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Ameliorative Effect of Mushroom Extracts against Butyl Paraben Induced Toxicity in Liver and Kidney in Female Albino Rats.

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Abstract

Parabens are group of preservatives chemical compounds used in cosmetics, personal hygiene product, food products and pharmaceuticals**.** In this study the hepatorenal toxicity due to exposure to paraben was evaluated. In this study design Twenty-four of albino rats experimentally used. Butyle paraben (BP) orally was given to animals 180 days in dose of 4.6 mg\kg.bw which equal to10 % of the LD50 of BP. The extract of Mushroom was given by stomach tube in dose of 10 mg/kg/day for six 180 days. Exposure to Parabens exhibited histopathological and biochemical alterations. In the line of biochemical analysis BP induced toxic changes in both liver and kidney, the hepatic cellular enzymes concentrations (AST, ALT), Bilirubin, urea and creatinine were raised. In contrast plasma proteins were decreased in comparison to the control group. In renal and hepatic tissues BP administration induced vascular congestion as well as necrosis in the hepatorenal epithelium. Both the biochemical and histopathological alteration was improved after giving mushroom extracts in comparison to BP given group. In conclusion, mushroom extracts exhibited biochemical and histopathological improvement in liver and kidney against the toxicity by Butylparaben.

Keywords:
Biochemical changes, Butylparaben, Extracts, Hepatorenal Toxicity, Histological alteration, Mushroom

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Introduction

Parabens groups, including various compounds such as butylparaben, isobutyl-paraben, methylparaben as well as their metabolite such as p-hydroxybenzoic acid. The Parabens have been mostly used in foods preservation, skin hygiene and care. They used also as cosmetics byproduct and in the pharmaceutical agents' production, where it acts as antimicrobial preservatives for several years. Parabens has wide famous names in the world commercial industry. This famous name comes due to the daily uses of parabens by human and even animals. Both human and animals are exposed to parabens compound through various ways (e.g. cosmetics powders, canned food products and the pharmaceuticals preservatives compounds Cosmetic products like cosmetic powder, eye shadows, lipsticks, perfumes, foundations. They are used as dermally applicants. Also, they are considered one of the sources of absorption and exposure to the parabens' compound in human body. Cosmetics are widely used in females other than males so that females are much higher in exposure to parabens other than the males (Giulivo et al., 2016). Published reports have emerged in recent years implicating parabens as potential carcinogens in breast cancer, uterine cancer, and most recently, skin cancer as well as a general toxic agent (Macrene, 2008). (Fransway et al., 2019). Biochemical properties of the parabens such as they can be stable at high range of temperature. In addition to, they keep their impact within high scale of pH values. Parabens have anti-microbial effects where they act as has anti-bacterial and anti-fungal agents (Alam et al., 2014; Abbas et al., 2010). Parabens have no noticeable taste and smell and they are also soluble in oils and water, so they appeared effective in liquefied phases. Humans orally exposed to parabens via consumption of the processed foods materials such as jellies, beverages, canned foods, canned fruits and jams etc. (Boberg et al., 2016). Liver is considered the site of toxin removal and toxic materials detoxification in the mammals' body. Liver has a big role in the synthesis of antioxidants as well as the regulation and maintaining the metabolic mechanisms in the body. Liver cells injury was noticed through increased the secretion and production of some enzymes like AST, ALP and ALT, which they are used as clinical indicators of its abnormality initiated by extrinsic or intrinsic factors like poisonous materials or other microbial agents. (Abbas et al., 2010; Boberg et al., 2010). Metabolic pathways in the body resulted in metabolic waste product formation such as drug toxin byproducts. The kidney function is to excrete and remove these products so that accumulation of kidney markers and other waste products are indicator for acute and chronic kidney injury (Mehat et al., 2007). It well known that exposure to BP causes serious damaging effects on the hepatorenal tissues. Exposure to BP leads to rise in the production of ROS in the hepatocytes as well as lowering the concentration of glutathione enzyme, superoxide dismutase and ascorbic acid (Watkins et al., 2015).

