Hepatoprotective Activity Of Adina Cordifolia Leaves Against Hepatotoxicity In Rats

Shikha Tiwari[1*], Govind Soni[2]

[1*]Research Scholors, Department of Pharmacy, Oriental University, Indore.
[2]Professor,Department of Pharmacy, Oriental University, Indore.

[*]**Corresponding Author:** Shikha Tiwari
[*]Research Scholors, Department of Pharmacy, Oriental University, Indore, Email:shikha.26088@gmail.com

Abstract
The hepatoprotective effects of Adina cordifolia, a member of the Rubiaceae family, were studied in Wister rats that had sustained liver injury due to ethanol (AEAC) and its aqueous extract (AQEAC). When given at a dose of 500 mg/kg of body weight, AEAC and AQEAC were shown to have hepatoprotective effects, notably lowering blood SGPT, SGOT, alkaline phosphatase, and total bilirubin while significantly increasing total protein. Additional proof of the hepatoprotective effect was found through histopathological analyses of liver tissue. Serum enzyme activities were significantly elevated in ethanol-treated rats' blood samples, indicating liver damage from the ethanol, while they were significantly decreased in animals given AEAC or AQEAC, suggesting that the hepatic cells in the latter group were protected from the ethanol-induced hepatocellular injury. Both AEAC and AQEAC were successful, with benefits comparable to those of the popular drug silymarin.

Keywords: Adina cordifolia, Pharmacological Potential, Extract, Taxonomy and Hepatoprotective properties.

INTRODUCTION

Over five millennia ago, early Indian and Chinese civilizations documented the use of plants as a source of medicine in their written records. Many traditional remedies based on plants remain a standard element of the routine treatment of many illnesses. In spite of incomplete knowledge of their chemical makeup, medicinal plants are widely recommended thanks to anecdotal reports of their use and effectiveness that have made it public. The usage of medicinal plants has greatly bolstered basic health care on a worldwide scale (Maciel et al., 2002). When compared to synthetic pharmaceuticals, which are seen to be harmful to both persons and the environment, herbal medications have become a symbol of security in modern society. Substance addiction and alcoholism are among the world's most pressing health and development issues. Alcohol use causes a variety of harmful metabolic alterations in the liver. Liver weight and volume fluctuate due to steatosis, alcoholic hepatitis, and cirrhosis from excessive alcohol usage over a lengthy period of time.

One of the worst outcomes of heavy alcohol use is alcoholic liver disease (ALD), which is the second largest cause of mortality among all liver illnesses (Rehm et al., 2003).The last stage of the disease is liver cirrhosis, which is a leading cause of death in developed nations (Fernández-Checa et al., 1993).Animal studies have shown that prolonged alcoholism causes liver damage via oxidative stress, which in turn causes fibrosis, reduced liver function, and increased apoptosis (Schuppan et al., 1995). The health risks associated with excessive alcohol use stem from the fact that it increases the body's production of reactive oxygen species (ROS), which in turn damages and kills cells. Damage to the liver from alcohol use is characterized by a lack of vitamin A in the body.

In India, people employ almost 25,000 different herbal combinations for treatment. Pharmaceutical firms are actively doing research on plant material for its potential medicinal components in response to a rise in demand for plant goods throughout the globe. Research into the active compounds that form the foundation of pharmaceuticals to combat diseases like psychiatric disorder, neuro-developmental disorder, diabetes, cancer, AIDS, and several other chronic diseases continues, despite the fact that the therapeutic benefits of many plants have not been shown.

Traditional medicinal herb use is as ancient as human civilization itself. Throughout history, every society has made use of herbs. Herbal medicine has become an essential element of our contemporary society. Prehistoric humans took note of and valued the wide variety of plant life they encountered. Many medical uses of plants have been discovered via careful study of wild animals and much trial and error. Over time, local herbal remedies became more comprehensive as different cultures discovered the healing properties of different plants. They used this strategy to compile data on plants and specify it precisely in the herbal pharmacopoeia. In fact, the majority of the pharmacopoeia of modern scientific medicine was developed from traditional herbal knowledge long into the 20th century. Many drugs in current use have botanical origins. Nearly a quarter of all prescriptions filled in the most advanced nation include botanical ingredients. Some are derived from plant extracts, while others are synthetic analogues of these substances.

