25.81% to -66.67% of control (+) group. Moreover, G3 (*Annona* pulp 5%), G4 (*Annona* pulp 7.5%) & G6 (*Annona* peel 7.5%) decreased TG more than control (-) group record. G4 (*Annona* pulp 7.5%) showed the highest decreased limit in serum triglycerides (TG) (mg/dl), with significant difference with the other groups.

It is obvious hepatointoxication lowered considerably the level of good cholesterol (from 41 to 29mg/dl). On the contrary, feeding experimental diets (G3, G4, G5, G6, G7, G8, G9 & G10) reversed such change, taking into consideration that the highest increased limit obtained for G4 (*Annona* pulp 7.5%) with significant difference with them. **Gupta *et al*., (2005)** demonstrated that blood HDL-C increased in alloxan-induced diabetic rabbits when treated with different extract fractions from *Annona* (*Annona squamosa*) pulp.

VLDL in serum was appreciably increased by hepatointoxication while decreased by nutritional intervention using experimental diets (G3, G4, G5, G6, G7, G8, G9 & G10) which ranging from -25.81% to -66.67% of control (+) group. The highest decreased limit obtained for G4 (*Annona* pulp 7.5%) with significant difference as compared to the other groups.

The intake of fruit parts diets lowered appreciably the LDL level. Best treatment recorded for G4 (*Annona* pulp 7.5%) which revealed non-significant different LDL content in comparison with control (-) group. Studies of **Adewole and Ojewole, (2009)** agree with results of present work in *Annona* pulp group decreased plasma LDL cholesterol levels.

Nutritional intervention with experimental diets (G3, G4, G5, G6, G7, G8, G9 & G10) lowered greatly the AI, in particular for the G3 (*Annona* pulp 5%) & G4 (*Annona* pulp 7.5%) which recorded -79.73% & -82.84% less AI compared to control (+) group and non-significant different AI value compared to control (-) rats.

Adeyemi *et al*., (2009) showed that treatment with methanolic extracts of *Annona muricata* led to a significant (P ≤ 0.05) reduction in the serum total cholesterol, triglyceride, low- density lipoprotein cholesterol and very low-density lipoprotein cholesterol; and a significant (P ≤0.05) increase in the serum high-density lipoprotein cholesterol of *A. muricata*-treated group when compared to untreated diabetic group of rats.

Table (4): Lipids fractions in serum of normal rats and hepatointoxicated rats (n=5 rats/groups)

Parameters / Groups	TC (mg/dl) Mean ± SD	TG (mg/dl) Mean ± SD	HDL (mg/dl) Mean ±SD	VLDL (mg/dl) Mean ± SD	LDL (mg/dl) Mean ± SD	AI (mg/dl) Mean ± SD
G1: Control –ve	98^{g} ±1.85	78^{h} ±1.05	41^{a}±1.3	15.6^{f}±0.88	41.4^{h}±0.04	1.39^{g}±0.39
G2: Control +ve	261^{a} ± 2.77	186^{a} ± 2.78	29^{e}±1.75	37.2^{a}± 1.23	194.8^{a}±1.23	8.04^{a}±0.25
G3: Annona pulp 5%	100^{g} ± 1.13	69^{i} ± 1.13	38^{abc}±1.81	13.8^{g}± 0.25	48.2^{g}±0.11	1.63^{fg}±0.06
G4: Annona pulp 7.5%	95^{h} ± 1.45	62^{j} ± 1.61	40^{ab}±1.12	12.4^{h}± 0.09	42.6^{h}±0.93	1.38^{g}±0.16
G5: Annona peels 5%	116^{e} ± 1.63	87^{f} ± 1.29	35^{cd}±1.68	17.4^{de}± 0.37	63.6^{e}±0.29	2.31^{de}±0.3
G6: Annona peels 7.5%	109^{f} ± 1.01	83^{g} ± 1.55	37^{bcd}±1.03	16.6^{ef}± 0.59	55.4^{f}±0.75	1.95^{ef}±0.22
G7: Annona seeds 5%	120^{d} ± 1.75	96^{d} ± 1.44	34^{d}±1.99	19.2^{c}±0.88	66.8^{d}±1.12	2.53^{d}±0.2
G8: Annona seeds 7.5%	118^{de} ± 1.29	90^{e} ± 1.34	36^{cd}±1.39	18^{d}±0.28	64^{e}±0.56	2.28^{de}±0.07
G9: Mixture of all 5%	130^{b} ±1.36	138^{b} ± 1.74	29^{e}±1.48	27.6^{b}±0.05	73.4^{b}±1.43	3.48^{b}±0.09
G10: Mixture of all 7.5%	127^{c} ± 158	135^{c} ± 1.93	31^{e}±1.51	27^{b}±0.37	69^{c}±0.66	3.10^{c}±0.14
LSD	2.81	2.82	2.61	1.086	1.43	0.36

