REVIEW ON CARDIO PROTECTIVE AND ANTI-OXIDANT ACTIVITY OF PAULOWNIA TOMENTOSA PLANT

Sudarshan Singh[1*], Arun Dev Pokharel[1,]Mrs. Kusu Susan Cyriac[2]
Karnataka College of pharmacy #33/2, Thirumenahalli, Bangalore – 560064, India.Department of pharmacology.
Corresponding author: sudarshan singh

ABSTRACT

Paulownia tomentosa is one of the most useful trees in China. Variousparts(leaves, flowers, fruits, wood, bark, roots and seeds) of Paulownia have been used for treating avariety of ailments and diseases. Each of these parts has been shown to contain one or morebioactive components, such as ursolic acid and matteucinol in the leaves; Paulownia and dsesaminin the wood/xylem; syringin and catalpinoside in the bark. The fruits contain fatty oils, alkaloids, flavonones as well as flavonoids with antioxidant properties. In vitro grownPaulownia fortunei Hemsl. Seedlings, inoculated with Agrobacterium rhizogenes have a potential toproduce hairy roots and synthesize bioactive compounds such as acteosides. Withvarious new studies describing isolation of therapeutic compounds and their probable application inhuman health, it is an opportune moment to revisit medicinal potential of this tree.

KEYWORDS

Paulownia tomentosa, cardioprotective activity, antioxidant activity, 5-Fluorouracil induced cardio toxic rats.

INTRODUCTION

Cardiovascular disease (CVD) is a group of disorders/diseases of the heart and blood vessels,including heart attack and stroke. Cardiovascular diseases include: coronary heartdisease (heart attacks), cerebrovasculardisease, raised blood pressure (hypertension), peripheral artery disease, rheumaticheart disease, congenital heart disease, andheart failure[1].

Cardiovascular diseases (CVDs) continue to be a leading cause of morbidity and mortality among adults around the world. Risk factors have included blood pressure, cigarette smoking, Total Cholesterol (TC), Low Density Lipoprotein Cholesterol (LDL-C), High Density Lipoprotein Cholesterol (HDL-C), and Diabetes Mellitus. Factors such as obesity, left ventricular hypertrophy, family history of premature CVD, and Estrogen Replacement Therapy (ERT) have also been considered in defining CVD risk. Data from population studies enabled prediction of Coronary Heart Disease (CHD) during a follow-interval of several years, based on blood pressure, smoking history, TC, LDL-C and HDL-C levels, Diabetes Mellitus, and left ventricular hypertrophy on the electrocardiogram ECG [2].

Cardiovascular disease is considered as the leading cause of death among high-income countries and is projected to be the leading cause of death worldwide by 2030. Much of the current research efforts have been aimed toward the identification, modification and treatment of individual-level risk factors [3].

Cardio toxicity is the occurrence of heart electrophysiologydysfunction or muscle damage. The heart becomes weakerand is not as efficient in pumping and therefore circulatingBlood[4].

Paulownia tomentosa belongs to the family Scrophulariaceae, it is commonly known as princess tree [5]. *Paulownia tomentosa* is a genus that is composed of a number of species. They are all native to China except *P. fortune* which extends into Vietnam and Laos. *Paulownia tomentosa.* Also name a princess or empress tree [6]. *P. tomentosa* is a rich source of Geranylated flavanones, furanoquinones, iridoides and flavonoids were also present. *Paulownia tomentosa* is a large indecidous tree planted mostly for its fast growing wood and decoratative purposes. The tree is also used in traditional Chinese medicine. As a part of our study of natural polyphenols, the fruits of *Paulownia tomentosa* although with the development of chemical and pharmacological analysis methods we can study natural compounds more thoroughly, a great number of compounds and plants still remain unexplored. One such plant is *Paulownia tomentosa.* In this plant only a few compounds have been identified, mostly of polar character and divided into five groups: phenolic glycosides, furofuran lignanes, furanoquinones, iridoides and flavonoids. A large group of essential oil substances has also been identified in the flowers. These compounds and especially the flavonoids were identified from different species, where they probably serve as UV irradiation protectors. The increase in free radical species (corresponding with a high UV irradiation) is nowadays considered to be the true cause and effect of many metabolic disorders connected to such diseases as neurodegeneration, cancer and diabetes mellitus. A screening assay of *P. tomentosa* fruit extracts showed an antiradical effect [7].

