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Assessment of the Possible Protective Effect of Sugarcane (*Saccharum officinarum*) Peels Extract for Experimentally Induced Hepatotoxicity and Renal Disorders of Adult Male Sprague Dawley Rats

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ABSTRACT

Liver and kidneys disorders are fundamental public health problems as they are critical to exogenous substances such as natural poisons and/or medications that eventually lead to various hepatic and renal disorders mostly due to interference with oxygen metabolism. This study was carried out to evaluate the impact of the sugarcane peel extract on hepatic and renal complications linked to toxicity. Forty Sprague Dawley male rats (150-180g), equally divided into four equal groups. On 13th day of the experiment, the group I and II received distilled water and a single dose of paracetamol (3g/kg bwt), respectively. Group III pretreated with *Saccharum officinarum* peel extract (SOPE) at 200mg/rat for 13 days plus paracetamol (3g/kg bwt) on the 13th day before 1hr of treatment and group IV rats received pretreatment with Silymarin at 0.3g/kg bwt for successive 13 days plus paracetamol (3g/kg bwt) on the 13th day before 1hr of treatment. At the end of the trial, biochemical parameters besides liver and kidney histopathology were examined. Results revealed that the toxin group with a single overdose of paracetamol caused a critical increase in liver enzymes and kidney markers, bilirubin, alkaline phosphatase, lipid levels, an increase in C-reactive protein values, and caused decreases in serum levels of albumin, total protein, oxidative stress parameters (CAT, SOD, and GSH). On the other hand, co-administration of (SOPE) pretreatment showed an impact in minimizing and preventing all of these risks represented in avoiding liver and kidney damage resulting from some medication overdoses. In conclusion, the possible mechanism of protective activity of *Saccharum officinarum* peels extract is owing to its antioxidant and anti-inflammatory effect.

Key words: Sugar cane peels, Oxidative stress, Acetaminophen, Hepatotoxicity, Renal disorders, C-reactive protein.

INTRODUCTION

Liver diseases have become one of the significant reasons for morbidity and mortality in humans and animals. So, studies on liver syndrome pathogenesis on the animal model have been established everywhere throughout the world (Gao et al. 2017; Marcellin and Kutala 2018; Moed and Zaman 2019). The primary capacity of the liver is to consume and detoxify food, medication, and chemicals. Hepatotoxicity due to medications seems to be the most widely recognized contributing component. Hepatocellular and cholestasis can be caused by medications or natural poisons, resulting from hepatic injuries. Liver injuries may lead to hepatic disorder and death (Roy et al. 2014; Singh et al. 2016; Al Kury et al. 2020). Hepato-renal complex is a multi-organ condition affecting both the liver and the kidney. Acute idney injuries can be found in those with acute or chronic liver disease (Amin et al. 2019; Ramadan et al. 2020).

The kidney is responsible for the regulation of fluid and acid-based balances; clearance of toxins whether endogenous (as urea and creatinine) or exogenous (as medications); re-absorption of some beneficial molecules. Amongst these functions, clearing xenobiotics may subject the kidney to acute or chronic damage according to the time and degree of risk (Delanghe and Speeckaert 2011).

Acetaminophen overdose remains one of the most significant poisonings in numerous pieces of the world. A dose of 200mg/kg bwt or 10g is worldwide rules propose and considered a lethal dose (Duffull and Isbister 2013). A particularly harmful complication of acetaminophen

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overdose is hepatic injury (Cermik et al. 2013). However, epidemiological studies have shown that chronic use of acetaminophen is associated with kidney failure (Vaillant et al. 2013). Acetaminophen causing liver toxicity is described as broad oxidative stress. Prior investigations contended that free molecules (oxygen metabolism) caused massive peroxidation in lipid and liver disorders. Reactive oxygen species, within mitochondrial, are responsible for cell signaling, leading to cell damage (Du et al. 2016).

Nutritional supplements and conventional therapeutic plants can give numerous significant medications to the modern drug industry. Hepatoprotective agents, dietary supplements, and herbal formulations with empirically revealed hepatocellular distribution activities can be listed in the therapy of liver ailments. Many medicinal plants have been utilized since ancient times attributed to their successful utilization just as anti-cytolytic and anti-inflammatory role. The medication for liver disorders can be revitalized by creating normalized and scientifically tried elective prescriptions with high protection and adequacy outlines (Chavan and Aniket 2019).

Saccharum officinarum (Sugar cane) fundamental biological activities to health care have been given in a great way against toxicity induced by chemicals or other medication. It comprises several of phytochemicals, among them phenolic mixes, plant sterols, and policosanols are of prime importance. Phenol relief in regular safeguarding of plants refers to maladies, meanwhile, plant sterols and policosanols are segments of wax and plant oils. The phytochemicals have achieved improved enthusiasm because of their cancer prevention agent action, cholesterol-lowering, and other potential medical advantages (Ali et al. 2019). Attributable to these bioactivities against toxicity, it is developed worldwide because of the affordable and therapeutic effect of its high yielding items (Hussein and EL-Shafey 2019).

