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Research Article
Therapeutic Potential of Virgin Coconut Oil in Ameliorating Diabetes Mellitus and Hepatotoxicity Using Rattus Norvegicus as Case Study

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Abstract

Background and Objective: The medicinal properties of many plants still remain unexplored for its enumerable activity of compounds, which is why plant materials remain important resources to combat serious diseases. Therefore this present study summarized the findings on the therapeutic potential of virgin coconut oil in improving Diabetes mellitus and Hepatotoxicity using Rattus Norvegicus as case study. **Materials and Methods:** Diabetes mellitus was induced intraperitoneally using alloxan monohydrate (single standard dose-150 mg dL^{-1} per body weight) dissolved in normal saline; while 50% CCl_4 dissolved in olive oil (v/v = 1:1) orally administered at a dosage of 1mL kg^{-1} body weight thrice weekly for 2 weeks was adopted as a measure to induce liver injury in rats. Treatments for both cases were carried out using virgin coconut oil (VCO) (daily dosage-1.42 mL kg^{-1} per b.wt.,). **Results:** Results obtained recorded significant decrease and increase ($p<0.05$) in body weights and blood glucose levels of diabetic rats from 7-21 days of the study when compared with diabetic rats treated with virgin coconut oil which significantly reversed ($p<0.05$) these changes close to normal levels. Results obtained from biochemical assays conducted on the lipid profile (TC, TG, LDL-C and HDL-C), liver enzyme markers (AST, ALT and ALP) and antioxidant status (SOD and MDA) of diabetic and CCl_4-induced rats treated with virgin coconut oil recorded significant changes ($p<0.05$) when compared to control, diabetic rats and CCl_4-induced rats in both cases. Liver tissues of CCl_4-Induced rats treated with VCO revealed a significant reduction in weight when compared with rats on CCl_4 dosage only. Histological studies revealed the protective and regenerative effects of virgin coconut oil on liver tissues. **Conclusion:** The findings in this study provided an insight into the therapeutic properties of virgin coconut oil which could serve as a benchmark for clinical trials.

Key words: Virgin coconut oil, diabetes mellitus, hepatotoxicity, rattus norvegicus, therapeutic, histological studies, intraperitoneally

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Diabetes mellitus is a type of metabolic disease identified as an irregular energy metabolism which leads most particularly to hyperglycemia and dyslipidemia as a result of lack in insulin secretion, insulin action or both[1]. The main signs of diabetes mellitus are polyuria (recurrent urination), polydipsia (dehydration), polyphagia (increased starvation) and weight loss[2]. The World Health Organization stated that approximately 422 million adults are suffering from diabetes mellitus worldwide[3]. The widespread of diabetes mellitus is expanding very quickly; thus 2013 report from the International Diabetes Federation sets the figure at 381 million cases[4]. About 20,000 deaths reported annually are attributed to hepatic disorder and diseases caused by ingestion or inhalation of hepatotoxins, thereby listing it as one of the foremost health issues globally especially in evolving countries[5]. Renewed attention to alternative medicines and natural therapies has raised researchers' interest in traditional herbal medicine because of their perceived effectiveness coupled with minimal side effects in clinical experience and relatively low costs[6]. Plant sources are becoming a target to explore new drugs in searching biologically active compounds or secondary metabolites. Thus there is an emerging interest in the utilization of medicinal plants as an alternative approach to current medications.

Virgin coconut oil (VCO) is a derivative of coconut which is obtained from a fully developed kernel of coconut by mechanical or natural process, with or without the use of heat, by not subjecting it to chemical refining, bleaching or deodorising, which does not lead to the alteration of the nature of the oil[7]. The complexity of the conditions surrounding the acceptability of virgin coconut oil as a remediation measure by many health organizations because of its high level of saturated fat, results from the current lack of researches completed so far on the medicinal properties of virgin coconut oil[8]. The role of virgin coconut oil on human health is generating scientific interest in researches and this issue continues to draw significant attention specifically in hyperglycaemia, hyperlipidemia and liver diseases. This current study therefore focused on the therapeutic potentials of virgin coconut oil in ameliorating diabetes mellitus and hepatotoxicity using wistar rats as case study.

