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

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ABSTRACT
Paulownia tomentosa is one of the most useful trees in China. Various parts (leaves, flowers, fruits, wood, bark, roots and seeds) of Paulownia have been used for treating a variety of ailments and diseases. Each of these parts has been shown to contain one or more bioactive components, such as ursolic acid and matteucinol in the leaves; Paulownia and desamin in 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 grown Paulownia fortunei Hemsl. Seedlings, inoculated with Agrobacterium rhizogenes have a potential to produce hairy roots and synthesize bioactive compounds such as acteosides. With various new studies describing isolation of therapeutic compounds and their probable application in human 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 heart disease (heart attacks), cerebrovascular disease, raised blood pressure (hypertension), peripheral artery disease, rheumatic heart disease, congenital heart disease, and heart 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 electrophysiology dysfunction or muscle damage. The heart becomes weaker and is not as efficient in pumping and therefore circulating Blood [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, furanocoumarins, iridoides and flavonoids were also present. Paulownia tomentosa is a large indeciduous tree planted mostly for its fast growing wood and decorative 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, furanocoumarins, 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 of 20 – 30 m under natural conditions and up to 50 m recorded in China, its origin land [9]. Its diameter can reach 2 m [10]. Paulownia plant has a tendency to form many branches if it is grown in open space, whereas in the forest it tends to form a straight trunk. Paulownia bark is brown to black, smooth but with visible lenticels in the young tree then gradually are developed vertical cracks together with its growth. Often all the parts except of the old branches are covered with glandular mucigel hair, thick hair and branched hairs or stelate (star shaped). Most of the Paulownia species have pseudo-dikomote ramification which are dried after the wither period. The rare leaves create a cylindrical crown or an umbrella shape. Leaves at the maturated tree reach the length of 15 – 30 cm and width of 10 – 12 cm, 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 not change, easily workable and suitable for carvings and isolations [12].

PLANT PARTS AND THEIR MEDICINAL USE

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 of tonsillitis, 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 decocation 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 second degree empyrosis [17].

**P. Tomentosa Flavonoids and Their Biological Activity**

Flavonoids represent the most numerous group of secondary 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 deliver health benefits. The activities of these flavonoids are frequently reviewed [18]. *P. Tomentosa* are rich in flavonoids, with concentrations over 1,000 times greater than those on the surfaces of the young leaves [19].

**Leaves**

Flavonoids isolated from *P. Tomentosa* leaves have 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*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Paeonibacillus alvei*, and *Candida albicans*. The inhibitory effects are more pronounced against gram-negative bacteria [21]. The leaves from *P. Tomentosa* (misidentified as *P. coreana*) contain isoatriplicolide tiglate (PCAC) that induces apoptosis in vitro studies on cervical and breast cancer cell lines [22].

**Flowers**

Among various parts of *Paulownia* tree, the flowers seem to be the most used plant part with multiple usages in folk herbal medicine [23]. Extracts of *P. Tomentosa* flowers have been of particular research interest due to the presence of flavonoids, specifically Apigenin. Apigenin has been shown to have hypotensive [24], anti-inflammatory [25], antispasmodic [26], and antioxidant [27] activities. Additionally, Apigenin has been reported to exert its anti-tumorigenic effect in vitro as well as in vivo not only via the inhibition of tumor cell proliferation, but also via the impairment of the invasive potential of tumor cells [29]. *Paulownia* flower extracts inhibit the growth of certain bacteria the strongest effect was seen on *Staphylococcus aureus*, whereas the effect on *Aspergillus niger*, *Saccharomyces cerevisiae*, and *Penicillium chrysogenum* were not significant [30]. Methanol extracts from dried flowers of *P. Tomentosa* have shown potent antiviral activity against enterovirus 71 (EV 71) and *Coxsackie virus A16* (CAV 16), the two main pathogens causing hand, foot and mouth disease (HFMD) [31]. Reported broad spectrum antimicrobial activity of the essential oils derived from *P. Tomentosa* flowers shows potential antiviral activity against enterovirus 71 (EV 71) and *Coxsackie virus A16* (CAV 16), the two main pathogens causing hand, foot and mouth disease (HFMD) [31].

