Research Article

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Antioxidant And Hepatoprotective Potential Of Tanacetum Parthenium In Pcm-Induced Experimental Hepatotoxicity.

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ABSTRACT

Many traditional medical systems employ herbal drugs for the hepatoprotection. Aim of the study was designed to evaluate the hepatoprotective potential of Tanacetum parthenium leaves against paracetamol (PCM) induced hepatotoxicity in wistar rats. Group -I animals were treated with 1ml CMC for 7 days. Group II to Group IV and V animals were administered with 1g/kg PCM for 7 days. In Group-II animals were treated with hepatotoxic drug Pcm (1g/kg) for 7 days, standard drug Silymarin (50mg/kg) was administered to Group-III for 7 days, Group-IV and Group-V were treated with (2mg/kg) and (4mg/kg) Tanacetum parthenium respectively for 7 days. 24 hours after the last dosing by PCM the blood was collected through Retro-orbital sinus under light anesthesia and the animals were sacrificed. Hepatoprotective potential was assessed by various biochemical parameters such as SGOT, SGPT and Bilirubin. Group-V shows decreased level of biochemical parameters when compared with Group-IV. However, Significant attenuation in biochemical and oxidative stress parameters were observed in the Group-III. Results of the study were well supported by the histopathological observations. Thus, this study confirms that Parthenolides present in Tanacetum Parthenium possess hepatoprotective potential as comparable to that of the standard drug.

Keywords : Hepatotoxicity, liver toxicity, Tanacetum parthenium, Reactive oxygen species Paracetamol, Silymarin.

INTRODUCTION

Liver is the major organ that is involved in the process of metabolism, detoxification of various endogenous chemicals [1]. Numerous causes are responsible for the progression of liver diseases such as, autoimmune disorder, viral infections and sedentary lifestyle, and all are associated with marked increase in biomarkers such as ALT, AST and bilirubin/ biliverdin. Hepatotoxicity is the medical term for liver damage that results in compromised liver function.

The principal cause of acute liver illness and a potential clinical and regulatory issue during the past few decades, drug-induced liver injury, (DILI) has garnered a lot of attention. [2] Several drugs are either withdrawn from the market like Ibufenac, Iproniazid, Nimesulide, sulfathiazole, troglitazone, etc. or issued a black box warning by the United States Food and Drug Administration (USFDA) like amiodarone, flutamide, isoniazid, methotrexate, propylthiouracil, etc. due to their potential to cause liver toxicity (DILI rank Dataset, USFDA) [3].

One of the most frequent pharmaceuticals to result in DILI is reportedly PCM. When taken at higher amounts, the common painkiller and fever reducer acetaminophen (APAP) might result in hepatotoxicity [1]. The liver is the primary site of metabolism for paracetamol, where it is converted into the more urine-excretable glucuronide and sulphate conjugates [4]. The majority of its metabolism results in pharmacologically inert glucuronide and sulphate conjugates, with a tiny portion (between 5 and 10 percent) being oxidised to a reactive metabolite termed N-acetyl-p-benzoquinone imine (NAPQI) [5]. By attaching to the sulfhydryl group of glutathione (GSH), NAPQI is successfully detoxified and is subsequently eliminated in the urine as conjugates of cysteine and mercapturic acid. The primary culprits behind PCM-induced hepatotoxicity are the hepatic cytochrome P-450 isoforms (CYP2E1 and CYP2A6), which also create NAPQ [6,7,8]. This saturation results in GSH depletion, which triggers the development of an oxidative stress state [9]. Oxidative stress, or an imbalance between the amount of reactive oxygen species (ROS) and the antioxidant capacity of cells, is one of the mechanisms of PCM toxicity. By producing hepatic ischaemia, necrosis, and apoptosis, ROS alter gene expression and cause severe liver damage.

Journal of Toxicological Research (ISSN 2996-1823)

Apoptosis-related signalling pathways such cytochrome c release and mitochondrial translocation of Bax are involved in PCM hepatotoxicity [10]. The search for a unique and effective formulation is crucial given the unreliability of modern medications and the severity of liver illnesses [9].

