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Effects of *Matricaria chamomilla* flower extract on hepatotoxic effect of 5-fluorouracil in rabbits

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Abstract

Background and objective: *Matricaria Chamomilla* extract has profound biological and pharmacological properties and it has been widely used for its medicinal effects. It may be helpful in preventing hepatic damage induced by drugs. The chemotherapeutic agent 5-FU has been widely used for solid types of cancer however, liver toxicity is one of its serious side effects. The present study was designed to evaluate the effectiveness of *Matricaria Chamomilla* flower extract for hepatotoxicity induced by administration of 5-FU into rabbits.
Methods: A total number of 20 rabbits were randomly divided in to four groups, group 1 received distilled water, group 2 treated with chamomile extract (100mg/kg/day),group 3 and 4 animals were injected with 20mg/kg/day of 5-FU for 5 consecutive days and on day 6 started to receive treatment with either distilled water or chamomile extract that continued up to day 14, in which animals were sacrificed to get liver samples for histopathological analysis. A Kruskal-Wallis H and Post-Hoc tests were used for the statistical analysis and comparisons between the groups.
Results: The histopathological study showed significant inflammation of hepatic tissue in the group using 5-FU compared to control and chamomile treated groups.However, using chamomile after 5-FU induced hepatotoxicity didn't show any significant reduction of inflammation of the hepatic tissue when compared to 5-FU treated group.
Conclusion: Although chamomile has profound biological and pharmacological properties such as anti-inflammatory and antioxidant activities that may be helpful in preventing hepatotoxicity induced by some drugs but in this study it didn't show effectiveness in treating 5-FU induced hepatotoxicity at the dose and duration used.
Keywords: Chamomile; Matricaria Chamomilla; 5-FU; Inflammation; Hepatotoxicity.

Introduction

5-Fluorouracil (5-FU) is uracil analogue that belongs to anti-metabolite class of chemotherapeutic agents. It is used for the treatment of solid types of cancer including colorectal, pancreatic, breast, head and neckcancer.[1,2] This chemotherapeutic agent generates acceptable outcomes in treating of various cancers, but also exhibit severe toxicity and undesirable side effects.[3]

Liver toxicity is one of the most serious adverse effects of anticancer treatments because it is actively involved in different metabolic functions including metabolism of toxins.[4] The increased generation of reactive oxygen and nitrogen species, together with the decreased antioxidant defense, promotes the development and progression of hepatotoxicity.[5] The chemotherapy induced hepatotoxicity in 5-FU based regimens can be an acute or a delayed outcome.[6]

The use of traditional medicine is widespread and plants still represent a large source of natural antioxidants that might leads to the development of novel drugs.[7] Therefore, several herbal medicines are experimented for their possible antioxidant and hepatoprotective

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effects against various chemicals that induced liver damages in animals. Chamomile is one of these medicinal herbs.[8]

Matricaria Chamomilla L (family Asteraceae), which is commonly known as chamomile, is one of the oldest; most widely used and well documented medicinal plant in the world, and has been recommended to enhance wound healing,[9] and used traditionally for numerous digestive disorders.[10] It has antioxidant,[11,12] antimicrobial,[13] anti-inflammatory,[14,15] immune-modulatory[16] and anticancer activity.[17,18] Gupta and Misra (2006) found that chamomile extract has hepatoprotective activity in paracetamol intoxicated albino rats.[19]

Chamomile contains a large number of active compounds classes. The most important ones are the components of the essential oils and the flavanoids.[8,20] The major components of the essential oils are alpha bisalol, alpha pharnesene and chamazulene.[21] The flavanoids are the major phenolic constituents of the flowers. Among the flavanoids, apigenin is the most promising compound.[22] The other components of chamomile include amino acids, poly saccharides, fatty acids and minerals.[23]

Nowadays, researches are focusing on exploring the pharmacological profile of compounds from natural origin, and few interventions are of proven efficacy in reducing the liver toxicity after cancer treatment and there are no universally accepted treatment protocols, but research activity is growing, so the present study was designed to evaluate the effectiveness of using *Matricaria Chamomilla* flower extract for hepatotoxicity induced by administration of 5-FU into rabbits.

Methods

Rabbits and housing:

Twenty healthy female albino rabbits were used in this study, each weighing 1- 1.5 kg, they were supplied and cared in the Animal House at the College of Medicine, Hawler Medical University, Erbil, Kurdistan Region of Iraq. The rabbits were acclimatized for 1 week before starting the study, and were kept under standard laboratory conditions, and maintained on a 12 hours light/dark cycle at 20 ± 5°C, and had free access to water and food during the study period.