Glycosides were the most abundant compounds isolated from the secretions of glandular hairs on the leaves and flowers of *P. tomentosa* these compounds were sticky but non-toxic to several insects surface of immature fruit were also rich in flavonoids. Oncidinol, a glyceride structurally related the glycerides of the glandular hairs, was isolated from the floral oil of Ornithophora radicans and may act as a reward for pollinating bees , also suggesting that the glycerides in the glandular hairs of *P. tomentosa* are not toxic. Therefore, the glandular hairs on the leaves and flowers may only physically obstruct herbivores. In contrast, the secretions of the glandular hairs [8].

BOTANIC DESCRIPTION

Paulownia is a deciduous tree and can reach a height of20 – 30 m under natural conditions and up to50 m recorded in China, its origin land[9]. Its diameter can reach 2 m[10]. Paulownia plant has a tendency to form many branchesif it is grown in open space, whereas in the forest it tendsto form a straight trunk. Paulownia bark is brown to black,smooth but with visible lenticels in the young tree thengradually are developed vertical cracks together with its growth.Often all the parts except of the old branches are coveredwith glandular mucigel hair, thick hair and branched hairsor stelate (star shaped). Most of the Paulownia specieshave pseudo-dikomote ramification which are dried afterthe wither period.The rare leaves create a cylindrical crown or an umbrella shape. Leaves at the maturatedtree reach the length of 15 – 30 cm and width of 10 – 12cm, with smooth and weaved sides. The new plants have big leaves and long stem, with trowel sides, placed in front of each other or in spiral shape[11]. Paulownia trunk is light, strong, dries quickly, aesthetically pleasant, with light colour that do notchange, easily workable and suitable for carvings andisolations [12].

PLANT PARTS AND THEIR MEDICINALUSE

Paulownia is one of the most exploited medicinal plants in terms of the plant parts that have been used in traditional medicine. In traditional Chinese medicine, the bark, fruit, xylem, and leaves of *P. tomentosa* var. *tomentosa* have been applied to treat or prevent a variety of diseases, such as hemorrhoid, carbuncle,inflammatory bronchitis, gonorrhea, upper respiratory tract infection, parotitis, asthma, traumatic bleeding, erysipelas, bacteriological diarrhea, swelling, bronchopneumonia, enteritis, conjunctivitis, hypertension, and tonsillitis [13,14]. The leaves, wood, and fruits of *P. tomentosa* have been traditionally used for the treatment oftonsillitis, bronchitis, asthmatic attack, and bacterial infections such as enteritis or dysentery. *Paulownia* may also have wound-healing properties, as the leaves have been used for the treatment of frostbite and leg ulcers [15]. Leaves, fruits, and flower are the most important plant parts employed in folk herbal medicine. Folk remedies in China use mashed *Paulownia* flowers to treat acne vulgaris and the decoction to treat fungal infection on the sole of the foot and the skin between toes [16]. Flowers are also used in treatment of first to seconddegree empyrosis [17].

P. TOMENTOSA FLAVONOIDS AND THEIR BIOLOGICAL ACTIVITY

Flavonoids represent the most numerous group ofsecondary metabolites isolated from *P. tomentosa*. Some of the flavonoid compounds found in *P.tomentosa* have been categorized as dietary flavonoids.Consuming this compound is believed to deliverhealth benefits. The activities of these flavonoids arefrequently been reviewed[18].P. tomentosa are rich in flavonoids, withconcentrations over 1,000 times greater than those onthe surfaces of the young leaves[19].

