

## Ethanollic Artichoke Extract improves outcome in a rodent model of 5- Fluorouracil Induced Cardio toxicity

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### ABSTRACT

**Background:** During treatment, many drugs may become cause of cardiac system toxicity, cytotoxic drugs therapy cause cardiac toxicity, including 5- Fluorouracil (5- FU). It is regarded as antimetabolite which cause its toxic effects during S phase of the cell cycle and got its activation by conversion of thymidine phosphorylase into fluorodeoxyuridylate (5 fluoro 2'deoxyuridine 5'monophosphate, 5-FdUMP) which cause inhibition of thymidylate synthase, which ultimately cause prevention of synthesis of DNA.

**Aim:** To focus on evaluation of ethanollic artichoke extract (*Cynara scolymus L*) with respect to its cardio protective properties against 5-fluorouracil (5-FU) induced cardio-toxicity in rabbits by estimation of Alanine aminotransferase, creatine kinase and aspartate aminotransferase enzymes in serum.

**Methods:** 4 groups consisting of 8 rabbits each were made for collected 32 rabbits who were albinos. Group I: (negative control) administered dimethyl sulfoxide (DMSO) (2 ml/kg /day) orally on daily basis for duration of 10 days. Group II: (positive control) administered DMSO (2 ml/kg /day) daily via oral route for duration of 10 days and subsequently received dose of 5-FU (150 mg/kg) (single) by intraperitoneal injection, on day 8<sup>th</sup> day in connection with DMSO. Groups III: administered ethanollic artichoke extract (200 mg/kg/day) orally on daily basis for duration of 10 days. Groups IV: administered ethanollic artichoke extract (200 mg/kg/day) daily on oral basis for 10 days with subsequently single intraperitoneal dose of 5-FU (150 mg/kg) on day 8<sup>th</sup> day.

**Results:** Before intoxication via 5-FU, treatment of ethanollic artichoke extract note worthily reduces the increase serum levels of AST,CK & ALT enzymes due to cardio toxicity induced via 5-FU- in case of rabbits .

**Conclusions:** With respect to present scenario, extracts of ethanollic artichoke serve as powerful modulator in reducing or masking cardiac toxicity cause by induction of 5-FU in case of rabbits.

**Keywords:** Artichoke Extract, Fluorouracil Induced Cardio toxicity, Ethanollic

### INTRODUCTION

One of the most escalating diseases in recent years is a Cardiovascular disease that remained one of the leading cause of death in many developing countries<sup>1</sup>. It may occurs during treatment with many cytotoxic drugs, such as 5- fluorouracil and that's why serve as dose limiting factor in case of cancer treatment and finally effecting tumor response<sup>2</sup>. Cardiac toxicity constitute of cardiac symptoms like from little alteration in blood pressure leading to arrhythmias and hence cardiomyopathy. In past researches variety of chemotherapy induced toxicity related to myocardium have ben postulated like damage at cellular level because of generation of free oxygen radicals and the generation of immunogenic reactions along with antigen in the myocardium cells. In addition to the effects of cytotoxic agents in relation to specific phospholipids, like cardiolipin, it also depict cardiac toxicity development<sup>2</sup>.

5- Fluorouracil (5-FU) is regarded as antimetabolite that execute its effects on cell cycle specially during the S phase and is catalyzed via thymidine phosphorylase into fluorodeoxyuridylate (5 fluoro 2'deoxyuridine 5'monophosphate, 5-FdUMP) that exhibits negative impact

over thymidylate synthase, thus stopping synthesis of DNA that leads to cell growth in imbalanced way leading to cell death<sup>3-5</sup>. It is regarded as significant antineoplastic substance that is used very often in treating various cancers such as breast, gastrointestinal head and neck tumors. Additionally, its effects on bone marrow depression, gastrointestinal related pathologies, thrombocytopenia and leucopenia<sup>6</sup>, myocardial system abnormalities leading to its toxicity, nephrotoxicity and hepatotoxicity, supports its restriction in administration widely and extensively. Moreover, it also leads to cause significant organ toxicity along with noteworthy increased in oxidative stress as well as apoptosis<sup>7</sup>.