Values with different letters indicate significant differences Between the groups (P≤0.05), and vice versa. LSD: least significant Differences (P≤0.05).

d-Kidney functions:

The results illustrated in table (5) indicate the serum creatinine (mg/dl), urea (mg/dl) & uric acid (mg/dl) of experimental rats. It could be noticed that hepatointoxication raised serum creatinine (mg/dl), urea (mg/dl) &uric acid (mg/dl). All rats of experimental diets (G3, G4, G5, G6, G7, G8, G9 & G10) showed significant decreases in serum creatinine (mg/dl), urea (mg/dl) &uric acid (mg/dl). Taking into consideration that the highest decreased limit of serum creatinine (mg/dl) , urea (mg/dl) & uric acid (mg/dl) obtained for G4 (*Annona* pulp 7.5%). This trend was also found by **Usunomena & Ngozi (2016)** who found that *Annona muricata* lowered the levels of urea nitrogen (UN), creatinine (Cr) & uric acid (UA) that were released into serum as a consequence of acute DMN-induced hepatic and renal damage. It significantly decreased (p< 0.05) acute DMN-induced (p< 0.05) urea, creatinine and uric acid levels when compared to DMN alone group, thus enhancing renal function.

Table (5): Kidney function (creatinine (mg/dl), urea (mg/dl) &uric acid (mg/dl) in serum of normal and hepatointoxicated rats (n=5 rats/groups)

Parameters / Groups	**Urea (mg/dl) Mean ±SD**	**Creatinine (mg/dl) Mean ± SD**	**Uric Acid (mg/dl) Mean ± SD**
G1: Control –ve	15^{f}±1.89	0.5^{c}±**0.07**	3.1^{d}±0.07
G2: Control +ve	54^{a}±1.25	1.7^{a}±**0.81**	8.3^{a}±1.15
G3: Annona pulp 5%	19^{de}±1.33	0.6^{c}±0.06	3.7^{bcd}±0.25
G4: Annona pulp 7.5%	17^{ef}±1.69	0.5^{c}±0.01	3.4^{cd}±0.09
G5: Annona peels 5%	24^{c}±1.09	0.9^{bc}±0.36	3.5^{bcd}±0.01
G6: Annona peels 7.5%	21^{d}±1.41	0.8^{bc}±0.07	4^{bcd}±0.19
G7: Annona seeds 5%	26^{c}±1.63	1.3^{ab}±0.02	4.3^{bc}±0.33
G8: Annona seeds 7.5%	29^{b}±1.14	1.4^{ab}±0.05	4.1^{bcd}±0.08
G9: Mixture of all 5%	29^{b}±0.99	1.4^{ab}±0.22	4.6^{b}±0.42
G10: Mixture of all 7.5%	30^{b}±1.07	1.4^{ab}±0.22	4.4^{bc}±0.01
LSD	2.35	0.51	0.71

Values with different letters indicate significant differences Between the groups (P≤0.05), and vice versa. LSD: least significant Differences (P≤0.05).

E- Serum protein fractions:

The results of table (6) show serum protein fractions (total protein (g/dl), albumin (g/dl), globulin (g/dl) & Alb/Glb ratio of experimental rats. It is evident that T. protein & albumin (g/dl) degenerated due to hepatointoxication, while were raised by feeding tested fruit parts, in particular G4 (*Annona* pulp 7.5%) which recorded the highest increase of T. protein, albumin & Alb/Glb ratio. hepatointoxication elevated the globulin (from 2.2 to 2.4 g / dl). The highest decreased limit of globulin obtained for G4 (*Annona* pulp 7.5%).