Preparation of the plant extract:

Matricaria Chamomilla was purchased as crude dry flowers from the local market of Erbil city / Iraq. The plant was taxonomically identified by the specialists (Dr. Ghazi Faiq Haji) at the department of field crops/ College of Agricultural Engineering Science/SU. The aqueous extract was prepared from the dried flowers that was weighed (100g) and crushed in to fine powder by a pestle and mortar to prepare 5% suspension (w/v) by adding hot boiling water to chamomile powder in a volumetric flask. The flask was placed over a shaker (200 rpm) for four hours at 37C^{o} using digital hot-plate magnetic stirrer by Wisestir. After shaking, the preparation was left over for cooling at room temperature and then it was filtered through Whatman's filter papers. The filtered aqueous extract wasdried under 50C^{o}, using hot-air oven by Memmert, to get a yield of 18.4g and stored at -20C^{o} and were used later for this study.[8] The aqueous chamomile extract was prepared to be used in this study in a dose of 100mg/kg/day.[24]

Induction of hepatotoxicity:

The 5-FU (100mg/20ml vial, Koçak Farma Company /Istanbul / Turkey) was administered intraperitoneally to each animal in the study groups in a dose of 20mg/kg for five consecutive days.[3,25]

Experimental design and grouping of animals:

The animals were divided randomly into:

Control groups (Normal saline groups): Consist of distilled water treated group and chamomile extract treated group (5 animals each). In the distilled water treated group, a volume of distilled water equal to chamomile extract was given by gavage tube, while the chamomile

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extract-treated group was given chamomile extract in a dose of (100mg/kg/day) once daily. The animals were intraperitoneally injected with normal saline (0.9% NaCl) in the same manner and dose like 5-FU for five days, and the treatment with distilled water or with once daily chamomile extract was initiated at day 6 and the treatment continued for 14 days.

Study groups (5-FU groups): After induction of hepatotoxicity using 5-FU, the animals in this group were also divided into two groups: the distilled water treated group and chamomile extract treated group (5 animals each) and treated in the same manner like the control group.

Histopathological analysis

At the end of the experiment (at day 15 from the starting of the treatments) all the animals were sacrificed by mild ether inhalational anesthesia, and the anterior abdominal wall was opened by a midline incision and the liver was dissected, the right lobe was removed, fixed 10% neutral formalin, embedded in paraffin, sectioned with microtome set at 5µm thicknesses and stained with hematoxylin and eosin and was examined under the light microscope for general morphology.[26]

Histological parameters such as (dilatation of portal tract, inflammatory cell infiltration, necrosis and fibrosis) were evaluated in five microscopic fields in each section preparation (linearly adjacent to each other) and preceded with scoring of these separate locations for all the groups. These parameters are determined by one blind evaluator, the inflammation scores classified into 4 categories, as described by Hadi et al (2012) and Ebada (2018): Score-0 (no or minimal), Score-1 (mild changes), Score-2 (moderate changes), and Score-3 marked or severe changes.[27,28]

Statistical analysis: The results were given as mean of ranking of data ± standard error. The potential difference among groups for histopathological data was evaluated using Kruskal-Wallis H test. All statistical calculations were done using computer programs SPSS (version 15). Statistical significance of differences between the groups was tested with the Post-Hoc test at 5% level of significance.

Results

The histopathological findings of control and study groups are as following:

1. Distilled water treated group:

Light microscopic observation revealed that the control hepatic tissue showed normal large polygonal cells with prominent round nuclei and eosinophilic cytoplasm, and few spaced hepatic sinusoids arranged in-between the hepatic cords (Figure 1).

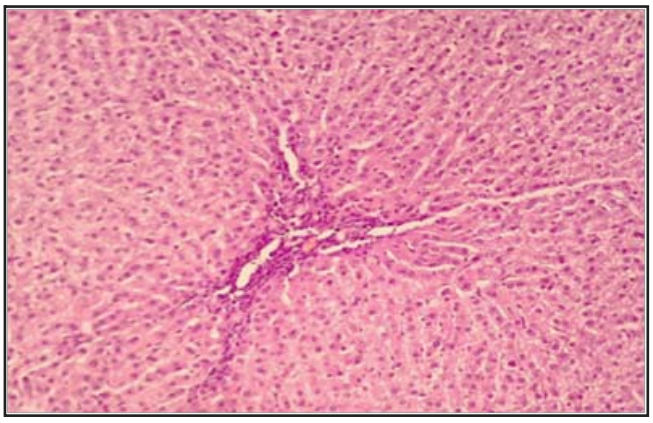

Figure 1 Photomicrograph from rabbit's liver of normal control rabbit showing normal liver architecture. Central vein, plates of hepatocytes some are binucleated, hepatic sinusoids with endothelial cells, Kupffer cells in their lining epithelium (H&E stain, Ax100)

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2. Chamomile extract treated group: This group showed slight hydropic degeneration of hepatocytes (Figure 2).

central vein, periportal inflammatory cells infiltration, dilatation of sinusoids, hydropic degeneration of the hepatocytes as well as micro abscess formation (Figure 3).