Mushrooms are fungi which bear fruiting structure that are large enough to be seen with naked eye. They can appear either below ground (hypogenous) or above the ground (epigeous) where they can be harvested by hand. (Chang et al., (1989). Mushroom has rich nutritional values as well as its flavor and texture which they make it as one of the most common food sources. Moreover, not only mushroom has nutritional values but also it has medicinal effects. Mushroom enhances the immune systems which lower the diseases and infections. The medicinal effects of mushroom include lowering blood glucose level, the serum lipid profiles in addition to it act as anticancer agent (Wong et al., 2008). Mushrooms contains high amount of proteins and carbohydrates on the other hand it has low level of fats. Mushrooms

also are rich in free amino acids and minerals. It found also mushrooms possesses high concentration of dietary compounds such as chitin and the beta-glucans. Some other biochemical compounds like volatile organic compounds, Some polysaccharides, some polyphenols with flavonoids and terpenoids are recorded in the chemical composition of mushrooms (Rathore et al., (2017).According to Soheir et al (2007), mushrooms have high anti-oxidant effects which play an important protective role against toxicity. The antioxidant effects were due to the presence of bioactive compounds that they act as scavengers to the reactive oxygen species in the body tissues. BP compounds enter the body via dermal application, or the oral intake then absorbed metabolized by the liver cells and its byproducts are eliminated out in the bile and urine (Nowak et al., 2018). The study was done to evaluate the Paraben effects on the kidney and liver with determination the ameliorative impacts of mushrooms extracts.

Materials and methods

Ethical approval:

All procedures in the present study were performed and approved in accordance with the Ethics Committee of the Faculty of Veterinary Medicine, South Valley University, Qena, Egypt.

Experimental Animals:

In this experiment twenty-four adult female Wistar albino rats 170-200 gm in weight and about 115- 120 days in age, were bought from animal home, Cairo, Egypt. The protocol of the study was approved by the Animal Ethics Committee at South Valley University, Egypt. Animals were housed in each 5 animals in one cage. Rats were left under good sanitizations and were given standard feeds and water *ad libitum*.

Chemical Substances:

a- B**utyl paraben**

N-butyl paraben crystalline powder was bought from Sigma Aldrich Co. USA.

b- Mushroom

Mushrooms (*Pleurotus ostreatus*) were purchased from hyper market Qena city, Egypt in form of fruiting bodies.

c- Biochemical Kits

ALT, AST, Total Protein, Albumin, Bilirubin, urea and Creatinine were analyzed using biochemical kits purchased from Biodiagnostic Laboratories, Dokki, Giza, Egypt.

Methods

Mushrooms extracts Preparation.

Mushrooms were brought and thoroughly cleaned by running water after well cleaning. The bodies were let to dry then cut into small parts. The mushrooms' parts were kept in well cleaned and dry place and left away from direct sun heat for keeping its nutritional values. Using electric mortar, the well insipid mushrooms pieces were broken into fine powder.

Mushroom extraction.

Depending on Lee et al., (2007), method (hot water extraction), as the following: in 100 mL of boiling water 10 grams of mushroom powder were added and well mixed. The contents were centrifuged at 5000×g for 40 minutes. Using Whitman's No.1 filter paper, the supernatants were filtered. 100 mL of water with 100 C° was drained to the residues. The mix was heated to evaporate slowly at 40 C° using the rotary evaporator. The component was dried using the freeze dryer then mushroom extracts were obtained. The obtained extracts were stored at - 18 ºC for until use.

Experimental design

The experimental design was as the following a twenty-four adult female Wister

albino rats were divided into 3 equal groups (each = 8). **Group 1:** Animals were served as control group and were given 0.2 ml pea nut oil orally for 180 days. **Group 2:** The experimental animals were administrated with 10 % of the lethal dose of the butyl paraben which equal to (4.6 mg/rat/day), according to Masten & Tice, (1999). The volume was concluded in 200 microliter of pea nut oil and was given by stomach tube for 180 days. **Group 3:** The rats was given the same dose of BP plus 10mg/kg/day mushroom extract, Wu, et al., **(2013)** concluded in 300 microliters of saline were administrated also per os for 180 days.

After finishing the designated work rats were euthanized and sacrificed by cervical dislocation. Whole blood specimens were collected by puncturing of the heart by fine needle syringe. Collected blood was added in clean tubes without using anti coagulants. Coagulated blood was left at room temperature for 10 -15 minutes then centrifuged for another 15 minutes at 3000 rpm. Collected serum was stored at -20 C then used for biochemical analyses using advanced spectrophotometer device (Bain et al., 2016). For histopathological examination Liver and kidney organs were harvested.

