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Evaluation of Hepatoprotective Activity of Ethanolic Extract of the Seed of *Flacourtia jangomas* against CCl_4-Induced Liver Damage in Rat Model

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Hepatotoxicity is a serious global concern caused by the increased use of non-pharmacological substances and drugs. There are numerous medications available to treat this condition, the most well-known of which being silymarin. Although few, silymarin has certain adverse effects, which is why many are looking for alternatives, and medicinal plants may be a

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viable option. According to studies, *Flacourtia jangomas* has the potential to scavenge free radicals among therapeutic plants. We carried out this research to determine the hepatoprotective effects of an ethanolic extract of *Flacourtia jangomas* seeds.

Methods: The experiment used 45 rats divided into 9 groups of five each. 25 of them developed hepatotoxicity as a result of regular CCl_4 administration. One of the groups was the disease control group, while the other four were given their respective treatments. The treatment groups received 300, 600, and 1200 mg/kg of *Flacourtia jangomas* seed extract, respectively. After 28 days of treatment, the rats were sacrificed and blood samples were obtained to assess several parameters.

Results: Based on the result of the tests, all of the abnormal levels of serum glutamate oxidoacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), creatinine, urea, total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride (TG) were restored to normal levels in a dose-dependent manner, but a high dose in the case of SGPT and creatinine, and a medium and high dose in the case of urea, HDL, LDL, and TG were required to significantly restore the abnormal level with 95% confidence intervals.

Discussion: This study provides evidence that *Flacourtia jangomas* seed extract has the ability to provide hepatoprotection by acting as a free radical scavenger, possibly due to the presence of components like flavonoids, phenolic acids, and tannins.

Conclusion: As the seed of *Flacourtia jangomas* has the potential to exhibit hepatoprotective activity, intensive research is needed to isolate the genuine therapeutic compounds utilizing hydrophilic and hydrophobic solvents and introduce novel compounds to the disease management system.

Keywords: Flacourtia jangomas; silymarin; hepatoprotective activity; hepatotoxicity; carbon tetra chloride.

1. INTRODUCTION

The liver performs a variety of functions and is a vital organ that provides support to almost every other organ in the body [1]. Numerous endogenous and exogenous compounds depend on it for detoxification and excretion, thus any harm to it or disruption of its functioning could have a detrimental effect on one's health in a variety of ways [2]. Hepatotoxicity is the term for injury or damage to the liver caused by exposure to nonpharmacological compounds such as carbon tetrachloride (CCl_4) or medications such as anti-tubercular treatments, general anesthetics, paracetamol, some anti-cancer drugs, etc. [1-11]. This is an uncommon but potentially fatal adverse medication event that can result in hepatocyte breakdown and death, mitochondrial inhibition, and altered lipid metabolism, all of which can raise oxidative stress [3, 12]. Within the last ten to fifteen years, there has been a thirtyfold increase in the incidence of hepatotoxicity, which ranges from 1.27 to 40.6 occurrences per 100,000 patients worldwide [4].

There are numerous drug classes on the market to treat hepatotoxicity, such as thalidomide, colchicine, resveratol, corticosteroid, interferon, silymarin, sulfoadenosylmethionine, etc. [13]. Among these drugs, silymarin, an extract from the *Silybum marianum* plant, has been shown to have hepatoprotective activity through a number of mechanisms. These include boosting RNA polymerase I and ribosomal RNA synthesis, which in turn stimulates hepatocyte protein synthesis and leads to hepatic regeneration and stabilizing membrane permeability by preventing lipid peroxidation. Additionally, it increases the amount of glutathione produced by the liver, which strengthens antioxidant defenses and helps activate antioxidant enzymes like superoxide dismutase [5,6,7,14,15,16,17]. Silymarin also protects liver cells from toxic chemicals by inhibiting the activation of hepatic nuclear factor kappa B (NF-κB), which stops TNF-α, interferon-gamma, IL-2, and IL-4 from being produced [16]. Headaches, skin problems, gastroenteritis, and cognitive events were the most often reported adverse responses; the toxicity and effectiveness are still being studied. Gastrointestinal symptoms were the most prominent adverse reaction [7, 8,14,18].