MATERIALS AND METHODS

This study was conducted in the Scientific & Medical Research Center (ZSMRC) in the faculty of medicine, Zagazig University (No P1-1-2018**).** The protocol was approved by the Institutional Animal Ethics Committee according to the regulation of the committee for controlling and follow-up of experiments on animals; (protocol No: 902 dated: 26/09/2009).

Plant Material Preparation

Sugar Cane (*Saccharum officinarum)* Peels Extract

Plant Material: Sugar cane peels were collected from peeling sugar cane chopsticks from the local center, Sharkia governorate, Egypt. Sugar cane chopsticks were cleaned, and the waste material (peels) were dried in the open air for 7 days in the shade. The dried peel was pulverized to powder by using a mechanical grinder.

Extraction: The sugar cane powder (650g) was extracted with the use of 20L of absolute ethanol by maceration at room temperature three times for 6 days, the extract was concentrated in conformity by reducing pressure by the usage of a rotary evaporator (Buchi, Switzerland), the concentrated extract was fractionated by using a separate funnel by n-hexane (40-60). The n-hexane solvent evaporated, using a rotary evaporator to yield 250g dried residues.

Preparation of Liquid Extraction for Dosage: Acacia gum dry extract (100g) was added to 100ml hot (60ºC) distilled water, after mixing total volume was made 1000ml by addition of distilled water. Out of this suspension, 2ml was used as a daily dose.

Chemical Agents (Drugs)

Paracetamol (500mg Paracetamol Per Tablet)

Acetaminophen, made by El Nasr Pharmaceutical Chemicals Co, is available on the market and was prepared as a suspension for orally single overdose using a metallic stomach tube (oral gavage) by concentration 3g/kg bwt in groups (II, III and IV) (Rekha et al. 2013).

Silymarin Plus Preparation

Silymarin plus was obtained from Sedeco Pharmaceutical Co. Egypt. Silymarin was dissolved in distilled water and then administered orally at 300mg/kg bwt (Toklu et al. 2007).

Experimental Animals

Forty Sprague Dewaley male rats were purchased from the Veterinary Laboratory Animal Farm, Zagazig University. Rats were kept in metal cages (5rats/cage) and sustained under the laboratory conditions model of aeration and temperature. The animals were allowed free access to a standard diet (the commercial rodent chow) and water *ad libitum*. All animals were kept under observation and acclimation for 2 weeks to the optimum environment before starting the experimental time.

Experimental Design

Rats with an initial body weight of 150-180g were randomly divided into four equal groups. Group I (control group) was orally given distilled water. Group II (toxin control) was dosed with a single overdose of acetaminophen (3g/kg bwt), 600mg/200g rat from prepared suspension orally on the 13th day of the trial to induce liver and kidney poisonous quality. Group III was pretreated with *Saccharum officinarum* peel extract dosed, 2ml (200mg)/every rat daily for 13 days, and dosed acetaminophen (3g/kg bwt), 600mg/200g rat once in the 13th day before 1hr of treatment and group IV rats received pretreatment with Silymarin (0.3g/kg bwt), 60mg/200g rats orally daily for successive 13 days with acetaminophen (3g/kg bwt) (single overdose), on the 13th day before 1hr of treatment. At the end of the trial (the 14th day), the blood samples were drawn from fasted rats to prepare serum samples. The liver and kidneys were removed from each rat in all groups, wiped with normal cold saline, dried with filter paper, and sustained in 10% formalin-Saline for the histological examinations.

Laboratory Analysis

On the final day of dosage, blood samples were brought under light ether anesthesia in non-heparinized tubes. Serum was separated by centrifugation for 20min at 4000rpm and serum was preserved at -20°C to determine

