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Amelioration of Capecitabine Toxicity in Albino Rats Using *Chrysanthemum* Extract

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Abstract

Cancer is a growing threat to human and animal health, The use of synthetic chemotherapy in the treatment of cancer is short because of lack of appropriate safety due to their drastic side effects. So, this study evaluated the ameliorative effect of *Chrysanthemum* on genotoxicity as well as renal and hepatic toxicity of capecitabine (xeloda), as a model of anticancer drug. Thirty six male albino rat were divided into 6 groups. Serum samples were taken at 21 and 45 days and bone marrow samples at 45 days. Comet assay, biochemical tests for liver and kidney functions were done also serum oxidative biomarker were measured. The results of the present study revealed that capecitabine (xeloda) caused harmful genotoxic effect, biochemical changes in oxidative biomarkers, liver and kidney function, however the use of capecitabine (xeloda) in combination with *Chrysanthemum* ameliorated these changes especially with high dose. In conclusion, capecitabine adverse effects could be successfully alleviated through the co-administration of the natural antioxidant *Chrysanthemum*.

KEYWORDS
Genotoxicity, Capecitabine, *Chrysanthemum*, Cancer, Oxidative biomarkers.

INTRODUCTION

Cancer is a growing threat to human and animal health, despite the growing research to improve treatment and find a cure. Cancer also is considered the main cause for human deaths worldwide, accounting for 7.6 million deaths in 2008 and is expected to rise to 13.1 million deaths in 2030 (Toolaram *et al*., 2014).

The use of chemotherapeutic agents in the treatment of cancer is deficit because of their side effects which are responsible of impaired organ function, most chemotherapeutics cause liver and kidney disorders. The vast majority induced oxidative stress and caused injury to the tissues (Premkumar *et al*., 2001).

Capecitabine is the prodrug of Fluorouracil (5-FU) which is the antimetabolite of activity against neoplasms. Capecitabine is effective against many types of cancers including prostate, renal cell, ovarian, and pancreatic, with evidence in metastatic breast and colorectal cancer. Therefore, capecitabine is currently approved by the FDA for use as a first-line treatment in patients with metastatic colorectal cancer (Walko and Lindley, 2005).

Capecitabine caused oxidative stress in the liver of rats as its effect observed in both enzymatic and non-enzymatic antioxidative markers. It affects superoxide dismutase (SOD) activity, glutathione s-transferase (GST) activity and malondialdehyde (MDA) (Olayinka *et al*., 2017). Capecitabine caused the formation of vast amount of reactive oxygen species and also reduction in plasma antioxidant levels (Altıner, 2020).

The idea of combining plant with anticancer drugs offers very valuable advantages such as the building of more potent anticancer therapies with less side effects, for example *Chrysanthemum* was reported as a protective agent against liver, kidney damage and genotoxic effect caused by anticancer drugs (Ahmad *et al*., 2015; Linjawi, 2015).

Chrysanthemum is a dicotyledonous genus from family *Asteraceae*. These herbaceous plants originally inhabit in East Asia and proved enormous ornamental, medicinal and industrial values (Hadizadeh *et al*., 2022).

Various compounds, including flavonoids, terpenoids, polysaccharides and unsaturated fatty acids have been identified in the genus *Chrysanthemum*. This unique combination imparted multiple biological features including antioxidant, antimicrobial, anti-inflammatory, anticancer, anti-allergic, anti-obesity, immune regulation, hepatoprotective and nephroprotective activities (Samiei and Shakeri, 2022),

Chrysanthemum aqueous extract was also reported to have hepatoprotective effect. It significantly reduced the levels of glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT) and alkaline phosphatase (ALP). The increase of these enzymes reflect damage of liver cell membrane and necrosis of hepatocytes (Jeong *et al*., 2013)

Chrysanthemum manifested a protective effect against the genotoxicity of the chemotherapeutic drug doxorubicin (DOX). The reduction of antioxidant defense during doxorubicin administration resulted in a decrease in the frequency of micronuclei and DNA damage. *Chrysanthemum* extract also prevented he-

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patic, kidney, and testicular injury by decreasing the oxidative stress and scavenging the free radicals, indicating the protective nature of this plant (Linjawi, 2015).

Chrysanthemum ethanolic extract showed antioxidant activity and preventive effect to oxidative DNA damage. The antioxidant activity was attributed to the phenolic and flavonoidal compounds present in the extracts. The ethanolic extract showed higher activity than that of aqueous extracts. In addition, the ethanol extract showed strong capacity on the prevention of oxidative DNA damage with minimal liver cell cytotoxicity (Debnath *et al*., 2013).

