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Acetaminophen-induced liver and kidney injuries in mice: treatment with *Alpinia officinarum* rhizome

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Abstract. *Paracetamol (acetaminophen) is widely used around the world as both an analgesic and antipyretic medication. It is effective and safe when taken in therapeutic doses; however, overdosing can result in liver and kidney toxicity in both humans as well as animals. Medicinal plants are important sources of nutrition and healthcare for humans, and many of them have demonstrated protective effects against liver and kidney injuries. This research investigates the liver and kidney protective effects of various Alpinia officinarum (galangal, l) extracts in mice exposed to acetaminophen. Specifically, it examines the effects of extracts obtained using different solvents, including polar and nonpolar organic solvents and aqueous solutions. The study's findings indicated that essential oil, hydroethanolic, and chloroform extracts have the most significant protective effects on the liver and kidney. These protective effects may attributed to the presence of flavonoids, alkaloids, terpenoids, fatty acids, and phytosterols in these extracts. In conclusion, essential oil, hydroethanol, and chloroform used for the extraction of galangal rhizome effectively isolated various bioactive components, which provided substantial protection against the liver and kidney injuries caused by paracetamol in mice.*

Keywords: *paracetamol, Alpinia officinarum (Galangal), liver and kidney injuries, medicinal plants, polar and nonpolar extracts*

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ФИЗИКО-ХИМИЧЕСКАЯ БИОЛОГИЯ

Научная статья
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Повреждения печени и почек у мышей, вызванные ацетаминофеном: лечение корневищем *Alpinia officinarum*

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Аннотация. *Парацетамол (ацетаминофен) широко используется во всем мире в качестве анальгетика и жаропонижающего средства. Он эффективен и безопасен при приеме в терапевтических дозах, однако его передо-*

зировка может привести к токсическому поражению печени и почек как у людей, так и у животных. Лекарственные растения являются важным компонентом в рационе питания человека, а также активно применяются в области здравоохранения, и многие из них обладают защитным эффектом от повреждений печени и почек. Данное исследование направлено на изучение защитных эффектов различных экстрактов Alpinia officinarum (галангал, I) для печени и почек у мышей, подвергшихся воздействию ацетаминофена. В частности, в ходе работы изучено влияние экстрактов, полученных с помощью различных растворителей, включая полярные, неполярные органические растворители и водные растворы. Результаты исследования показали, что эфирные масла, этанольные и хлороформенные экстракты оказывают наиболее выраженное защитное влияние на печень и почки. Это защитное влияние может быть обусловлено наличием флавоноидов, алкалоидов, терпеноидов, жирных кислот и фитостеролов в указанных экстрактах. В заключение следует отметить, что эфирное масло, этанол и хлороформ, использованные для экстракции корневища галангала, эффективно изолировали различные биоактивные компоненты, что обеспечило существенную защиту от поражения печени и почек, вызванного парацетамолом у мышей.

Ключевые слова: *парацетамол, Alpinia officinarum (галангал), заболевания печени и почек, лекарственные растения, полярные и неполярные растворители*

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INTRODUCTION

The drug-induced liver toxicity (DIL) is a common cause of liver injury, responsible for about half of the cases of acute liver failure. While the drug-induced liver injury usually resolves after discontinuation of the offending medication, it presents significant diagnostic as well as therapeutic challenges for physicians. The most common clinical presentations include acute hepatitis and cholestasis, but various other clinical pathological patterns of both acute and the chronic liver disease may occur as well.

The development of the drug-induced liver disease typically involves either the parent drug or its metabolites, which can affect cellular biochemistry or trigger an immune response directly. Per hepatotoxin is associated with a specific pattern of injury as well as latency. However, some drugs can lead to more than one type of injury pattern [1–3].

The drug-induced nephrotoxicity (DIN) is a main cause of the kidney damage, contributing to high rates of mortality and morbidity. This serious issue restricts the clinical use of various therapeutic and diagnostic agents, including antineoplastic drugs, antibiotics, immunosuppressive agents, non-steroidal anti-inflammatory drugs (NSAIDs), as well as contrast agents [4, 5].