Physiological functions are mostly controlled by the liver. It plays an important role in several processes, including detoxification. In addition, the liver is responsible for the detoxification of many different medications and xenobiotics. This is why liver illnesses are so devastating. Acute and chronic hepatitis (inflammatory liver illness) and hepatitis (non-

inflammatory disease) are two examples; cirrhosis (a degenerative condition that causes fibrosis of the liver) is still another. Toxic substances (particular medicines, chemotherapeutics, peroxidized oil, aflatoxin, carbon tetrachloride, paracetamol, chlorinated hydrocarbons, etc.), excessive alcohol intake, infection, and autoimmune condition are the leading causes of liver damage. Therefore, protecting the liver from all of these toxins is crucial.

Ethylene glycol is the most well-known medication used to produce liver injury in experimental settings due to its extreme toxicity. Due to the liver's role in the metabolism and detoxification of ethylene glycol and other substances, it caused fibrosis, cirrhosis, and hepatocarcinoma in those who were exposed to it.

Plants play an important part in medicine because they contain chemical components with varying effects on the human body. Some parts have been credited with biological qualities that help fight cancer, bacteria, ulcers, liver damage, inflammation, diabetes, amoebas, and pain. This plant's traditional medicinal uses include, but are not limited to, alleviating symptoms of rheumatism, digestive problems, headaches, the common cold, toothaches, fever, pain, swelling, bacterial infections, urinary problems, conjunctivitis, and infertility.

LITERATURE REVIEW

Tanya Yadav, Tofeeq Khan, Umesh Patel, Ubhay Pandey, Abhishek Soni (2023), In terms of mortality rates, cancer ranks second globally. Significant limitations and space for improvement remain despite remarkable advances in the treatment and management of cancer development. Chemotherapy is associated with a variety of unpleasant side effects in certain patients. The use of plant-based products in cancer treatment is one example of a natural therapy that may have fewer negative side effects. A small number of plant-based medicines are now in use for cancer treatment. Numerous plant compounds, however, have shown very encouraging anti-cancer capabilities in vitro but have not yet been tested on people. The potential of these plant compounds as cancer treatments for humans must be investigated further. In this article, we'll look at the numerous chemical components found in plants and discuss their probable mode of action as anticancer medicines. Cancer has a devastating impact on people all around the world. New medicines to treat and prevent this fatal illness are always in demand. Natural substances are attracting the attention of the scientific community since their potential adverse effects are less severe than those of conventional therapies like chemotherapy. Secondary metabolites are produced naturally by plants; their potential anticancer effects are being studied with an eye toward developing novel therapeutic medications. As a result of the effectiveness of these chemicals as standard medications for cancer therapy, new technologies are appearing to further the field. Nanoparticles for nano-medicines are one emerging technology with the potential to improve the efficacy of plant-derived pharmaceuticals in the treatment of cancer by regulating the release of the active ingredient and exploring other routes of administration. The features of medicinal plants that make them attractive candidates for prospective anticancer therapies are discussed in this overview, along with the corresponding increase in demand for these chemicals.

(Iliyasu, U., Ibrahim, H., Katsayal, U.A., et al., 2022), For thousands of years, people have relied on medicinal plants to cure a wide range of illnesses. It is impossible to overstate the value of ethnomedicinal plants in the research and development of new medicines. The leaf, stem bark, and root of the plant Breonadia salicina (Vahl) Hepper and J.R.I.Wood (Rubiaceae) are widely used in traditional medicine for the treatment of cancer, arthritis, inflammation, wound infections, fever, diarrhoea, and vomiting. ScienceDirect, ResearchGate, Sci-Hub, Wiley Online Library, and Google Scholar were searched for relevant articles, and their abstracts were compiled for this study. While studies published between 2010 and 2021 were prioritized for this evaluation, we also included references from before that time period because of the prevalence of references to earlier work in more current works. The ethnomedical applications and supporting experimental evidence of the plant's pharmacological activity, including antibacterial, antifungal, and antitrypanasomal effects, are the primary subject of this study. Identifying and identifying the bioactive chemicals in this plant is a necessary first step toward determining whether or not it has the potential to be developed into a new medicinal drug.