These results are in agreement with **Saleem *et al*., (2010)** who showed that the extracts of *Annona squamosa* had a significant increase in total protein as compared to the hepatotoxic group. Similarly, **Offor *et al*., (2015)** showed that the levels of total protein and albumin were decreased in hepatointoxicated rats,and there was a significant dose-dependent increase (P≤0.05) in total protein and albumin concentrations in the albino rats that received the ethanol extract of *Annona muricata* at high level of doses.

Table (6): Serum protein fractions (total protein (g/dl), albumin (g/dl), globulin (g/dl) & Alb/Glb ratio in serum of normal and hepatointoxicated rats (n=5 rats/groups)

Parameters / Groups	**T.P (g/dl) Mean ±SD**	**Alb. (g/dl) Mean ± SD**	**Glb. (g/dl) Mean ± SD**	**A/G (g/dl) Mean ± SD**
G1: Control –ve	7.2^{b}± 0.11	5^{b}± 0.03	2.2^{cd}±0.03	2.27^{c}±0.107
G2: Control +ve	4.6^{f}± 0.25	2.2^{g}±0.01	2.4^{bc}±0.01	0.92^{g}±0.001
G3: Annona pulp 5%	6.9^{bcd}±0.09	4.6^{c}± 0.11	2.3^{c}±0.17	2^{d}±0.05
G4: Annona pulp 7.5%	7.9^{a}± 0.46	6.1^{a}± 0.25	1.8^{e}±0.08	3.39^{a}±0.102
G5: Annona peels 5%	6.8^{bcd}±0.08	4.1^{de}± 0.09	2.7^{a}±0.05	1.52^{f}±0.025
G6: Annona peels 7.5%	7^{bc}± 0.01	4.4^{cd}± 0.36	2.6^{ab}±0.19	1.69^{e}±0.093
G7: Annona seeds 5%	6.3^{cde}±0.64	4^{def}±0.07	2.3^{c}±0.08	1.74^{e}±0.111
G8: Annona seeds 7.5%	6.1^{de}±0.03	4.3^{cde}±0.42	1.8^{e}±0.16	2.39^{b}±0.005
G9: Mixture of all 5%	5.8^{e}±0.19	3.6^{f}±0.06	2.2^{cd}±0.02	1.64^{e}±0.011
G10: Mixture of all 7.5%	5.9^{e}±0.72	3.9^{ef}±0.04	2^{de}±0.18	1.95^{d}±0.025
LSD	0.61	0.34	0.20	0.17

Values with different letters indicate significant differences Between the groups (P≤0.05), and vice versa.LSD:least significant Differences (P≤0.05).

F- Serum bilirubin fraction:

Data of table (7) show the effect of feeding by experimental diets on serum levels of total bilirubin, direct bilirubin and indirect bilirubin in hepatointoxicated rats.

Total bilirubin, direct bilirubin and indirect bilirubin improved when rats fed on the above mentioned fruit parts powders and their mixture

It is obvious that due to hepatointoxication total bilirubin, direct bilirubin and indirect bilirubin activity increased. All rats of tested fruit parts showed a significant decrease in serum levels of total bilirubin ranging from -14% to -41% of control (+) group. G4 (*Annona* pulp 7.5%) showed the highest decreased limit in serum levels of total bilirubin with non-significant difference with G3 (*Annona* pulp 5%) & control (-) group. **Saleem *et al*., (2010)** showed that the extracts of *Annona squamosa* had a significant decrease in total bilirubin as compared to the hepatotoxic group.

Feeding on experimental diets (G3, G4, G5, G6, G7, G8, G9 & G10) reduced greatly the direct bilirubin level, in particular that of G4 (*Annona* pulp 7.5%) -57.89% decrease in comparison with control (+) group, which reversed highest decrease direct bilirubin activity with non-significant difference with control (-) group.

