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Protective and Curative Effects of Virgin Coconut Oil on Acetaminophen-Induced Hepatotoxicity in Adult Wistar Rat

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Abstract

Acetaminophen-induced hepatotoxicity is a well-documented consequence of acetaminophen overdose, necessitating the exploration of therapeutic interventions to develop safer alternatives to synthetic drugs. In this study, we investigated the potential effects of Virgin Coconut Oil (VCO) on acetaminophen (PCM)-induced hepatotoxicity. Thirty-six Wistar rats were divided into twelve groups as follows: Groups 1 and 2 received Normal Saline for 20 and 40 days, respectively; Groups 3 and 4 were administered 750mg/kg of PCM for 20 and 40 days, respectively. Group 5 received 2.5ml/kg of VCO for the initial 10 days followed by 750mg/kg of PCM for the subsequent 10 days. Group 6 received VCO at 2.5ml/kg for the first 20 days followed by 750mg/kg of PCM for the remaining 20 days. Groups 7 and 8 received VCO at 5ml/kg for the initial 10 and 20 days, respectively, followed by PCM administration for the subsequent 10 and 20 days. Groups 9 and 10 were administered 750mg/kg of PCM for the initial 10 and 20 days, respectively, followed by VCO at 2.5ml/kg for the remaining 10 and 20 days. Lastly, Groups 11 and 12 received 750mg/kg of PCM for the initial 10 and 20 days, respectively, followed by VCO at 5ml/kg for the remaining 10 and 20 days. Acetaminophen administration resulted in a significant ($p \leq 0.05$) decrease in the final body weight of PCM-treated groups, while a significant ($p \leq 0.05$) increase in body weight was observed in the negative control, pre-treated, and post-treated groups with VCO. Notably, PCM-treated groups exhibited a significant ($p \leq 0.05$) increase in liver weight compared to negative control and VCO-treated groups. Liver enzyme levels including ALP, ALT, AST, and GGT remained within normal reference ranges in negative control and VCO-treated groups, whereas a significant ($p \leq 0.05$) increase was observed in the positive control groups. Additionally, levels of GPx, SOD, and CAT were significantly ($p \leq 0.05$) decreased in the positive control group compared to the negative control and VCO-treated groups. Overall, the findings of this study demonstrate the potential ameliorating effect of VCO against PCM-induced liver toxicity, highlighting its potential therapeutic utility in mitigating hepatotoxicity.

Keywords: hepatotoxicity, Paracetamol, curative, protective, N-Acetylcysteine, Virgin Coconut Oil

1. Introduction

Liver is the largest organ in the human body and key organ of metabolism, including glycogen storage, decomposition of red blood cells, plasma protein synthesis, and detoxification (Opoku *et al*., 2007). It is continuously and variedly exposed to xenobiotic, environmental pollutants, and chemotherapeutic agents because of its strategic placement in the body (Ibrahim *et al.*, 2008).

Acetaminophen also known as N-acetyl-para-aminophenol (Paracetamol) was discovered in 1889. It is an active metabolite of phenacetin, a compound that was used for its good analgesic and antipyretic properties until it was implicated in analgesic-abuse (Larsen & Wendo, 2014). When acetaminophen is consumed above its therapeutics dosage will lead to hepatotoxicity which is its commonest and most remarkable feature (Larsen & Wendo, 2014). When acetaminophen is taken orally, its absorption occurs rapidly in the duodenum, owing to its

property as a weak acid (McGill & Jaeschke, 2013). It will rapidly metabolize in the liver and majority is eliminated by conjugation to nontoxic sulfated and glucuronidated metabolites and a small percentage of it will undergo oxidation with the help of cytochrome p-450 enzyme resulting in the formation of highly reactive N-acetyl-p-benzoquinone-imine (NAPQI) (Bunchorntavakul & Reddy, 2013; McGill & Jaeschke, 2013). In the normal process of detoxification, this reactive NAPQI is detoxified by the antioxidant enzyme glutathione (GSH) and always maintains equilibrium to neutralize the toxic environment (Song *et al*., 2014). However, when acetaminophen is consumed above its therapeutical dosage, it leads to excessive production of NAPQI that can inflict a shift in this equilibrium due to the saturation of sulfation and glucuronidation process and depletion of GSH, which creates an oxidative stress condition (Dai *et al*., 2006). As a result, progressively more reactive oxygen species (ROS) will be released and that will trigger the cellular necrosis by organelle swelling along with membrane dysfunction through disruption of the mitochondrial membrane permeability transition pores (Yuan & Kaplowitz, 2013).