Researchers are presently looking for synthetic drug alternatives in medicinal plants because of their potential as an economical source, little to nonexistent adverse effects, and wide range of secondary byproducts with pharmacological action [9, 10]. Furthermore, it is possible to genetically modify plants to increase their production of the desired secondary

metabolites [17,18,19]. Many plants, including *Allium sativum*, *Nigella sativa*, *Capparis spinosa*, *Flacourtia jangomas*, *Launaea procumbens*, *Spondias mombim*, and others, have been discovered by researchers to have hepatoprotective properties recently [20-25]. *Flacourtia jangomas*, a plant belonging to the Salicaceae family, is also referred to as Paniala, coffee plum, Indian plum, or Painnagola. Although it originated in India, Bangladesh, and Myanmar, tropical areas of east Africa and south-eastern Asia are also home to the species. It's a little tree that grows to a height of 5 to 10 m with low branches, though it can occasionally reach 14 m [26–28]. Bark, roots, leaves, fruits, and seeds are among the body parts that contain a variety of compounds, including lignans and flavanolignans, terpenoids, alkaloids, flavonoids and tannins, coumarins and isocoumarins, and glucosides. These compounds have been shown to exhibit pharmacological activities such as hepatoprotective, anti-diarrheal, antioxidant, anti-diabetic, and anti-bacterial properties [23, 26, 29-31]. *F. jangomas* is safe and doesn't have any hazardous effects compared to silymarin [32,33].

F. jangomas seeds have components that have good free radical scavenging properties, according to a recent study [32]. Additionally, a study demonstrating strong hepatoprotective efficacy was conducted in vitro using a particular hepatotoxic model [23]. Nevertheless, no research has been conducted to assess the hepatoprotective properties of *F. jangomas* seed using animal models. Therefore, the current study's objective is to assess the hepatoprotective properties of *F. jangomas* seeds against hepatotoxicity induced by CCl_4 by assessing biochemical parameters such as lipid profile and tests for liver and kidney functioning.

2. MATERIALS AND METHODS

2.1 Plant Collection and Extract preparation

F. jangomas seeds were procured from the local market in Dhaka and authorized by the University of Dhaka's Department of Pharmacy. Fresh seeds were air-dried, ground to a fine powder and then immersed in 50% ethanol for a duration of 15 days. Every three days, the extract was filtered. The extracted material was dried at low temperature and pressure using a rotary evaporator. Finally, the raw residue underwent the required pharmacological testing.

2.2 Drugs and Chemicals

The well-known hepatotoxic chemical carbon tetrachloride (CCl_4) was bought from the Sigma company in the US. Livasil 140 mg, a frequently used anti-oxidant marketed drug form of silymarin, was acquired from Incepta Pharmaceuticals Ltd.

2.3 Experimental Animal Procurement, Nursing and Grouping

45 male rats weighing between 120-150 grams were taken from Jahangirnagar University in Savar, Dhaka, which were randomly divided into 9 groups each group having 5 rats. The University of Dhaka's Institute of Nutrition & Food Science (INFS) maintained a climate-controlled environment for the test subjects, with a 12-hour light/dark cycle, a temperature of 25±3 ºC, and a relative humidity of 55±5%. They were given access to clean water to drink and regular meals to eat. To allow for adaptation, the animals were housed in the environment for a minimum of one week prior to the study. The Institutional Animal Ethics Committee (IEAC) rules have been complied to in all experimental procedures. Both positive and negative control groups were included in our investigation.

2.4 Induction of Hepatotoxicity

Carbon tetrachloride (CCl_4) is a common chemical used in laboratories to study a wide range of acute and chronic liver problems. The CYP2E1 isoenzyme produces the trichloromethyl free radical (CCl_3), a CCl_4 metabolite that reacts with proteins and lipids in cells to form trichloromethylperoxy radical. This free radical causes lipid peroxidation and lobular necrosis by attacking lipids on the endoplasmic reticulum membrane more quickly than the trichloromethyl free radical. To induce liver damage, each group—aside from the control group—received a single oral dosage of CCl_4 and olive oil at a 1:1 ration (3 ml/kg of rat body weight) every day on an empty stomach. Animals received different dosages (300, 600, and 1200 mg/kg) of *F. jangomas* seed extracts orally afterwards as treatment to hepatic injury.