Experimental diets (G3, G4, G5, G6, G7, G8, G9 & G10) showed a significant decreasing in serum levels of indirect bilirubin ranging from -14.29% to -39.56% of control (+) group, taking into consideration that the highest increased limit obtained for G4 (*Annona* pulp 7.5%), with no significant differences with G3 (*Annona* pulp 5%) & control (-) group. These results are in agreement with **Gupta *et al*., (2005)** who observed that feeding fruit pulp of *Annona muricata* had decreased serum bilirubin levels.

Table (7): Total bilirubin, direct bilirubin and indirect bilirubin activity of normal rats and hepatointoxicated rats (n=5 rats/groups)

Parameters / Groups	T.B (mg/dl) Mean ±SD	D.B (mg/dl) Mean ± SD	I.B (mg/dl) Mean ± SD
G1: Control –ve	0.58^{c}±0.009	0.040^{g}±0.0001	0.54^{f} ± 0.009
G2: Control +ve	1.00^{a}±0.25	0.095^{a}±0.0009	0.91^{a} ± 0.001
G3: Annona pulp 5%	0.61^{c}±0.001	0.044^{f}±0.0002	0.57^{f} ± 0.008
G4: Annona pulp 7.5%	0.59^{c}±0.008	0.040^{g}±0.0008	0.55^{f} ± 0.002
G5: Annona peels 5%	0.69^{bc}±0.013	0.045^{f}±0.0007	0.65^{d} ± 0.007
G6: Annona peels 7.5%	0.66^{bc}±0.006	0.046^{f}±0.0005	0.61^{e} ± 0.004
G7: Annona seeds 5%	0.74^{bc}±0.026	0.093^{b}±0.0006	0.66^{d} ± 0.005
G8: Annona seeds 7.5%	0.73^{bc}±0.003	0.079^{d}±0.0025	0.65^{d} ± 0.012
G9: Mixture of all 5%	0.86^{b}±0.048	0.085^{c}±0.0011	0.78^{b} ± 0.024
G10: Mixture of all 7.5%	0.80^{bc}±0.004	0.076^{e}±0.0005	0.72^{c} ± 0.038
LSD	0.14	0.0017	0.026

Values with different letters indicate significant differences between the groups (P≤0.05), and vice versa. LSD: least significant Differences (P≤0.05).

G-Antioxidants enzymes:

Data of table (8) show the effect of feeding by experimental diets on serum levels of antioxidants enzymes (CAT(mmol/L), SOD (mmol/L) & GPx(ng/ml)) in hepatointoxicated rats.

It is obvious that due to hepatointoxication CAT(mmol/L), SOD (mmol/L) & GPX(ng/ml) activity reduced. All rats of tested fruit parts showed a significant increase in serum levels of CAT(mmol/L) ranging from +344.44% to +655.56% of control (+) group. G4 (*Annona* pulp 7.5%) showed the highest increased limit in serum levels of CAT (mmol/L) as compared to all diets formulae, with non-significant difference with control (-) group.

Feeding on experimental diets (G3, G4, G5, G6, G7, G8, G9 &

G10) raised greatly the SOD activity, in particular that of G4 (*Annona* pulp 7.5%) +754.55% increase in comparison with control (+) group, which reversed highest increase SOD activity.

Experimental diets (G3, G4, G5, G6, G7, G8, G9 & G10) showed a significant increasing in serum levels of GPX (ng/ml) ranging from +90% to +255% of control (+) group, taking into consideration that the highest increased limit obtained for G4 (*Annona* pulp 7.5%) with no significant differences with control (-) group. These results are consistent with previous reports which indicated that CCl_4 brought about significant decreases in liver SOD, CAT, GPx in hepatointoxicated positive rats compared with those of normal control rats **(Adewole and Ojewole, 2009). Abbas *et al*., (2015)** showed that Graviola is an excellent source of the trace mineral manganese, which is an essential cofactor in a number of enzymes important in energy production and antioxidant defenses. For example, the key oxidative enzyme superoxide dismutase, which disarms free radicals produced within the mitochondria (the energy production factories within our cells), requires manganese. **Arthur *et al*., (2012)** reported that hepatointoxicated positive rats have significant decrease GPx activity in serum compared with those of normal control rats.