MATERIALS AND METHODS

Experimental animals: Twenty-four wistar albino rats (*Rattus norvegicus*) were acquired from the animal house, Department of Biochemistry, University of Benin, Benin. The sexes and weights of the rats were determined and they were preferably males ranging from 150-170 g. The rats were accommodated in metabolic cages under standard laboratory conditions, with access to feeds (pelletized growers mash) and water ad libitum. Experimental animals were acclimatized for a week before induction begun. The experimental protocol was approved by the Faculty of Life Science Ethical Committee of University of Benin.

Preparation and extraction of virgin coconut oil: Fresh mature coconuts obtained from New Benin market, Benin were identified and authenticated in the Herbarium Center, by Mr. Kingsley Ugwu of the Department of Pharmacognosy, University of Benin. After dehusking, the solid endosperm was crushed and prepared into thick slurry which was later compressed through a cheese cloth to obtain coconut milk. The coconut milk was chilled for 12 h to solidify the lipid which were further left to dissolve (containing liquid moisture at this stage). In other to obtain a pure virgin coconut oil, the emulsion was heated slightly for 3 min to eliminate the moisture which was filtered and kept at room temperature.

Experimental design: Twenty-four male Wistar albino rats (weighing 150-170 g) were randomly selected for use. Twelve of the rats were classified in three equal groups as control, diabetic group and diabetic+VCO (1.42 mL kg^{-1}), while the other 12 rats were grouped same way as control, CCl_4 group and CCl_4+VCO (1.42 mL kg^{-1}), respectively.

Induction of diabetes mellitus: Alloxan monohydrate 150 mg kg^{-1} b.wt., was suspended in normal saline and injected intraperitoneally after 18 h of fasting to induce hyperglycemia in rats through the method of Federiuk *et al.*[9]. The blood glucose level was examined after alloxanization in blood samples collected by tail tipping method using a glucometer and test strips. Rats diagnosed with blood glucose level greater than 200 mg dL^{-1} were considered diabetic.

Induction of hepatic injury: About 50% carbon tetrachloride (CCl_4) dissolved in olive oil (v/v = 1:1) at a dosage of 1 mL kg^{-1} b.wt., thrice weekly for 2 weeks was adopted as a measure to induce liver injury in rats.

Collection of blood sample for biochemical analysis: The blood glucose levels and body weights were recorded for rats in all groups at day 1, 7, 14 and 21. At the closing stages of the experiment, blood samples were collected by cardiac

puncture under mild ether or chloroform anesthesia and centrifuged at 3500 rpm for 15 min and the respective sera separated for biochemical analysis viz: High density lipoprotein-cholesterol, triglyceride, total cholesterol, alanine aminotransferase, aspartate aminotransferase, alkaline phosphate, superoxide dismutase and malondialdehyde.

Collection of organ tissue sample for histopathological analysis: Liver specimens of rats from the control, CCl_4 and CCl_4+VCO (1.42 mL kg^{-1}) groups were excised and blotted dry for their respective wet weights to be taken using analytical weighing scale. They were further sliced/trimmed (few mm thickness) and fixed in 10% formal saline for preservation which was used for histological study at the University of Benin Teaching Hospital (UBTH), Benin.

Data analysis: Data were demonstrated as Mean±Standard Error Mean. The results were evaluated using the one-way analysis of variance (ANOVA). *Post-hoc* several comparison tests were carried out using Turkey HSD test to evaluate pair-wise differences among group means. Differences between groups were considered significant at $p<0.05$. All statistical analyses were done using the SPSS software (version 16).