**Fruits**

Extracts of *P. Tomentosa* flowers have been shown to suppress asthmatic tracheal inflammation, while the essential oil from the flowers also alleviated the allergic airway inflammation in mice [32].

**Wood and Bark**

*Paulownia* wood serves for making paper pulp, musical instruments, furniture, and is also used in construction [36]. Antioxidant activity of extracts from *P. Tomentosa var. tomentosa* bark has also been demonstrated that might lead to medicinal applications. The latter study showed that isocampneoside II plays a critical role in neuroprotection by acting as a free radical scavenger and antioxidant [37].

**Root**

Roots have been used to treat chronic retrograde inflammation of the shoulder joint capsule and...
Surrounding ligaments, muscles, tendons and bursa mucosa, also known as scapulohumeral periarthritis in medical terms [38].

**SEED**

Paulownia seeds can also be used as a non-traditional material for the production of oil which is rich in bioactive compounds such as sterols and tocopherols for nutritive purposes [39].

**SYRINGIN**

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

**FLAVONOID**

The four main groups of flavonoids are flavones, flavanones, catechins, and anthocyanins [41]. The geranylated flavanones from P. tomentosa was shown to inhibit levels of nitrite oxide in LPS stimulated rat macrophages [42].

**GLYCOSIDE**

Glycosides are a large and very significant class of carbohydrate derivatives that are characterized by replacement of the anomeric hydroxyl group by some other substituent [43]. With the advancement in chromatographic methods and modern spectroscopic techniques, studies on natural products from the genus Paulownia continue to reveal new compounds. The most notable ones are iridoid glycosides, phenylpropanoid, lignin glycosides, flavonoids, sesquiterpene and triterpenes. Many of these compounds have been proven to contain a certain degree of bioactivity [44]. Phenylethanoid derivatives which are incorporated by ether or ester bond to iridoid glycosides have recently been isolated [45]. Phenylethanoid glycosides Campneosid I extracted from P. tomentosa have a high biological activity. Campneosid I was found to have significant antibacterial activity against several pathogenic strains of Streptococcus and Staphylococcus including S. aureus [46].

**CHEMICAL COMPOUND OF THE PAULOWNIA LEAF**

<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>IN %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organic matter</td>
<td>91.4</td>
</tr>
<tr>
<td>Proteins</td>
<td>22.6</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>2.8-3.0</td>
</tr>
<tr>
<td>Kappa</td>
<td>0.4</td>
</tr>
<tr>
<td>Potassium</td>
<td>0.6</td>
</tr>
<tr>
<td>Calcium</td>
<td>2.1</td>
</tr>
<tr>
<td>Iron</td>
<td>0.6</td>
</tr>
<tr>
<td>Zinc</td>
<td>0.9</td>
</tr>
<tr>
<td>Metabolisation energy</td>
<td>15-18mg /kg</td>
</tr>
</tbody>
</table>

**CULTIVATION OF PAULOWNIA TOMENTOSA**

Paulownia consumes about 2000 liters of water per tree to reach a production of 4.3 t/ha during the first cut. Paulownia has a high adaptability with land climacteric conditions. In the Mediterranean climate conditions the Paulownia production is negatively affected by the high evapotranspiration but not from the rainfalls and temperatures. This species is very adaptable and widely dispersed. It has natural distribution from the tropical zones till the ones with moderated climate. And to the zones where the annual rainfalls are between 500 to 2000 mm and a height from the sea level up to 2400 m. The adequate conditions for the Paulownia cultivation are attained in a height of 200 – 1300 m above the sea level with an average of the...
annual temperature 15 – 23°C and annual rainfalls 1400 – 2800 mm. Paulownia is not affected from pests and diseases; the plant is very flexible and usually not affected by diseases.\textsuperscript{[48]}