LEAVES

Flavonoids isolated from *P. tomentosa* leaveshave antiradical and cell protective effects [20]. Aqueous extracts of fresh *P.elongata* leaves and silage show *in vitro*antimicrobial activity against *Salmonella enterica,Pseudomonas aeruginosa, Staphylococcusaureus, Streptococcus pyogenes, Paenibacillusalvei,* and *Candida albicans.* The inhibitory effectis more pronounced against gram-negativebacteria [21]. The leaves from *P. tomentosa*(misidentified as *P. coreana*) containisoatriplicolide tiglate (PCAC) that inducedapoptosis in *vitro* studies on cervical and Breast cancer cell lines [22].

FLOWERS

Among various parts of *Paulownia* tree, theflowers seem to be the most used plant part withmultiple usages in folk herbal medicine[23]. Extracts of *P. tomentosa* flowers have been ofparticular research interest due to the presenceof flavonoids, specifically Apigenin. Apigenin has been shown to have hypotensive [24],anti-inflammatory [25], antispasmodic [26],antioxidant [27], and vasorelaxant properties [28]. Additionally, Apigenin has beenreported to exert its anti-tumorigenic effect *invitro* as well as *in vivo* not only via the inhibitionof tumor cell proliferation, but also via theimpairment of the invasive potential of tumorcells [29].*Paulownia* flower extracts inhibit the growth ofcertain bacteria the strongest effect was seen on*Staphylococcus aureus*, whereas the effect onAspergillus niger, Saccharomyces cerevisiae,and Penicillium chrysogenumwere not sosignificant [30]. Methanol extracts from driedflowers of *P. tomentosa* have shown potentialantiviral activity against enterovirus 71 (EV 71)And Coxsackie virus A16 (CAV 16), the twomain pathogens causing hand, foot and mouthDisease (HFMD) [31].Reportedbroad spectrum antimicrobial activity of theessential oils derived from *P. tomentosa* flowers the flavonoids extracted from *Paulownia* flowershave been shown to suppress asthmatic tracheainflammation, while the essential oil from theflowers also alleviated the allergic airwayinflammation in mice [32].

FRUITS

It has been noted that certain compounds of*Paulownia* fruits may have high inhibitory activityagainst Staphylococcus epidermidis, apathogenic gram-positive bacteria [33]. A studyreported that the *P. tomentosa* fruits can be afeasible source of natural antioxidant substances[34]. Purification of the methanol extract of*P. tomentosa* fruits yielded potentacetyl cholinesterase (hAChE) andbutyrylcholinestrase (BChE) inhibitory flavonoidswhich have been linked to amelioration ofAlzheimer's symptoms in addition to being a richsource of various geranylated flavonoids [35].

WOOD AND BARK

Paulownia wood serves for making paper pulp,musical instruments, furniture, and is also usedin construction[36].Antioxidantactivity of extracts from *P. tomentosa* var.*tomentosa* bark has also been demonstratedthat might lead to medicinal applications.The latter study showed that isocampneoside IIplays a critical role in neuroprotection by actingas a free radical scavenger and antioxidant.[37]

ROOT

Roots have been used to treat chronic retrogradeinflammation of the shoulder joint capsule and

Surrounding ligaments, muscles, tendons and bursa mucosa, also known as scapulohumeralperiarthritis in medical terms [38].

SEED

Paulownia seedscan also be used as a non-traditional material forthe production of oil which is rich in bioactivecompounds such as sterols and tocopherols fornutritive purposes [39].

SYRINGIN

Syringin is a Phenylpropanoid glycoside pertaining to eleutheroside derivative.The pharmacological properties of syringininclude free radicals scavenging, neuronal celldamage prevention, apoptosis inhibition, antidiabeticeffect, anti-inflammatory potential, antinociceptiveeffect, and anti-allergic actions[40].

