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Abstract

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Introduction

Is escalating in recent year's and remains as a leading cause of mortality in developing countries (1). It is can occur during the therapy with several cytotoxic drugs, including 5-fluorouracil and may be the dose limiting factor in cancer treatment and hence tumor response (2). Cardiac toxicity includes a wide range of cardiac effects from small changes in blood pressure and arrhythmias to cardiomyopathy. In literature, different mechanisms of chemotherapy induced cardiac toxicity are postulated including cellular damage due to the formation of free oxygen radicals and the induction of immunogenic reactions with the presence of antigen presenting cells in the heart. Moreover, the influence of the cytotoxic agents on certain phospholipids, especially cardiolipin, may also explain the development of cardiac toxicity (2).

5- Fluorouracil (5-FU) is an antimetabolite that acts during the S phase of the cell cycle and is activated by thymidine phosphorylase into fluorodeoxyuridylate (5 fluoro 2'deoxyuridine 5'monophosphate, 5-FdUMP) that inhibits thymidylate synthase, thus preventing DNA synthesis that leads to imbalanced cell growth and ultimately cell death (3-5). It is a potent antineoplastic agent commonly used for treatment of various malignancies including gastrointestinal, breast and head and neck cancer. In addition to bone marrow depression, gastrointestinal tract reaction, or even leucopenia and thrombocytopenia ⁽⁶⁾, it has diverse adverse effects such as cardiac toxicity, hepatotoxicity and nephrotoxicity which restrict its wide and extensive clinical usage, also it

Cardiovascular disease

causes marked organ toxicity coupled with increased oxidative stress and apoptosis (7).

Medicinal plants and their derivatives are widely used all over the world as medicinal, salutistic or functional food. Some medicinal plants are promising natural source (8). Artichoke (*Cynara scolymus L.*) is one of the world's oldest medicinal plants.

It is an important crop of ancient Greece, grows in Egypt, Mediterranean area and other countries .It is belonging to the family (Asteraceae) (9). It has medical properties and used in traditional folk medicine mainly because of their choleric (increasing bile secretion), diuretic and hypocholesterolemic activities (10). It is a good source of natural antioxidants such as vitamin C, hydroxycinnamic acids and caffeoylquinic acid derivatives (cynarin and chlorogenic acid) (11). Artichoke plant is rich with flavonoids (luteolin, apigenin), which its potential protective effect as antioxidant have been demonstrated for the extracts of this vegetable in reducing reactive oxygen species (ROS) from stimulated human neutrophil and in protection of hepatocyte from t-butyl

hydrogen peroxide induced cytotoxicity (12). The artichoke extracts were assessed for their protective role in the control of oxidative damage to biological molecules (proteins, lipids and DNA), caused by free radicals such as RCOO and/or OH, using the b- potential antioxidant effect. Several *in vitro* studies have shown that the antioxidant potential effect of ALE is dependent on radical scavenging and metal ion chelating effect of its constituents such as cynarin,



chlorogenic acid and flavonoids. Pure constituents of ALE have also been shown to produce less inhibitory activity on free radical production than the extract itself (13).

Materials and Methods Chemicals and drugs

5-Fluorouracil (5-FU) obtained from EBEWE pharma, AUSTRIA. Dimethyl sulfoxide (DMSO) and ethanol solvent obtained from warehouse chemicals of College of Pharmacy/ University of Baghdad.

Reagents

Standard assay rat's kits for AST/GOT and ALT/GPT were obtained from Egyptian Company For Biotechnology (S.A.E) and for CK obtained from Biolabo SA, 02160, Maizy, France.

Plant materials

The plant was collected from the Garden of Medicinal Plants at the Department of Pharmacognosy and Medicinal plants / College of Pharmacy / University of Baghdad. The leaves of the plant were dried in shade at room temperature, then rendered into a fine powder by using electrical mill and weighed.

Extraction of the plant

Four grams of powdered leaves were extracted by maceration with 2500 ml of absolute ethanol for one week, then the extract was filtered and evaporated to dryness under reduced pressure by using rotary evaporator, after that the collected amount was weighted (14).

Preparation of the extract for injection

A specific weight (4.5 gm.) from the dried ethanolic artichoke extract was dissolved in dimethyl sulfoxide (112.5 ml) to get a concentration of 40 mg/ml (as a stock solution) (13).

Experimental animals

Twenty -four female albino rats of 1-2 month old (average body weight 150-200gm), were obtained from

animal house of the college of pharmacy/ university of Baghdad. The animals were acclimatized under standard laboratory conditions for 2 weeks prior to treatment. They had free access to standard diet and water. They were maintained under standard condition of temperature (30°C), humidity and light / dark cycles. All the experimental studies were conducted in conformity with the guidance for care and standard experimental animals of our College ethical protocol. The animals were used in this study divided equally into four groups, each group with 6 rats they were treated as following: Group I: (negative control) received oral daily dose of DMSO (2 ml/kg /day) for 10 successive days. Group II: (positive control), received oral daily dose of DMSO (2 ml/kg /day) for 10 successive days with administered single dose of 5-FU (150 mg/kg) intraperitoneally on 8th day 7 in association with DMSO. Group III: received 200 mg/kg/day 13 of ethanolic artichoke extract orally for 10 successive days. Groups IV: received 200 mg/kg/day 13 of ethanolic artichoke extract orally 10 successive days with subsequently single intraperitoneal dose of 5-FU (150 mg/kg) on 8th in association with the ethanolic artichoke extract (13). After 24 h of the end of the experimental period (10 days), all the animals were anesthetized under light diethyl ether anesthesia and blood samples were collected in clean test tubes by intracardiac puncturing and allowed to clot at room temperature.