Hence the present study was designed to evaluate the impact of *Chrysanthemum* on genotoxicity and kidney and hepatic function in the anti-cancer drug capecitabine (Xeloda®) exposed albino rat.

MATERIALS AND METHODS

The source of capecitabine was (XELODA®) 500 mg tablets of Roche Registration Inc. A total of 36 healthy male albino rats were used in this study, weighting 80.0±10.0 g were obtained from the Laboratory Animal Resource Center, Faculty of Veterinary Medicine, Suez Canal University, Ismailia, Egypt. They were kept for 2 weeks for acclimatization. The animals were kept in stainless steel cages at temperature of 27°C ±5, 12 h dark–light alternation under good ventilation and fed a standard ration (72% corn, 72% soya bean, and 1% fish meal) with free access to water and food. Each cage was provided with a mesh drawer for wastes disposal daily. The scheme of this study was approved by the animal ethical committee of Faculty of Veterinary Medicine, Suez Canal University, Egypt.

Chrysanthemum extract preparation

Extract of *Chrysanthemum* was prepared from the corolla of the *Chrysanthemum* purchased from local market. Extract was obtained from (500g) via extraction with 4 L of Ethanol 95 % at room temperature over 3 days. The resulting solution was centrifuged and filtered, and the supernatant drawn, evaporated, and freeze-dried. The residue (100 mg) was then dissolved in 10 ml of water (Tsuji-Naito *et al*., 2009).

Experimental Design

Animals were divided into 6 groups, each group consisted of 6 rats. Drug and/or extract was given orally to the groups according to the following scheme:

Group 1: Capecitabine 30 mg/kg/day (Olayinka *et al*., 2017).
Group 2: Capecitabine 30 mg/kg/day + *Chrysanthemum* 5mg/kg/day (Ahmad *et al*., 2015).
Group 3: Capecitabine 30 mg/kg/day + *Chrysanthemum* 10mg/kg/day.
Group 4: *Chrysanthemum* extract 5mg/kg/day.
Group 5: *Chrysanthemum* extract 10mg/kg/day/
Group 6: no treatment (negative control).

Blood samples were collected after 21 and 45 days of experiment initiation, while bone marrow samples were collected after 45 days.

Determination of biomarkers levels

Serum was analyzed for Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Creatinine, uric acid and Total proteins, spectrophotometrically using commercially available Diamond Diagnostics kits (Germany). GSH, SOD and MDA using commercially available diagnostic kits (BioVision's ApoGSH TM Colorimetric Assay Kit, USA)

Bone marrow samples were collected for comet assay. End-frosted slides were pre-coated with 0.5% normal melting point agarose and were allowed to dry at room temperature overnight. Cell suspensions were mixed with 0.5% low melting point agarose and 40 ml aliquots were mounted on glass slides and covered with a 24* 24 mm glass coverslip. Two gels were made on each slide from bone marrow sample. The gels were allowed to set on a cold plate and then the coverslips were removed. Slides were immersed in lysis solution (2.5 mol/l NaCl, 100 mmol/l EDTA disodium salt, 10 mmol/l, pH 10, Tris buffer, 10% DMSO and 1% Triton X-100) and stored at 4°C overnight. Slides were placed on an electrophoresis platform, covered with electrophoresis buffer (1 mmol/l EDTA disodium salt and 0.3 mol/l NaOH) and DNA was allowed to unwind for 20 min before electrophoresis (0.7 V/cm, 300 mA) for a further 20 min. DNA unwinding and electrophoresis were performed in the dark in a cold unit set at 4°C. Slides were immersed in three changes of neutralizing buffer (0.4 mol/l, pH 7.5, Tris–HCl) for 5 min at room temperature and then stained with 50 ml propidium iodide (20 lg/mL). Twenty min later, slides were scored, 50 nuclei per gel, using a comet IV capture system (Perceptive Instruments). Tail intensity (TI) was used as the measure of damage and was defined as the percentage of DNA that had migrated from the head of the comet into the tail (Smith *et al*., 2008).