Determination of liver function tests (LFT).

Serum Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) were detected according (Reitman and Frankel, 1957). The total Protein analyzed depending on (Gornal et al., 1949) method. According to (Doumas et al., 1971) albumin was estimated. Globulin calculated from the following formula subtraction albumin concentration from the total protein level according to (Howard, 1937).

Determination of kidney function tests (KFT).

Depending the method recorded by Teitz, (1986) serum Creatinine was detected and according to Tiffany et al., (1972), urea concentration in serum was evaluated.

Histopathological examination:

Liver and kidney samples were collected after animal scarification. The samples were by phosphate puffer saline then priced into small pieces 1.5 cm in diameter then fixed in freshly prepared 10% neutral buffered formalin. The tissues samples were dehydrated gradually using ethyl alcohol in multiple concentrations starting with 70% alcohol concentration then 80%, 90%, 95% and end with 100% alcohol concentration. Then, paraffinized in in paraffin blocks. In the end, multiple sections about 5µm thickness were obtained using manual microtome. The processed sections were stained with Harries hematoxylin and eosin for histopathological evaluation, (Drury and Willington, 1980).

Statistical analysis:

One-way analysis of variance (ANOVA) was used to analyze the obtained data statistically. It was done using SPSS program version 17 according to (Borenstein et al., 1997). The difference was statistically significant when p values were less than 0.05.

Results

A. Biochemical findings

A.1. Liver function test

Liver function tests exhibited changes in its reference values when the Butyl paraben was given orally. Oral administration of BP irritated the hepatocytes which manifested by increase the liver enzymes activity. The increased in ALT and AST was non – significant when compared with control group. Not only the alterations were in the liver enzymes, but also total protein, albumin, globulin and serum bilirubin were increased. Recovery in the liver function tests was noticed either by increase or

decrease in these parameters after oral administration of mushroom extract. As seen in (Fig. 1 & Fig. 2), in the line of nutritional values of mushroom there was a significant increase ($p \leq 0.05$) in the concentration of total protein in comparison with both Paraben and control treated groups.

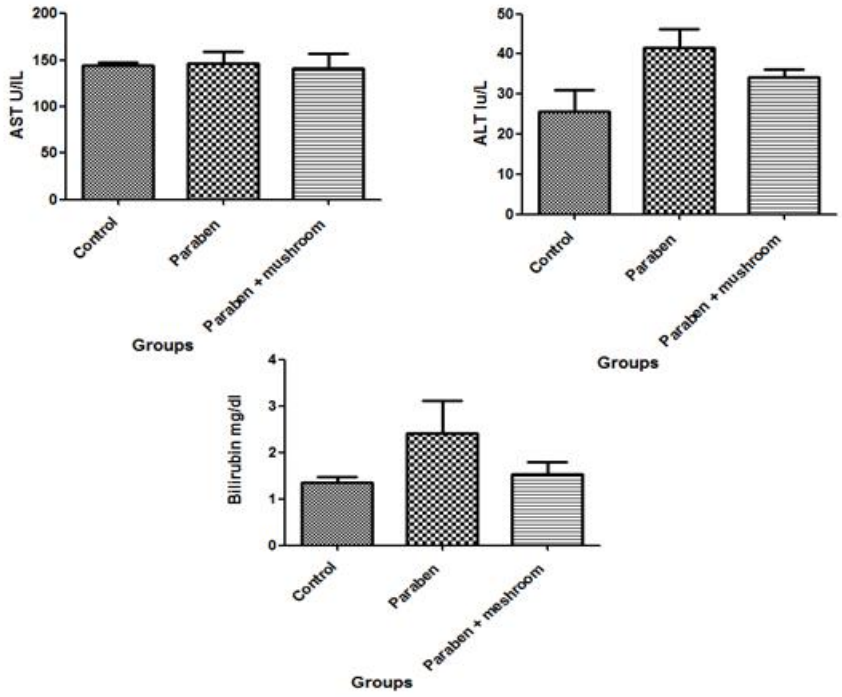

Fig. 1. Exhibited the toxic impact of BP on ALT, AST and Bilirubin with the ameliorative impact of mushroom extracts in comparison to control animals. Data are shown with mean ± SE ($P < 0.05$).