the activities of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), albumin, (Total & Direct) bilirubin, alkaline phosphatase, total protein, albumin, cholesterol, and triglycerides. In addition, kidney parameters (creatinine and urea) and inflammatory markers (CRP) were evaluated. Oxidative stress, MDA, SOD, GSH, and CAT were also determined. After the rats were sacrificed, the whole liver and kidney were removed from each rat in all groups, scrubbed with normal saline, dehydrated with filter paper, and stayed in 10% formalin-Saline at room temperature for the histological examinations. The serum activity of ALT and AST were solved by the kinetic method utilizing at once made packs as in conformity with the procedure according to the International Federation of Clinical Chemistry (IFCC) using a fully automated analyzer Ellipse system (Bergmeyer et al. 1986). Serum total and direct bilirubin using Elitech clinical systems are intended for the quantitative in vitro diagnostic determination of bilirubin by Sherwin and Thompson (2003). Serum alkaline phosphatase was determined using Elitech clinical system catalog number PASL-0400. AMS Kit was used for diagnostic determination of total protein according to the procedure of Henry 1974 (Sylvan 1975). Albumin was determined according to Doumas et al. (1971). Serum cholesterol levels were determined according to the procedure of Tietz 1995 and triglycerides according to Rifai et al. (1999). Serum creatinine levels were determined using a BioMed kit by Young et al. (1975). Serum urea levels were determined using Spectrum kits, according to Tietz (1990). BioMed kit was used for the determination of serum C-reactive protein, described by Okamura et al. (1990). Serum GSH levels were determined using a biodiagnostic kit (GSH catalog # GR2511). Serum SOD was determined by a biodiagnostic kit adapted to the procedure of Nishikimi et al. (1972). Serum CAT was determined by using the kit with catalog # CA2517 and serum MDA was specified using the bio-diagnostic kit adapted to the procedure of Satoh (1978).

Statistical Analysis

Numerical data were indicated as mean±SD. The levels of markers were analyzed by ANOVA. The Mann-Whitney U-test was used for comparisons between unrelated groups (Schwartz et al. 2018).

RESULTS

Effect of *Saccharum officinarum* peel extract (SOPE) 2ml/Rat on Various Liver Enzymes and Drug Silymarin Plus in Normal and Induced Toxicity Rats

The data presented in Table 1 showed that oral administration of a single overdose of the drug acetaminophen (3g/kg bwt) (+ve control) caused significant elevations to liver enzymes and alkaline phosphatase in acetaminophen group P<0.0001 when compared with the control group. While pretreatment with sugar cane peel extract and administration of toxin dose of acetaminophen showed a non-significant increase and reduced values compared to the positive control group in these indices. So, an extract showed a good impact according to silymarin plus as a reference drug and according to normal control.

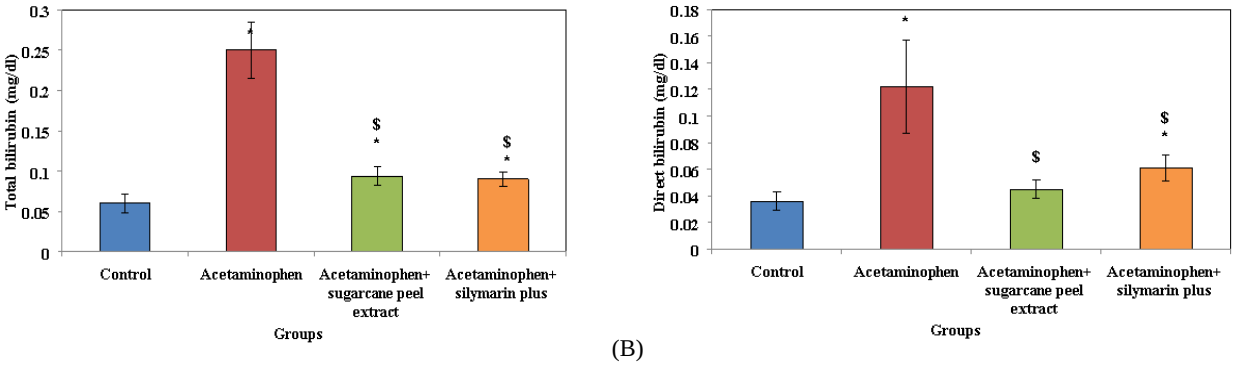
Effect of SOPE on Albumin, Total Protein and Lipid Indices in Normal and Induced Toxicity Rats

As declared in Table 2, positive control group acetaminophen showed a significant decline in levels of albumin and total protein. In contrast, combined with sugar cane peels extract resulted in improving the abnormalities of these parameters. The toxin control group (Acetaminophen group) with a single overdose exhibited significant dyslipidemia as rising to cholesterol and triglycerides values compared to the normal control group. However, pretreatment and co-administration of sugar cane peel extract with overdosing to acetaminophen lowered cholesterol and triglyceride levels.

Table 1: Effect of *Saccharum officinarum* peel extract (SOPE) 2ml/rat on various liver enzyme levels and drug silymarin plus in normal and induced toxicity rats.

Treatment	ALT (U/L)	AST (U/L)	ALP (U/L)
Control	37.0±5.89	127±21.57	63.54±3.77
Acetaminophen	299.0±143.86*	562±165.15*	80.03±4.39*
Acetaminophen+Sugar cane peel extract	73.50±14.95$	206.90±23.12*$	72.99±2.5*$
Acetaminophen+ Silymarin Plus	73.50±31.90$	227.50±13.34*$	77.89±3.19*#

Means±SEM in the same column bearing different superscripts is significantly different at *P<0.0001, $P<0.01, #P<0.05 at P<0.05.