Table (8): Antioxidants enzymes (CAT(mmol/L), SOD (mmol/L) & GPX(ng/ml) activity of normal rats and hepatointoxicated rats (n=5 rats/groups)

Groups \ Parameters	CAT (mmol/L) Mean ±SD	SOD (mmol/L) Mean ± SD	GPX (ng/ml) Mean ± SD
G1: Control –ve	67^{a}±1.95	96^{a}±1.08	69^{a}±1.83
G2: Control +ve	9^{f}±1.65	11^{f}±1.82	20^{g}±1.05
G3: Annona pulp 5%	66^{a}±1.47	92^{b}±1.16	66^{b}±1.75
G4: Annona pulp 7.5%	68^{a}±1.73	94^{ab}±1.73	71^{a}±1.17
G5: Annona peels 5%	52^{c}±1.81	44^{d}±1.25	52^{d}±1.62
G6: Annona peels 7.5%	59^{b}±1.52	45^{d}±1.64	56^{c}±1.28
G7: Annona seeds 5%	41^{e}±1.36	52^{c}±1.39	43^{e}±1.56
G8: Annona seeds 7.5%	46^{d}±1.23	39^{e}±1.52	45^{e}±1.38
G9: Mixture of all 5%	40^{e}±1.18	38^{e}±1.91	40^{f}±1.41
G10: Mixture of all 7.5%	42^{e}±1.89	36^{e}±1.47	38^{f}±1.93
LSD	2.72	2.59	2.59

Values with different letters indicate significant differences Between the groups ($P \leq 0.05$), and vice versa. LSD: least significant Differences ($P \leq 0.05$).

H-Serum glucose:

Data of table (9) show the effect of feeding by experimental diets on serum glucose levels in hepatointoxicated rats.

It is obvious that due to hepatointoxication serum glucose level increased. All rats of tested fruit parts showed significant decreases in serum levels of glucose ranging from -2.22% to -17.57% of control (+)

group. G3 (CCL_4 injected rats fed on 5% Annona pulp) & G4 (CCl_4 injected rats fed on 7.5% *Annona* pulp)showed the highest decrease limit in serum levels of glucose as compared to all diets formulae, with significant difference with control (-) group. This result is in agreement with **Adeyemi *et al*., (2010**) who reported that after administration of STZ, the blood glucose level was significantly higher in animals. The blood glucose levels of animals gradually decreased with treatment with extracts of *A. muricata* over the period of five weeks; there was a significant reduction in the blood glucose levels.

Table (9): Serum glucose (mg/dl) levels of normal rats and hepatuintoxicated rats
(n = 5 rats / gruops)

Parameters / Groups	**Glucose (mg/dl) Mean ±SD**
G1: Control –ve	136^{h}±1.83
G2: Control +ve	239^{a}±1.75
G3: Annona pulp 5%	197.4^{g}±0.96
G4: Annona pulp 7.5%	197^{g}±1.38
G5: Annona peels 5%	210.2^{d}±0.48
G6: Annona peels 7.5%	209^{d}±1.16
G7: Annona seeds 5%	201^{f}±1.61
G8: Annona seeds 7.5%	206.7^{e}±1.54
G9: Mixture of all 5%	233.7^{b}±0.99
G10: Mixture of all 7.5%	215.7^{c}±1.00
LSD	2.27

Values with different letters indicate significant differences Between the groups ($P \leq 0.05$), and vice versa. LSD: least significant Differences ($P \leq 0.05$).