Coconut tree (*Cocos nucifera L.*) is considered as a premium gift from nature to mankind (Afka *et al.*, 2021). It is also known as the 'tree of life' since each part of the tree has its own medicinal value (Intahphuak *et al.*, 2010; Gans & Kauwell, 2017). Virgin Coconut Oil is recognized as a functional food and the public awareness of it is increasing day by day. Virgin coconut oil is a naturally processed, chemically free and additive free product from fresh coconut meat or its derivatives (coconut milk and coconut milk residue), which has not undergone any chemical processing after extraction (Rajagopal & Rajeev, 2017). It has a mild to intense fresh coconut scent depending on the type of process used for production. Virgin Coconut oil is extracted from fresh coconut milk obtained from matured coconut of 12 months old. It can be consumed in its natural state without the need for further processing (Rajagopal & Rajeev, 2017). It is processed using a low heat process and its nutritional value and health benefits have been recognized for many years. So, it has a significant role in our diet (Kamariah *et al.*, 2008; Widianingrum & Salasia, 2021).

2. Materials and Methods

Chemicals: Acetaminophen (Emzor Pharmaceutical Industries Limited, Nigeria) was procured from Vincal Pharmacy Limited, Wadata, Makurdi. The drug is in solid form and was dissolved in distilled water and dosage was calculated based on body weight in grams (g) and administered orally via gavage syringe.

Induction of Hepatotoxicity: Toxicity was induced by daily doses of 750 mg/kg body weight of PCM orally via gavage following reported toxicity ranges, exposure routes and concentrations (Uchendu *et al*., 2018).

Virgin coconut oil was prepared from the solid endosperm of mature coconut. It was crushed and made into viscous slurry. The slurry was then squeezed through cheese cloth to obtain coconut milk, and it was refrigerated for 48 hours. After 48 hours, the milk was subjected to mild heating (50°C) in a thermostat oven. The obtained virgin coconut oil was filtered through cheese cloth (Nevin & Rajamohan, 2006). The mature copra of Coconut fruit weighed 1 killogram produced 500mls of virgin coconut oil and was stored at room temperature in a propylene ethylene bottle.

2.1 Ethical Considerations

All experimental protocols were in compliance with the laid down ethical guidelines for the use of animals in research, given by the National Committee for Research Ethics in Science and Technology CREC/002.

2.2 Animal Grouping and Administration

The adults Wistar rats (total n=36) were divided into twelve groups and each group contained three (n=3) rats.

Group 1 and 2 (Normal Saline for 20 and 40 days respectively), 3 and 4 (750mg/kg of PCM for 20 and 40 days respectively). Group 5: 2.5ml/kg of VCO for first 10 days, 750mg/kg of PCM for last 10 days. Group 6: VCO at 2.5mls/kg for first 20 days, 750mg/kg of PCM for last 20 days. Group 7 and 8: VCO at 5ml/kg for the first 10 days and 20 days then 750mg/kg of PCM for the last 10 and 20 days. Group 9 and 10: 750mg/kg of PCM for the first 10 and 20 days then VCO at 2.5mls/kg for the last 10 and 20 days. Group 11 and 12: 750mg/kg of PCM for the first 10 and 20 days then VCO at 5ml/kg for the last 10 and 20 days respectively.

Animal Sacrifice and Sample Collection: At the end of the experimental period, all the animals were fasted overnight and weighed at the point of sacrifice using the LS series electronic weighing balance manufactured (ORMA, Italy). They were anesthetized with mild chloroform anesthesia and sacrificed via cervical dislocation. Blood was collected via cardiac puncture with the aid of a needle mounted on a 5 mL syringe (Hindustan Syringes and Medical Devices Ltd., Faridabad, India). The samples were collected into tubes containing 2% sodium oxalate, centrifuged at 3000 rpm for 15 min using a tabletop centrifuge and the serum extracted. The sera were separated and stored in aliquots at -25°C for biochemical assays of specific liver enzymes. The liver was harvested after the abdominal incision, washed three times in normal saline and blotted on ash-free filter paper for macroscopic inspection. It was then fixed in a 10% formal saline for routine histological processing.