Synthetic medications used to treat liver problems today are inefficient and may have negative side effects. As a new and promising way to treat liver damage, natural substances derived from herbal plants have so recently attracted the attention of scientists [11]. An essential member of the Asteraceae family of medicinal plants is feverfew (Tanacetum parthenium) [12]. Insect bites, menstruation irregularities, infertility, fever, toothaches, stomachaches, migraines, arthritis, helminthiasis, and asthma have all been treated using this plant [12]. The primary mechanisms by which PTL exerts these biological effects in tumour and inflammatory illnesses involve the suppression of NF-κB and the targeting of various NF-κB signalling cascade stages. For instance, PTL binds IκB-kinase, an activator of NF-κB (IKK) [13]. Additionally, molecular mechanism studies have demonstrated that PTL can activate p53, suppress NF-kB, and disturb the redox balance in leukaemia stem cells (LSCs) [14]. PL has been known to have many biological activities including anti -inflammatory and anti-hyperalgesic effects [15].

Silymarin, a complex blend of flavonolignans, is an ethanol extract from milk thistle [16]. Its treatment increases levels of enzymes involved in the body's removal of free radicals, including superoxide dismutase, glutathione peroxidase, glutathione S-transferase, quinone reductase, and catalase [17]. Silymarin demonstrates a variety of pharmacological actions that can shield liver cell membranes, stop liver cell ageing, encourage liver purification, and aid in liver detoxification [18]. Silymarin has an antioxidant activity at least ten times more powerful than that of vitamin E guarding the liver against liver damaging pharmaceuticals, such as acetaminophen and tetracycline [10]. Hence the study has been pharmacologically designed to explore the role of Tanacetum Parthenium (Parthenolide) on hepatic disorders.

MATERIALS AND METHODS

Chemicals and drugs

All the drug solutions were freshly prepared before use. Paracetamol and Silymarin was purchased from Haustus Biotech Pvt. Ltd, India. Tanacetum Parthenium (parthenolide) was purchased from Herbo Nutra Extract Pvt, Ltd India. Diagnostic Kits used in study were purchased from Reckon Diagnostics Pvt, Ltd. India.

Animals

Wistar rats of either sex, weighing 200-250 gm employed in the present study and procured from approved animal laboratory. Experimental animals were housed in the animal house of Rayat-Bahra University and they maintained under standard condition of relative humidity, 12 hours light-dark cycle, adequate ventilation and ambient room temperature. The experimental protocol used in the present study was duly approved by the Institutional Animal Ethical Committee (IAEC) and were fed on standard chow diet (Ashirwad Industries, Ropar, India) and water ad libitum. The care of animals carried out as per the guidelines of the ethics Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

Experimental Design

38 Wistar rats were divided into five groups containing 8 rats (n=8) in each group except normal control (n=6)

Group 1: (Normal Control)

Animals in this group were treated with carboxymethylcellulose (CMC) for 7 days.

Group 2: (Paracetamol Control)

Animals in this group were treated with PCM . (1g/kg) p.o for 7 days

Group 3: (Silymarin pre -treated PCM)

Animals in this group were treated with Silymarin (50mg/kg) p.o. for 7 days

Group 4: (Parthenolide (2mg/kg) Pre-treated PCM)

Animals in this group were treated with low dose (2mg/kg) of parthenolide and PCM for 7 days.

Group 5: (Parthenolide (4mg/kg) Pre-treated PCM)

Animals in this group were treated with high dose (4mg/kg) of Parthenolide and PCM for 7 days.

Preparation of liver tissues

On the eighth day of experiment, animals were anesthetized with intraperitoneal injection of thiopental 50 mg/kg (Somanawat and Thong-Ngam, 2013).Afterward, the livers were isolated and cleaned. Each isolated liver was divided into two parts: the first part was fixed in 10% neutral formalin solution, preserved in 70% ethanol and dehydrated with ascending grades of ethanol. Then, it was cleared with xylene and embedded in paraffin wax to get paraffin blocks. Paraffin blocks were cut to obtain serial sections of 5 µm, then, they were put on the top of glass slides and stained with hematoxylin and eosin (H&E) stain. The second part was homogenized in ice-cold phosphate buffer (pH 8) at a concentration of 15% (w/v), and then was centrifuged in cooling centrifuge (Hettich Zentrifugen, Tuttlingen, Germany) at 960 xg for 5 min. The supernatant was separated and further centrifuged at 7840 xg for 45 min at 4 °C. The supernatant was collected and transferred to a new tube for estimation of total antioxidant capacity and total oxidant status.