Suksungworn R, Duangsrisai S. (2021), Antioxidant activity is only one of several pharmacological qualities found in plants in the family Rubiaceae that might be harnessed in the future. The antioxidant activity and phenolic and flavonoid content of methanolic extracts of bark and wood from five species of the Rubiaceae family were studied. Mitragyna diversifolia wood (437.57 9.90 mg GAE g-1) and Haldina cordifolia wood (30.11 0.20 mg QE g-1) had the greatest total phenolic content (TPC) and total flavonoid content (TFC) in terms of phytochemical contents and antioxidant activity. Catunaregam tomentosa bark showed the highest antioxidant activity against nitric oxide radicals (IC50 = 13.96 5.32 g ml-1), Morinda coreia wood showed the highest activity against superoxide radicals (IC50 = 918.27 0.16 g ml-1), and Morinda coreia bark showed the second-highest activity against DPPH radicals (IC50 = 360.58 19.28 g Strong relationships were found between the TPC and TFC in M. diversifolia wood and DPPH and FRAP in M. diversifolia bark and wood. TFC and FRAP were shown to have a strong link in all plant extracts with the exception of C. tomentosa wood, whereas no correlation was identified between TFC and NO. The antioxidant capacity of C. tomentosa bark was the greatest among the Rubiaceae species tested. In general, it's worth noting that the plants in the family Rubiaceae show promise as a source of natural antioxidants.

Adina cordifolia is a member of the Rubiaceae family, according to Dalu, A.P., Zagare, V.S., Avchar, P.E., Kadam, M.P., Ingole, A.S., Nagrik, S.U., and Patil, P.A. (2021). Adina cordifolia plant extracts included flavonoids, carbohydrates, alkaloids, saponins, phenols, tannins, terpenoids, and cardiac glycosides. Since the dawn of medicine, herbal remedies have been held in the highest regard. Their widespread use now suggests that herbal remedies are being integrated into cutting-edge medical practice. The medicinal plants offer natural therapeutic properties against different illnesses, and much research has been conducted on these plants for the treatment of chronic bronchitis, jaundice, stomachaches, cancer,

diabetes, and other conditions. The focus of the present study is on a botanical description of Adina cordifolia as well as its different pharmacological actions and therapeutic applications.

Khadijeh Alsadat Tahamtan and M. S. Sharada (2019), In order to determine whether or not Adina cordifolia, Careya arborea, Cassia angustifolia, Hiptage benghalensis, and Lannea coromandelica are able to protect the liver from alcohol-induced damage, HepG2 cell lines were used in the current investigation. Toxic dosage investigation was performed on leaf extracts before determining hepatoprotective capacity. Extracts' hepatoprotective potency was evaluated using MTT test, which measures the proportion of viable cells in the sample. Qualitative analysis was used to begin identifying the phytochemical makeup of leaf extracts. Alcohol intoxication followed 72 hours of pretreatment of HepG2 cells with varying doses of leaf extracts (below hazardous dosage). The results indicated that compared to HepG2 cells pretreatment with conventional silymarin, which exhibited 80% cell viability, HepG2 cells pretreated with Cassia angustifolia ethanolic leaf extract showed 92% cell vitality. Adina cordifolia showed the greatest hepatoprotection compared to the other herbs studied. Cassia angustifolia and Adina cordifolia leaf extracts have shown promise as a source of secondary metabolites with hepatoprotective properties, according to a bio-efficacy research.

Materials and Methods:

Procurement and Authentication of the Plan

The leaves of the Adina cordifolia plant were identified and validated by Dr. S. K. Billore, professor and head of the college of plant and environmental management at Vikram University in Ujjain, Madhya Pradesh.

Preparation of extracts of Adina cordifolia

The leaves of the Adina cordifolia plant are the source of this essence. The leaves of the plant were collected, dried in the sun, and then processed into a powder in a commercial grinder. A No. 40 mesh filter was used to separate the powder, and then it was stored in an airtight container.

Figure 1 Leaves of Adina cordifolia

Pharmacological studies

Animals

Wistar albino female rats (weighing between 150 and 200 g) were procured from the Central Drug Research Organization in Lucknow for use in the acute toxicity investigations. They were housed in polypropylene pens and fed a standard rat pellet diet by Hindustan Lever Ltd. of Bangalore. The rats were put through a constant 12-hour cycle of light and shade. The animal ethics committee of the university examined and approved the experimental methods, and the rats fasted for at least 12 hours beforehand. In accordance with the CPCSEA's ethical guideline and the criteria for the care of laboratory animals, all experiments were conducted first thing in the morning. A standard orogastric cannula was used to orally administer medicine to the rats.