Several medications, such as chemotherapy drugs, antimicrobials, immunosuppressants, NSAIDs, and radiocontrast agents, can adversely affect the liver and kidneys. Research has shown that the hepatic and nephrotoxic effects of some of these medications may be mitigated by the use of natural products. While certain NSAIDs, like acetaminophen (N-acetyl-p-aminophenol, APAP), are generally safe at therapeutic doses, they can lead to liver and kidney toxicity in cases of overdose, which poses an increasingly significant public health concern [4–7].

Recent studies have proved that various natural products, like phytochemicals, plant extracts, herbal formulations, and animal-derived compounds, provide protective effects against drug-induced liver (DIL) and kidney injury (DIN). These natural products operate through multi-target therapeutic mechanisms, like inhibiting oxidative stress, inflammation, apoptosis, fibrosis, and necroptosis. Additionally, they help to regulate autophagy and maintain cell polarity by influencing various signaling pathways and new molecular targets. Such compounds also show a diverse set of activities, like immunomodulatory and antiviral effects [8, 9].

Alpinia officinarum, commonly known as galangal (I), is a perennial, rhizomatous herb that belongs to the Zingiberaceae family. It's typically found in both tropical and subtropical regions of South Asia. This plant serves both medicinal and culinary purposes. Its dried rhizome has been traditionally used for centuries to relieve symptoms such as stomach aches, colds, ulcers, and diarrhea. Recent pharmacological studies have proved that galangal offers a range of beneficial effects, like anti-inflammatory, antioxidant, antidiabetic, anti-ulcer, anti-diarrheal, antiemetic, analgesic, anticoagulant, and antitumor properties. Other research has identified the primary components of galangal as volatile oils, flavonoids, glycosides, and diarylheptanoids, which contribute to its diverse medicinal qualities [10].

Recent studies have highlighted the pharmacological properties of galangal, which are primarily attributed to its flavonoids and diarylheptanoids. These compounds are significant for their anti-inflammatory, antioxidant, and anticancer properties, as well as their ability to combat multi-drug-resistant strains. One particularly notable compound found in galangal, galangin, is a bioflavonoid that shows considerable potential in treating various diseases [11].

In this work, according to the mentioned pharmacological activities of this plant, the therapeutic effects of galangal extracts obtained using organic and organo-aqueous solvents with different polarities on liver and kidney injuries caused by acetaminophen were studied, and the results were compared to the control and other groups in mice.

MATERIAL AND METHODS

Chloroform, ethanol, carbon tetrachloride, and the other chemicals were provided from Sigma-Aldrich (USA) and Merck (Darmstadt, Germany) chemical companies.

Gas chromatographic analysis was conducted on an Agilent 7890N chromatograph paired with a mass-spectrometer 5975C, MODE EI. A capillary column, HP-5MS (30 m × 0.25 mm i.d.; the film thickness 0.25 μm) was applied. Its column function program was as follows: 60 °C for 2 min and then 7 °C/min to 280 °C. The carrier gas was helium at the rate of 3 ml/min. The samples (1 μl) of diluted essential oils were injected by hand. The parts of extracts were noticed through the retention time, the retention indices which are related to C_6-C_{35} phytochemicals computer matching with Wiley/NIST library and comparing their mass spectra with the genuine samples or with available data in the literature. The proportion of the mixture of the seen compounds was evaluated from the GC peak area with no correction factors, and relatively calculated.

Rizhomes of *Alpinia officinarum* (I) were obtained from the local market in Tehran and authenticated in the herbarium laboratory of the Iranian Institute of Medicinal Plants (Voucher Numbers: IMPHM-8). These parts of I were kept away from sunlight. Then air-dried in the shade, powdered well, then extracted by maceration with mentioned solvents with different polarities (96% hydroethanol, chloroform, carbon tetrachloride, and aqueous) separately for 72 hours (100 g of the powdered plant macerated in 500 ml solvent). The compositions were filtered and concentrated to yield extracts that were used for GC-MS analysis and protective effects on acetaminophen-induced liver & kidney injuries in mice.