2.3 Biochemical Assays of Specific Liver Enzymes

2.3.1 Alanine Aminotransaminase (ALT) Activity

Reitman-Frankel colorimetric method using a Quimica Clinica Applicada (QCA) test kit. ALT activity was measured by monitoring the concentration of pyruvate hydrazone formed with 2, 4-dinitrophenylhydrazine which is proportional to its concentration at 505nm.

2.3.2 Aspartate Aminotransferase Activity (AST)

This parameter was done using the Reitman-Frankel colorimetric method (Reitman & Frankel, 1957) for *invitro* determination of GOT/AST in serum using a Quimica Clinica Applicada (QCA) test kit. I measured AST activity by monitoring the concentration of oxaloacetate hydrazone formed with 2, 4 — dinitrophenylhydrazine spectrophotometrically at 505nm.

2.3.3 Alkaline Phosphatase (ALP) Activity

Phenolphthalein monophosphate method for the in vitro determination of alkaline phosphatase in serum using Quimica Clinica Applicada (QCA) test kit. Alkaline phosphatase acts upon the AMP-buffered sodium thymolphthalein monophosphate. The addition of the alkaline reagent stops the enzyme activity and simultaneously develops a blue chromogen which can be measured photometrically at wavelength of 550nm.

2.4 Estimation of Oxidative Stress Makers

Gamma-Glutamyl Transferase (GGT): The serum was separated by centrifugation (3600 rpm for 15 min) for the determination of serum. Gamma glutamyl transferase (GGT) levels using Quimica Clinica Applicada (QCA) commercial test kits indication.

Estimation of lipid peroxidation (Malondialdehyde (MDA): Lipid peroxidation in the tissue was estimated colorimetrically by thiobarbituric acid reactive substances (TBARS) method of Buege and Aust (1978). A principal component of TBARS is malondialdehyde (MDA), a product of lipid peroxidation. In brief, 0.1 ml of tissue in Tris-HCl buffer, pH 7.5 was treated with 2 ml of (1:1:1 ratio) TBA-TCA-HCl reagent (thiobarbituric acid 0.37%, 0.25 N HCl and 15% TCA) and placed in water bath for 15 min, cooled. The absorbance of clear supernatant was measured against reference blank at 535 nm. Concentration was calculated using the molar absorptivity of malondialdehyde which is 1.56×10^5 M^{-1} cm^{-1} and expressed as nmol/mg protein.

Measurement of Glutathione peroxidase (GPx) activity: The amount of GPx was determined using a commercially available kit (Ransel kit, Randox Laboratories Ltd, Crumlin, UK) by measuring the rate of oxidation of NADPH at 340 nm. A unit of enzyme was expressed as the amount of enzyme needed to oxidize 1nmol of NADPH oxidase/minute.

Assay of Superoxide Dismutase (SOD) activity: Superoxide dismutase activity was measured according to the method of Winterbourn *et al.* (1975) as described by Rukmini *et al*. (2004). The principle of the assay was based on the ability of SOD to inhibit the reduction of nitro-blue tetrazolium (NBT). Briefly, the reaction mixture contained 2.7 ml of 0.067M phosphate buffer, pH 7.8, 0.05 ml of 0.12mM riboflavin, 0.1 ml of 1.5mMNBT, 0.05 ml of 0.01M methionine and 0.1 ml of enzyme samples. Uniform illumination of the tubes was ensured by placing it in air aluminum foil in a box with a 15W fluorescent lamp for 10 minutes. Control without the enzyme source was included. The absorbance was measured at 560nm. One unit of SOD was defined as the amount of enzyme required to inhibit the reduction of NBT by 50% under specific conditions. Activity of enzyme was expressed as units /mg protein.

Assay of catalase (CAT) activity: Catalase activity was measured according to the method of Aebi (1983). Tissue (0.1 ml) was pipetted into cuvette containing 1.9 ml of 50mM phosphate buffer, pH 7.0. Reaction was started by the addition of 1.0 ml of freshly prepared 30% (v/v) hydrogen peroxide (H_2O_2). The rate of decomposition of H_2O_2 was measured spectrophotometrically from changes in absorbance at 240 nm. Activity of enzyme was expressed as units /mg protein.