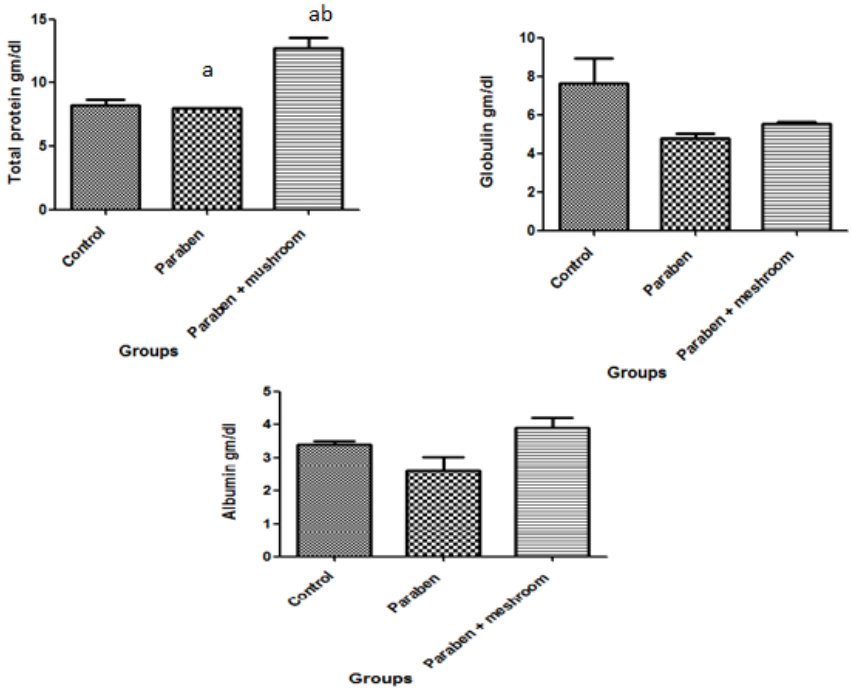

Fig. 2. Exhibited the toxic impact of BP on total protein, globulin and albumin with the ameliorative impact of mushroom extracts in comparison to control animals. Data were shown with mean ± SE ($P < 0.05$).

A.2. Kidney function test

Oral inoculation of butyl paraben for rats for successive six months induced alterations in the renal tissues. BP induced significant increase ($p \leq 0.05$) in the serum urea and creatinine concentrations in comparison to control group. When mushroom was given by stomach tube, the toxic changes in the renal epithelial tissues was diminished that manifested by reduction in the mentioned parameters as shown in (Fig. 3).

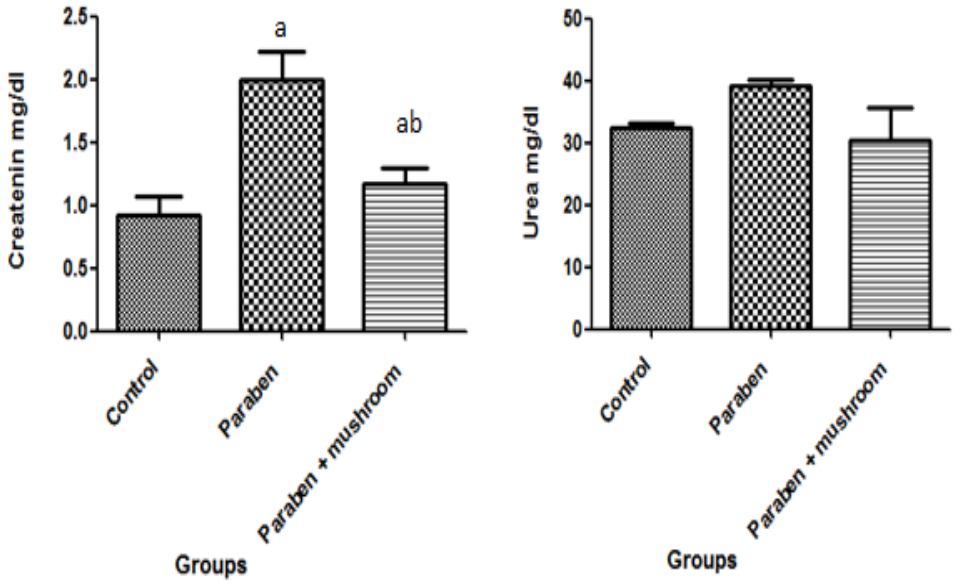

Fig. 3. Exhibited the toxic impact of BP on serum creatinine and urea with the ameliorative impact of mushroom extracts in comparison to control animals. Data were shown with mean ± SE ($P < 0.05$).

