



Corn Silk Extract attenuates Acetaminophen-induced Hepatotoxicity in Rats

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ABSTRACT

Paracetamol (acetaminophen-N-acetyl-p-aminophenol, PCM), a most common antipyretic & analgesic compound is widely used for the treatment of cold, cough, fever, pain including chronic pain, muscular ache, migraine, menstrual cramps, headache, backache and toothache. Acetaminophen over dosage is considered as one of the major causes of hepatic toxicity. The current study aimed to investigate the protective effect of corn silk methanolic extract (CSME) against acetaminophen (APAP)-induced hepatic toxicity. Therefore, the present study was carried out on 40 male Wistar albino rats, which were randomly allocated into four groups (n=10). Control group; orally administered with 0.9% normal saline. CSME group, orally received CSME, 400 mg/kg BW daily for 5 weeks; APAP group, orally administered with a single dose of APAP, 2g/kg BW; APAP+ CSME group, orally administered with CSME as in CSME group, followed by a single oral dose of APAP as in APAP group. The results of this study revealed that APAP caused a significant elevation in alanine transaminase (ALT) and aspartate transaminase (AST) activities. Also, APAP caused significant increases in malondialdehyde (MDA) and nitric oxide (NO) concentrations compared with control group. However, pre-treatment with CSME restored all biochemical parameters toward the normal levels as the control group. In conclusion, oral administration of CSME protected rats against APAP hepatic toxicity through its antioxidant protective mechanisms.

Keywords: Acetaminophen, Hepatic toxicity, Corn silk, Malondialdehyde.

1. Introduction

Liver is the chief organ associated with different phases of metabolic and physiologic homeostasis of the organism (Valko et al. 2007). Hepatitis, cirrhosis and alcoholic liver diseases can result from free radicals, alcohol, xenobiotics, food additives and pollutants (Valko et al. 2007). Acetaminophen or paracetamol (N-acetyl-p-aminophenol) (APAP) marketed as Panadol or Tylenol and other preparations belongs to a group of drugs called antipyretics (fever reducers) and analgesics (pain killers) which in overdosage result in hepatotoxicity (Coresh et al. 2007; Baleni et al. 2015). Paracetamol can treat pain including muscular ache, chronic pain, migraine, headache, backache fever, cough, cold and toothache (de Carvalho et al. 2004; Goyal et al. 2005; Kachoosangi et al. 2008).

It has no side effect when used at the therapeutic doses but the chronic use and overdosage may result in hepatic toxicity or even death (Goyal et al. 2010; Goyal et al. 2011; Fan et al. 2011; Raof et al. 2012). Hepatotoxicity can occur after the ingestion of a single overdose of paracetamol. About 80% of the liver failure cases associated with drugs is due to paracetamol toxicity (Larson et al. 2005).

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Paracetamol administration result in lipid peroxidation which has been postulated to be the destructive process in liver injury, enhancement of lipid peroxidation is suggested by the increase in MDA level of liver causing tissue damage and failure of antioxidant defense mechanisms to prevent formation of excessive free radicals (Abirami et al. 2015). Paracetamol-associated hepatotoxicity results in an increase of nitric oxide (NO) and thus causes oxidative stress (Kisaoglu et al. 2014). Herbs assume a significant job in the development of current drugs which have been utilized in treating numerous illnesses for quite a long time (Wan Rosli et al. 2010). One of these herbs is corn silk dried cut stigmata of maize (*Zea mays L.*) female flowers which is a well-known traditional Chinese herbal medicine and also identified as a functional food (Wang, 2011). These herbs contain natural antioxidants, especially phenolic compounds so that they have a therapeutic effect (Liu et al. 2011). These phenolic compounds may prevent various diseases related to oxidative stress such as cancer, hypertension, and cognitive dysfunction because they have the ability to scavenge reactive oxygen species (ROS) (Hu et al. 2010). Corn silk (*Zea mays L.*) contains sodium, potassium, magnesium, calcium salts, carbohydrates, proteins, vitamins, saponins, alkaloids. It also contains volatile and fixed oils, steroids such as stigmaterol and sitosterol, flavonoids and tannins (Velazquez et al. 2005; Olaniyan and Babatunde, 2016) Corn silk has been used for the treatment of kidney stones, nephritis, prostatitis, cystitis, edema and gout in numerous parts of the world (Cott, 2003; EbrahimZadeh et al. 2008). Although, there is limited investigations on corn silk effect on body weight, lipid, hematological, hepatocellular, nephrological and histopathological indices, it is used as a medicinal plant for treatment of diabetes, depression, fatigue, kidney stones, urinary infections, and as a slimming tea (Ikpeazu et al. 2018). The bioactivities of corn silk were widely discussed in different studies, which included antioxidant activity (Maksimovic and Kovacevic, 2003), anti-diabetic activity (Zhao et al. 2012), anticoagulant activity (Choi and Choi, 2004), anti-inflammatory activity (Wang et al. 2012), anti-cancer (Yang et al. 2014) and anti-obesity activity (Chaiitianan et al. 2016). Lipid peroxidation can be reversed by methanolic extract of corn silk due to its antioxidant effects (Ebrahimzadeh et al. 2008). The present study aimed to investigate the protective potential of CSME against APAP over dosage in rats, and to elucidate the underlying molecular mechanism of its protective potentials.