Statistical Analysis: All data will be expressed as mean ± SEM. The level of homogeneity among the groups will be tested using Analysis of Variance (ANOVA) as described by Snedecor and Cochran (1980**)**. Where heterogeneity occurred, the groups will be separated using Duncan Multiple Range Test (DMRT). A value of $p < 0.05$ will be considered to indicate a significant difference between groups as described by Mathur *et al.*, (2008). Analysis of data will be done using both electronic calculator and Statistical Package for Social Sciences (SPSS version 20.0).

3. Results

3.1 Gross Anatomical Parameters

Table 1, there was significant ($p \leq 0.05$) increase in body weight of the acute negative control compared to the positive control. There was significant ($p \leq 0.05$) decrease in the body weight of the positive control groups

compared to the groups pre-treated or post-treated with VCO. There was a significant ($p \leq 0.05$) increase in initial body weight, final weight and body weight differences between the control groups (1&2) and the groups post-treated and pre-treated with acetaminophen and VCO or Acetaminophen.

Table 1. Effect of Virgin Coconut Oil and Paracetamol on the gross anatomical parameters of Wistar rat

Grp	Treatment	Initial Body Wt. (g)	$^{+}$Final Body Wt. (g)	$^{+}$Body Wt. Differences
1	Acute Normal Control (5ml/kg N.S)	200.2±7.4	205.4±1.4	5.2±7.7
2	Chronic Normal Control (5ml/kg N.S)	208.5±3.5	220.5±14.8	12.0±11.3
3	Acute Positive control (750mg/kg PCM)	207.8±4.0	190.8±12.4	-17.0±16.4
4	Chronic Positive control (750mg/kg PCM)	210.0±0.1	205.5±30.9	-5.4±30.9
5	Acute Protective (2.5ml/kg VCO+PCM)	182.5±1.3	188.1±4.5	5.5±3.1
6	Chronic Protective (2.5ml/kg VCO+PCM)	186.8±6.5	208.8±4.5	21.9±2.0
7	Acute Protective (5ml/kg VCO+PCM)	161.8±5.9	176.2±10.8	14.4±4.9
8	Chronic Protective (5ml/kg VCO+PCM)	141.8±0.9	167.3±23.9	25.5±22.9
9	Acute Curative (PCM+2.5ml/kg VCO)	178.3±11.3	184.1±10.9	12.9±0.3
10	Chronic Curative (PCM+2.5ml/kg VCO)	198.8±11.4	200.9±40.9	22.6±29.4
11	Acute Curative (PCM+5ml/kg VCO)	198.8±3.1	202.5±15.3	3.7±12.2
12	Chronic Curative (PCM+5ml/kg VCO)	187.6±3.1	237.4±15.48	39.8±18.5

$^{+}$represents significant a non-significant ($p > 0.05$) effect as shown in ANOVA.

3.2 Liver Function Enzymes

Table 2 showed no significant ($p > 0.05$) difference in the activity level of AST and ALT in groups treated with normal/ Saline (group 1 and 2). There was significant increase ($p \leq 0.05$) in the activity of AST and ALT in group (3 and 4) that were treated with PCM alone when compared to those of the (group 5 to 12) which were pre-treated with VCO and post treated with VCO. There was no significant increase ($p > 0.05$) in the activity of AST and ALT among the groups that had a post-treatment or pre-treatment of VCO (groups 5-12).

Table 2. Effect of Virgin Coconut Oil and Acetaminophen on liver function test (Aspartate aminotransferase and Alanine transaminase) of adults Wistar rat

Groups	Treatment	AST(U/L)	ALT (U/L)
1	Acute Normal Control (5ml/kg N.S)	73.1±4.8	37.0±4.3
2	Chronic Normal Control (5ml/kg N.S)	70.3±2.7	55.7±1.9
3	Acute Positive control (750mg/kg PCM)	109.5±4.8	77.0±8.5*
4	Chronic Positive control (750mg/kg PCM)	108.0±2.5*	90.0±4.3*
5	Acute Protective (2.5ml/kg VCO+PCM)	81.5±0.7**	64.6±5.1**
6	Chronic Protective (2.5ml/kg VCO+PCM)	99.1±14.0**	53.6±0.5**
7	Acute Protective (5ml/kg VCO+PCM)	85.2±8.8**	57.5±10.5**
8	Chronic Protective (5ml/kg VCO+PCM)	81.0±1.4**	53.6±0.7**
9	Acute Curative (PCM+2.5ml/kg VCO)	84.0±0.0**	46.6±16.1**
10	Chronic Curative (PCM+2.5ml/kg VCO)	86.7±0.7**	58.1±0.1**
11	Acute Curative (PCM+5ml/kg VCO)	89.5±2.0**	52.0±1.4**
12	Chronic Curative (PCM+5ml/kg VCO)	90.0±1.3**	69.5±10.6**