Journal of Toxicological Research (ISSN 2996-1823)

Biochemical parameters

Blood samples were collected using non-heparinized tubes. The nonheparinized blood samples were centrifuged at 1000 ×g for 20 min; sera samples were stored at −20 °C until the time of analysis. The separated sera were used for determination of alanine aminotranseferase (ALT), aspartate aminotranseferase (AST) and Billirubin using specific diagnostic kits.

Determination of Oxidative stress parameters

Estimation of catalase (CAT)

Catalase activity was determined spectrophotometrically by the method of Koroliuk et al. 1988.

Estimation of Superoxide Dismutase (SOD)

Superoxide dismutase (SOD) activity will be measured according to a method described epinephrine at Ph10.4. In this method, supernatant of the tissue is mixed with 0.8ml of 50mMglycine buffer, ph 10.4, and the reaction is started by addition of 0.02ml (-) epinephrine. After 5min, the absorbance will be measured at 480nm. The activity of SOD expressed as percent activity of vehicle-treated control.

Estimation of Glutathione (GSH)

The method of Ellman, 1959 will be used to measure the reduced glutathione (GSH) level. To precipitate the tissue proteins, the tissue homogenate in 0.1 M phosphate buffer pH 7.4 is combined with an equal volume of 20% trichloroacetic acid (TCA) containing 1 mM (Ethylene diamine tetra acetic acid) EDTA. After allowing the mixture to stand for 5 minutes, it is centrifuged for 10 minutes at 200 rpm.Following the transfer of the supernatant (200µl), Ellman's reagent (DTNB:5,5-dithio bis-2-nitrobenzoic acid) (0.1 nM) will be produced in 0.3 M phosphate buffer with 1% of sodium citrate solution. The total volume of all the test tubes is then 2 ml. The absorbance of the solution will be measured at 412nm against blank and the amount of reduced GSH expressed as nM /mg of tissue.

Histopathological Examination

Liver samples will be fixing in neutral buffered formalin overnight, washed well in running tap water, dehydrated, cleared in xylene and embedded in paraffin. Sections of 5µm thickness will cut with microtome device and stain with hematoxyline and Eosine. Paraffin wax will be removed by warming the glass slide gently. The melted wax will be removed with Xylene washing then slide will be washed with absolute alcohol and water to hydrate the section was then stained with Hematoxylin -Eosine method. In brief micrograph of the liver sections will be capture and necrotic areas will define and areas will be calculated.

Statistical Analysis

The observations were statistically analysed with the help of InStat3. All of the results were expressed as the mean ± SEM. Results were analysed using one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison test and $p< 0.05$ was considered to be statistically significant.

RESULTS

Effect of *Tanacetum parthenium* (Parthenolide) on Catalase (CAT) in PCM-induced hepatotoxicity in rats

Treatment with PCM produced a significant decrease ($p<0.001$) in the level of catalase (CAT) when compared with normal control. However, treatment with standard drug Silymarin (50mg/kg) produced significant ($p<0.001$) increase in CAT level when compared with disease group. Moreover, treatment with Parthenolide (2mg/kg, 4mg/kg) showed significant ($p<0.001$) increase in the level of CAT in dose dependent manner when compared with disease control as standard.

All values are expressed as mean ± SEM, a = $p < 0.001$ vs Normal control, b = $p < 0.001$ vs PCM – induced hepatotoxicity, d = $p < 0.001$ vs low dose of parthenolide.