(A) (B)

Fig. 1: Effect of SOPE and drug Silymarin on Bilirubin in combination pretreatment. (A) Total bilirubin, (B) Direct bilirubin where Control, *=Significant *VS* control, $=Significant *VS* Acetaminophen, #=Significant *VS* SOPE.

Table 2: Effect of *Saccharum officinarum* peel extract (SOPE) on Albumin, Total Protein, and Lipid indices in normal and induced toxicity rats.

Treatment	Total protein (g/dl)	Albumin (g/dl)	Total cholesterol (mg/dl)	Triglycerides (mg/dl)
Control	6.69±0.28	4.04±0.15	46.0±4.76	79.60±10.72
Acetaminophen	05.86±0.24*	3.67±0.08*	61.30±9.55*	112.40±17.97$^{\$}$
Acetaminophen+Sugar cane peel extract	6.28±0.29$^{*\$}$	3.81±0.08$^{*\$}$	49.3±2.71$^{\$}$	84.40±13.33$^{\$}$
Acetaminophen+Silymarin Plus	6.70±0.28$^{\$\#}$	3.69±0.11$^{*\$}$	67.1±8.41$^{\#}$	87.30±12.69

Means±SEM in the same column bearing different superscripts is significantly different at *P<0.0001, $P<0.01, #P<0.05 at P<0.05.