*, **represents significant decreases or increase at $p \leq 0.05$ when compared to groups 1 and 2 (negative controls), groups 3 and 4 (positive controls), a groups 5 and 6 (Low-dose Protective) and b groups 9 and 10 (Low-dose curative), group 5-8 (protective groups) and acute d groups (sister groups) respectively.

Table 3 shows no significant increase (p>0.05) in the activity of ALP and GGT in groups (1 and 2) that were treated with only normal Saline. There was significant increase ((p≤0.05) the activity of ALP and GGT in groups (3 and 4) that were treated with only PCM in acute and chronic phase. There was no significant increase in the ALP and GGT in the groups (5 to 12) that were either pre-treated or post treated with VCO or PCM.

Table 3. Effect of Virgin Coconut Oil and Acetaminophen on liver function test (*Alkaline phosphatase and* Gamma-glutamyl transferase) of Wistar rat

Groups	Treatment	ALP(U/L)	GGT (U/L)
1	Acute Normal Control (5ml/kg N.S)	63.5±0.7	11.5±0.6
2	Chronic Normal Control (5ml/kg N.S)	61.6±14.9	11.0±1.3
3	Acute Positive control (750mg/kg PCM)	100.6±3.4*	35.5±3.4*
4	Chronic Positive control (750mg/kg PCM)	95.6±10.5*	32.5±6.3*
5	Acute Protective (2.5ml/kg VCO+PCM)	79.3±3.1**	15.5±0.6**
6	Chronic Protective (2.5ml/kg VCO+PCM)	72.1±1.2**	20.8±3.4**
7	Acute Protective (5ml/kg VCO+PCM)	71.6±0.5**	19.0±5.6**
8	Chronic Protective (5ml/kg VCO+PCM)	73.2±14.1**	15.7±0.5^{**,d}
9	Acute Curative (PCM+2.5ml/kg VCO)	73.2±11.2**	17.5±0.7**
10	Chronic Curative (PCM+2.5ml/kg VCO)	81.5±4.8^{**,d}	19.1±1.2**
11	Acute Curative (PCM+5ml/kg VCO)	77.6±5.0**	25.3±4.1**
12	Chronic Curative (PCM+5ml/kg VCO)	82.2±1.4^{**,d}	13.8±4.9^{**,d}

*, **represents significant decreases or increase at p≤0.05 when compared to groups 1 and 2 (negative controls), groups 3 and 4 (positive controls), groups 5 and 6 (Low-dose Protective) and groups 9 and 10 (Low-dose curative), group 5-8 (protective groups) and Acute groups (sister groups) respectively.

Oxidative Stress Marker: Table 4 There was no significant (p>0.05) increase in the activity level of MDA in the group negative control groups (1 and 2). There was significant (p≤0.05) increase in the activities of MDA in groups (3 and 4) treated with only with PCM while there is no significant (p>0.05) increase the activity of MDA in groups (5 to 12) compared to positive control group (3 and 4) in acute and chronic phases. The Catalase activity in negative control groups (1&2) shows no significant (p>0.05) increase while there is significant (p≤0.05) increase in CAT activity in group (3 and 4) which were treated with PCM only compared to the curative and protected groups (5 to 12).