Figure 1

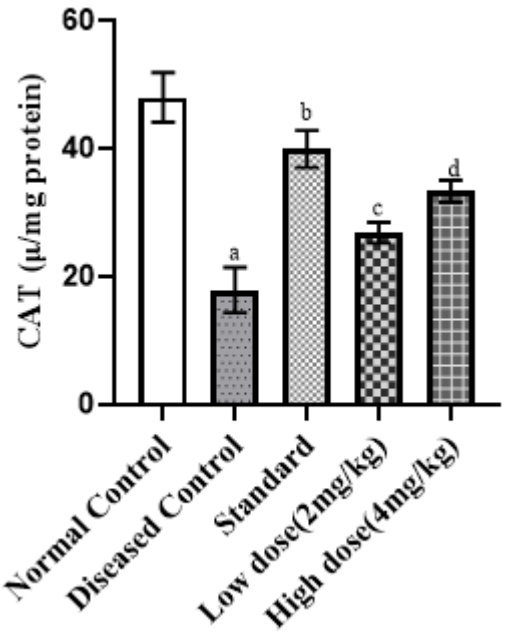


Fig. 1: Effect of Parthenolide (2mg,4mg/kg) respectively on CAT expressed as µ/mg protein. All values are expressed as mean ± SEM, a = $p < 0.001$ vs Normal control, b = $p < 0.001$ vs PCM – induced hepatotoxicity, d = $p < 0.001$ vs low dose of parthenolide.

Journal of Toxicological Research (ISSN 2996-1823)

Effect of Parthenolide on Superoxide-dismutase (SOD) in PCM-induced hepatotoxicity in rats

Significant reduction (p<0.001) in level of SOD was noted in PCM – induced Hepatotoxicity when compared with normal control. However, treatment with standard drug Silymarin (50mg/kg) produced significant (p<0.001) increase in superoxide dismutase (SOD) level when compared with disease group. However, treatment with Parthenolide (2mg/kg,4mg/kg) showed significant (p<0.001) increase in the level of SOD in dose dependent manner when compared with disease control as standard are expressed as mean ± SEM, a = p < 0.001 vs Normal control, b = p < 0.001 vs PCM – induced hepatotoxicity, d = p < 0.001 vs low dose of Parthenolide.

Figure 2

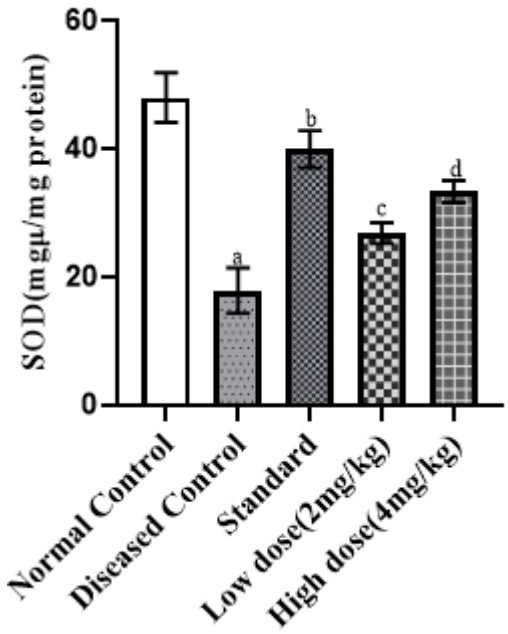


Fig. 2: Effect of Parthenolide (2mg,4mg/kg) on SOD expressed as μ/mg protein. All values are expressed as mean ± SEM, a = p < 0.001 vs Normal control, b = p < 0.001 vs PCM – induced hepatotoxicity, d = p < 0.001 vs low dose of Parthenolide.

Effect of Parthenolide on Glutathione (GSH) in PCM-induced hepatotoxicity in rats

Treatment with PCM causes significant depletion (p<0.001) in GSH level when compared with normal control. However, treatment with standard drug Silymarin (50mg/kg) produced significant (p<0.001) increase in GSH level when compared with disease group. However, treatment with parthenolide (2mg/kg,4mg/kg) showed significant (p<0.001) increase in the level of GSH in a dose dependent manner when compared with disease control as standard.

are expressed as mean ± SEM, a = p < 0.001 vs Normal control, b = p < 0.001 vs PCM – induced hepatotoxicity, d = p < 0.001 vs low dose of Parthenolide.