96 NMRI mice weighing 20 to 25 g (Pasteur's Institute in Tehran-Iran) were kept in an air-conditioned animal house room at 22±2 °C and obtained with a standard diet and tap water. The procedures were in compliance with NIH guidelines for the care and use of the research animals.

Mice were desultorily divided into control, acetaminophen, acetaminophen + chloroform, acetaminophen + carbon tetrachloride, acetaminophen + hydroalcoholic extracts, and the acetaminophen + essential oil groups. These extracts (200 mg/kg) are dissolved in the cold physiologic saline and fed daily by gavage to mice one week before acetaminophen injection (300 mg/kg, i.p.) for liver and kidney toxicity.

Liver and kidney homogenates were prepared based on a published report [12].

The homogenate protein content was determined according to a published report[1].

Then, liver & kidney serum markers included: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), malondialdehyde (MDA), catalase (CAT), blood urea nitrogen (BUN), Creatinine, and superoxide dismutase (SOD) were analyzed by standardized procedures using commercial kits (Pars azmoon Company, Tehran, Iran, and Kia zist, Hamedan, Iran), following the instrument manufacturer's protocol.

All the data were shown as means ±*SEM*. Statistical analysis was done with the aid of Graph Pad Prism Software version 8.0 and one-way analysis of variance (ANOVA), followed by a coupled Tukey post-hoc statistical test. The Kolmogorov-Smirnov test was used for verification of normal distribution. A statistical *p*-value under 0.05 was considered significant.

RESULTS AND DISCUSSION

The mentioned extracts and essential oil were made from the maceration of **I** in the stated organic and aqueous solvents. GC-MS results were summarized in Table.

According to the outcomes of GC-MS data (Table), different extracts and ethereal oil of *Alpina galanga* (Galangal, I) are rich in flavonoids, alkaloids, terpenes, fatty acids, phytosterols, and phenols which have been mentioned in several articles for their antioxidant and anti-inflammatory properties [13–20].

Mortality (the death rate), morbidity (considered as any abnormal condition or behavior), irritability (a condition of aggressiveness or increased response to handling), and the other relevant abnormal states were witnessed in the animals.

Figure 1 shows the results of ALT enzyme activity in serum in different groups. As can be seen, in the acetaminophen group, there was a strong and significant rise ($P < 0.001$) compared to the control group. The same significant rise was obtained to a lesser extent in the acetaminophen groups treated with hydroethanol

The quantitative analysis of some phytochemicals in hydroethanolic, chloroform, carbon tetrachloride extracts, and volatile oil of *Alpinia officinarum* was identified by gas chromatography – mass spectrometry

Количественный анализ некоторых фитохимических веществ в экстрактах, полученных с помощью этанола, хлороформа, четыреххлористого углерода, и эфирном масле *Alpinia officinarum*, идентифицированных методом газовой хроматографии – масс-спектрометрии

Chemical family	Chloroform, %	Carbon tetrachloride, %	Essential oil, %	Hydroethanolic 96%, %
Fatty acids	55.68	–	–	5.32
Terpenes	0.75	8.49	34.02	–
Alkaloids	4.11	–	10.45	12.91
Galangin (flavonoid)	8.35	8.35	–	19.00
Phytosterols	–	–	–	9.32
Other flavonoids	8.35	–	–	–
Phenols	–	–	4.65	–
Others	17.07	83.16	50.88	53.45

[1] Becker J.M., Caldwell G.A., Zachgo E.A. Biotechnology: a laboratory course. San Diego: Academic Press; 1996, 283 p.

($P < 0.05$), carbon tetrachloride ($P < 0.001$), chloroform ($P < 0.05$) extracts and essential oil ($P < 0.05$) compared to the control group. Also, in the three acetaminophen groups treated with hydroethanol, chloroform extracts, and ethereal oil ($P < 0.05$), a significant fall in alanine aminotransferase activity was obtained compared to the acetaminophen group.