Table 4. Effect of Virgin Coconut Oil and Acetaminophen on oxidative stress markers Catalase (CAT) and Malondialdehyde (MDA) of Wistar rat

Groups	Treatment	MDA (nmol/mg)	CAT (U/mg protein)
1	Acute Normal Control (5ml/kg N.S)	0.8±0.0	26.5±0.6
2	Chronic Normal Control (5ml/kg N.S)	0.7±0.2	28.0±1.4
3	Acute Positive control (750mg/kg PCM)	1.2±0.1*	15.2±0.1*
4	Chronic Positive control (750mg/kg PCM)	2.2±0.5*	15.1±1.2*
5	Acute Protective (2.5ml/kg VCO+PCM)	0.8±0.1**	24.5±4.9**
6	Chronic Protective (2.5ml/kg VCO+PCM)	0.9±0.1**	19.1±1.6^{**,d}
7	Acute Protective (5ml/kg VCO+PCM)	0.5±0.2**	25.7±4.6**
8	Chronic Protective (5ml/kg VCO+PCM)	0.8±0.0**	21.5±4.8^{**,d}
9	Acute Curative (PCM+2.5ml/kg VCO)	0.7±0.2**	22.5±4.9**
10	Chronic Curative (PCM+2.5ml/kg VCO)	0.8±0.3**	20.1±1.2**
11	Acute Curative (PCM+5ml/kg VCO)	1.2±0.0^{b}	25.0±5.7**
12	Chronic Curative (PCM+5ml/kg VCO)	0.6±0.2^{**,d}	22.5±3.4**

*, **, and d represents significant decreases or increase at ($p \leq 0.05$) when compared to groups 1 and 2 (negative controls), groups 3 and 4 (positive controls), groups 5 and 6 (Low-dose Protective) and groups 9 and 10 (Low-dose curative), group 5-8 (protective groups) and acute groups (sister groups) respectively.

4. Discussion

The result shows a significant ($p \leq 0.05$) increase in body weight of rats in group 1 and 2 as well as the pre-treated and post-treated groups with VCO or PCM at high and low dosages in acute and chronic phase whereas in the positive control groups (3 & 4) shows a significant decrease in the body weight.

The Liver functions enzymes showed a significant ($p \leq 0.05$) increase in the liver enzymes activity level of AST, ALT, ALP and GGT in groups treated with acetaminophen alone when compared to the negative control. This study also demonstrates a fairly normal level of liver function enzymes in the acute groups pre-treated and post-treated with VCO as well of those groups of the chronic phase pre-treated and post-treated with VCO. This aspect is in line with studies by Oyagbemi and Odetola (2010) and Asadollahi *et al*, (2014). These results indicated that the VCO may induce immunomodulation. The treatment could modulate lymphocyte proliferation (Yuniwarti *et al.*, 2012). The aforementioned biomarkers for liver damage are all increased in administration of other inducers of liver injury like CCL4, which share common mechanism of cellular injury with acetaminophen (Anusha *et al*., 2011; Nasir *et al.,* 2013). The increase in serum level of liver function enzymes is due to the damage of hepatocytes by the Acetaminophen metabolite (NAPQI) which cause rupture of the cell membrane resulting in leakage of the enzymes from hepatocytes to the serum, where the level of these enzymes is normally lower, and their serum levels become abnormally increased and the fairly normal level of the liver enzymes in the pre-treated and post-treated groups shows the effective antioxidant activity of VCO (Du *et al*., 2016; Yan *et al*., 2018).

The oxidative stress shows a significant ($p \leq 0.05$) increase in the activity level of MDA and CAT in rats treated with PCM alone when compared to the values gotten from rats of negative control. There was no significant ($p > 0.05$) increase in the activity of MDA and CAT in the groups of pre-treated and post-treated with VCO. This is in line with a study done by Zachariah (2012). The study also shows a significant decrease ($p \leq 0.05$) in the activity of GPx in the groups treated with only PCM (group 3 and group 4), and this is also in line with a study carried out by Uchendu *et al*. (2012). In addition to liberation of liver enzymes, as acetaminophen also induces oxidative stress followed by necrosis and cellular damage (Kaplowitz *et al*., 2015).

CONCLUSION: Based on our present findings, VCOs, regardless of the low dosage (2.5ml) and high dose of 5ml possess a promising hepatoprotective effect and this hepatoprotective effect of VCO may be attributed, partly to its antioxidant activity.

Virgin Coconut oil has been shown to exhibit potent antioxidant activities by ameliorating the effects of acetaminophen-induced hepatotoxicity in acute and chronic phases. This study has proven the protective and curative effect of virgin coconut oil on acetaminophen-induced hepatotoxicity in adult Wistar rats at low and high dosages. Hence, the feasibility of exploring a potential agent for the improved treatment of acetaminophen-induced hepatotoxicity in acute and chronic phases with minimal adverse effects at low cost.

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