RESULTS

Body weight of rats: The results obtained for the body weight of rats in the various groups as shown in Table 1 indicated that the diabetic group recorded significant reductions ($p<0.05$) in body weight from 7-21 days of the study when compared with control and diabetic+VCO (1.42 mL kg^{-1}) groups, respectively. Also the diabetic+VCO (1.42 mL kg^{-1}) group revealed a significant increase ($p<0.05$) in body weight which was close to the control group but different from the diabetic group.

Blood glucose level of rats: Results shown in Table 2 revealed that the fasting blood glucose levels of the diabetic group recorded a high significant increase ($p<0.05$) from 7-21 days of the study when compared with control and diabetic+VCO (1.42 mL kg^{-1}) groups, respectively. A gradual decrease ($p<0.05$) in blood sugar levels occurred in the diabetic+VCO (1.42 mL kg^{-1}) group from 7-21 days when compared with the diabetic group.

Lipid profile level of rats: The results obtained from the lipid profile of rats in the various groups as shown in Table 3, indicated that the diabetic group recorded a high significant

Table 1: Body weight (g) of rats

	Days			
Groups	1	7	14	21
Control	167.55±2.33[a]	172.76±6.74[a]	178.32±3.99[a]	180.21±3.7[a]
Diabetic group	132.24±6.39[b]	129.29±2.84[b]	127.41±2.74[b]	125.79±2.85[b]
Diabetic+VCO (1.42 mL kg^{-1})	141.31±6.80[c]	150.37±6.71[c]	163.12±2.41[c]	175.18±1.47[a,c]

Values are stated as Mean SEM of 4 rats each group, [b]Significantly different from the values of control ($p<0.05$), [c]Significantly different from the values of diabetic group ($p<0.05$)

Table 2: Blood glucose level (mg dL^{-1}) of rats

	Days			
Groups	1	7	14	21
Control	91.75±8.16[a]	93.50±1.94[a]	97.00±1.58[a]	102.00±1.97[a]
Diabetic group	365.25±15.21[b]	371.00±16.71[b]	371.75±10.70[b]	379.25±11.56[b]
Diabetic group+VCO (1.42 mL kg^{-1})	321.50±6.71[c]	280.75±9.23[c]	241.75±7.88[c]	196.25±5.81[c]

Values are stated as Mean SEM of 4 rats each group, [b]Significantly different from the values of control ($p<0.05$), [c]Significantly different from the values of diabetic group ($p<0.05$)

Table 3: Lipid profile activity of rats

	Lipid profile (mmol L^{-1})			
Groups	Total cholesterol	Triglyceride	HDL-C	LDL-C
Control	107.34±1.20[a]	85.00±1.37[a]	37.88±1.08[a]	52.46±1.06[a]
Diabetic group	145.94±2.05[b]	118.33±2.33[b]	21.67±1.11[b]	100.63±3.39[b]
Diabetic group+VCO (1.42 mL kg^{-1})	128.37±1.01[c]	96.32±1.74[c]	33.76±0.65[a,c]	75.35±0.85[c]

Values are stated as Mean SEM of 4 rats each group, [b]Significantly different from the values of control ($p<0.05$), [c]Significantly different from the values of diabetic group ($p<0.05$)

increase ($p<0.05$) in the serum levels of Total Cholesterol (TC), Triglyceride (TG) and Low-Density Lipoprotein-Cholesterol (LDL-C), while High Density Lipoprotein-Cholesterol (HDL-C) was significantly reduced ($p<0.05$) when compared to control and diabetic+VCO (1.42 mL kg^{-1}) groups. Consequently, the diabetic+VCO (1.42 mL kg^{-1}) group revealed a significant decrease ($p<0.05$) in the serum levels of the TC, TG and LDL-C and an increase ($p>0.05$) in HDL-C levels when compared to the diabetic group.