2. Material and methods

2.1. Experimental animals.

The present study was carried out on 40 male Wistar albino rats, weighing from 110 to 120 g, 4 weeks old, obtained from Al-Zyade experimental animal production center, Abo rawash, Giza, Egypt. All animals kept for two weeks for adaptation before in polypropylene cages under hygienic measures and supplied with a balanced ration and clean water ad libitum with a 12 h light / 12 h dark cycle. Animal Care and Use Committee of University of Sadat City approved all procedures of the experiment under approval No. (-VUSC-006-1-16).

2.2. Chemicals.

Acetaminophen was purchased as Panadol® from Alexandria Co. for Pharmaceuticals and Chemical Industries, Egypt (GlaxoSmithKline, Egypt). Other chemicals used in this study were of analytical grades.

2.3. Preparation of plant extract.

Corn silk was collected from corn farms in Al Akhmas village, Menoufia, Egypt during its annual cultivation season in August which used for preparation of CSME extract according to the method of Sepehri et al.

(2011). To prepare methanolic extract, the corn silk was shade-dried at room temperature then ground into powder. A total of 250 g of powder was soaked in 1 liter of 80% methanol for 72 h with intermittent shaking. The mixture was then filtered, and the filtrate was left to evaporate until dryness. A semi-solid mass was obtained with a total 12% (w/w) yield ratio. The extract was then kept at 4°C until used. The CSME extract was dissolved in distilled water before administration to rats.

2.4. Experimental design.

A total of forty albino rats were randomly assigned into 4 groups (n=10), each as follows: Control group, rats were orally administered with a single dose of 1.8 ml 0.9 % normal saline at the last day of the experiment. CSME group, rats were orally administered with corn silk methanolic extract, 400 mg/kg BW dissolved in distilled water daily for 5 weeks (Mehboob and Tahir, 2015). APAP group, rats were orally administered with a single dose of APAP, 2 g/kg BW dissolved in 0.9% normal saline at last day of the experiment (Abirami et al. 2015). APAP+CSME group, rats were orally administered with CSME, 400 mg/kg BW dissolved in distilled water daily for 5 weeks, then received orally a single dose of APAP, 2g/kg BW dissolved in saline.

2.5. Blood and tissue sampling.

At the end of the experiment, animals were anaesthetized, then blood samples were collected from the medial canthus of the eye with heparinized capillary tube, serum samples were separated and stored at -80°C until being used for measuring the biochemical parameters. Livers were removed and stored at -80°C for further investigation of malondialdehyde (MDA) and nitric oxide (NO). The second part was preserved in 10% formalin for histopathological studies.

2.6. Biochemical assays.

Kits were purchased from Biodiagnostic Company (Dokki, Giza, Egypt) to determine serum activities of AST (CAT.NO. AS 1061(45)), ALT (CAT.NO. AL1031(45)); according to the instructions provided by the manufacturer. Also, MDA (CAT.NO.MD 2529), NO (CAT.NO. 2533) Kits were purchased from Biodiagnostic Company to determine lipid peroxidation (MDA and NO) in liver homogenate.

2.7. Histopathological examination.

Following necropsy, tissue specimens from the livers were collected and rapidly fixed in 10% neutral buffered formalin solution. The fixed specimens were trimmed, washed, dehydrated in ascending grades of ethyl alcohol, cleared in methyl benzoate and processed through the conventional paraffin embedding technique. 3-5 μ microns sections were obtained from paraffin blocks using microtome (LEICA RM 2135) then routinely stained by hematoxylin and eosin (H & E) stain according to the method of Bancroft and Gamble, (2008). Stained slides were microscopically analyzed using light microscopy. Histopathological Photos were photographed using a digital Leica photomicroscope (LEICA DMLB Germany).