2.5 Evaluation of Hepato-Protective Activity

For this experiment, 45 rats were selected at random and were evenly divided into nine groups (Table 1).

Table 1. Application of treatment efficacy

Group number	Group specification	Treatment species	Dose treatment species (mg/kg)	Abbreviation of Groups
1	Negative control	Physiological saline	10 ml/kg	N
2	CCl_4 control	N/A	N/A	CCl_4
3	CCl_4 + Silymarin	Silymarin	80	$CCl_4 + S_{80}$
4	CCl_4 + *Flacourtia jangomas*	*Flacourtia jangomas*	300	$CCl_4 + FJ_{300}$
5	CCl_4 + *Flacourtia jangomas*	*Flacourtia jangomas*	600	$CCl_4 + FJ_{600}$
6	CCl_4 + *Flacourtia jangomas*	*Flacourtia jangomas*	1200	$CCl_4 + FJ_{1200}$
7	*Flacourtia jangomas*	*Flacourtia jangomas*	300	FJ_{300}
8	*Flacourtia jangomas*	*Flacourtia jangomas*	600	FJ_{600}
9	*Flacourtia jangomas*	*Flacourtia jangomas*	1200	FJ_{1200}

Out of the 9 groups, group 1 was the negative control group. It was fed physiological saline and a standard diet to create an optimal, neutral environment. In group 2, liver damage was caused using CCl_4, and no medication was administered. This group was compared to groups 4, 5, and 6, where seed extract was used as a treatment, with the potency of the plant extract being determined using a "One-way ANOVA test." In group 3, hepatic damage developed, and a commercial drug was administered to see if a conventional medication would be effective in treating the condition. After liver damage was induced in groups 4, 5, and 6, seed extract was administered at low, medium, and high doses (300, 600, and 1200 mg/kg) as a form of treatment. In groups 7, 8, and 9, no disease was developed; however, the drug was administered at doses of 300, 600, and 1200 mg/kg to see if any side effects were noticed in healthy rats by monitoring changes in blood parameters. This is primarily carried out for toxicological research.

After 28 days of treatment, all of the rats were euthanized, and a cardiac puncture was performed to obtain blood. Then, in order to determine the impact of CCl_4, silymarin, and plant extract on the pathological condition of rats, various parameters were measured in each group, including serum glutamate oxidoacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), creatinine, urea, total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride (TG).

2.6 Statistical Analysis

The Microsoft Excel program was used to capture and analyze all of our discoveries (raw data) in terms of numerical parameters on a broadsheet. Descriptive statistics were applied to the collected data, and the results were presented as mean SD. We interpreted inter-group heterogenicity in terms of many biological parameters using the "One-way Anova test" feature of the SPSS 16 software to assess statistical significance. The statistical significance of the occurrences is established by the fact that the 'p' value was less than 0.05 ($p<0.05$).

3. RESULTS

The effect of *F. jangomas* extract on liver function tests is listed in Table 2. When compared to the negative control group, the CCl_4 treated group's SGPT and SGOT levels were higher. With increasing doses of *F. jangomas* seed extract, the SGPT and SGOT levels declined correspondingly; however, the SGPT level only decreased significantly ($p<0.05$) in case of a high dose.

Table 2. Rat liver function test following medication administration and *F. Jangomas* extract

Group	SGPT (U/L)	SGOT (U/L)
N	38.24±2.91	45.54±5.32
CCl_4	114.25±15.31	122.38±11.32
$CCl_4 + S_{80}$	61.5±9.29	69.24±7.58
$CCl_4 + FJ_{300}$	111.22±13.61	120.25±9.63
$CCl_4 + FJ_{600}$	109.201±10.22	118.21±7.93
$CCl_4 + FJ_{1200}$	107.52±12.41*	115.25±10.24
FJ_{300}	34.23±3.92	47.79±5.39
FJ_{600}	39.21±4.51	44.3±5.21
FJ_{1200}	38.47±3.20	47.38±6.16