FLAVONOIDS

The four main groups of flavonoidsare flavones, flavanones, catechins, andanthocyanins [41]. The geranylated flavanones from *P. tomentosa* was shown to inhibit levels ofnitrite oxide in LPS stimulated rat macrophages[42].

GLYCOSIDE

Glycosides are a large and very significant classof carbohydrate derivatives that arecharacterized by replacement of the anomerichydroxyl group by some other substituent [43].With the advancement in chromatographicmethods and modern spectroscopic techniques,studies on natural products from the genus*Paulownia* continue to reveal new compounds.The most notable ones are iridoid glycosides,phenyl-propanoid, lignin glycosides, flavonoids,sesquiterpene and triterpenes. Many of thesecompounds have been proven to contain acertain degree of bioactivity [44]. Phenylethanoidderivatives which are incorporated by ether orester bond to iridoid glycosides have recently been isolated [45]. Phenylethanoid glycosidesCampneosid I extracted from *P. tomentosa* havea high biological activity. Campneosid I wasfound to have significant antibacterial activityagainst several pathogenic strains of*Streptococcus* and *Staphylococcus* including *S.aureus*[46].

CHEMICAL COMPOUND OF THE PAULOWNIA LEAF[47]

COMPOUND	IN %
Organic matter	91.4
Proteins	22.6
Nitrogen	2.8-3.0
Kappa	0.4
Potassium	0.6
Calcium	2.1
Iron	0.6
Zinc	0.9
Metabolisation energy	15-18mg /kg

CULTIVATION OF PAULOWNIA TOMENTOSA

Paulownia consumes about 2000 liters of water per treeto reach a production of 4,3 t/ha during the first cut.Paulownia has a high adaptability with land climactericconditions. In the Mediterraneanclimate conditions the Paulownia production is negativelyaffected by the high evapotranspiration but not from the rainfalls and temperatures .This species is very adaptable and widely dispersed. It hasa natural distribution from the tropical zones till the oneswith moderated climate. And to the zones where theannual rainfalls are between 500 to 2000 mm and a highfrom the sea level up to 2400 m. Theadequate conditions for the Paulownia cultivation areattained in a height of 200 – 1300 m above the sea levelwith an average of the annual temperature 15 – 23oC andannual rainfalls 1400 – 2800 mm.Paulownia is not affected from pests and diseases; theplant is very flexible and usually not affected by diseases.[48]

Cultivation requirement of Paulownia tomentosa[49]

Temperature	25-47°c (optimum 27°c)
Water	500-2000 mm (700 mm during vegetative growth or over 150 mm/ month
Sea level height	2400 m (preferred 750-800m)
Soil temperature	15-16°c
Soil PH	5-8.9
Clay	<25-30%
Total porosity	≥ 50%
Salinity	<1%

MATERIALS AND METHODS

Plant material

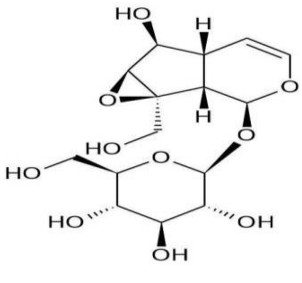
Fresh leaves and fruits of *Paulownia tomentosa*.Were collected from Agricultural Museum, Dokki, Giza, Egypt in July and September respectively. The plant materials were identified by Mrs. Terase Labib, head of the taxonomy at El-Orman Botanical Garden. A voucher specimen (No.06-06-03-16) was kept at the Herbarium of El-Orman Botanical Garden.

Extraction & Isolation

Mature fresh fruits of *P. tomentosa*.Were subjected to complete extraction by cold maceration in absolute methanol. The extract was collected, filtered and evaporated under vacuum. The residue was mixed with distilled water and successively extracted on cold with chloroform, ethyl acetate, methanol respectively. The different extracts were evaporated separately under vacuum till dryness. The methanol extract were subjected to silica gel column chromatography (CC) by (Chloroform – Methanol – Water) to give catalpol (1), Aucubin (2) and paulownioside (3) and new hydrocarbon.