Statistical Analysis

Data were expressed as means ± standard error of means (SE). The Statistical Processor System Support (SPSS) version 10 computer program was used to evaluate all the acquired data. The significance of variations in mean values between control and treatment rates (a) was determined using the one-way analysis of variance (ANOVA) test followed by Duncan s post hoc test for multiple group comparisons. Statistical significance was defined as a value of $p<0.05$. The percentages of change between the various experimental groups and the normal control group were determined (Tello and Crewson, 2003).

RESULTS

Effect of treatment on ALT, AST, uric acid and creatinine serum levels

On detecting ALT, AST, total protein (TP), uric acid and creatinine measurement from the data tabulated in Tables 1 and 2, it was denoted that a significant increase in the level of serum ALT, AST, uric acid and creatinine and significance decrease in TP ($p < 0.05$) was recorded in anticancer treated rats (group 1) after 21, 45 days of the experimental period compared with the negative control group (group 6). Anticancer (30mg) +*Chrysanthemum* (5 and 10 mg/kg bw) treated animals (groups 2 and 3) showed a significant decrease ($p < 0.05$) in the level of serum ALT, AST, uric acid and creatinine and significance increase in TP compared to positive control rats. While administration of *Chrysanthemum* ethanolic extract only (5 and 10 mg/kg bwt) in groups 4 and 5, induced no significant changes compared to the control negative group.

Effect of treatment on the serum GSH, MDA and SOD levels

From the data tabulated in Tables 3 and 4, it was denoted

that a significant decrease in the level of serum GSH, SOD and significance increase in serum MDA ($p < 0.05$) was recorded in anticancer treated rats (group 1) after 21, 45 days of the experimental period compared with the negative control group (group 6). Anticancer (30mg) +*Chrysanthemum* (5 and 10 mg/kg bw) treated animals (groups 2 and 3) showed a significant increase ($p < 0.05$) in serum GSH, SOD and significance decrease in serum MDA compared to positive control rats. While administration of *Chrysanthemum* ethanolic extract only (5 and 10 mg/kg bwt) in groups 4 and 5, induced no significant changes compared to the control negative group.

Effect of treatment on DNA damage

It was denoted that a significant increase in the level of DNA damage shown in increase tail length, DNA in tail and tail moment ($p < 0.05$) was recorded in anticancer treated rats (group 1) after 45 days of the experimental period compared with the negative control group (group 6). Anticancer (30mg) +*Chrysanthemum* (5 and 10 mg/kg bw) treated animals (groups 2 and 3) showed a significant decrease ($p < 0.05$) in the level of DNA damage (tail length, DNA in tail and tail moment) compared to positive control rats (group 1). While administration of *Chrysanthemum* ethanolic extract only (5 and 10 mg/kg bwt) in groups 4 and 5, induced no significant changes compared to the control negative group (group 6). These data are shown in Table 5.

DISCUSSION

The present study demonstrated that the ethanolic extract

Table 1. Effect of capecitabine and/or *Chrysanthemum* treatment on the serum levels of ALT, AST, TP, uric acid and creatinine on day 21.

	Group 1	Group2	Group3	Group4	Group5	Group 6
ALT (U/L)	60.67±2.12[a]	37.50±1.25[b]	35.50±1.33[b]	25.33±1.76[c]	25.33±1.76[c]	23.33±1.15[c]
AST (U/L)	175.66±3.21[a]	143.83±3.60[b]	136.66±3.38[b]	93.83±2.70[c]	103.33±4.07[c]	104.33±2.04[c]
TP (g/dl)	2.950±0.14[a]	4.733±0.20[b]	4.800±0.07[b]	6.483±0.43[c]	6.866±0.23[c]	7.166±0.40[c]
Uric acid (mg/dl)	3.1333±0.18[a]	1.7833±0.03[b]	1.7167±0.07[b]	1.000±0.06[c]	0.983±0.10[c]	0.950±0.13[c]
Creatinine (mg/dl)	3.1333±0.11[a]	1.5833±0.13[b]	1.4667±0.07[b]	0.783±0.06[c]	0.650±0.04[c]	0.6833±0.07[c]

Values are presented as means ± S.E. Different small superscript letters indicate significancy in the same column ($p<0.05$).

Table 2. Effect of capecitabine and/or *Chrysanthemum* treatment on the serum levels of ALT, AST, TP, uric acid and creatinine on day 45.