This Table 2 shows the standard deviation and average SGPT and SGOT values for 9 distinct groups, each with five rats. U/L is the unit of SGPT and SGOT. Following a 28-day course of

Table 3. Rat kidney function test following medication administration and *F. Jangomas* extract

Group	Creatinine (mg/dL)	Urea (mg/dL)
N	0.57±0.12	37.21±3.16
CCl_4	2.79±0.84	103.46±8.21
$CCl_4 + S_{80}$	1.27±0.79	61.75±6.29
$CCl_4 + FJ_{300}$	2.61±0.85	100.25±6.39
$CCl_4 + FJ_{600}$	2.39±0.29	95.91±7.2*
$CCl_4 + FJ_{1200}$	2.01±0.82*	91.67±6.58*
FJ_{300}	0.77±0.76	36.21±4.21
FJ_{600}	0.85±0.63	32.46±7.21
FJ_{1200}	0.89±0.69	37.92±6.29

Table 4. Rat lipid profile test following medication administration and *F. Jangomas* extract

Group	Total cholesterol (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	Triglyceride (mg/dL)
N	104.26±5.21	86.29±4.23	47.39±4.73	58.62±2.94
CCl_4	200.29±11.63	41.26±5.39	154.5±12.24	110.53±9.89
$CCl_4 + S_{80}$	146.41±8.29	63.39±5.12	81.7±9.98	75.25±12.31
$CCl_4 + FJ_{300}$	197.98±10.21	42.89±5.39	149.5±14.75	107.42±9.08
$CCl_4 + FJ_{600}$	193.24±9.82	45.73±6.91*	145.28±12.2*	101.25±7.63*
$CCl_4 + FJ_{1200}$	191.57±12.21	49.73±5.87*	141.25±6.28*	95.86±8.8*
FJ_{300}	106.27±7.51	83.21±2.2	49.2±3.73	59.95±4.4
FJ_{600}	109.29±3.2	87.75±3.79	51.93±5.08	55.29±5.01
FJ_{1200}	105.5±5.23	82.2±5.08	48.63±4.53	59.73±6.68

treatment, the values were obtained from blood serum.

When compared to the control group, the administration of CCl_4 significantly raised the levels of kidney functioning test markers such as creatinine and urea (Table 3). *F. jangomas* seed extract and silymarin reduced the elevation of creatinine and urea levels. Significant ($p<0.05$) results were observed with a high dose of seed extract for creatinine and both medium and high doses for urea.

This Table 3 shows the standard deviation and average creatinine and urea values for 9 distinct groups, each with five rats. For creatinine and urea, the measurement is mg/dL. Following 28 days of treatment, the values were obtained from blood serum.

In comparison to the control group, the rats who received CCl_4 had higher levels of total cholesterol, LDL, and triglycerides, but their HDL levels were lower (Table 4). Although the elevated total cholesterol level was gradually lowered in a dose-dependent way, it was non-significant ($p>0.05$). However, both medium and high doses of seed extract significantly restored the abnormal levels of LDL, HDL, and TG ($p<0.05$).

This Table 4 shows the standard deviation and average values for total cholesterol, HDL, LDL, and triglycerides over 9 groups, each with five rats. The units for triglycerides, HDL, LDL, and total cholesterol are mg/dL. Following a 28-day course of treatment, the values were obtained from blood serum.

4. DISCUSSION

Our findings confirm the idea that the ethanolic extract of *Flacourtia jangomas* seeds has hepatoprotective effect against carbon tetrachloride-induced hepatic injury, suggesting that it does so via scavenging free radicals and gradually reducing liver cellular necrosis.