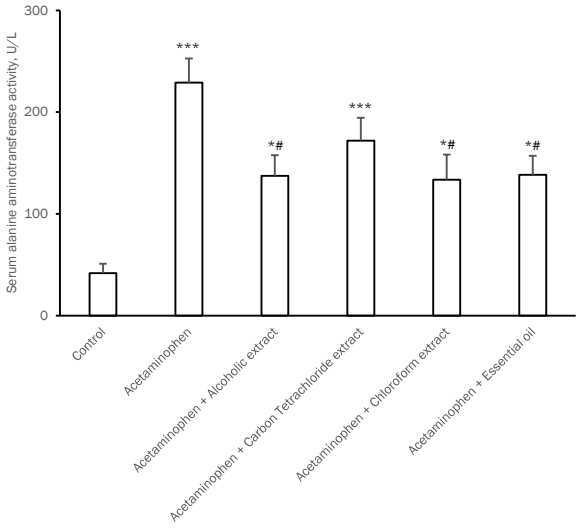

Fig. 1. Serum alanine aminotransferase activity in various groups: * – $p < 0.05$, ** – $p < 0.01$, *** – $p < 0.001$ (compared to the control group); # – $p < 0.05$, ## – $p < 0.01$, ### – $p < 0.001$ (compared to the acetaminophen group)

Рис. 1. Результаты определения активности сывороточной аланинаминотрансферазы в различных группах: * – $p < 0,05$, ** – $p < 0,01$, *** – $p < 0,001$ (по сравнению с контрольной группой); # – $p < 0,05$, ## – $p < 0,01$, ### – $p < 0,001$ (по сравнению с группой, принимавшей ацетаминофен)

Figure 2 shows the results of AST activity in serum in different groups. As can be seen, in the acetaminophen group, a significant rise in the activity of the enzyme was obtained compared to the control group ($P < 0.001$). The same significant rise was obtained to a lesser extent in the acetaminophen groups treated with hydroethanol, chloroform, carbon tetrachloride ($P < 0.001$) extracts, and essential oil ($P < 0.01$) compared to the control group. On the other hand, in the acetaminophen groups treated with hydroethanol, chloroform, carbon tetrachloride extracts ($P < 0.001$), and volatile oil ($P < 0.01$), there was a significant fall in the activity of this enzyme compared with the acetaminophen group.

Figure 3 shows the results of ALP enzyme activity in serum in different groups. As can be seen, in the acetaminophen group, there was a strong and significant rise ($P < 0.001$) compared to the control group. The same significant rise was obtained to a lesser extent in the acetaminophen groups treated with hydroethanol, chloroform, carbon tetrachloride extracts, and volatile oil ($P < 0.001$) compared to the control group. Also, only in the acetaminophen group treated with essential oil ($P < 0.01$), a significant fall in alanine aminotransferase activity was obtained compared to the acetaminophen group.

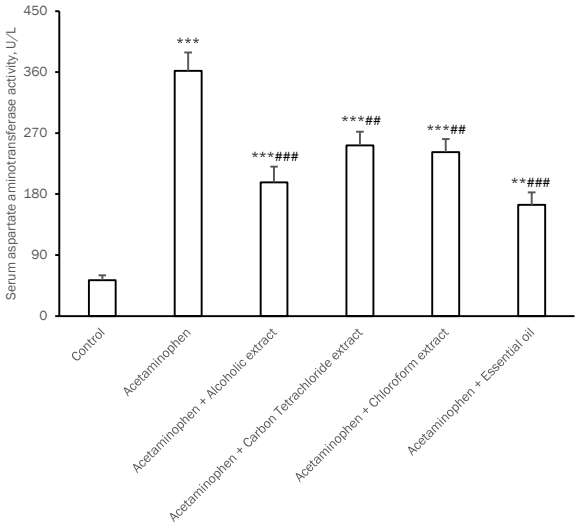

Fig. 2. Serum aspartate aminotransferase activity in various groups: * – $p < 0.05$, ** – $p < 0.01$, *** – $p < 0.001$ (compared to the control group); # – $p < 0.05$, ## – $p < 0.01$, ### – $p < 0.001$ (compared to the acetaminophen group)