Figure 3

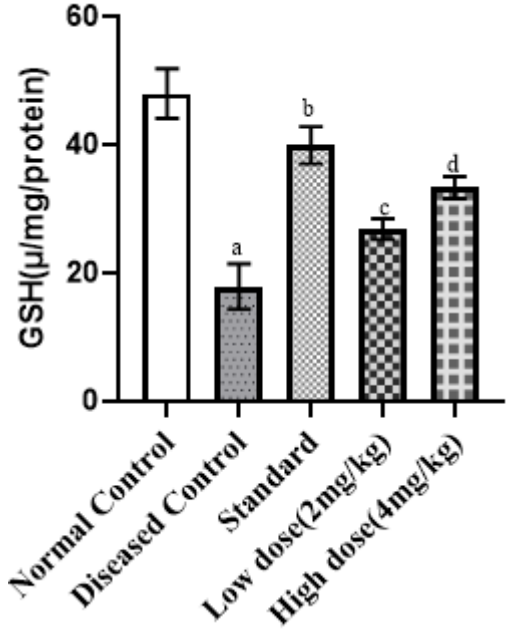


Fig. 3: Effect of Parthenolide (2mg,4mg/kg) on GSH expressed as μ/mg protein. All values are expressed as mean ± SEM, a = p < 0.001 vs Normal control, b = p < 0.001 vs PCM – induced hepatotoxicity, d = p < 0.001 vs low dose of Parthenolide.

Journal of Toxicological Research (ISSN 2996-1823)

Effect of Parthenolide on SGOT, SGPT, (U/L) and BILLIRUBIN (mg/dl) in PCM-induced hepatotoxicity in rats

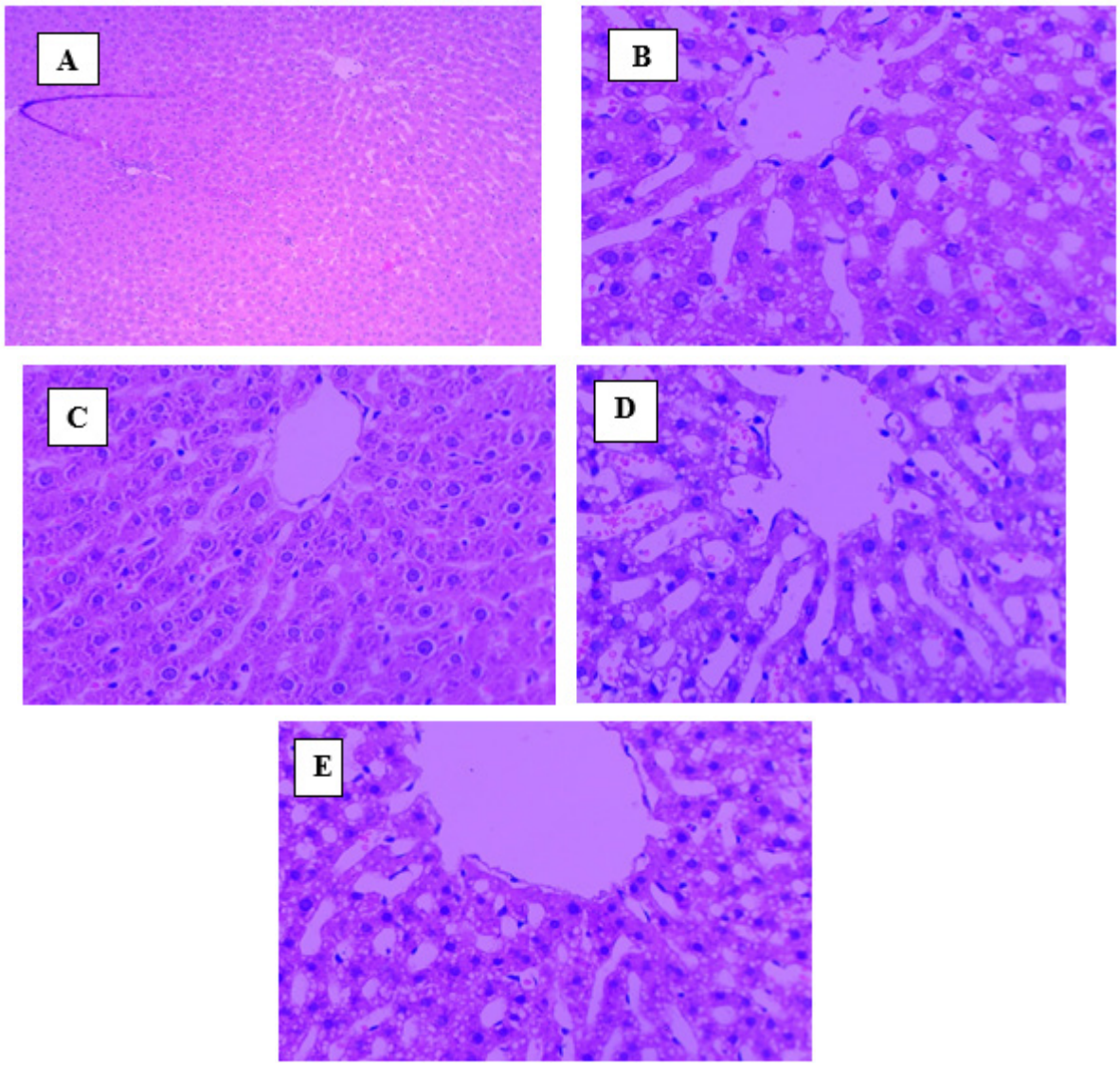
Table 1. Effect of Silymarin and Parthenolide on SGOT, SGPT, (U/L) and Billirubin (mg/dl).