Antioxidant status of rats: Alloxan monohydrate administration resulted in a significant decrease ($p<0.05$) in superoxide dismutase activity (SOD) and a significant increase ($p<0.05$) in malondialdehyde (MDA) levels in the diabetic group when compared to control and diabetic+VCO (1.42 mL kg^{-1}) groups, respectively as shown in Table 4. Consequently, administration of VCO (1.42 mL kg^{-1}) to diabetic rats resulted in a significant increase ($p<0.05$) and decrease ($p<0.05$) in SOD and MDA levels when compared with the diabetic group.

Liver weight of rats: As shown in Table 5, the liver tissues of CCl_4 group revealed significant increase ($p<0.05$) in weight when compared with those of control and CCl_4+VCO (1.42 mL kg^{-1}) groups, respectively. Consequently the CCl_4+VCO (1.42 mL kg^{-1}) group recorded a significant decrease ($p<0.05$) in liver weight when compared with CCl_4 group.

Liver enzyme markers of rats: Results obtained for the assessment of liver enzyme markers in rats (Table 6) indicated that the CCl_4 group recorded a high significant increase ($p<0.05$) in the activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphate (ALP) respectively when compared with control and CCl_4+ VCO (1.42 mL kg^{-1}) groups. Consequently, the CCl_4+VCO (1.42 mL kg^{-1}) group produced a significant reduction ($p<0.05$) in the activities of ALT, AST and ALP when compared with CCl_4 group.

Antioxidant status of rats: There was a significant decrease ($p<0.05$) and increase ($p<0.05$) in serum superoxide dismutase (SOD) and malondialdehyde (MDA) levels of CCl_4 group when compared with control and CCl_4+VCO (1.42 mL kg^{-1}) groups, respectively (Table 7). Consequently, CCl_4+VCO (1.42 mL kg^{-1}) group recorded significantly changes ($p<0.05$) in SOD and MDA levels when compared to the CCl_4 group.

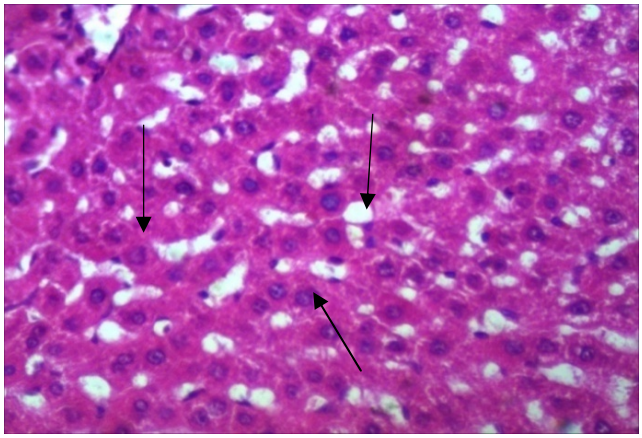

Fig. 1: Sections of liver tissue of control group shows normal cords of hepatocytes, central vein and portal triad, with round nuclei and eosinophilic cytoplasm (thin arrows). Haematoxylin and eosin. Magnification: x400

Table 4: Serum superoxide dismutase (SOD) and malondialdehyde (MDA) levels (mean SEM)

Groups	Superoxide dismutase (U mL^{-1})	Malondialdehyde (mmol mL^{-1} ($\times10^{-3}$)
Control	8.79 ± 0.11^{a}	10.53 ± 0.26^{a}
Diabetic group	6.64 ± 0.19^{b}	15.39 ± 1.34^{b}
Diabetic+VCO (1.42 mL kg^{-1})	7.55 ± 0.14^{c}	$9.49\pm0.42^{a,c}$

Values are stated as Mean SEM of 4 rats each group, [b]Significantly different from the values of control ($p<0.05$), [c]Significantly different from the values of diabetic group ($p<0.05$)

Liver histology: Histological studies revealed the liver tissues of the control, CCl_4 and CCl_4+VCO groups respectively as shown in Fig. 1-3. The liver tissues of the CCl_4 group showed severe necrosis of hepatocytes around the central vein with partial involvement of the mid-zonal areas, loss of nuclei and eosinophilic cytoplasm and cellular infiltration indicating centrilobular necrosis. Thus CCl_4-induced rat treated with virgin coconut oil (1.42 mL kg^{-1}) revealed mild to moderate recovery when compared with the CCl_4 group.