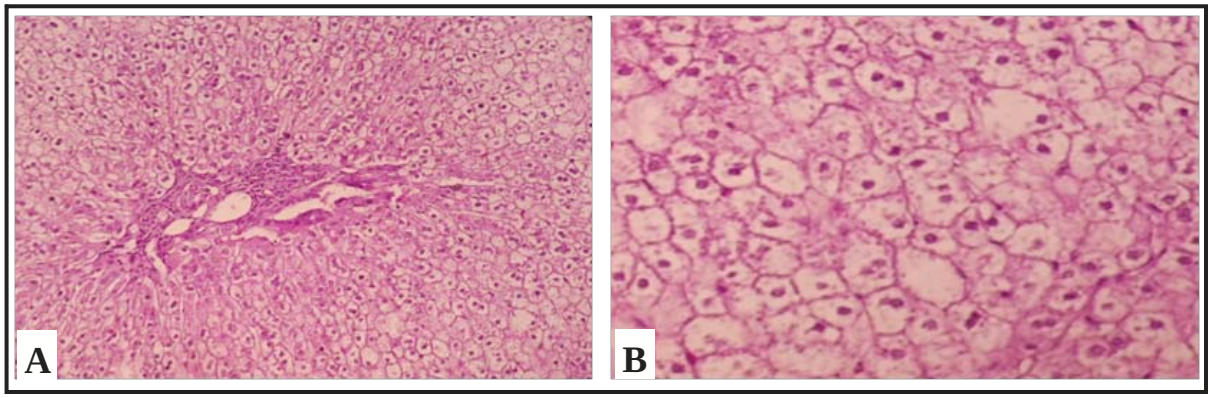

Figure 2 Photomicrograph from rabbit's liver of chamomile control rabbit showing hydropic degeneration (H&E stain, Ax100, Bx400)