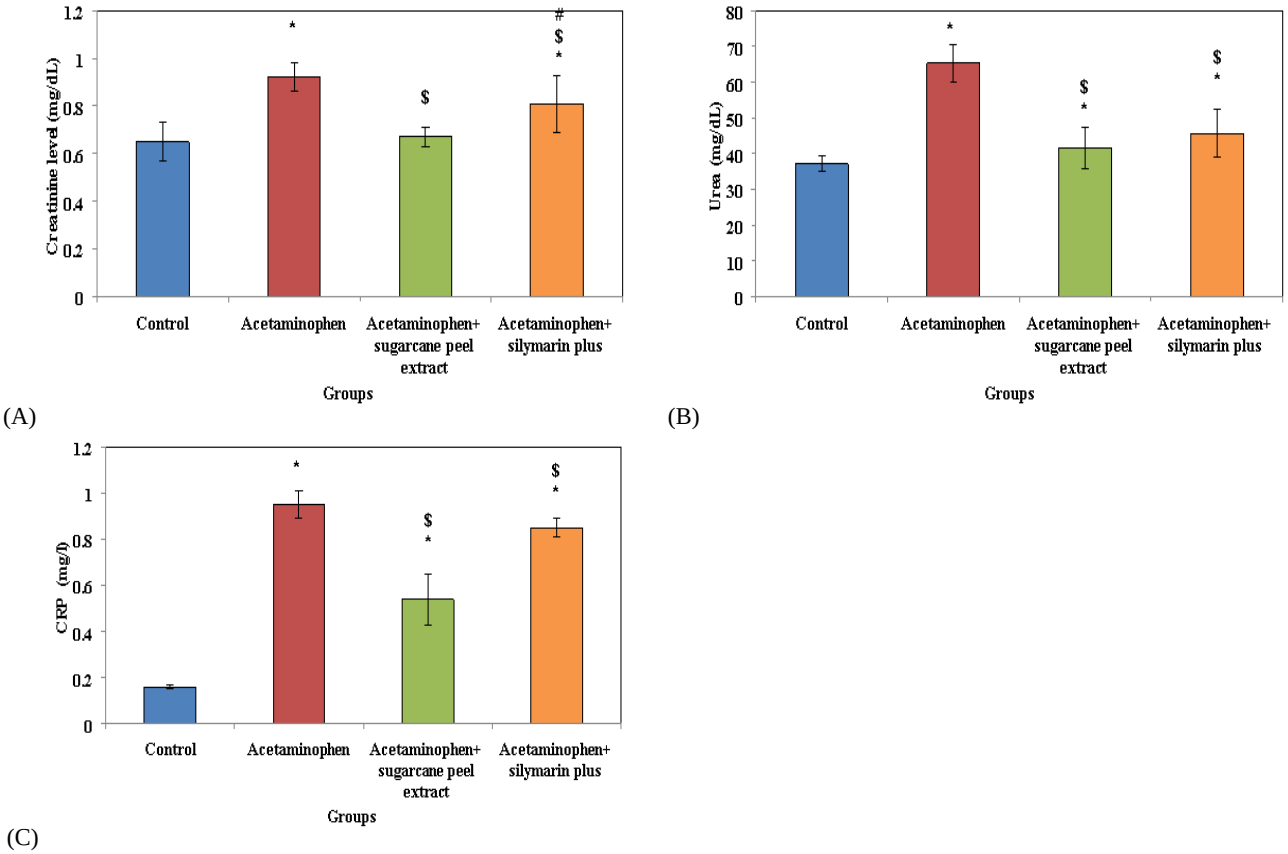


Fig. 2: *Saccharum officinarum* peel extract (SOPE) improves renal function and vital role as an anti-inflammatory effect. **(**A) Creatinine, (B) Urea, (C) CRP where Control, *=Significant *VS* control, $=Significant *VS* Acetaminophen, #=Significant *VS* SOPE.

The Effects of SOPE and the drug Silymarin on Bilirubin in Combination Pretreatment

According to Fig. 1 (A & B), elevation to serum total and direct bilirubin in G2 in comparison with the control group and the combination with sugar cane peels extract (G3) protected against levels elevation as it caused a reduction in the levels of bilirubin and that indicated the ability of SOPE for curing bilirubin.

***Saccharum officinarum* Peel Extract (SOPE) Improves Renal Function and Vital Role as an Anti-Inflammatory Effect**

The results (Fig. 2A, B & C) revealed a highly marked increase (P<0.0001) in the values of creatinine, urea and C-reactive protein in the toxin group II are 0.92±0.06, 65.0±5.12, and 0.95±0.07mg/L, respectively compared with the control group. Pretreatment rats with SOPE described a significant decrease (P<0.0001) in the values of (Cr, Urea, and CRP) which are 0.67±0.04, 41.6±5.7, and 0.54±0.11mg/L, respectively versus toxin rats in the pretreated rats with silymarin plus and acetaminophen group (G4).

***Saccharum officinarum* Peel Extract (SOPE) and Oxidative Stress Activities**

The results (Fig. 3) revealed a substantial increment (P<0.0001), (14.86±2.88)nmol/g in serum MDA in Acetaminophen (G2) and decrease (P<0.0001) in serum GSH, SOD, and CAT) with values 0.72±0.05mmol/g, 1.61±0.42U/g, and 284.4±4.35U/g, compared with a control group. Pretreatment with SOPE caused a significant reduction (P<0.0001) in serum MDA levels in Acetaminophen + Sugar cane peel extract (G3): (6.97±1.76) nmol/g and marked rise (P<0.0001) in serum CAT, GSH, and SOD levels (G3) : (428.8±68.26U/g, 1.10±0.13mmol/g, and 3.097±0.72U/g) to reach normal values of control group than using drug silymarin plus respectively versus toxin rats in acetaminophen group and rats pretreated with Silymarin Plus.

Photomicrographs of Liver Tissues of Normal and Treatment Groups

In the present study (Figure 4), extract group (G3) treated with Sugar cane peels extract and then exposed to

acetaminophen showing regeneration of the liver cells and a small area of necrosis (Fig. 4C1), and showed normal liver tissue following the control group (Fig. 4A) except mild fatty changes (Fig. 4C2) in contrast with Fig. 4B (G2) positive control of acetaminophen group, and liver tissue of a rat (G4) handled with the drug Silymarin Plus, exposed to a single overdose of acetaminophen (Fig. 4 D1 & D2).

Histopathological Examination of Kidneys

The present study, (Fig. 5) revealed improvement in renal tissue of a rat processed with Sugar cane peels extract and exposed to a single overdose of acetaminophen (Fig. 5C) in accordance with the control group (Fig. 5A), showing normal renal tubules and glomerulus with few aggregates of inflammatory cells comparing with acetaminophen group (Fig. 5B) and (Fig. 5D) dealt with silymarin and susceptible to a single overdose of acetaminophen.