B. Histopathology

Histopathological changes in livers inoculated with BP were manifested by severe vascular congestion in the central and portal veins.

Vacuolar degeneration was noticed in association with mild coagulative necrosis, severe periportal inflammatory cells infiltration, biliary epithelial degeneration, vasculitis, high mitotic frequency, dilated blood sinusoids, in some cases the hepatic necrosis observed clearly with edema.

When Mushroom extracts administrated with BP recovery was observed and characterized by mild hepatic congestion, and hepatic vacuolar degeneration.

Disappearance of inflammatory reaction in some cases, and others showed mild inflammation (Fig. 4). BP administration also effects on the renal tissues and characterized by severe vascular congestion with interstitial leukocytic cell infiltration, glomerular necrosis, necrotic tubular epithelium, narrowing of the tubular lumen and mesangial cell proliferation in the renal glomeruli with congested blood capillaries.

Treatment with BP plus mushroom extracts exhibited recovery of the glomerular structure and most of the epithelial lining of renal tubules becomes normal without any features of degenerations or necrosis and diminished the inflammatory cells infiltration (Fig. 5).

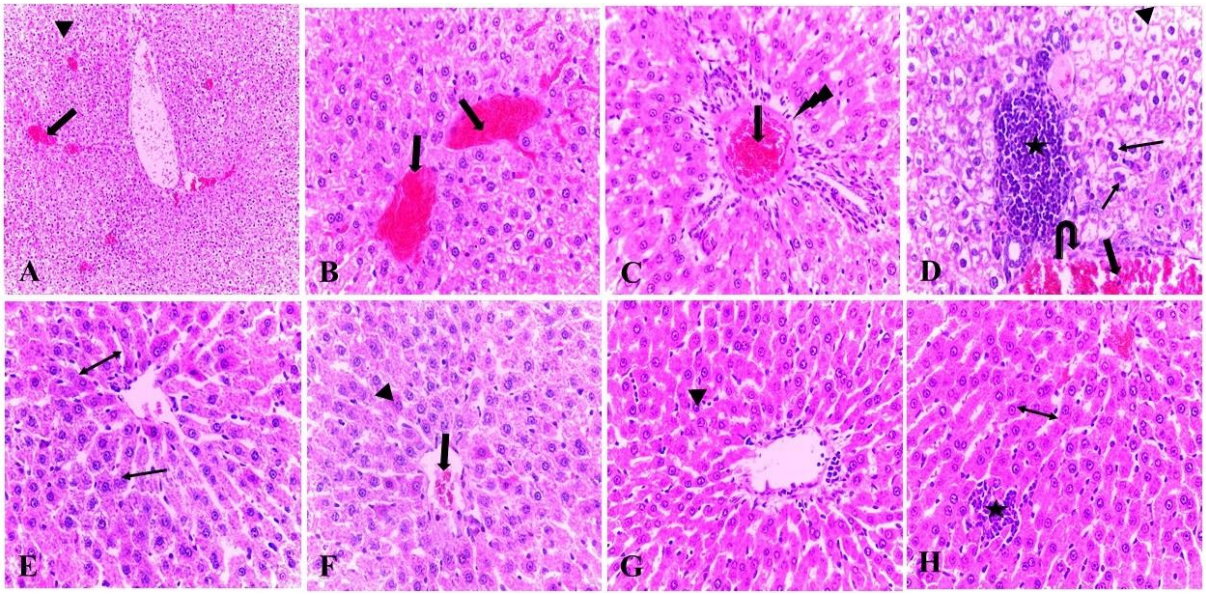

Fig. 4. Histopathological figure of the livers in rats treated with BP (A-D) and rats treated with BP+ ME (E-H). Severe vascular congestion was observed in liver (thick arrow) (A-D) with mild vascular congestion (thick arrow) (F), vacuolar degeneration (arrow head) (A & D) with mild degenerative alteration (arrowhead) (F & G), notable large (asterisk) (D) and small focal inflammatory cellular aggregation (asterisk) (H). Periportal edema (lightning Bolt) (C), necrotic vascular lining (U-turn arrow) (D), mild dilated hepatic sinusoids (double line arrow) (E & H), high mitotic frequency (thin arrow) (D) and low mitotic frequency (thin arrow) (E).