DISCUSSION

Alloxan is used to induce experimental diabetes due to the selective destruction of the insulin-producing pancreatic beta-islets[9]. This particular alloxan-induced insulin release occurs for short duration followed by the complete suppression of the islet response to glucose[10].

In this present study, diabetes mellitus was induced in rats through alloxan monohydrate injection which caused the destruction of beta cells of the pancreas as proposed by Lenzen and Munday[11]. As shown in Table 1 and 2, results

Table 5: Liver weight (g) of rats

	Samples				
Groups	I	II	III	IV	Mean±SEM
Control	4.5	5.1	4.7	5.2	4.88±0.17[a]
CCl_4 only	6.5	6.4	6.7	6.5	6.53±0.06[b]
CCl_4+VCO (1.42 mL kg^{-1})	6.0	5.8	5.7	5.5	5.75±0.10[c]

Values are stated as Mean±SEM of 4 rats in each group, [b]significantly different from the values of control ($p<0.05$), [c] significantly different from the values of CCl_4 group ($p<0.05$)

Table 6: Liver enzyme markers of rats (Mean±SEM)

	Liver enzyme markers (units L^{-1})		
Groups	ALT	AST	ALP
Control	32.30±1.57[a]	40.58±1.53[a]	37.80±1.63[a]
CCl_4 only	65.60±1.31[b]	77.10±3.[b]	71.84±1.55[b]
CCl_4+VCO (1.42 mL kg^{-1})	39.92±0.44[c]	48.50±1.21[a,c]	46.99±1.30[c]

Values are stated as Mean±SEM of 4 rats in each group, [b]Significantly different from the values of control ($p<0.05$), [c]Significantly different from the values of CCl_4 group ($p<0.05$)

Table 7: Serum superoxide dismutase (SOD) and malondialdehyde (MDA) levels (Mean±SEM)

Groups	Superoxide dismutase (U mL^{-1})	Malondialdehyde (mmol mL^{-1} ($\times 10^{-3}$)
Control	6.60±0.19[a]	41.18±0.76[a]
CCl_4 only	2.51±0.03[b]	50.31±1.21[b]
CCl_4+VCO (1.42 mL kg^{-1})	5.53±0.19[c]	45.14±0.31[c]

Values are stated as Mean±SEM of 4 rats in each group, [b]Significantly different from the values of control ($p<0.05$), [c]Significantly different from the values of diabetic group ($p<0.05$)

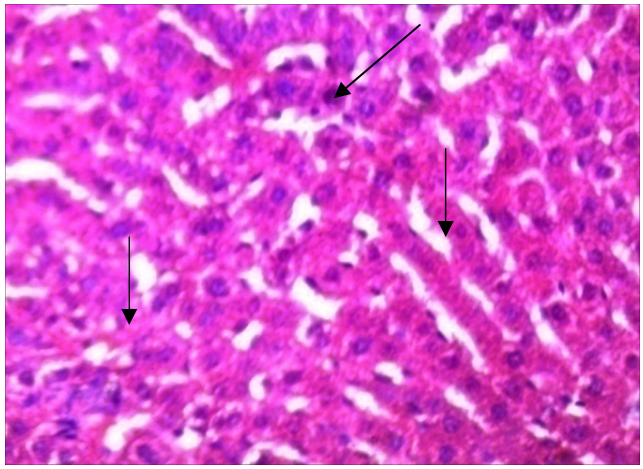

Fig. 2: Sections of liver tissue of CCl_4-induced rat (1 mL kg^{-1}) shows severe necrosis of hepatocytes around the central vein with partial involvement of the mid zonal areas. There is also loss of nuclei and eosinophilic cytoplasm, scattered portal triad and inflammatory cellular infiltration indicating centrilobular necrosis (thin arrows). Haematoxylin and eosin. Magnification: x400