Hepatotoxins like CCl_4 cause damage to liver cells by overproducing reactive oxygen species (ROS) and trichloromethyl free radicals during hepatic metabolism by cytochrome P-450. These free radicals then cause lipid peroxidation, covalent bonding of radicals with structural proteins, and ultimately, degradation of cellular membranes. Serum levels of important biomarkers, such as SGPT and SGOT, indicate the physiological activity of the liver. While SGOT is primarily bound in mitochondria, SGPT is the primary metabolic enzyme found in intracellular components. CCl_4 affects the liver's transport capacity and membrane permeability, which increases the amount of the vital liver biomarkers SGPT and SGOT that leak into the circulation [20,34,35,36,37]. Our research showed that the

disease control group's SGPT and SGOT levels increased significantly, supporting previous studies that found CCl_4 to be the cause of the hepatic damage [20]. The *F. jangomas* seed's ethanolic extract reduced the levels of SGPT and SGOT in a dose-dependent manner, demonstrating the seed's hepatoprotective qualities by healing liver damage, raising serum antioxidant enzyme levels through oxidative stress detoxification, and reducing ROS production [37] While a study found that a methanolic extract of the fruit and leaves of *F. jangomas* exhibited hepatoprotective activity, our study found that the higher dose had a better capacity to lower SGOT and SGPT levels, which may have resulted from the use of different extraction medium [23]. Nonetheless, the majority of research indicates that escalating the dosage enhances the ability to decrease SGPT and SGOT levels [20].

According to studies, use of CCl_4 can also result in nephrotoxicity by impairing glomerular function and producing free radicals, as seen by a rise in plasma creatinine and urea levels [38,39]. Similar to conventional silymarin, *F. jangomas* restored the CCl_4-induced changes in serum creatinine and urea in a dose-dependent manner, demonstrating the plant's possible hepatoprotective activity and confirming the hepatoprotective properties of the seed. Other investigations that were conducted on plants that had hepatoprotective action also indicated a decrease in serum creatinine and urea levels [40].

CCl_4 affects the lipid profile by increasing total cholesterol, LDL, and triglyceride levels while decreasing HDL levels through decreased protein synthesis and disturbance in phospholipid metabolism, which may contribute to this abnormality [41]. Following administration of *F. jangomas* ethanolic seed extract, levels of HDL were up and triglyceride, cholesterol, and LDL were lowered. Similar findings for other therapeutic plants were also shown in other investigations [41].

Flacourtia jangomas contains a wide range of phytochemical elements, including anthocyanin, alkaloids, β-carotene, flavonoids, tannin, saponin, and phenolic compounds, which are often, found in fruits and have a variety of pharmacological effects [42]. Seeds may also include these components. These ingredients exhibit antioxidant properties that protect against hepatotoxicity, according to several studies [43–49]. Because phenolic groups serve as hydrogen donors, phenolic compounds—including tannins, phenolic acids, and flavonoids—have the ability to scavenge free radicals and limit the oxidation of proteins while also increasing the activity of antioxidant enzymes [32,37]. However, screening should have been done to determine the chemical contents contained in the seed and measurements should have been made to determine the quantity of components present in order to improve the comprehensiveness of this study. All things considered, *Flacourtia jangomas* may represent a viable, clinically relevant, natural remedy against side effects caused by drugs when prolonged or multiple drug therapy is necessary for a strong hepatoprotective effect.

5. CONCLUSION

The present investigation of *F. jangomas* in rat models sheds light on its potential hepatoprotective properties. A potential hepatoprotective effect of the plant extract was established by a decrease in SGPT, SGOT, ALP, creatinine, TC, LDL, and TG and an increase in HDL level in rats treated with CCl_4. To identify the responsible active chemicals and their potential mechanism of action, and to obtain extractions using different hydrophobic and hydrophilic solvents to assess the activity of different compounds so they may be used in different disease management systems, rigorous research is required.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Animal Ethic committee approval has been collected and preserved by the author(s)