Chemicals

The solvents and chemicals were all of analytical grade. The common medication silymarin (25 mg/kg, b.w.) was utilised.

Acute toxicity studies

Acute oral toxicity is evaluated by first identifying the lethal dose, which is part of the acute toxic category method. Young adult rats are fasted before receiving a single oral gavage dose of the test substance. All of the animals are necropsied after up to 15 days of careful observation and weighing. The study medications were given in doses of 5, 50, 300, 2000, and

5000 milligrams per kilogram of body weight. We now know the deadly doses. All of the rats used in this study were females, and there were a total of three rats used in each of the different treatment groups.

Hepatoprotective studies

Carbon tetrachloride (CCl4) induced hepatotoxicity

During drug metabolism in the endoplasmic reticulum and mitochondria, reactive oxygen species O—are generated, leading to an increase in intracellular reactive Fe+2 ions, aldehyde, GSH depletion, and calcium sequestration. Both direct covalent contact and oxidative CCl3 O - contribute to the degradation of Ca+2 sequestrations. Increased intercellular Ca+2, aggregation by proteolytic enzymes, and an increase in Fe+2 ions all contribute to the precipitation of aldehyde cytotoxicity by lipid peroxidation in the absence of sequestration.

Paracetamol induced hepatotoxicity

The liver damage caused by paracetamol is caused by a hepatotoxic metabolite. At therapeutic concentrations, the most prevalent metabolites of paracetamol are the sulfate and glucuronide conjugates. By forming reactive intermediates with glutathione, the residual chemicals are neutralized. An overdose results in a higher percentage of the drug being transformed into the reactive metabolite because the sulphate and glucuronide pathways have been depleted. The reactive metabolite may be flushed out through the conjugation route if the liver is supplied with glutathione-like molecules, such as acetyl cysteine. This shields the liver's cells from harm and stops the damage from spreading.

Results and Discussion

Acute toxicity study

To evaluate a drug's effectiveness and safety in people, acute toxicity tests are carried out. Experimental animals are often subjected to acute toxicity tests in order to establish the LD50. According to OECD Guideline 423, the acute toxicity of acetone and water extracts of A. cordifolia was tested. In a dose-escalation investigation, rats given up to 5,000 mg/kg showed no signs of death, toxicity, or aberrant behavior. This suggests that all of the extracts were similarly benign, with no negative effects on the test subjects (rats).

Table 1 Acute toxicity studies of extracts of A. cordifolia

Sr. No.	No. of Animals	Extract	Dose (mg/kg)	Results
1	3	AEAC	5	No death
2	3		50	No death
3	3		300	No death
4	3		2000	No death
5	3		5000	No death
6	3	AQEAC	5	No death
7	3		50	No death
8	3		300	No death
9	3		2000	No death
10	3		5000	No death

LD50: 5000 mg/kg, ED50: 500 mg/kg

Hepatoprotective activity

Carbon tetrachloride (CCl_4) induced hepatotoxicity

Thiopentone sodium (40 mg/kg) administered intravenously caused sleep in all animal groups. When compared to the control group, CCl4-treated rats required considerably more time to fall asleep and remained sleeping for longer durations of time (min) after they were asleep. Pretreated animals with AEAC, AQEAC (500 mg/kg p.o.), and silymarin slept much more quickly and for a shorter amount of time than CCl4-exposed and silymarin-pretreated mice. The initial sleep period for the CCl4 group was 80.2 5.28 sec, while the AEAC group slept for 110.2 4.48 sec, the AQEAC group slept for 130.8 4.76 sec, and the silymarin group slept for 130.8 4.76 sec. The CCl4 group slept for 235.8 6.80 minutes, whereas the AEAC group slept for 210.8 5.88 minutes, the AQEAC group slept for 192.2 5.76 minutes, and the silymarin group slept for 0 minutes.

Table 2 Effect of extracts of *A. cordifolia* leaves on functional parameters in CCl4 induced hepatotoxic rats.