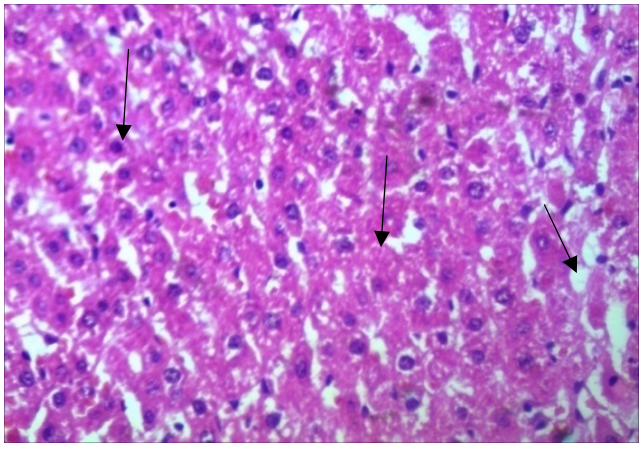

Fig. 3: Sections of liver tissue of CCl_4-induced rat treated with virgin coconut oil (1.42 mL kg^{-1}) shows mild to moderate recovery from centrilobular necrosis with partial cord of hepatocytes, central vein, portal triad, round nuclei and eosinophilic cytoplasm, (Thin arrows) Haematoxylin and eosin. Magnification: x400

obtained for the body weight and fasting blood glucose levels of rats in the diabetic group revealed a decrease in body weight and a significant increase in blood glucose level which indicate loss or ineffective use of glucose by peripheral tissues due to the destruction of beta cells of the pancreas. This agrees with the study of Lachin and Reza[12]. However all of the above changes were found to be reversed in the diabetic+VCO (1.42 mL kg^{-1}) group. This indicated that VCO possesses blood glucose lowering effects due to medium chain fatty acids present in the extract which ensured the recovery of affected beta cell functions and change in body weight. Although this finding is consistent with the study of Iranloye *et al.*[13] it further shows that VCO improves body weight consistently when used on a daily basis.

Dyslipidemia is a significant coronary heart disease risk factor in type 1 diabetes mellitus[14]. The increase in the blood levels of total cholesterol (TC), triglyceride (TG), low density lipoprotein-cholesterol (LDL-C) and a decrease in high density lipoprotein-cholesterol (HDL-C) contribute to secondary complications of diabetes[15].

Results obtained from this study as shown in Table 3 revealed significant increases in TC, TG, LDL-C and a decrease in HDL-C levels. Administration of VCO (1.42 mL kg^{-1}) to diabetic rats resulted in the decrease in serum levels of TC, TG, LDL-C and an increase in HDL-C levels. These observed effects of VCO in the blood levels of lipid profile in diabetic rats suggested that the extract is effective in ameliorating diabetic complications such as cardiovascular disease, arteriosclerosis, coronary artery disease etc., due to its high content of polyphenols which are bioactive components in the extract. Although this finding is consistent with the study of Akinnuga *et al.*[16] it further showed that VCO is even more effective in ameliorating the lipid profile of rats without undergoing any mechanical mixing with any substance.

Results in Table 4 depicted the alterations in the antioxidant defense system of diabetic rats as a result of the significant reduction in the superoxide dismutase (SOD) activity of rats. The decrease in SOD activity in the diabetic group could be due to oxidative stress which led to the formation of free radicals. This is consistent with the studies of Seven *et al.*[17]. Also the significant increase in the malondialdehyde (MDA) levels of the diabetic group may be due to protein damage and inactivation of membrane bound enzymes through direct attack by free radicals. Thus administration of VCO to diabetic rats led to a significant increase ($p<0.05$) and decrease ($p<0.05$) in SOD and MDA levels, respectively in contrast with the diabetic group. This can be attributed to the antioxidant properties contained in the polyphenolic compounds present in VCO extract which serves to restore membrane integrity and oxidative stress generated by free radicals.