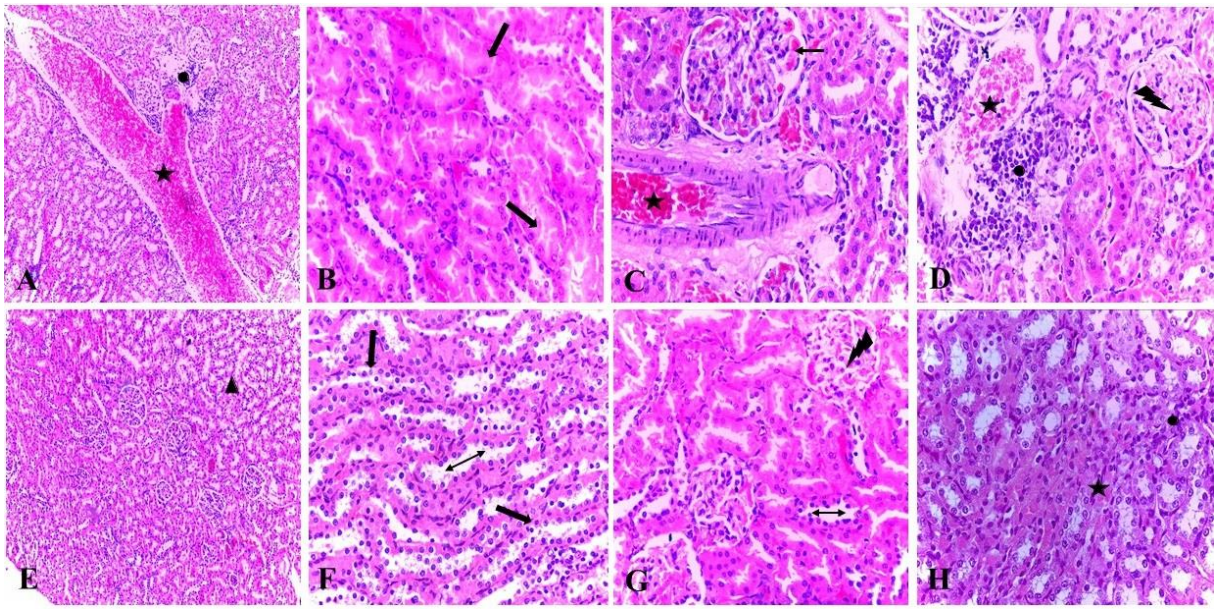

Fig. 5. Histopathological figure of the kidneys treated with butyl paraben (A, B, C & D) and others treated with butylparaben and mushroom (E, F, G & H). Kidneys are showing severe vascular congestion (asterisk) (A, C & D) and mild congestion (asterisk) (H), apparent leukocytic infiltration (oval) (A & D) and mild inflammatory reaction (H), complete tubular epithelium necrosis (thick arrow) (B) and restoration of a tubular structure (triangle & thick arrow) (E&F), congestion of glomerular capillaries (thin arrow) (C), necrotic glomeruli with mesangial cell proliferation (Lightning Bolt) (D) and mild mesangial proliferation (Lightning Bolt) (G), and wide tubular lumen (double line arrow) (F&G). (H& E: A & E: X50, B-D & F-H: X100 respectively.