Compound 1

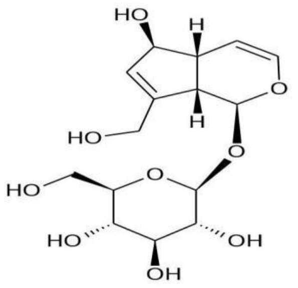
It was isolated as white crystalline powder by preparative TLC from fractions (1-15) CHCl3-MeOH-H2O (80:20:2) then purified and crystallized from methanol its m.p.= 203-205, It is highly soluble in water and methanol also soluble in ethanol, acetone, but almost insoluble in lipophilic organic solvents such as chloroform, benzene, and petroleum ether & Rf value is (0.21) in solvent system *n*-butanol-H2O (9:1).



Catalpol

Compound 2

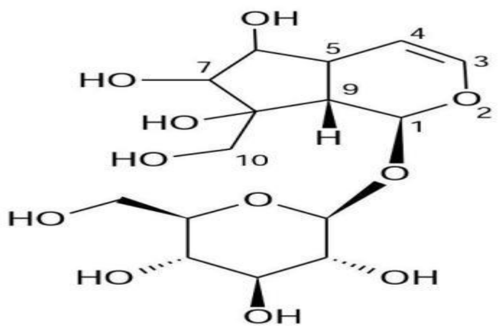
It was isolated as white crystalline powder by preparative TLC from fractions (31-45) CHCl3-MeOH-H20 (80:20:2) then purified and crystallized from methanol, its m.p. =181°C, soluble in water, insoluble in chloroform, ether, petroleum ether and Rf values (0.5 & 0.8) in two different solvent systems *n*-butanol-H2O (9:1) &*n*-butanol-MeOHH2O (7:2:1).



Aucubin

Compound 3

It was isolated as white crystalline powder by preparative TLC from fractions (31-45) CHCl3-MeOH-H2O (80:20:2) then purified and crystallized from methanol its m.p. is 308°C (decomposed) soluble in water, methanol and insoluble in chloroform & Rf values (0.38 & 0.68) in two different solvent systems *n*-butanol-H2O (9:1) &*n*-butanol-MeOH H2O (7:2:1) as shown.



Paulownioside

Compound 4

It was isolated as white amorphous powder from the choroformic fractions (20 fractions). Crystallized by methanol, its m.p. = 201, soluble in chloroform, insoluble in methanol and Rf value (0.75) in solvent system *n*-butanol-H2O (9:1).

Chemicals and biochemical kits

All chemicals used in the present study were of high analytical grade, products of Sigma (USA), Merck (Germany), BDH (England) was used for the induction of diabetes in rats. Glibenclamide (Daonil) (Sanofi Aventis) was used as standard antidiabetic drug. Kits used for the quantitative determination of different parameters were purchased from Bio-diagnostic (Egypt).

Animals

Male albino rats weighting (120-150g), supplied from the animal house of National Research Centre (Dokki, Giza, Egypt) were used for experimental investigation. The rats were kept in our laboratory under controlled environmental conditions. Anesthetic procedures complied with the legal ethical guidelines approved by the Ethical Committee of the Federal Legislation and National Institutes of Health Guidelines in USA and were approved by the ethical committee of the National Research Centre in Egypt with registration No. 13-015.[50]

Experimental Design

Wistar Albino rats of either sex, weighing (150-250 g) will be used in this study. Rats will be housed at constant temperature (20 ± 1.8°C) and relative humidity (50 ± 10%) in standard polypropylene cages, six per cage, under a 12-h light/dark cycle, and allowed food and water freely.