Sr. No.	Treatment/ Dose	Onset of sleep(Sec.)	Duration of sleep (Min.)
1	Normal	170.0 ± 2.06	110.2 ± 2.80
2	Induced (CCl4)	80.2 ± 5.28*	235.8 ± 6.80*
3	Standard (Silymarin)	156.2 ± 3.48***	149.7 ± 2.49***
4	AEAC (500mg/kg)	110.2 ± 4.48**	210.8 ± 5.88**
5	AQEAC (500mg/kg)	130.8 ± 4.76***	192.2 ± 5.76***

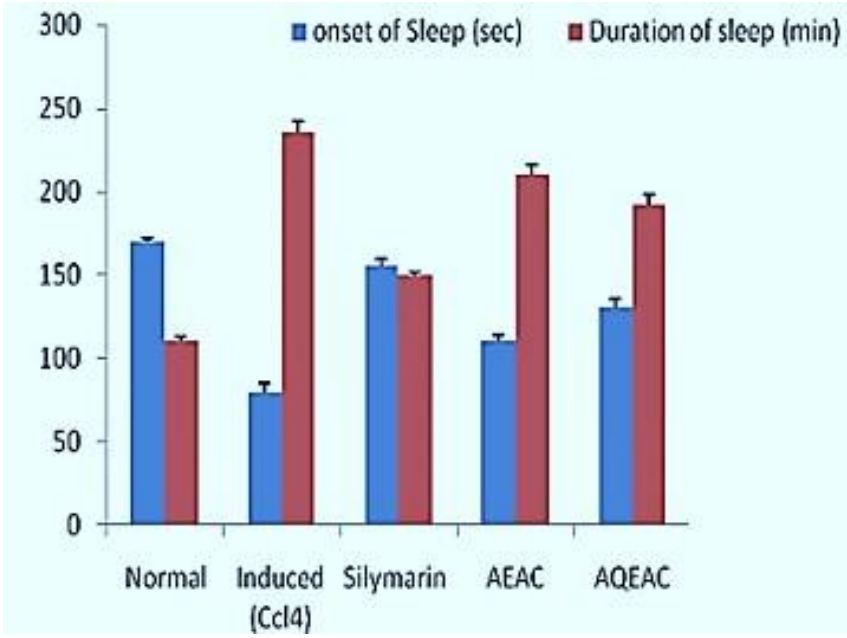

Figure 2 Effect of A. cordifolia leaves extracts on functional parameters in CCl4 induced hepatotoxic rats.

Effect of *A. cordifolia* leaves extracts on physical parameters

Table 3 Effect of *A. cordifolia* leaves extracts on physical parameters in CCl4 induced hepatotoxic rats.

Sr. No.	Treatment/ Dose	Liver weight (wt/100gm b.w)	Liver Volume
1	Normal	6.84 ± 0.06	6.85 ± 0.07
2	Induced (CCl4)	9.12 ± 1.28*	9.52 ± 1.18*
3	Standard (Silymarin)	7.04 ± 1.48***	7.02 ± 1.49***
4	AEAC (500mg/kg)	8.38 ± 0.48**	8.39 ± 0.88**
5	AQEAC (500mg/kg)	7.80 ± 0.76***	7.91 ± 0.76***

Values are mean ± SEM, n = 6.

Effect of *A. cordifolia* leaves extracts on serum marker enzyme levels of carbon tetrachloride induced hepatotoxic rats

Table 4 Effect of *A. cordifolia* leaves extracts on serum marker enzyme levels of carbon tetrachloride induced hepatotoxic rats

Sr. No.	Treatment/ Dose	SGPT U/L	SGOT U/L	ALP U/L
1	Normal	62.0 ± 3.71	168.04 ± 2.80	190.0 ± 8.01
2	Induced (CCl4)	128.18 ± 7.24*	272.8 ± 8.24*	280.42 ± 6.46*
3	Standard(Silymarin)	65.06±6.41***	170.16±8.17***	198.20±8.27***
4	AEAC (500mg/kg)	98.18 ± 7.20**	231.0 ± 8.13**	260.0 ± 6.31**
5	AQEAC(500mg/kg)	89.56±5.61***	188.0 ± 8.66***	240.15±6.28***

Effect of *A. cordifolia* leaves extracts on biochemical parameter

Table 5 Effect of *A. cordifolia* leaves extracts on biochemical parameters carbon tetrachloride induced hepatotoxic rats

Sr. No.	Treatment/ Dose	Total Bilirubin (mg/dl)	Total Protein (gm/dl)
1	Normal	0.38 ± 0.06	9.57 ± 0.24
2	Induced(CCl4)	9.20 ± 0.24*	6.02 ± 1.46*
3	Standard (Silymarin)	0.54 ± 0.20***	9.24 ± 1.26***
4	AEAC (500mg/kg)	0.70 ± 0.02**	7.22 ± 1.12*
5	AQEAC (500mg/kg)	0.62 ± 0.42***	7.28 ± 0.42**