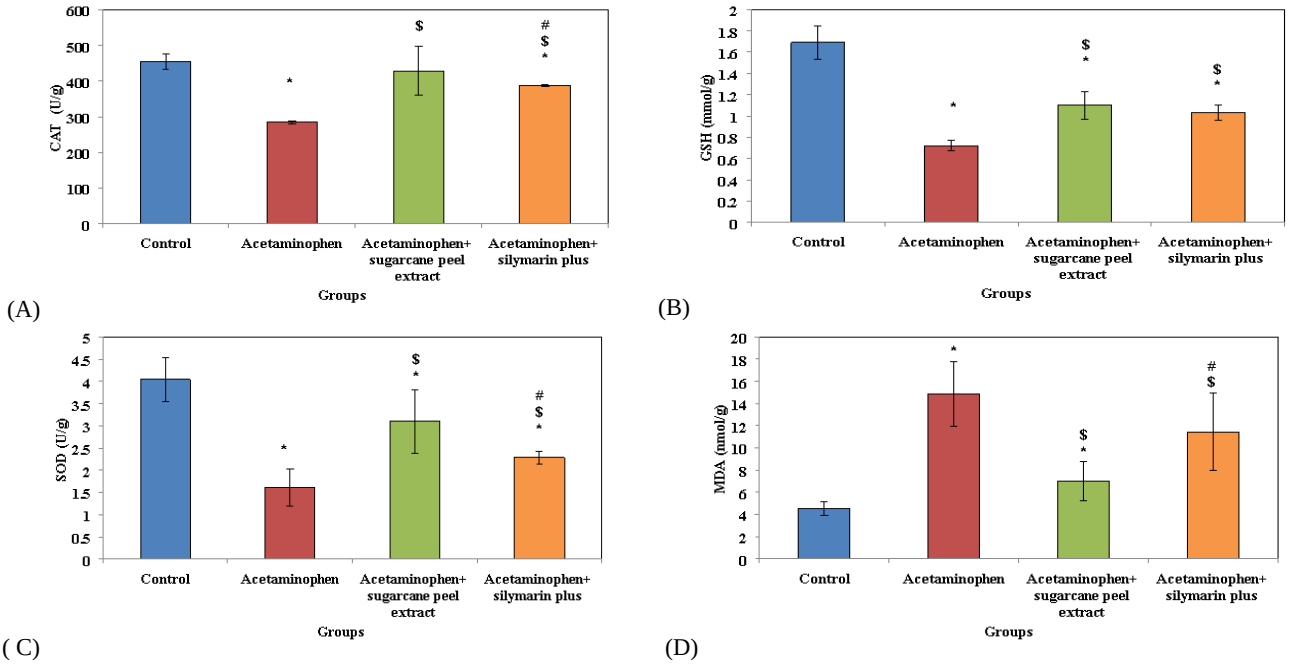


Fig. 3: *Saccharum officinarum* peels extract (SOPE) and oxidative stress activity. (A) CAT, (B) GSH, (C) SOD, (D) MDA where Control, *=Significant *VS* control, $=Significant *VS* Acetaminophen, #=Significant *VS* SOPE.