2.8. Statistical analysis.

All statistical analyses of results were performed using SPSS program software version 16 (IBM®, USA). Statistical significances were determined by one-way ANOVA. The results expressed as the mean \pm standard errors (SE), Results were statistically significant at $P < 0.05$.

3. Results

3.1. Effect of acetaminophen and corn silk extract on serum biochemical parameters, lipid peroxidation and antioxidant activity.

As shown in table 1, 2 administration of APAP to the rats (Group III) significantly increased serum level of ALT activity, AST activity, NO, MDA levels compared with control group (Group I). Administration of CSME prior to APAP treatment (Group IV) significantly decreased AST activity and MDA levels compared with APAP group. The administration of CSME alone to (Group II) caused no significant changes in all tested parameters compared with control group.

3.2. Histopathological findings.

In Table 3 and Fig 1, the histopathological examination of liver sections obtained from control and CSME groups showed normal hepatic architecture of liver tissue. In contrary, the liver of APAP group exhibited severe histopathological changes, such as centrilobular hepatic necrosis, fatty changes, ballooning degeneration, congestion of central vein & portal vein, sinusoidal congestion and inflammatory cell infiltration. The group received APAP+CSME showed nearly normal hepatocytes, congestion in central vein and a remarkably reduction in necrosis and other alterations seen in acetaminophen group.

4. Discussion

Acute liver failure can frequently result from severe APAP hepatotoxicity (Larson et al. 2005). Detoxification pathway of paracetamol results in production of a reactive intermediate metabolite N-acetyl-p-benzoquinone imine (NAPQI) which causes cellular injury, paracetamol-induced toxicity takes two phases in animal, initial metabolic phase followed by an oxidative phase. During the metabolic phase, paracetamol conjugation metabolites present in the liver. Hepatotoxicity results when a reactive metabolite NAPQI forms protein adducts on mitochondrial proteins which deplete cellular glutathione resulting in oxidative stress, mitochondrial injury and cell death (Ramachandran and Jaeschke, 2017).

Corn silk is also an old herbal medicine in china, which plays a role in reduction of hyperglycemia (Guo et al. 2009), reduction of weight gain (Du and Xu, 2007). It also showed anti-tumor, anti-proliferative effects (Habtemaram, 1998), anti-fatigue (Hu et al. 2010) anti-fungal (El-Gorab et al. 2007) and anti-obesity activities (Du and Xu, 2007). The results of this study revealed that acetaminophen produced a significant increase in the activities of ALT and AST compared with control group, this might be due to the damaging effect of acetaminophen on hepatic cells. This harmful effect of APAP can be explained by oxidative stress resulted from APAP treatment as indicated by elevation in hepatic MDA which in turn can increase the membrane permeability to the aminotransferases, increasing their activities and cause liver damage. These results go in line with those of Akther et al. (2013) who attributed their result to the liver damage which can be explained that these enzymes are present in the cytoplasm; then due to the cell damage they are released in blood producing hepatotoxicity; and Abirami et al. (2015) who assigned this hepatic injury to the disturbance caused in the transport functions of hepatocytes resulting in leaking of cellular enzymes such as plasma ALT and AST. Furthermore, our results agreed with Yayla et al. (2014), Kisaoglu et al. (2014) and Hamza and Al-Harbi, (2015) who attributed these findings to the increase in cell membrane permeability and aminotransferase levels which result in increasing the activities of these enzymes and cause liver damage. and this is in agreement with Akther et al. (2013), Kisaoglu et al. (2014) and Abirami et al. (2015) who attributed this increase to the excessive oxygen radical production and also increase in the synthesis of hepatic nitric oxide and this is similar to the results of Kisaoglu et al. (2014) who stated that NO is another factor leading to lipid peroxidation. These results are in a harmony with the histopathological finding which showed varying degrees of hepatitis and hepatic damage and these findings are in a line with Abirami et al. (2015) who attributed these damage to that the paracetamol toxic overdose reduces hepatic GSH content so that cellular mitochondrial proteins binds to free NAPQI which suppresses mitochondrial fatty acid β -oxidation and results in massive necrosis and apoptosis of hepatocytes (Chen et al. 2009; Bhattacharyya et al.2013). On the other hand, treatment with CSME led to improvement of liver tissue which can be attributed to the antioxidant activity of corn silk due to its total phenolic and flavonoids content (Liu et al. 2011; Tanideh et al. 2018). In conclusion, in this study we conveyed the hepatic damage caused by APAP overdose which signified by of liver function tests elevations, alterations in antioxidant activities, changes of liver tissue histopathological findings. CSME protected the hepatic tissue against acetaminophen through its antioxidant activity.