The liver is a unique organ anatomically located to serve its dual role as a metabolic and biochemical transformation factory[18]. The ability of the liver to perform these functions is often compromised by numerous substances that we are exposed to on a daily basis; these substances include certain drugs and chemicals (such as carbon tetrachloride, paracetamol, etc) which are associated with hepatotoxicity[19,20].

In this study the significant increase in liver weights of CCl_4 group could be as a result of damaged liver cells exposed to carbon tetrachloride as shown in Table 5. However, the CCl_4+VCO (1.42 mL kg^{-1}) group had their liver weights reduced close to normal levels due to the regenerative properties of VCO.

Results shown in Table 6 revealed the remarkable elevations of serum liver enzyme markers (AST, ALT and ALP) which can be attributed to the destruction of the membrane structures of hepatocytes; hence enzymes are released into circulation after hepatocyte damage. This agrees with the reports of Sallie *et al.*[21]. The CCl_4+VCO (1.42 mL kg^{-1}) group revealed significant reductions ($p<0.05$) in the liver enzyme markers of CCl_4-induced rats due to the active components in VCO such as polyphenols which protect the liver from leakage of enzymes and toxicity of foreign substances.

Superoxide dismutase (SOD) is an important antioxidant enzyme that catalytically scavenges superoxide radicals and provides defense against oxygen toxicity. Thus it is found in high levels in the liver, adrenal glands, kidneys and spleen[22]. Results shown in Table 7 recorded a significant decrease in SOD activities in the CCl_4 group due to the formation of free radicals caused by oxidative stress which led to the damage of membrane lipids, cell injury and cell death. Consequently virgin coconut oil (VCO) (1.42 mL kg^{-1}) administration reversed the SOD activity of CCl_4-induced rats close to normal levels due to its free radical scavenging properties which stabilizes the plasma membrane of hepatocytes. An increase in the serum MDA levels is an indication of elevated level of lipid peroxidation which leads to the decrease in membrane fluidity and death of cells which agrees with the reports of Halliwell and Gutteridge[22]. The CCl_4+VCO (1.42 mL kg^{-1}) group revealed significant decrease in their MDA levels which suggested that VCO may possess necessary bioactive components such as saponins and phenols for protection against free radical damage induced by carbon tetrachloride in rats.

In the histological studies conducted in this research as shown in Fig. 1-3, a section of the liver tissue of the control group revealed normal cords of hepatocytes, central vein and portal triad, with round nuclei and eosinophilic cytoplasm. Some damages such as severe necrosis of hepatocytes, loss of nuclei and eosinophilic cytoplasm, cellular infiltration etc., caused by carbon tetrachloride were observed in sections of liver tissues of the CCl_4 group. Administration of VCO to CCl_4-induced rats brought about mild to moderate recovery of liver tissues from centrilobular necrosis with partial cord of hepatocytes, central vein, portal triad, round nuclei and eosinophilic cytoplasm. This possibly implies that virgin coconut oil may be beneficial to liver cells due to its therapeutic properties.

CONCLUSION

Finally it is believed that bioactive components present in virgin coconut oil are able to improve hyperglycemia, dyslipidemia and liver toxicity in rats thus disregarding the facts that VCO cannot be employed as a remediation measure and also adding to the little literature available. Thus further research on virgin coconut oil may reveal its potential as a source of phyto-medicine which can be presented as a recommendation for clinical trials.

SIGNIFICANCE STATEMENT

This study has successfully provided an insight into the therapeutic properties of virgin coconut oil by rebuking the fact that coconut oil is not accepted as a remediation measure by many health organizations due to its high level of saturated fat. Also the data presented explained the importance of virgin coconut oil as an anti-diabetic, hepato-protective and antioxidant agent in disease states.

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