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" الإقتصاد المنزلى والتنمية المستدامة 2030 "
15 ديسمبر2020م

http://homeEcon.menofia.edu.eg ISSN 1110-2578

التأثير العلاجي الطبيعي المحتمل للأغذية المحتوية على أجزاء نباتية من فاكهة القشطة على الفئران المصابة بالتسمم الكبدي

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قسم التغذية وعلم الأطعمة – كلية الاقتصاد المنزلى– جامعة المنوفية– شبين الكوم– مصر

المستخلص العربي:

تم إجراء الدراسة الحالية لمعرفة التأثيرالغذائي المحتمل للأجزاء النباتية المختلفة لفاكهة القشطة والتي تشمل (اللب الداخلى–القشرة الخضراء– البذور السوداء) ومخلوطهم علي تحسن التسمم الكبدي لبعض الفئران المصابة برابع كلوريد الكربون. تم استخدام ٥٠ فأر أبيض بالغ يتراوح وزن الفأر ١٨٠ ± ١٠ جرام، تم تغذيتها على الوجبة الأساسية لمدة أسبوع ثم قسمت بعد ذلك إلي ١٠ مجموعات متساوية وتركت إحداها كمجموعة ضابطة سالبة، أما المجموعات ٩ الأخرى فتم إصابتها تجريبيا باستخدام مادة رابع كلوريد الكربون، (٠,٢ ملجم / كجم من وزن الجسم) لمدة أسبوعين لتحفيز اصابه الكبد. تركت المجموعة ٢ كمجموعة ضابطه موجبة وتمت تغذية المجموعات ٣و ٤و ٥و ٦و ٧و ٨و ٩و ١٠ على نظام غذائي باضافة مساحيق الاجزاء النباتية وهي اللب الداخلي بنسبه ٥%، اللب الداخلي بنسبه ٧،٥%، القشرة الخارجيه بنسبه ٥%، القشره الخارجيه بنسبة ٧،٥%، البذور السوداء بنسبه ٥%، البذور السوداء بنسبه ٧،٥% وخليط منهم بنسبه (٥%،٧،٥%)على التوالي. استمرت التجربة لمدة ٢٨ يوم وفى نهاية التجربة تم وزن الفئران ثم ذبحهم وتجميع عينات الدم بعد صيام ١٢ ساعة ثم فصل السيرم لتقدير مستوى السكر في الدم ، وظائف الكبد (الجلوتاميك أوكسالو أستيك ترانس أمينيز، الجلوتاميك بيرفيك ترانس أمينيزوالألكالين فوسفاتيز)، ووظائف الكلى والبروتين الكلي والألبيومين و الكولسترول الكلى و الجلسريدات الثلاثية،(HDL–c LDL–c and VLDL–c) ومؤشر (AI) وكذلك مستوي البليروبين الكلي المباشر والغير مباشر، وانزيمات منع الأكسدة (CAT,GPX,SOD) ثم تم فصل الأعضاء الداخلية (الكبد والكلى والطحال والرئتين والقلب) ووزنها، وأيضا تم تقدير وزن الجسم المكتسب، والمأخوذ من العلف ونسبة الاستفادة من الغذاء. وقد أظهرت نتائج هذه الدراسة أن تناول الأجزاء المختلفة من فاكهه القشطة(G3 و G4 و G5 و G6 و G7 و G8 وG9 وG10) قد نتج عنه زيادة معنوية في كل من وزن الفئران وكذلك المأخوذ من العلف ونسبة الاستفادة من الغذاء وكذلك زيادة نسبة البروتين الدهني عالي الكثافة و تحسن في مستوى سكر الدم و كذلك تحسن في وظائف الكبد و الكلي ولكن مع انخفاض ملحوظ ($P \leq 0.05$) في بقية التحليلات مقارنة مع مجموعة الضابطة الموجبة(+ ve) ، بما يشير إلي تعزيز وظائف الكلى والكبد مع انخفاض ALT، AST، ALP ، الكرياتينين ، حمض اليوريك ، اليوريا الذي يعكس التأثير العلاجي القوي للتغذية على الاجزاء النباتية المختلفه لفاكهه القشطة على الفئران المصابه بالتسمم الكبدي الناجم عن الحقن برابع كلوريد الكربون. أفضل المعاملات كان للب الداخلي للفاكهة بنسبه 7.5%.

الكلمات المفتاحية:

رابع كلوريد الكربون–تسمم الكبد–القشطة–الاجزاء النباتية–انزيمات الكبد– الانزيمات المضادة للأكسدة.