All over the world, Medicinal plants along with their derivatives are used extensively assalutistic, medicinal, and functional food. The souce of these plants are mostly natural<sup>8</sup>. One of the oldest medicinal plants is Artichoke (*Cynara scolymus*. It is a significant ancient Greece crop, that cultivates in Mediterranean area, Egypt and other countries.It belongs to the family (Asteraceae)<sup>9</sup>. It has many medical benefits that can be used as medicine because of its hypocholesterolemic choleric (increasing bile secretion), and diuretic effects<sup>10</sup>.

It serves as a wonderful natural source antioxidants such as caffeoylquinic acid derivatives (cynarin and chlorogenic acid) vitamin C and hydroxycinnamic acids<sup>9,11</sup>.

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Artichoke plant is enriched with flavonoids like apigenin and luteolin, which exhibits protective antioxidant effects in decreasing reactive oxygen species (ROS) from catalyzing human neutrophil and in proving shield to hepatocyte from t-butyl hydrogen peroxide causing cytotoxicity<sup>12</sup>. The assessment of the artichoke extracts was made with respect to protective role against oxidative damage to molecules like DNA proteins and lipids, due to presence of free radicals like RCOO and/or OH, utilizing the metmyoglobin assay, b- carotene/linoleate assay, t and he deoxyribose assay. rtichoke leaf extracts (ALE) have significant antioxidant properties. Many research studies depicted that antioxidant property of ALE is relied upon effects like radical scavenging as well as metal ion chelating property of its constituents like flavonoids cynarin, and chromogenic acid. It has been shown that pure constituents of ALE exhibits decreased inhibitory effects on synthesis of free radical production as compared to extract itself<sup>13</sup>.

**Experimental animals:** Albino rabbits about 32 in number owing weight 250-300gm were selected from animal house. Before giving treatment, the rabbits were acclimatized for about two weeks maintaining standardized laboratory conditions .The standardized food and diet was provided to the rabbits. Temperature was maintained at 30°C humid in light / dark cycles. All this experiment was conducted keeping in view standardized conditions with respect to College ethical protocol. Four groups of rabbits were made in such a manner that each group consisted of 8 rabbits:

Group I: (negative control) administered dimethyl sulfoxide (DMSO) (2 ml/kg /day) orally on daily basis for duration of 10 days. Group II: (positive control) administered DMSO (2 ml/kg /day) daily via oral route for duration of 10 days and then received dosage of 5-FU (150 mg/kg) (single) by IP injection, on day 8th day in connection with DMSO. Groups III: administered ethanollic artichoke extract (200 mg/kg/day) orally on daily basis for

duration of 10 days. Groups IV: administered ethanollic artichoke extract (200 mg/kg/day) daily on oral basis for 10 days with subsequently single intraperitoneal dose of 5-FU (150 mg/kg) on day 8<sup>th</sup> day in liked with ethanollic extract .After 24 hours of the experiment, all the rabbits were anesthetized via using light diethyl ether anesthesia and finally samples of blood were taken in test tubes via intracardiac puncturing and then at room temperature , blood was allowed to clot .

**Biochemical assessment:** The separation of serum was done by aid of centrifugation for duration of 15 min at 4000 r.p.m and then its storage was made in eppendorf tubes at temperature of – 25 °C in order to evaluate enzymes like AST, alanine aminotransferase ALT and creatine Kinase CK<sup>15</sup>.

**RESULTS**

Analysis of data was made for statistical assessment. Data of study samples was expressed as the mean values mean±standard deviation (SD). The Statistical significance with respect to differences among different groups was estimated via student unpaired t- test. Data was considered statically noteworthy for p-value < 0.05.

5-FU (Group II) noteworthy (P<0.05) raised levels of ALT, and CK and AST engymes in serum was observed as compared to rabbits belonging to Group After treating rabbits with ethanollic artichoke extract associated with 5-FU (Group IV) note worthily (P<0.05) decline in ALT and CK and AST enzymes in serum in realtion to Group II was noted. Groups III depicted no noteworthy differences (P<0.05) in CK and ALT in relation to Group I, but noteworthy difference were noted in AST in relation to group I. whereas group IV depicted noteworthy increase (P<0.05) in ALT CK and AST enzymes in relation to Group I, as depicted in Table 1.