5. References

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Table 1: Effects of CSME and / or APAP on serum ALT and AST activities in different groups of rats.

| Groups | Control | CSME | APAP | APAP+CSME |
|-----------|-------------|-------------|--------------|--------------|
| AST (U/L) | 67.38±1.22c | 62.94±2.11c | 111.86±6.7a | 90.22±9.21b |
| ALT (U/L) | 20.69±0.51b | 16.82±0.92b | 67.28±12.17a | 56.98±14.26a |

The values are expressed as the means ±SE, number of rats =10, values carrying different letters in the same row are significantly different.

Table 2: Effects of CSME and / or APAP on hepatic (MDA, NO) levels in different groups of rats.

| Groups | Control | CSME | APAP | APAP+CSME |
|------------------------------|-------------------------|--------------------------|-------------------------|---------------------------|
| Hepatic MDA (nmol/g. tissue) | 28.49±3.15 ^b | 33.41±2.17 ^b | 61.46±2.97 ^a | 35.11±4.08 ^b |
| NO (mmol/g. tissue) | 45.87±1.78 ^b | 49.40±3.11 ^{ab} | 55.22±0.92 ^a | 48.02±3.118 ^{ab} |

The values are expressed as the means± SE, number of rats=10, values carrying different letters in the same row are significantly different.

Table (3): Histopathologic alterations induced by acetaminophen and ameliorative effect of corn silk in liver tissues:

| Groups & Histopathological grades | Histopathological grades | | | |
|--|--------------------------|------|------|-----------|
| | Control | CSME | APAP | APAP+CSME |
| Lesions | | | | |
| Centrilobular coagulative necrosis | - | - | ++++ | + |
| Focal area of coagulative necrosis infiltrated by inflammatory cells | - | - | ++ | - |
| Inflammatory reaction | - | + | ++ | + |
| Fatty changes | - | - | +++ | - |
| Signet ring appearance | - | - | ++ | - |
| hepatocellular ballooning degeneration | - | - | ++ | + |
| Congestion of central vein, portal vein & hepatic sinusoids | - | - | +++ | + |
| Dilatation of central vein | - | - | ++ | - |

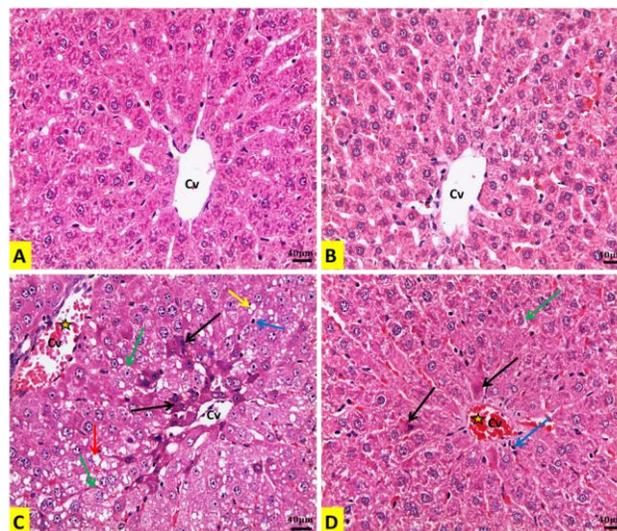


Fig (1): Representative photomicrographs of liver sections of rats in different groups (Haematoxylin and Eosin stain; X20; Scale bar 40 µm) A: Control group showing normal histologic architecture of liver. B: Corn silk group showing normal architecture as control group. C: Acetaminophen group showing severe centrilobular hepatic coagulative necrosis (black arrows), fatty changes (yellow arrows), signet ring appearance (red arrow), ballooning degeneration (green arrows), congestion of central vein (star) and inflammatory cell infiltration (blue arrow). D: Acetaminophen + Corn silk group showing somewhat normal hepatic cords, congestion of central vein (star), remarkable reduction in necrosis only sporadic necrotic cells (black arrows), mild inflammatory cell infiltration (blue arrow) and mild hepatocellular hydropic degeneration (green arrows).