Biochemical assessment

The serum was separated by centrifugation for 20 min at 3600 round per minute (r.p.m.) and stored into eppendorff tubes at - 20 °C to be used for determination creatine (14).

Result

Data were subjected to statistical analysis and expressed as mean \pm standard deviation (SD). Statistical significance between groups was determined using the unpaired Student's t-test. Differences were considered statistically significant at $p < 0.05$.

5-FU (Group II) significantly ($P < 0.05$) increased serum levels of AST, ALT, and CK compared to Group I. Administration of ethanolic artichoke extract with 5-FU significantly ($P < 0.05$) decreased serum levels of AST, ALT, and CK compared to Group II.

Group IV showed a significant increase ($P < 0.05$) in AST, ALT, and CK compared to Group I, as shown in Table (1).

Discussion

Cardiac toxicity is one of the most serious side effects of 5-FU, commonly presenting as myocardial ischemia, and less frequently as arrhythmias, hypertension or hypotension, left ventricular dysfunction, cardiac arrest, and sudden death. The incidence of 5-FU-induced cardiotoxicity ranges from 0–35%, depending on dose, pre-existing cardiac conditions, and chemotherapy schedule.

The mechanisms underlying this toxicity are not fully understood; however, several hypotheses have been proposed, including vascular endothelial damage leading to coagulation, coronary artery spasm-induced ischemia, direct myocardial toxicity, and thrombogenic effects due to altered blood properties.

Oxidative stress is considered a key factor, as 5-FU increases superoxide anion levels while reducing antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px). This imbalance

promotes the formation of highly reactive hydroxyl radicals via the Haber–Weiss

reaction, leading to cellular damage. Elevated reactive oxygen species (ROS) can oxidize lipids, proteins, and nucleic acids, impairing cellular function.

Additionally, pro-inflammatory cytokines such as TNF- α , IL-1, and IL-6 contribute indirectly to tissue damage induced by chemotherapy.

The present study confirms the cardiotoxic effect of 5-FU, demonstrated by elevated serum levels of AST, ALT, and CK, which are well-established biomarkers of cardiac injury.

Importantly, treatment with ethanolic artichoke extract significantly reduced these biomarkers, indicating a protective effect against 5-FU-induced cardiac toxicity in rats.

This protective effect is likely attributed to the antioxidant properties of artichoke extract, particularly its phenolic compounds such as chlorogenic acid, cyanins, luteolin-7-glucoside, tannins, and caffeoylquinic derivatives. These compounds exhibit strong free radical scavenging activity, reducing ROS production and protecting against oxidative damage caused by cytotoxic drugs.

Table 1. Effects of ethanolic artichoke extract (200 mg/kg) on the serum levels of AST, ALT and CK in albino female rats with 5-FU induced cardiac toxicity, data are expressed as Mean \pm SD, n

=6, * p <0.05. Standard deviation

(SD), 5-Fluorouracil (5-FU) and dimethyl sulfoxide (DSMO).

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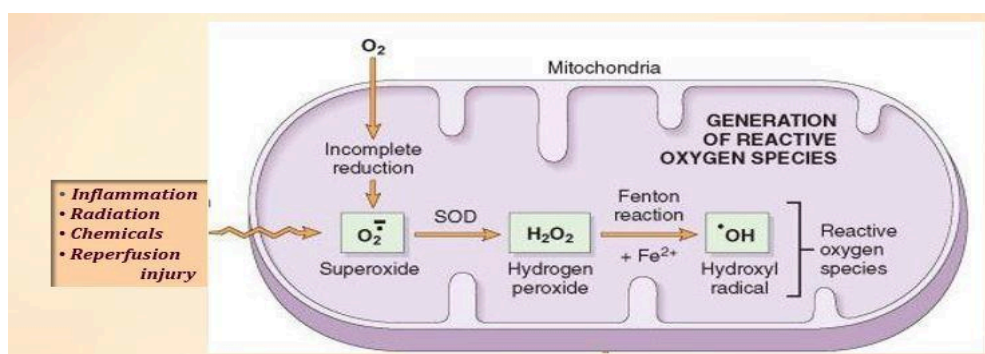
Treatment group n=6	Type of treatment	Serum Aspartate aminotransferase (S.AST) Up to 40 IU/L (Mean \pm SD)	Serum Alanine aminotransferase (S.ALT) Up to 40 IU/L (Mean \pm SD)	Serum Creatine kinase (S.CK) Up to 190 IU/L (Mean \pm SD)
I	Dimethyl sulfoxide (DMSO) only	27.33 \pm 0.42	7.33 \pm 0.81	51.33 \pm 4.35
II	5-Fluorouracil (5-FU)	74.06 \pm 11.52 *	32.53 \pm 1.43 *	555.66 \pm 67.77 *
III	200 mg/kg of Ethanolic artichoke extract	22.33 \pm 2.60 *	7.2 \pm 4.73	48.42 \pm 9.40
IV	200 mg/kg of Ethanolic artichoke extract + 5-FU	31 \pm 1.93 ^s	16 \pm 0.44 ^{*s}	63.6 \pm 5.05 ^{*s}

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(s): Significant difference with respect

(*): Significant difference with respect to negative control group (P< 0.05) to 5-FU treated group.

Figure 1. cellular damage due to the formation of free oxygen radicals → Time New Roman, Size10



Conclusion

The results of this study suggested that the

ethanolic artichoke extract has protective effects against 5-FU-induced cardiac toxicity in albino female rats. However, before a conclusive statement can be made on the potential antioxidant activity of artichoke extract as an adjunct to 5-FU therapy, there is a need for further.

References

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عرض الصفحة و ليس ضمن الاعمدة مع
مراعاة ان تكون في مكانها المناسب من
البحث.