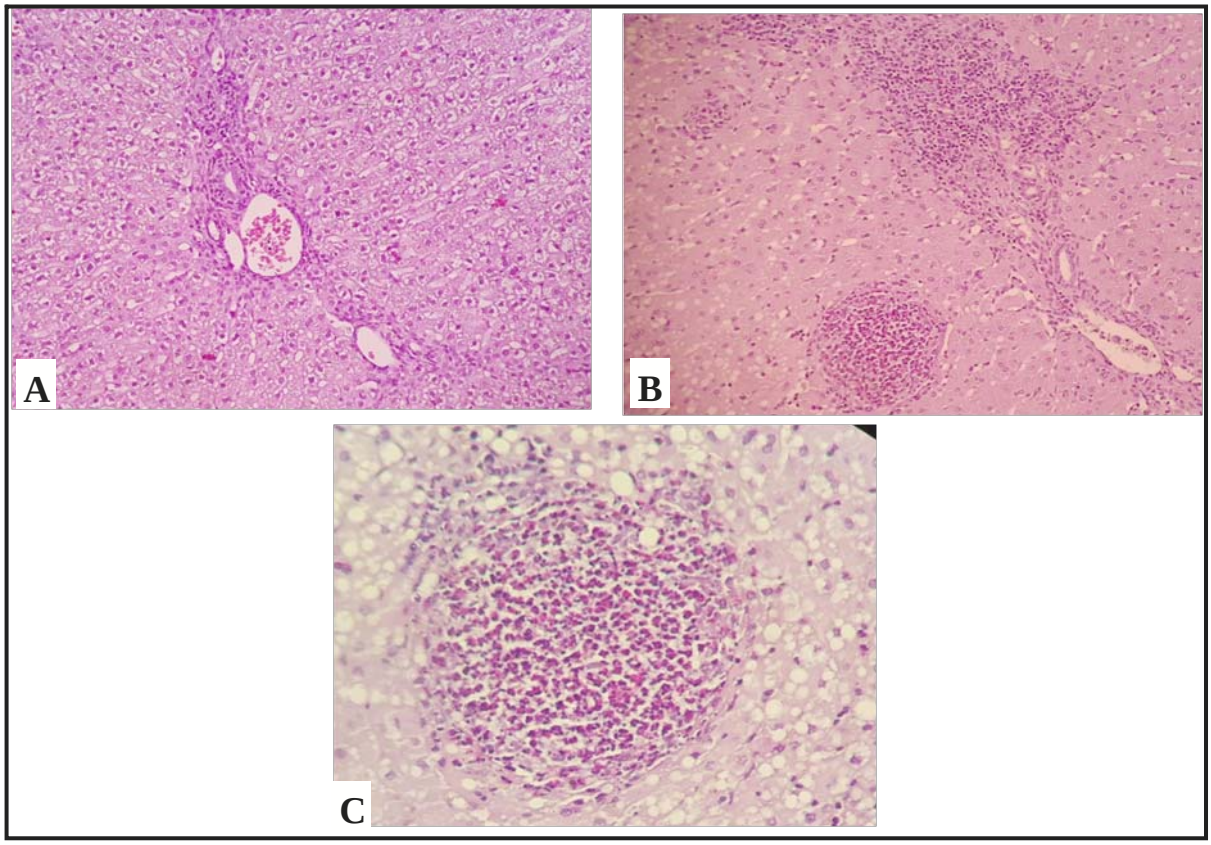

Figure 3 Photomicrograph from rabbit's liver of 5-FU study rabbit shows congestion of central vein, periportal inflammatory cells infiltration, dilatation of sinusoids, hydropic degeneration of the hepatocytesas well as micro abscess formation (H&E stain, Ax100, Bx100, C x400)

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4. 5-FU and chamomile treated group: the hepatic tissue in this group shows periportal inflammatory cells infiltration, dilatation of sinusoids and hydropic degeneration of the hepatocytes (Figure 4).

In the present study, the Kruskal-Wallis H test indicated that there was a significant difference among the different groups (P = 0.002). The histopathological examination of liver tissues from both the control and chamomile groups revealed normal architecture with no to minimal grade of inflammation as shown in Figure 1 and 2, and there was no statistical difference observed between the two groups. There were statistically significant differences between control group and 5-FU treated groups which showed severe degree of liver tissue inflammation. Using chamomile for the study group of rabbits after 5 days from using 5-FU and comparing the histopathological finding and degree of inflammation with 5-FU treated group showed no any significant improvement in the degree of inflammation and there was statistically significant difference with the control group. The mean and mean of ranks for each group are shown in Table 1 and the statistical comparisons between the groups are shown in Table 2.

Table 1 The mean and mean of ranks for each group

Groups	Mean	Mean of Ranks
Saline/water	0	4.5
Saline/chamomile	0.4	7.3
5-FU/water	1.4	13.2
5-FU/chamomile	2	17

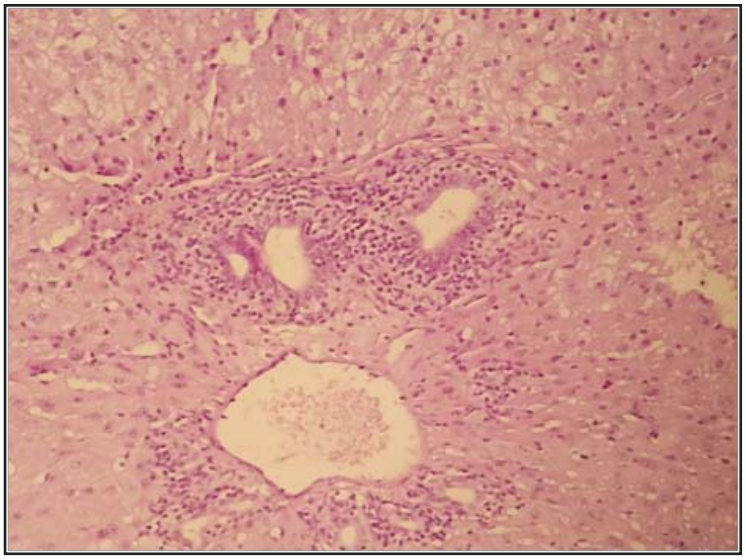

Figure 4 Photomicrograph from rabbit's liver of 5-FU and chamomile study rabbit shows periportal inflammatory cells infiltration, dilatation of sinusoids, hydropic degeneration of the hepatocytes (H&E stain, x100)

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Discussion

Although 5-FU is the most commonly used chemotherapeutic agent for the treatment of breast cancer and other various types of solid cancers, but its use may cause systemic side effects on liver, kidney and heart.[6,29] While many studies done to prevent hepatotoxicity, this is the first study done to investigate the effectiveness of using *Matricaria Chamomilla* flower extract in treating hepatotoxicity induced by 5-FU.