	Group 1	Group2	Group3	Group4	Group5	Group 6
ALT (U/L)	77.16±3.87[a]	39.83±1.24[b]	38.50±0.88[b]	26.33±1.76[c]	25.83±1.40[c]	24.66±1.56[c]
AST (U/L)	180.00±2.63[a]	146.66±3.35[b]	134.16±2.89[b]	93.33±2.07[c]	102.50±1.66[c]	104.16±3.51[c]
TP (g/dl)	2.666±0.19[a]	4.416±0.19[b]	4.633±0.15[b]	6.466±0.38[c]	6.700±0.26[c]	6.950±0.35[c]
Uric acid (mg/dl)	3.3667±0.16[a]	1.8167±0.040[b]	1.633±0.07[b]	1.050±0.08[c]	0.933±0.12[c]	0.883±0.14[c]
Creatinine (mg/dl)	3.2333±0.08[a]	1.5833±0.137[b]	1.500±0.05[b]	0.8±0.06[c]	0.666±0.04[c]	0.683±0.06[c]

Values are presented as means ± S.E. Different small superscript letters indicate significancy in the same column ($p<0.05$).

Table 3. Effect of capecitabine and/or *Chrysanthemum* treatment on the serum levels of GSH, MDA, and SOD of albino rats after 21 days.

	Group 1	Group2	Group3	Group4	Group5	Group 6
GSH (mg/dl)	0.30±0.057[a]	0.70±0.03[b]	0.833±0.03[b]	1.566±0.05[c]	1.866±0.10[c]	1.366±0.11[c]
MDA (nmol/ml)	59.95±2.21a	34.000±1.19b	33.216±0.57 b	17.016±0.99c	20.016±1.77 c	18.866±1.76 c
SOD (U/L)	313.00±2.87[a]	354.000±3.05[b]	360.33±2.15[b]	387.833±9.21[c]	401.00±5.26[c]	389.00±7.03[c]

Values are presented as means ± S.E. Different small superscript letters indicate significancy in the same column ($p<0.05$).

Table 4. Effect of capecitabine and/or *Chrysanthemum* treatment on the serum levels of GSH, MDA, and SOD of albino rats after 45 days.

	Group 1	Group2	Group3	Group4	Group5	Group 6
Tail length	11.1645±0.14[a]	8.9965±0.25[b]	7.9043±0.25[b]	5.682±0.20[c]	5.2308±0.17[c]	5.232±0.17[c]
DNA in tail (%)	13.225±0.33[a]	10.745±0.26[b]	9.578±0.41[b]	5.382±0.206[c]	5.378±0.202[c]	5.435±[0.166c]
Tail moment (%)	1.713±0.68[a]	0.8111±0.009[b]	0.607±0.005[b]	0.381±0.005[c]	0.3635±0.007[c]	0.3485±0.004[c]

Values are presented as means ± S.E. Different small superscript letters indicate significancy in the same column ($p<0.05$).

Table 5. Effect of capecitabine and/or *Chrysanthemum* treatment on DNA damage in rats after 45 days of experiment start.

	Group 1	Group2	Group3	Group4	Group5	Group 6
Tail length	11.1645±0.14[a]	8.9965±0.25[b]	7.9043±0.25[b]	5.682±0.20[c]	5.2308±0.17[c]	5.232±0.17[c]
DNA in tail (%)	13.225±0.33[a]	10.745±0.26[b]	9.578±0.41[b]	5.382±0.206[c]	5.378±0.202[c]	5.435±[0.166c]
Tail moment (%)	1.713±0.68[a]	0.8111±0.009[b]	0.607±0.005[b]	0.381±0.005[c]	0.3635±0.007[c]	0.3485±0.004[c]

Values are presented as means ± S.E. Different small superscript letters indicate significancy in the same column ($p<0.05$).

of *Chrysanthemum* when given orally for 45 days to albino rats ameliorated the genotoxic effect of capecitabine and improved the liver and kidney functions.

Capecitabine (xeloda) when given orally at dose of 30mg/kg for 45 day caused significant increases in the levels and activities of ALT, AST, uric acid and creatinine and a significant decrease in total protein level after 21 and 45 days of the experiment.

This effect could be justified on the basis that capecitabine was shown to lead to liver damage in rats through oxidative stress. In addition, capecitabine affected the kidney leading to an increase in the plasma levels of urea, and creatinine (Olayinka *et al*., 2017).

This was also observed by Tabata *et al*. (2004) who reported that administration of capecitabine (30 mg/kg BW twice daily) caused abnormal liver functions, severe inflammatory lesion to the liver as well as an increase in serum AST, ALT and ALP activities in rats.