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Gulati K. et al. Hepatotoxicity: its mechanisms, experimental evaluation and protective strategies', American Journal of Pharmacology. 2018;1(1):1004.
2. Abou Seif HS. Physiological changes due to hepatotoxicity and the protective role of some medicinal plants', Beni-Suef University Journal of Basic and Applied Sciences. 2016;5(2):134–146.
   DOI: 10.1016/j.bjbas.2016.03.004
3. Paniagua AC, Amariles P. Hepatotoxicity by drugs', in Ntambwe Malangu (ed.) Pharmacokinetics and Adverse Effects of Drugs - Mechanisms and Risks Factors. Rijeka: IntechOpen; 2018.
   Available:http://dx.doi.org/10.5772/intechopen.72005
4. Shmanko V, Shmanko O, Lazarchuk T. The current state of the problem of drug hepatotoxicity and measures of its prevention and treatment', Journal of Education, Health and Sport. 2023;30(1):1106–1115.
   DOI: 10.12775/JEHS.2023.30.01.010
5. Mishra AK. et al. Rationally designed nanoparticulate delivery approach for silymarin with natural bio-enhancer: *In vitro* characterization and in vivo evaluations of hepatoprotective effects in a mouse model', Journal of Drug Delivery Science and Technology. 2023;86:104580.
   DOI: 10.1016/j.jddst.2023.104580
6. Anupama Sekar J. et al. Silymarin enriched gelatine methacrylamide bioink imparts hepatoprotectivity to 3D bioprinted liver construct against carbon tetrachloride induced toxicity', European Journal of Pharmaceutics and Biopharmaceutics. 2024;198:114272.
   DOI: 10.1016/j.ejpb.2024.114272.
7. Karimi G, et al. Silymarin a promising pharmacological agent for treatment of diseases, Iranian Journal of Basic Medical Sciences. 2011;14(4):308-317.
8. Mulrow C. et al. Milk thistle: effects on liver disease and cirrhosis and clinical adverse effects', Evidence Report/Technology Assessment (Summary). 2000;21:1-3.
   Available:http://europepmc.org/books/NBK33277
9. Shakya AK. Medicinal plants: Future source of new drugs', International Journal of Herbal Medicine. 2016;4(4):59-64.
   DOI: 10.13140/RG.2.1.1395.6085
10. Fotsing YSF. et al. Extraction of bioactive compounds from medicinal plants and herbs', in Hany A. El-Shemy (ed.)Natural Medicinal Plants. Rijeka: IntechOpen; 2021.
    Available:https://doi.org/10.5772/intechopen.98602.
11. Thompson M. et al. Hepatotoxicity: Treatment, causes and applications of medicinal plants as therapeutic agents', The Journal of Phytopharmacology. 2017;6(3):186-93.
    DOI: 10.31254/phyto.2017.6308
12. Mihajlovic M, Vinken M. Mitochondria as the target of hepatotoxicity and drug-induced liver injury: molecular mechanisms and detection methods', International Journal of Molecular Sciences. 2022; 23(6):3315.
    DOI: 10.3390/ijms23063315
13. Muriel P, Rivera-Espinoza Y. Beneficial drugs for liver diseases', Journal of Applied Toxicology. 2007;28(2):93–103.
    DOI:10.1002/jat.1310
14. Federico A, Dallio M, Loguercio C. Silymarin/Silybin and chronic liver disease: a marriage of many years', Molecules. 2017;22(2):191.
    DOI: 10.3390/molecules22020191
15. Abenavoli L. et al. Milk thistle (*Silybum marianum*): A concise overview on its chemistry, pharmacological, and nutraceutical uses in liver diseases', Phytotherapy Research. 2018;32(11):2202–2213.
    DOI:10.1002/ptr.6171
16. Gillessen A, Schmidt HH-J. Silymarin as supportive treatment in liver diseases: A narrative review', Advances in Therapy. 2020;37(4):1279–1301.
    DOI:10.1007/s12325-020-01251-y
17. Wadhwa K. et al Mechanistic insights into the pharmacological significance of Silymarin, Molecules. 2022;27(16):5327.
    DOI: 10.3390/molecules27165327
18. Bindu KH, Mythili JB, Radhika RM. Chapter 12 - Genetic engineering in medicinal and aromatic plants', in GyanaRanjan Rout and K.V. Peter (eds.) Genetic Engineering of Horticultural Crops. Cambridge: Academic Press; 2021.
    Available:https://doi.org/10.1016/B978-0-12-810439-2.00012-X
19. Bharti PK. et al. Genetic manipulation in medicinal plants for enhancement of secondary metabolites', in Ravi Singh and Nitish Kumar (eds.) Genetic Manipulation

of Secondary Metabolites in Medicinal Plant. Springer: Singapore; 2023.
Available: https://doi.org/10.1007/978-981-99-4939-7_6