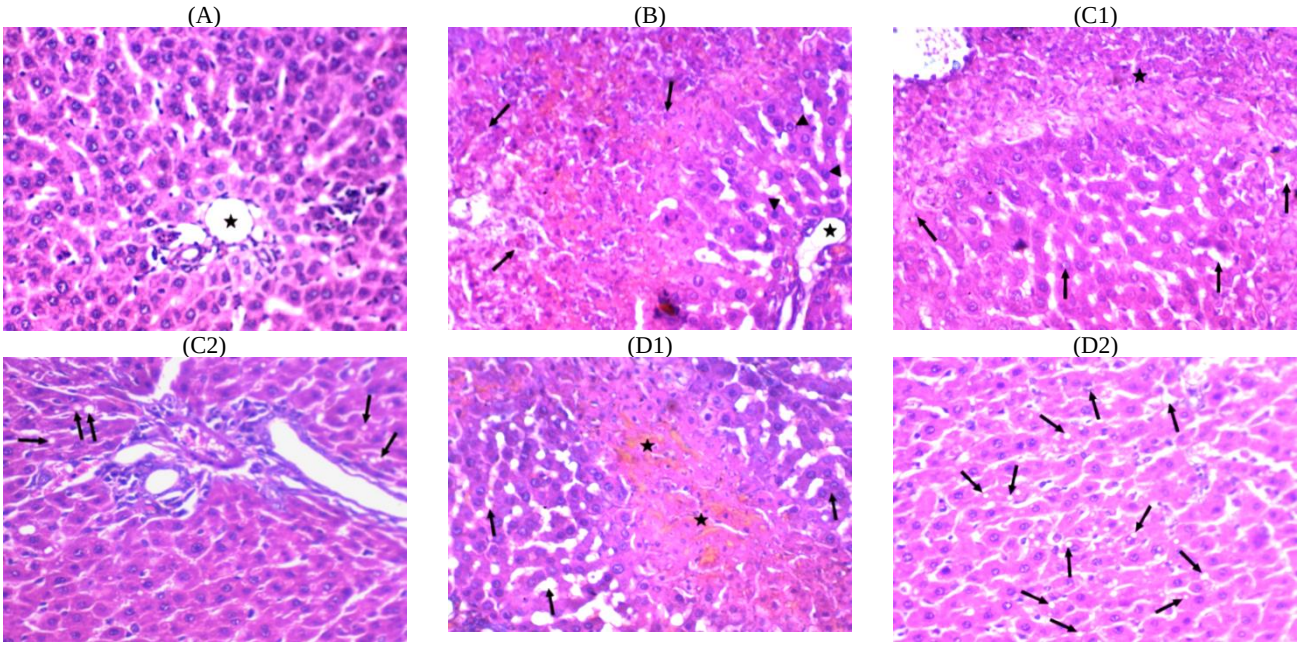


Fig. 4: Photomicrographs of liver rats of all studied groups (H & Eosin X 400), Fig. 4A showing normal-sized central vein ★ encircled by rows and cords of normal hepatocytes, Fig. 4B showing central veins ★ and a large number of necrotic liver cells ◥ surrounded by a small group of viable liver cells (arrows), Fig. 4C1 showing regeneration of the liver cells and a small area of necrosis, Fig 4C2 showing normal liver tissue and few liver cells showing mild fatty changes, Fig. 4D1 shows the regeneration of liver cells around large areas of necrotic liver cells and Fig. 4D2 showing moderate fatty changes in liver cells.

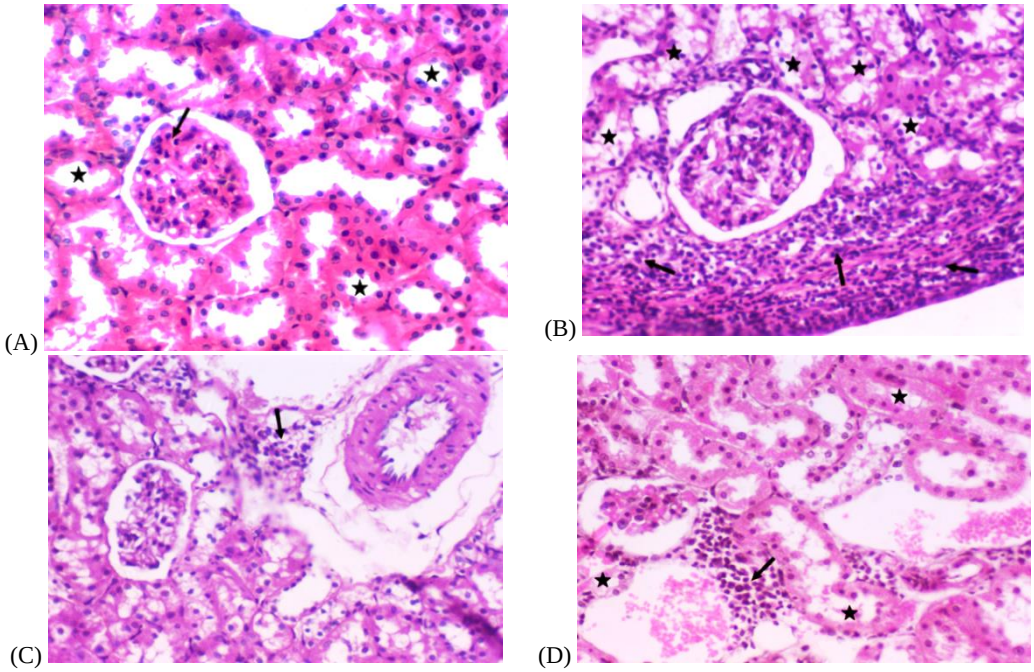


Fig. 5: photomicrographs of kidney rats of all studied groups (H & Eosin X 400), Fig. 5A showing normal glomerulus ↘ surrounded by normal proximal and distal renal tubules ★, Fig. 5B shows heavy aggregates of inflammatory cells and hydropic degeneration of the tubular epithelial cells, Fig. 5C showing normal renal tubules and glomerulus with few aggregates of inflammatory cells and Fig. 5D showing the moderate aggregate of inflammatory cells and hydropic degeneration of the tubular epithelial cells.

DISCUSSION

Humans are exposed to various xenobiotics including medications, chemical substances, and poison (Atashgahi et al. 2018), It is gradually being concluded now that the superiority of the disease/disorders is mostly associated with an imbalance between free radicals (pro-oxidant) and antioxidant homeostatic aspects (Phaniendra et al. 2015). Certain medicinal agents, when taken in overdoses now and again in any event, can lead to organ damage. Acetaminophen is one of the most common analgesic medications, it is a safety profile when expended in remedial portions. However, overdoses can cause both liver and kidney injuries in rodents. The regularity of acute kidney damage is about 2-10% in those with acetaminophen overdose (El Faras and Elsawaf 2017; Saleem and Iftikhar 2019).