In the present study the administration of 5-FU showed significant changes in hepatic tissue, and it was manifested microscopically as severe inflammation that was significantly different from both controls (NS) & chamomile groups, in which both groups showed minimal to no effect on the liver after administration.

The side effects of 5-FU on hepatic tissue were documented in several studies.[6,30] In general, the mechanism of chemotherapy – induced hepatic injury is by the production of reactive oxygen species (ROS) which is mainly a part of cytotoxic drug action to kill the tumour cells.[31] A study done by Sommer et al 2017 revealed that the molecular mechanism for 5FU-induced inflammation and steatosis of the hepatic tissue is due to its effect on mitochondrial function that resulted in the oxidative stress.[32]

The group of animals that received 5FU then chamomile extract didn't show any improvement in the histopathological features but there was significant increase in inflammation of hepatic tissue and this could be due to the dose of chamomile or the duration of using it during the study wasn't enough to treat hepatic inflammation induced by 5-FU. No study was found regarding using chamomile flower extract for the treatment of hepatoxic side effects of drugs, however, some studies showed the effectiveness of using chamomile extract in preventing liver injury induced by different drugs, as in a study done by Manna et al 2015 which concluded that the administration of 200mg/kg of methanolic extract of chamomile with azathioprine had hepatoprotective effect on rats' hepatic tissue due to the induced anti-oxidant capacity and reduced lipid peroxidation

Table 2 Comparisons between groups (mean of ranks ± standard error) of the hepatic inflammatory scores

Groups	Mean of inflammatory scores (mean of ranks±SE)	Post-Hoc test *P*-value
Saline/water Saline/chamomile	-2.8±3.5407	0.429
Saline/water 5-FU/water	-8.7±3.5407	0.014*
Saline/water 5-FU/chamomile	-12.5±3.5407	0.00*
Saline/chamomile 5-FU/water	-5.9±3.5407	0.04*
Saline/chamomile 5-FU/chamomile	-9.7±3.5407	0.006*
5-FU/water 5-FU/chamomile	-3.8±3.5407	0.283

* *P* value ≤0.05 is considered significant.

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which resulted in improved histological picture of the liver,[33] but these findings wasn't compared statistically to show a real significant differences of the results. Another study done by Tavakol et al suggested that the use of 50mg/kg of chamomile aqueous extraction prevent liver injury induced by paraquat herbicide in rats through lowering hepatic enzymes (ALT & AST) and increase in the activity of antioxidant enzymes (CAT, TAC & TTG) but no histological study on liver tissue was done in their studyto prove the effectiveness of chamomile on hepatic tissue inflammation.[34]

Recently a study by Shebbo et al 2020 revealed that the chemoprotective and antitumor role of chamomile aqueous extract in a dose of 150 mg/kg, against DMH-induced carcinogenic hepatic damage in mice; was attributed to antioxidant, antiproliferative and anti-inflammatory properties of the plant extract.[14]

A study done by Sayde et al 2018 showed that using chamomile extract (400 mg/kg) for three weeks before and after inducing hepatotoxicity by lipopolysaccharide has resulted in protective effect on liver by reducing liver enzymes, lipid peroxidation & markers of oxidative stress which resulted in improvement of the architecture of the liver in pre and post treated rats with chamomile.[35] In a study done by Ebada et al 2018 found that the administration of chamomile essential oil in a dose of 250 mg/kg for 2 weeks before the induction of hepatotoxicity in rats using acetaminophen resulted in partial protection of the liver.[28]

The present study showed that treating rabbits with 100mg/kg of chamomile extract after using 5-FU for 5 days resulted in no improvement of histopathological findings but on the contrary there were a significant inflammation of hepatic tissue, and this may indicate that either that the used dose or the duration of treatment with chamomile was not enough to treat the hepatic side effects of 5-FU since few studies indicated that the hepatoprotective effect of anti-inflammatory effect of chamomile extract has a dose and time dependent manner.[36] Many studies support the anti-oxidant power of *Matricaria chamomilla*,[12,14] and also its hepatoprotective, antitumor and anti-inflammatory activities is documented, and is related to the bioactive substances found in chamomile extract which is mainly represented in its phenolic compounds such as flavonoids tannins coumarins, lignans and quinons.[14,17,20]

Conclusion

Hepatotoxicity is a serious side effect of cancer chemotherapy that needs more attention for preventing or treating it if it occurs. Chamomile extract has profound biological and pharmacological properties that may be helpful in preventing hepatic damage induced by drugs but in the present study it wasn't effective in treating 5-FU induced hepatotoxicity at the dose and duration used and hence further investigation are needed for the assessment of other doses and durations for treating chemotherapy induced hepatotoxicity.

Competing interests

The author declares that he has no competing interests.

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