S.NO.	GROUP NAME	SGOT	SGPT	BILLIRUBIN
1.	Normal Control	96.66 ± 1.24	65.48 ± 1.36	0.15 ± 0.009
2.	Disease Control	157.19 ± 1.19	386.30 ± 4.70	1.17 ± 0.005
3.	Standard (Silymarin 50mg/kg)	122.66 ± 0.49	224.02 ± 5.96	0.22 ± 0.005
4.	Treatment dose (parthenolide 2mg/kg)	135.32 ± 1.40	305.18 ± 4.66	0.28 ± 0.007
5.	Treatment dose (parthenolide 4mg/kg)	126.98 ± 0.66	263.99 ± 2.58	0.24 ± 0.004

Effect of PT, Pcm and Silymarin on liver's histology

In histopathological studies, rats administered with PCM (1g/kg) had cytoplasmic vacuolization of hepatocytes and dilated sinusoids along with hyperplasia of Kupffer cell. In contrast, liver tissue architecture in normal control study group was normal. Treatment with silymarin (50mg/kg) showed cytoplasmic vacuolization of hepatocytes are clear, Kupffer cells are normal. Treatment with parthenolide (2mg//kg) showed some cytoplasmic vacuolization of hepatocytes, dilated sinusoids along with minimal hyperplasia of Kupffer cell. Further, treatment with (4mg/kg) of parthenolide showed significant effect on decreasing the cytoplasmic vacuolization of hepatocytes, dilated sinusoids and also hyperplasia of Kupffer cells.

Figure 4. A: Normal control; B: PCM- Induced (1g/kg); C: Silymarin Treated (50mg/kg); D: Parthenolide Treated (2mg/kg); E: Parthenolide Treated (4mg/kg).



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DISCUSSION

The finding of the present study revealed that the Tanacetum Parthenium has a therapeutic potential to ameliorate paracetamol induced hepatic changes in rats.

Exposure to various environmental contaminants or as an adverse effect of medications, as nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycoside antibiotics, and anticancer treatments results in hepatotoxicity [19,20].