20. Naji KM. et al. Hepatoprotective and antioxidant effects of single clove garlic against CCL_4-induced hepatic damage in rabbits', BMC Complementary and Alternative Medicine. 2017;17(1).
DOI: 10.1186/s12906-017-1916-8
21. Ada G.O. et al. Hepatoprotective effects of *Nigella sativa* seed extract against acetaminophen-induced oxidative stress', Asian Pacific Journal of Tropical Medicine. 2016;9(3):221–227.
DOI: 10.1016/j.apjtm.2016.01.039.
22. Aghel N, Rashidi I, Mombeini A. Hepatoprotective activity of *Capparis spinosa* root bark against CCl_4 induced hepatic damage in mice', Iranian Journal of Pharmaceutical Research. 2007;6(4):285-90.
DOI: 10.22037/ijpr.2010.734
23. Pai A, Shenoy C. Hepatoprotective activity of *Flacourtia jangomas* (Lour.) Raeuschleaves and fruit methanolic extract on paracetamol-induced hepatotoxicity in hepG2 cells', Biomedicine. 2021;41(3):587–591.
DOI: 10.51248/.v41i3.1197
24. Khan RA. et al. Hepatoprotection with a chloroform extract of *Launaea procumbens* against CCl_4-induced injuries in rats', BMC Complementary and Alternative Medicine. 2012;12(1).
DOI: 10.1186/1472-6882-12-114
25. Nwidu LL. et al. Hepatoprotective and antioxidant activities of *Spondias mombin* leaf and stem extracts against carbon tetrachloride-induced hepatotoxicity', Journal of Taibah University Medical Sciences. 2018;13(3):262–271.
DOI: 10.1016/j.jtumed.2018.03.006
26. Rai A, Mishra T. Ethnomedicinal and therapeutic values of *Flacourtia jangomas'*, The Journal of Indian Botanical Society. 2020;100(3and4):169–176.
DOI: 10.5958/2455-7218.2020.00037.6
27. Barbhuiya RI. et al. Mass modeling of Indian Coffee Plum (*Flacourtia jangomas*) fruit with its physicochemical properties', International Journal of Fruit Science. 2020;20(1):1–24.
DOI:10.1080/15538362.2020.1775161
28. Hossain MA. et al. Propagation of *Flacourtia jangomas*: an approach towards the domestication of a wild fruit species in Bangladesh', Dendrobiology. 2011;65:63-71.
29. Parvin S. et al. *In vitro* studies of antibacterial and cytotoxic properties of *Flacourtia jangomas* , International journal of pharmaceutical sciences and research. 2011;2(11):2786–1790.
DOI: 10.13040/ijpsr.0975-8232.2(11).2786-90
30. Singh AK, Singh J. Evaluation of anti-diabetic potential of leaves and stem of *Flacourtia jangomas* in streptozotocin-induced diabetic rats', Indian Journal of Pharmacology. 2010;42(5):301–305.
DOI: 10.4103/0253-7613.70238
31. Barua U. et al. Morpho-physiological, proximate composition and antioxidant activity of Flacourtia jangomas (Lour.) raeus', Plant Physiology Reports. 2022;27(1):56–64.
DOI: 10.1007/s40502-022-00644-1
32. Ripa FA. et al. Deciphering *In vitro* and *In vivo* pharmacological properties of seed and fruit extracts of *Flacourtia jangomas* (Lour.) Raeusch', Advances in Pharmacological and Pharmaceutical Sciences. 2024;2024(1).
DOI:10.1155/2024/4035987
33. Pai A, Shenoy KC. Toxicity and safety profiling of *Flacourtia jangomas (*Lour.) raeusch fruit and leaf methanolic extract in Sprague Dawley rats', Journal of Applied Biology & Biotechnology. 2023;12(1):258–264.
DOI: 10.7324/jabb.2024.152315.
34. Marslin G. et al. Oral delivery of curcumin polymeric nanoparticles ameliorates CCl_4-induced subacute hepatotoxicity in wistar rats', Polymers. 2018;10(5):541.
DOI: 10.3390/polym10050541
35. Gazwi HS, Soltan OI, Abdel-Hameed SM. Cakes fortified with papaya seeds effectively protects against CCl_4-induced immunotoxicity', Environmental Science and Pollution Research. 2023;30(51):111511–111524.
DOI: 10.1007/s11356-023-30172-w
36. Johra FT. et al. Amelioration of CCl_4-induced oxidative stress and hepatotoxicity by *Ganoderma lucidum* in long evans rats, Scientific Reports. 2023;13(1).
DOI: 10.1038/s41598-023-35228-y
37. Khan MZ. et al. Investigation of polyphenol profile, antioxidant activity and hepatoprotective potential of *Aconogonon alpinum* (all.) Schur roots', Open Chemistry. 2020;18(1):516–536.