**Table (1): Effects of ethanollic artichoke extract (200 mg/kg) on the serum levels of AST, ALT and CK in albino rabbits with 5-FU induced cardiac toxicity**

Group n=8	Management	AST (Mean ± SD)	ALT (Mean ± SD)	CK (Mean ± SD)
1	Dimethyl sulfoxide (DMSO) only	29.01 ± 0.34	8.02 ± 0.04	49.26 ± 5.89
2	5-Fluorouracil (5-FU)	81.00 ± 12.52	34.03 ± 1.01	62.78 ± 7.26
3	200 mg/kg of Ethanollic artichoke extract	23.56 ± 3.01	6.9 ± 3.94	50.33 ± 8.29
4	200 mg/kg of Ethanollic artichoke extract + 5-FU	29 ± 2.46	1 ± 0.8	59.3 ± 4.06

**DISCUSSION**

One of the most dangerous side effects of 5-FU administration is cardiac toxicity, that depicted symptoms such as cardiac arrhythmia, myocardial ischemia, hypo and hypertension, left ventricular malfunction, cardiac arrest and ultimately sudden death<sup>8</sup>.

The cardiac toxicity induced via 5-FU induced lies

between 0-35% which is further more dependent upon its dosage, patents cardiac health and chemotherapy schedule (4, 8). The handling with respect to cardiac toxicity due to 5-FU-induction is tough since pathophysiological circumstances remained un identified beneath this cardiac toxicity<sup>3,11</sup>.

Many mechanisms have been put forward that include damage to vascular endothelial system,

coagulation, ischemia coronary artery spasm, cardiac ischemia, myocardium toxicity and thrombogenicity because of rheological factors alterations<sup>1</sup>. The science behind cardiac toxicity due to 5-FU include oxidative stress with superoxide anion increased levels after treatment<sup>19</sup>.

The glutathion peroxidase (GSH-Px) and superoxide dismutase (SOD) activities were decreased in case of guinea pigs who were treated with 5-FU<sup>17</sup> depicting a decline capacity with respect to antioxidant. If not removed via cellular antioxidant systems, these superoxide anions have ability to synthesize the highly toxic as well as reactive hydroxyl radicals via undergoing into Haber-Weiss reaction, that can be catalyzed via iron<sup>2,3</sup>. Inside cells, inclination of reactive oxygen species (ROS) may lead to macromolecules oxygenation, including nucleic acids, lipids as well as proteins, hence misbalancing functions of cell<sup>6</sup>. Along with ROS, pro-inflammatory cytokines like interleukins (IL)-1, tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukins 6, also participate indirectly in generation of toxicity and becoming source of damage to organ with chemotherapeutic agents like 5-FU<sup>26</sup>.

Recent case study depicted and assured cardiac toxicity induced via 5-FU, as witnessed via noteworthy (P<0.05) inclination in CK, AST and ALT serum enzymes. Evidence of increased levels of cardiac biomarkers in serum is a clear cut indication of injury to myocardium which could be because of imbalances with respect to supply-demand, haemodynamic stress and toxic effects<sup>18</sup>. Examples of such markers are lactate dehydrogenase Creatine kinase (CK), AST, troponins and myoglobin<sup>10</sup>.

This case reach depicted a positive results with respect to cardiac toxicity reduction due to induction of 5-FU in case of albino rabbits after receiving treatment with extracts of ethanolic artichoke since there was visible declining levels of ALT, CK and AST enzymes level in serum. These results clearly shows that extracts of artichoke exerts a positive cardio protective effects again toxicity included by 5-FU. Artichoke extract depicted a positive as well a strong antioxidant effect of phenolic acids specially cyanine and chlorogenic acid<sup>13</sup>. As far as biological activity with respect to extracts of artichoke is taken into consideration, the luteolin-7- glucoside and hydrolysable tannins presence behind deratotoxicities of caffeoylquinic, in the phenolic fraction must be taken into consideration: All of these phenolics exhibits a powerful antioxidant property against hydroxyl and peroxy radicals by declining ROS release induced by cytotoxic drugs induction, when examined using the metmyoglobin assay and beta-carotene/linoleate assay<sup>14</sup>.

## CONCLUSION

In a nut shell, this case research depicted that extracts of ethanolic artichoke exhibits protective effects against cardiac toxicity induced due to administration of 5-FU in case of albino rabbits. However, before making a conclusion on the significant antioxidant property of artichoke extract in 5-FU therapy, there is further requirement of an extensive research and studies via different research scholars for different artichoke extracts

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