Discussion

Butyl paraben induced renal and hepatic toxicity. The parameters evaluated in this study were liver function tests (ALT, AST, serum bilirubin, total protein, albumin and globulin) and kidney function tests (serum creatinine and urea) as these parameters are good markers for hepatorenal toxicity. In our study we recorded serum biochemical changes and histological lesions in the tissues of liver and kidney due to PB poisoning. The results of biochemical analysis exhibited higher concentrations in the liver enzymes ALT and AST associated with lowering in the values of total protein, albumin and globulin in animals exposed to BP. These results come in agreement with the data recorded by Darbre et al. (2008). In this study the liver enzymes activity was increased as well as decrease the plasma protein were due to the response of the hepatocytes against the toxic effect of BP. These mentioned changes were because the liver enzymes increased directly in response to many toxic and metabolic reactions in hepatocytes. As well-known the main function of liver is to detoxify the toxic compounds as well as it participates in the antioxidant mechanisms in the body through production of the catalase enzyme which break down the hydrogen peroxide which is toxic to the tissues (Henryk, 2010). A lot of studies stated the same results, which revealed that the balance of hepatic enzymes disturbed due to any extrinsic or intrinsic toxic compounds or microorganisms (Abbas et al., 2010).

In accordance, administration of BP to the rats induced increase in urea and creatinine concentrations in in comparison to control animals and (BP + Mushroom extracts) group as well as lowering the glomerular filtration power of the renal glomeruli and renal tubules. These findings come in agree with the results observed by Wahlang et al. (2013). As bilirubin values were increased due to the inability of hepatic cells to remove the hem's metabolites. In the same, the working mechanisms of renal cells and glomerular filtration power affected leading to high concentrations of urea and creatinine. In the normal hemostasis creatinine waste product is produced as a metabolite of muscular creatine then removed by the renal tubular epithelium through urine. During kidney injuries and not work properly due to the effects of any endogenous and exogenous insults, its levels get raised (Harvey et al., 2006).

For confirmation of the biochemical findings histopathological examination was done. In our study the histological examination exhibited a promise results which revealed necrosis and degeneration in the hepatocytes in BP treated animals. In addition, BP administration affects strongly on the hepatic portal veins with congestion. Same results due to butyl paraben toxicity were recorded in the study was done by Martin et al. (2010). Co-administration of BP with mushroom extracts induced relive to the toxic effect of BP on the hepatic tissues which manifested by mild regenerative changes. Same study proved the positive impacts of mushroom on the liver. Depending on this study the damaged epithelium was improved due to the antioxidant effects of mushroom extracts (Soheir et al., 2012). Disorders in the renal glomerular epithelium resulted in malfunction of kidney function. Due to exposure of the rats to BP some debris were seen in both upper and distal renal tubules in association with disruptive and necrosed cells in the glomeruli as well as bowman's space. Same histopathological changes also were observed in the study done by Verma et al. (2007). Given mushroom extracts with BP improved the renal glomerular filtration rate and relieve the toxic effects of BP which manifested by decrease renal epithelium necrosis.

The co- administration of BP and mushroom extracts significantly diminished the increased concentrations of the analyzed biochemical parameters (AST, ALT, Serum Bilirubin, Urea and Creatinine). In contrast, mushroom extracts increased the plasma proteins values (total protein, albumin and globulin) as well as the histopathological alterations were recorded in the liver and kidneys were significantly ameliorated. Our obtained data gave full explanation about the protective power of mushroom extracts against the toxic effects of BP through activation of the oxidative system in the renal

and hepatic tissues by removal and scavengering the reactive oxygen species ending with remolding of the hepatorenal epithelium. Our results were similar to the observation of Nada et al. (2010). Same data also were observed by Soheir et al. (2012) who said that mushroom extracts have the power to significantly refine the toxicity induced by Ochratoxin in liver and kidneys in the examined albino rats. The power of the mushroom extracts to remove and ameliorate the toxic materials was due to immunity enhancement and active cytokines downregulation (Vetvicka and Yvin, 2004). Additionally, Mushroom extracts are rich components with some vitamins (D2, B1, C, B2 and vitamin C). Also the extracts have high amount of polysaccharides and glycoprotein compounds (eg.: chitin, mannans and galactans) and other bioactive compounds which they have powerful antioxidant effects, free radical scavengering with some other medical biological mechanisms (Manzi et al., 1999; Mattila et al., 2000; Synytsya et al., 2009).

Conclusion

In conclusion the study was done to evaluate the toxic effects of paraben on the liver and kidney depending on the biochemical analysis and histopathological examinations as well as efficacy of mushroom extracts as a protective agent against toxicity.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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