Animals are divided into 5 groups each group consist of 6 rats.

Group-1: Control (normal saline for 7 days).

Group-2: Normal saline for 7 days +5 fluorouracil (150mg/kg/ I.P) on 5th day (48 hr. before scarification).

Group-3: Vitamin-E (for 7 days) +5-fluorouracil.

Group-4: Low dosEthanolic extract of *Paulownia tomentosa*, for 7 days +5 fluorouracil.

Group-5: High dose of Ethanolicextract of *Paulownia tomentosa*,for 7 days +5 fluorouracil.

Forty-eight hours after the 5-fluorouracil administration, blood will be collected from the retro orbital route under ether anesthesia, the rats will be sacrificed and the parameters going to be studied are general appearance, gross morphology, heart weight, histopathology, hematological and biochemical parameters and tissue antioxidant markers.[51]

Preparation of serum and tissue homogenate

After The experimental regimen, the animals were scarified by cervical dislocation under mild chloroform anaesthesia. Blood was collected on decapitation. The heart were excised immediately and thoroughly washed with ice cold physiological saline. The collected blood was centrifuged at 2500 rpm for 10 min and collects the serum. The serum was used for various biochemical experiments.1 g of heart was taken and Homogenized with 0.1M cold buffer (pH-7.4) in a potter Homogenizer fitted with Teflon plunger at 600 revolution per for 3min. the homogenate was used for various biochemical assays. The protein Urea, Uric acid and Creatinine were estimated by colorimetric method. Lipid profile in serum Triglycerides,Cholesterol, HDL LDL and Phospholipids were assayed in serum using standard kits. Cardiac markers enzymes such as AST, ALT, LDH, ACP, and ALP.Enzymatic antioxidants such as SOD, Catalase, Lipid peroxidation[52]

HISTOPATHOLOGICAL STUDIES

Heart was washed in saline and a small portion of it was quickly fixed in 10% formalin. Then the tissue were proceed by standard histopathological technique (i.e.) dehydration through graded isopropyl alcohol, cleaning through xylene and impregnated in paraffin wax for 2 hours. Then wax blocks were made, sections were used for cutting microtone and stained by haematoxylin eosin method and photographed.

STATISTICAL ANALYSIS

The results of cardio protective and antioxidant activities are expressed as mean ± SD from six animals in each group. The results were statistically analysed using one way ANOVA followed by Tukey-Kramer post test for version 3.00 of graph Pad software, Inc. (San Dego CA), was used for statistical analysis.

ACUTE TOXICITY STUDIES

The acute toxicity study will be performed by using up and down procedure (OECD-425, guidelines).

ANTIOXIDANT STUDY

Estimation of superoxide dismutase:

Add 2.78 ml sodium carbonate buffer (0.05 mM, pH 10.2), 100 µL of EDTA (1 mM, 0.0037 g in 10 ml distilled water). Add 20µL supernant / sucrose for blank and Incubate at 30˚C for 45 min. Thereafter, the reaction will be initiated by adding 100µL of adrenaline. The change in the absorbance will be recorded at 480nm for 3 min.

Catalase estimation

Pipette out 100µL of supernant to 1.9 ml phosphate buffer (pH 7), add 1 ml H2O2 and measure the changes at the 240 nm for three min.

Lipid peroxidation

1 ml homogenate will be combined with 2 ml (TBA- TCA-HCl). Solution will be heated for 15 min in a boiling water bath, keep it for cooling at room temp, centrifuge at 4000 rpm for 10 min. Take supernatant and measure at 532 nm.