Paracetamol is reported to produce hepatic injury at the dose of 1g/kg p.o.[21,22,23], in the well reported model for screening of hepatoprotective agents against drug induced liver injury. It is mainly metabolized in the liver into non-toxic glucuronide and sulfate conjugates. [24] However, in overdose, the reactive metabolite N-acetyl-p-benzoquinonimine (NAPQI) is produced that covalently binds to cellular macromolecules and initiates cell damage. [25]. Further, paracetamol induced hepatotoxicity, has been thought to increase oxidative stress and promote narcotic cell death. This oxidative stress is noted to induce mitochondrial dysfunction through activation of mitochondrial permeability transition pore (MPTP) and adenosine triphosphate (ATP) depletion in present study [26]. PCM administration for a period of one week produces oxidative stress, inflammation, and causes apoptosis that play a pivotal role in the pathogenesis of hepatotoxicity [27,28]. Further PCM has been reported to produce hepatotoxicity by increasing oxidative stress. The oxidative stress has been documented to play a major role in the progression of hepatotoxicity [29,30,31]. Oxidative stress is measured in terms of CAT, SOD and GSH levels, A reduction in the activities of these antioxidant enzymes can result in lead to initiation and propagation of LPO & oxidative stress respectively [32]. This concentration is supported in our studies too where PCM cause decrease in CAT, SOD and GSH.

Paracetamol on overdose cause liver injury via formation of NAPQI by cytochrome P4502E1 is reported to cause hepatotoxicity [33] which further cause increase in expression of INOS [34], leading to oxidative stress and also increase the release of pro inflammatory mediators (IL-12, IL-18) upon activation of kupffer cells, TNF-α hepatic steatic cell. These consequences lead to mitochondrial dysfunction which is characterized by increase in Ca2+ and leads to ATP depletion [35].

In the present study higher concentration of paracetamol 1g/kg, 2g/kg and 3g/kg body weight cause severe liver injury damage as observed increase level of SGOT, SGPT and bilirubin in rodents [21,22,23].

In the present study paracetamol treatment cause severe cytoplasmic vacuolization, dilation of sinusoids and hyperplasia of Kupffer cells, Central vein shows congestion destruction, PCM induced these histopathological changes are supported by earlier literature [21]. However, parthenolide (4mg/kg) significantly restored normal architecture of liver and ameliorated PCM induced histopathological changes and this protection was found to be attenuated on treatment with Silymarin.

Tanacetum parthenium (feverfew) is a member of the daisy family. The term feverfew comes from the Latin word *febrifugia* and means fever reducer [36]. It has various pharmacological activities like the prevention of Cancer [37], Anti-inflammatory [38], analgesic, antipyretic, and anti-asthmatic [39]. Anti-oxidant [40], Anti-diabetic [41].

The protective effects of Parthenolide in ameliorating PCM induce hepatic changes by preventing the MPTP opening is confirmed by the treatment of Silymarin. Therefore, in present study Parthenolide treatment showed significant increase in the level of CAT and level of GSH. Hence Parthenolide as potential to attenuated cellular events responsible for mitochondrial dysfunction and thereby preventing MPTP opening. It has been observed that Parthenolide up regulate JNK/STAT, MAP Kinase and activities of ROS. [42,43,44] , leading to hepatoprotection responsible for increase the above mechanism in serum upon PCM induced liver dysfunction.....

The pharmacological treatment with Parthenolide, a sesquiterpene lactone causes significant decrease in the level of SGOT, SGPT and bilirubin. SGOT and SGPT are the metabolic enzymes, increase in the level of these enzymes significantly are probably due to hepato-biliary duct damage by ROS generation, COX, 5-ALOX, TNF-α, [45], NF kappa B [46] and decreased ATP [47]. Therefore, Parthenolide has been shown to significantly blocks ROS generation nitric oxide [48] Interleukins formation, TNF-α induced NF-κB activation and increased ATP generation [49]. Therefore, the protective effect of parthenolide was achieved due to its biological potential which was further confirmed by its attenuation using Silymain an MPTP opener in the present study.

CONCLUSION

The present results shows that the Pcm elicited deleterious hepatotoxic and other adverse effects as indicated by significant decrease in CAT,SOD and GSH. These effects appeared to be mediated, at least in part due to Pcm induced perturbation in antioxidant defense mechanism. Use of Tanacetum parthenium (parthenolide) prevents Pcm- induced hepatotoxicity parameters by increasing them and by strengthening the antioxidant defense mechanism. Our findings suggest that the use of Tanacetum parthenium protects the liver from Pcm induced hepatotoxicity, and may serve as a guide for future research strategies regarding hepatoprotective studies.

Journal of Toxicological Research (ISSN 2996-1823)

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Journal of Toxicological Research (ISSN 2996-1823)

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