However, co-administration of *Chrysanthemum* extract (in doses of 5mg/kg/day and 10mg/kg/day) with capecitabine showed significant decreases in serum activities of liver enzymes (ALT and AST), and in serum levels of uric acid and creatinine in rats (groups 2 and 3, respectively) as compared to group 1 (control positive group) after 21and 45 days from the start of the experiment.

These results were in accordance with (Ahmad *et al*., 2015) who stated that *Chrysanthemum* extract caused a significant decrease in the elevated serum level of enzymes (ALT and AST) upon co-administration with chemotherapeutic agent. They also reported that serum levels of uric acid and creatinine were significantly decreased.

Chrysanthemum extract administration significantly ameliorated the elevated plasma biomarkers of the liver and played a hepatoprotective role (Soni *et al*., 2014). In this study, administration of *Chrysanthemum* extract by doses of 5mg/kg and 10mg/kg (groups 4 and 5, respectively) did not cause any significant changes in serum levels of AST, ALT, uric acid and/or creatinine compared to group 6 (control negative group).

These results were in agreement to earlier studies (Li *et al*., 2010). It was reported that upon oral administration of *Chrysanthemum* ethanolic extract to albino rats, even in high doses, no significant changes in liver serum enzymes activities were detected.

Concerning oxidative biomarkers, the present study demonstrated that *Chrysanthemum* ethanolic extract when given orally at doses (5mg/kg Bw + *Chrysanthemum* 10mg/kg Bw) concomitantly with capecitabine at (30 mg/kg Bw) caused significant decrease in serum level of MDA and significant increases in serum activities of GSH and SOD compared to the positive control group. These results were in agreement to(Dong *et al*., 2017) who reported that *Chrysanthemum* decreased oxidative stress and inflammatory responses and caused increases in the activities of SOD and GSH .

Chen *et al*. (2021) reported that *Chrysanthemum* exhibited remarkable antioxidant activity in scavenging free radicals and significantly decreased the level of MDA. The possible explanation for these findings is that *Chrysanthemum* is rich in chemical constituents, like flavonoids and phenolic acids which attenuate the elevation of reactive oxygen species (ROS) level (Kim *et al*., 2006).

In this study, administration of *Chrysanthemum* extract by doses of 5mg/kg and 10mg/kg Bw, in groups 4 and 5, respectively, did not cause any significant changes in serum levels of MDA, SOD, and GSH compared to group 6 (control negative group). In the current study, capecitabine at a dose 30 mg/kg for 45 day caused significant increase in DNA damage represented by increases the tail length, and the tail moment.

The result agree with Wisniewska-Jarosinska *et al*. (2011) who recoreded that capecitabine has a genotoxic effect as it significantly decreased the viability of the cell. and damaged DNA in both cancer and normal cells. Also, capecitabine induced apoptosis in the cells.

The genotoxic effect of capecitabine because it is consider cytotoxic antimetabolic that interfere with nucleic acid metabolism in both normal and cancer cells (Ison *et al*., 2016).

The present study showed significant decrease in DNA damage of capecitabine anti-cancer drug in rat groups 2 and 3, which received *Chrysanthemum* ethanolic extract in doses of 5mg/kg Bw + *Chrysanthemum* 10mg/kg Bw, along with capecitabine (30 mg/kg Bw) compared to the control positive group which received xeloda only in a dose of (30 mg/kg Bw).

These results were in agreement with Ahmad *et al*., (2015) who reported that *Chrysanthemum* extract (5 mg) for 45 days significantly reduced the frequency of chromosomal aberration in both somatic and germ cells and DNA damage.

The ethanol-based extract of *Chrysanthemum* prevented induced DNA damage due to its strong antioxidant activities which resulted from the phenolic and flavonoid contents present in the extracts and did not show any cytotoxicity (Debnath *et al*., 2013).

Thus, the current experiments suggest that treatment with *Chrysanthemum* as natural antioxidant is effective for reducing the mutagenic and biochemical effects of capecitabine (xeloda) treatment in chemotherapeutic program.

Chrysanthemum ethanolic extract, being rich in flavonoids and phenolic compounds, could have hepatoprotective and nephroprotective activity. Thus, it could alleviate the adverse effects of the chemotherapeutic agent, capecitabine.

CONCLUSION

The complimentary use of *Chrysanthemum* with capecitabine (xeloda) treatment could be beneficial to reduce the adverse effect of capecitabine (xeloda) in cancer chemotherapy.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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