The current investigation was intended to analyze the protective effects of sugar cane (*Saccharum officinarum*) peel extract and its antioxidant role in hepatic and renal complications linked to toxicity with a single overdose of acetaminophen using silymarin plus as a reference drug including oxidative stress. A single overdose of acetaminophen-induced was a real reason for the occurrence of liver enzyme elevation that is considered one of the most important biochemical risk indicators of toxicity in the liver (Adewale et al. 2019). Our outcomes are in agreement with many investigators who noted that increasing liver enzymes, ALT, and AST are major risk factors to toxicity, liver damage is strongly associated with an increase in systemic oxidative stress. When the liver is injured, liver enzymes spill into the blood, causing elevation to liver enzyme levels (El Menyiy et al. 2018), the significant rise in these enzymes in circulation indicates significant hepatocellular damage (Zhang et al. 2019). In our investigation, Acetaminophen raised serum levels of AST, ALT, ALP, urea, creatinine, and lowered levels of total protein and serum albumin in agreement with the findings of Hassan and Rahman (2016). The current study showed liver damage is characterized by hypoproteinemia as decreased albumin (Yousef et al. 2010; Sedky et al. 2019) who state that hypoproteinemia could be the result of a decreased number of hepatocytes accountable for protein synthesis due to apoptosis and necrosis, which were indicated in our findings. Moreover, Acetaminophen causes oxidative stress in the liver of rodents with an increment of MDA and a reduction in GSH, SOD, and Catalase.

In our analysis, an excessive dose of paracetamol resulted in an increase in the level of serum creatinine and urea and necrosis in the renal units of rats and the occurrence of cell death and wear, which is represented by a polymorphic nucleus unit through the reduction of the nuclear factor and erythrocytes associated factors (2Nrf2) (Jayaraman and Namasivayam 2011). The mechanism occurs through a disturbing convention of special events as it contains the metabolism of the cytochrome P-450 into a reactive metabolite that makes tired glutathione and interconnections to proteins and reduces glutathione with increasing form and nitrogen species in past hepatocytes through modification necrosis and is taken to higher oxidation conditions making matters difficulty related to changes in calcium homeostasis. The initiation of a re-transduction marker leads to changes in the mitochondrial permeability of the commercial ATP group that causes necrosis and therefore acetaminophen is administered to central liver necrosis which may be fatal. There are several inflammatory medicinal substances that can produce different toxicities associated with these underlying events (Hinson et al. 2010).

The Acetaminophen treatment group showed a rise in both serum TC and TG, these results are indicative of

cellular leakage and loss of functional integrity of the cell membrane in the liver (Egbung et al. 2017). Inflammation is the source of acute liver harm. Sugar cane peel extract documented considerably higher harm in APAP caused hepatotoxicity, SOPE additionally eliminated the release of these cytokines, which may fractionally lower the inflammatory injury in the liver. Significantly, the results prove that the hepatoprotective effect of SOPE might also be due to its capacity to inhibit potent anti-inflammatory cytokines (Wu et al. 2019)**.** A substantial reduction in serum albumin levels together, and the significant rises in serum levels of ALT, AST, ALP, and (total and direct) bilirubin are in accordance with the findings of Forouzandeh et al. (2013) who showed severe APAP-intoxicated group exhibit severe necropathic changes, such as centrilobular hepatic necrosis and fatty changes associated with histopathological changes. Treatment with *Saccharum officinarum* significantly prevented biochemical changes resulting from toxicity. Oxidative stress commonly actuates lipid peroxidation by increasing rates of MDA, and our findings are in concurrence with the hypolipidemic effect of sugar cane peel extract, in rat role modeling as reported by Iwara et al. (2015), which involved flavonoids and other bioactive basic principles for the consequences. They are in concurrence with a report by Johnson et al. (2017) where lowering MDA values prevented the dismutation of lipids in PC-3 cells (Mathur et al. 2016).

Various proofs highlighted the potential contribution of oxidative stress via the production of ROS in APAP-induced organ toxicity. In our investigation, these results are based on flavonoids, a biologically active compound that is efficient to significantly decrease levels of ALT and AST, protein carbonyl content, bilirubin, ALP, and increasing the activity of superoxide dismutase (SOD), and catalase (CAT) (Jayaraman and Namasivayam 2011; Roy et al. 2014). The co-organization of SOPE with acetaminophen reduced oxidative stress and optimum apoptosis in the liver and kidney.

Conclusions and Future Prospective

It can be concluded that the possible mechanism of hepatorenal protective activity of *Saccharum officinarum* peels extract may be owing to its antioxidant and anti-inflammatory effect. Hepatoprotective and antioxidant activity of SOPE was confirmed by biochemical, antioxidant, and histopathological studies when compared with other medications (silymarin plus).

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Author's Contributions

Nabil A. Soliman supervised the experiment. Samih I. El Dahmy, ShalabyA.A designed the experiments and reviewed the manuscript. Khadija A. Mohammed performed the practical parts of this study and wrote the manuscript. All authors approved the final version of the manuscript.

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