Estimation of Glutathione Peroxidase

To 0.2 ml of tris buffer, 0.2 ml of EDTA, 0.1 ml of sodium azide and 0.5 ml of tissue homogenate will be added. To this mixture, 0.2 ml of glutathione and 0.1 ml of hydrogen peroxide will be added. The contents will be mixed well and incubated at 37°C for 10 minutes along with a tube containing all the reagents except sample. After 10 minutes the reaction will be arrested with the addition of 0.5 ml of 10 % TCA, centrifuged and the supernatant will be assayed for glutathione by Ellman's method.To 2.0 ml of the supernatant, 3.0 ml disodium hydrogen phosphate solution and 1.0 ml of DTNB reagent will be added. The color developed will be read at 412 nm. Standards in the range of 200-1000 jag will be taken and treated in the similar manner. The activity will be expressed in term of fig of glutathione consumed/min/mg protein.[53]

RESULT

Results of cardiac biomarkers were showed a significant increase in serum concentrations of CK-MB in FU-treated group in comparisonto control group. This elevation was significantlydecreased in LS-treated group, indicating the cardioprotectiverole of the plant. 5-FU treatment significantlyincreased the serum TAG and TC levels in FU-treated group incomparison to control group indicating hypertriglyceridemia andhypercholesterolemia. Serum LDL-c and VLDL-c concentrationsare significantly increased while the serum HDL-cconcentration is significantly decreased in FU-treated group incomparison to control group. Pre-co-post-treatment with *LS* significantlyimproved the tested parameters. Results showed a significant increase in thisratio in the FU-treated group which was significantly decreasedby *LS* treatment. Itshowed a significant increase in inflammatory markers suchas myocardial IL-1β and MPO activity and a significant decreasein GSH concentration in the FU-treated group whencompared to control rats. LS treatment reversed the results ofthese tested parameters. However, cardiac MDA and NO concentrationswere non-significantly increased in the FUtreatedgroup in comparison to control group and were nonsignificantlydecreased in the LS-treated group.[54]

DISCUSSION

The mechanisms of 5-FU-induced cardio toxicity are hemorrhagicinfarction, myocardial inflammatory reaction withinterstitial fibrosis; arterial endothelial injury followed by thrombosis increased metabolism leading todepletion of ATP, increased levels of superoxide anion and adecreased antioxidant capacity, arterial vasoconstriction andaltered plasma levels of substances involved in coagulation andfibrinolysis . Oxidative stress causes cellulardamage, coronary artery spasm and the decreased affinityof RBCs to transfer oxygen, resulting in myocardial ischemia,cardiac arrest and sudden death. Myocardium contains high concentrations of diagnosticmarkers for myocardial infarction and once metabolicallydamaged, it releases its content into the extracellular fluid. Serum Creatinine kinase (CK) and troponins are some of these markers.The increasedactivity of serum CK-MB isoenzyme reflects thealterations in the plasma membrane integrity and permeability. In the present study, 5-FU treated rats showeda significant elevation in the activity of serum CK-MB and cTnIlevel. Which indicated 5-FU induced myocardialnecrotic damage and the leakiness of the plasmamembrane. LS treatment resulted in lower activity of the CKMBand cTnI level in serum. It was demonstrated that LS couldmaintain membrane integrity, thereby limiting the leakage ofthese biomarkers.Hyperlipidemia plays an important role in cardiovasculardiseases and the development of atherosclerosis.A significant elevation in the serumTC, TAG, VLDL-c and LDL-c fractions along with a decrease inHDL-c were observed in 5-FU treated rats compared to controlrats. These observed changes concerning lipid profilecome in agreement.And couldbe attributed to the enhanced lipid synthesis via cardiac cyclic[55]

CONCLUSION

Our results confirmed the existence of cardio toxicity due to5-FU therapy, which was indicated by an elevation of serumcardiac cTnI, CK-MB, altered lipid profile and atherogenic indexwith enhanced oxidative stress and the release of some inflammatorymarkers. It can be concluded that LS seed exertscardioprotective activity that could be partly contributed by itsantioxidant and anti-inflammatory activities. So, *Lepidiumsativum* can be considered a candidate to protect againstcardio toxicity commonly encountered with 5-FU treatment. [56]

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