DOI: 10.1515/chem-2020-0062
38. Makni M. et al. Carbon tetrachloride-induced nephrotoxicity and DNA damage in rats', Human & Experimental Toxicology. 2012;31(8):844–852.
DOI: 10.1177/0960327111429140.
39. Rahmat AA, Dar FA, Choudhary IM. Protection of CCl_4-induced liver and kidney damage by phenolic compounds in leaf extracts of *Cnestis ferruginea* (de Candolle)', Pharmacognosy Research. 2014;6(1):19–28.
DOI: 10.4103/0974-8490.122913
40. Shaban NZ. et al. Prophylactic and curative effects of *Carica papaya* Linn. pulp extract against carbon tetrachloride-induced hepatotoxicity in male rats', Environmental Science and Pollution Research. 2022;30(10):27815–27832.
DOI: 10.1007/s11356-022-24083-5
41. Mahmoodzadeh Y, Mazani M, Rezagholizadeh L. Hepatoprotective effect of methanolic *Tanacetum parthenium* extract on CCL_4-induced liver damage in rats', Toxicology Reports. 2017;4:455–462.
DOI: 10.1016/j.toxrep.2017.08.003
42. Sasi S, Anjum N, Tripathi YC. Ethnomedicinal, phytochemical and pharmacological aspects of *Flacourtia jangomas*: A Review, International Journal of Pharmacy and Pharmaceutical Sciences. 2018;10(3):9–15.
DOI: 10.22159/ijpps.2018v10i3.23998
43. Hou F. et al. Hepatoprotective and antioxidant activity of anthocyanins in black rice bran on carbon tetrachloride-induced liver injury in mice', Journal of Functional Foods. 2013;5(4):1705–1713.
DOI: 10.1016/j.jff.2013.07.015
44. Raj VP. et al. *In vitro* and *In vivo* hepatoprotective effects of the total alkaloid fraction of Hygrophila auriculata leaves', Indian Journal of Pharmacology. 2010;42(2):99–104.
DOI: 10.4103/0253-7613.64500
45. Morakinyo AO. et al. Anti-oxidative and hepatoprotective effect of beta-carotene on acetaminophen-induced liver damage in rats', Biology and Medicine. 2012;4(3):134-140.
46. Gajenderet al. A comprehensive review of the pharmacological importance of dietary flavonoids as hepatoprotective agents, Evidence-Based Complementary and Alternative Medicine. 2023;2023(1):4139117.
DOI:10.1155/2023/4139117
47. Sobeh M. et al. Hepatoprotective and hypoglycemic effects of a tannin rich extract from *Ximenia americana* var. Caffra Root', Phytomedicine. 2017;33:36–42.
DOI: 10.1016/j.phymed.2017.07.003
48. Qu L. et al. Hepatoprotective activity of the total saponins from *Actinidia valvata* dunn root against carbon tetrachloride-induced liver damage in mice', Evidence-Based Complementary and Alternative Medicine. 2012;2012:1–13.
DOI: 10.1155/2012/216061
49. Shehab NG, Abu-Gharbieh E, Bayoumi FA. Impact of phenolic composition on hepatoprotective and antioxidant effects of four desert medicinal plants', BMC Complementary and Alternative Medicine. 2015;15:401.
DOI: 10.1186/s12906-015-0919-6

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