Hepatoprotective activity of *A. cordifolia* leaves extracts on paracetamol induced hepatotoxic rats

All animal groups were sedated after receiving an oral dose of 40 mg/kg thiopentone sodium. Paracetamol-treated mice slept for much longer periods of time than their untreated counterparts (min). Rats treated with AEAC, AQEAC (500 mg/kg, p.o.), and silymarin extracts slept and recovered much more quickly than those treated with paracetamol.

Table 6 Effect of *A. cordifolia* leaves extracts on functional parameters in paracetamol induced hepatotoxic rats

Sr. No.	Treatment/ Dose	Onset of sleep (Sec)	Duration of sleep (Min)
1	Normal	170.0 ± 2.06	110.2 ± 2.80
2	Induced (Paracetamol)	98.4 ± 6.28*	255.8 ± 5.90*
3	Standard (Silymarin)	176.6 ± 4.48***	140.2 ± 4.49***
4	AEAC (500mg/kg)	121.5 ± 4.80**	228.2 ± 5.02**
5	AQEAC (500mg/kg)	140.8 ± 5.76***	199.2 ± 5.96***

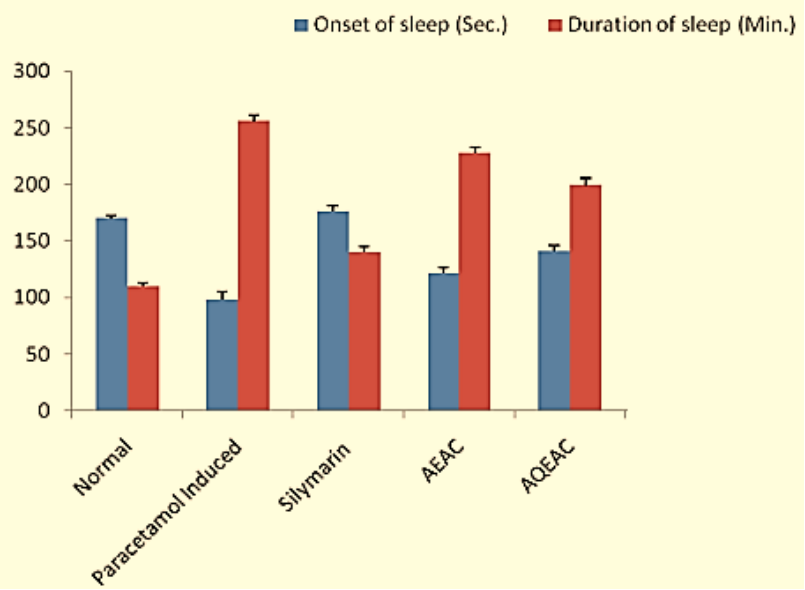

Figure 3 Effect of *A. cordifolia* leaves extracts on functional parameters in paracetamol induced hepatotoxic rats

CONCLUSION

The hepatoprotective chemicals were extracted from the coarsely powdered, shade-dried plant parts by soaking them in various solvent solutions. The quality of the plant material and the presence of active components are first determined by conducting physical and phytochemical tests on the concentrated extracts. The stem bark and powdered leaves were analyzed physicochemically. This study quantified the worth of ash. The phytochemical analysis revealed the presence of many phytoconstituents in the sampled material. Among the more significant ones were glycosides, carbohydrates, proteins, amino acids, sterols, triterpenes, total phenolic compound, flavonoids, and saponin. Hepatoprotective treatment is used to treat liver damage in rats brought on by CCl4, paracetamol, ethanol, and INH-RIF. Extracts of AEAC, AQEAC, and silymarin (25 mg/kg, p.o.) were given to six mice, whereas a control group of six mice received 500 mg/kg of AEAC. The total bilirubin and total protein levels of the hepatotoxicant-exposed groups both rose, respectively. Regeneration of hepatocytes was also seen, which may have had hepatoprotective benefits. The hepatoprotective effects of AEAC and AQEAC were determined by their ability to improve blood marker enzyme levels, physical measurements, functional parameters, and histological examinations. This supports the continuous scientific inquiry into the same medications that were employed in the past.

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