**Cultivation requirement of Paulownia tomentosa**\textsuperscript{[49]}

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>25–47°C (optimum 27°C)</td>
</tr>
<tr>
<td>Water</td>
<td>500–2000 mm (700 mm during vegetative growth or over 150 mm/ month)</td>
</tr>
<tr>
<td>Sea level height</td>
<td>2400 m (preferred 750-800 m)</td>
</tr>
<tr>
<td>Soil temperature</td>
<td>15-16°C</td>
</tr>
<tr>
<td>Soil pH</td>
<td>5-8.9</td>
</tr>
<tr>
<td>Clay</td>
<td>&lt;25-30%</td>
</tr>
<tr>
<td>Total porosity</td>
<td>≥ 50%</td>
</tr>
<tr>
<td>Salinity</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

**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](image)

**Compound 2**
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. =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-MeOH-H2O (7:2:1).
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.

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 dose Ethanolic extract of *Paulownia tomentosa*, for 7 days +5 fluorouracil.

Group-5: High dose of Ethanolic extract 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 Diego 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 comparison to control group. This elevation was significantly decreased in LS-treated group, indicating the cardioprotective role of the plant. 5-FU treatment significantly increased the serum TAG and TC levels in FU-treated group in comparison to control group indicating hypertriglyceridemia and hypercholesterolemia. Serum LDL-c and VLDL-c concentrations were significantly increased while the serum HDL-c concentration is significantly decreased in FU-treated group in comparison to control group. Pre-co-post-treatment with LS significantly improved the tested parameters. Results showed a significant increase in this ratio in the FU-treated group which was significantly decreased by LS treatment. It showed a significant increase in inflammatory markers such as myocardial IL-1β and MPO activity and a significant decrease in GSH concentration in the FU-treated group when compared to control rats. LS treatment reversed the results of these tested parameters. However, cardiac MDA and NO concentrations were non-significantly increased in the FU-treated group in comparison to control group and were nonsignificantly decreased in the LS-treated group[54]

DISCUSSION

The mechanisms of 5-FU-induced cardio toxicity are hemorrhagic infarction, myocardial inflammatory reaction with interstitial fibrosis; arterial endothelial injury followed by thrombosis increased metabolism leading to depletion of ATP, increased levels of superoxide anion and decreased antioxidant capacity, arterial vasoconstriction and altered plasma levels of substances involved in coagulation and fibrinolysis. Oxidative stress causes cellular damage, coronary artery spasm and the decreased affinity of RBCs to transfer oxygen, resulting in myocardial ischemia, cardiac arrest and sudden death. Myocardium contains high concentrations of diagnostic markers for myocardial infarction and once metabolically damaged, it releases its content into the extracellular fluid. Serum Creatinine kinase (CK) and troponins are some of these markers. The increased activity of serum CK-MB isoenzyme reflects the alterations in the plasma membrane integrity and permeability. In the present study, 5-FU treated rats showed a significant elevation in the activity of serum CK-MB and cTnI level. Which indicated 5-FU induced myocardial necrotic damage and the leakiness of the plasmamembrane. LS treatment resulted in lower activity of the CKMB and cTnI level in serum. It was demonstrated that LS could maintain membrane integrity, thereby limiting the leakage of these biomarkers. Hyperlipidemia plays an important role in cardiovascular diseases and the development of atherosclerosis. A significant elevation in the serum TC, TAG, VLDL-c and LDL-c fractions along with a
decrease in HDL-c were observed in 5-FU treated rats compared to control rats. These observed changes concerning lipid profile come in agreement. And could be attributed to the enhanced lipid synthesis via cardiac cyclic [55].

**CONCLUSION**

Our results confirmed the existence of cardio toxicity due to 5-FU therapy, which was indicated by an elevation of serum cardiac cTnI, CK-MB, altered lipid profile and atherogenic index with enhanced oxidative stress and the release of some inflammatory markers. It can be concluded that LS seed exert cardioprotective activity that could be partly contributed by its antioxidant and anti-inflammatory activities. So, *Lepidium sativum* can be considered a candidate to protect against cardio toxicity commonly encountered with 5-FU treatment. [56]

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