Рис. 2. Результаты определения активности сывороточной аспартатаминотрансферазы в различных группах: * – $p < 0,05$, ** – $p < 0,01$, *** – $p < 0,001$ (по сравнению с контрольной группой); # – $p < 0,05$, ## – $p < 0,01$, ### – $p < 0,001$ (по сравнению с группой, принимавшей ацетаминофен)

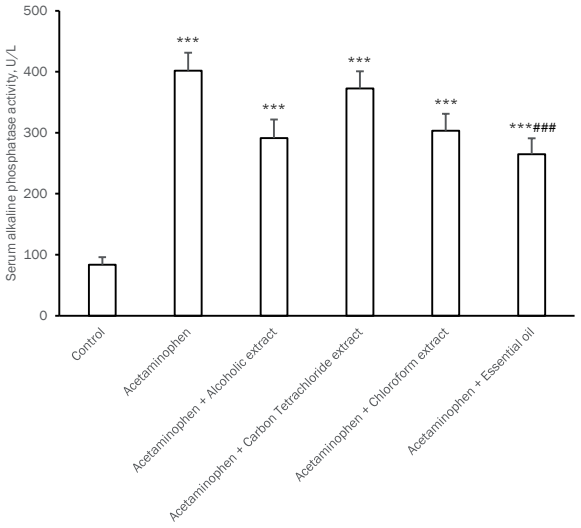

Fig. 3. Serum alkaline phosphatase activity in various groups: * – $p < 0.05$, ** – $p < 0.01$, *** – $p < 0.001$ (compared to the control group); # – $p < 0.05$, ## – $p < 0.01$, ### – $p < 0.001$ (compared to the acetaminophen group)

Рис. 3. Результаты определения активности сывороточной щелочной фосфатазы в различных группах: * – $p < 0,05$, ** – $p < 0,01$, *** – $p < 0,001$ (по сравнению с контрольной группой); # – $p < 0,05$, ## – $p < 0,01$, ### – $p < 0,001$ (по сравнению с группой, принимавшей ацетаминофен)

Figure 4 shows the level of MDA in liver tissue as an index of lipid peroxidation and oxidative stress in different groups. As it is shown in the acetaminophen group, there is a strong and significant rise in MDA compared with the control group ($P < 0.001$). This significant rise was seen in the acetaminophen groups treated with carbon tetrachloride ($P < 0.01$) extract compared to the control group but it was not significant in chloroform extract ($P > 0.05$). Also, in the acetaminophen groups treated with hydroethanol extracts and volatile oil, a none-significant fall in MDA was obtained compared to the acetaminophen group.

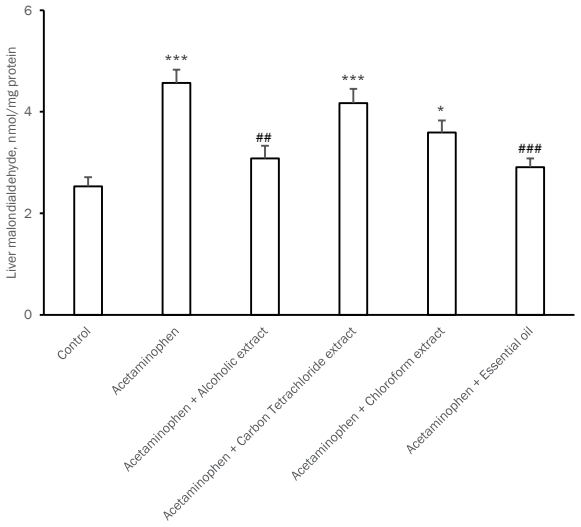

Fig. 4. Liver malondialdehyde levels in various groups: * – $p < 0.05$, ** – $p < 0.01$, *** – $p < 0.001$ (compared to the control group); # – $p < 0.05$, ## – $p < 0.01$, ### – $p < 0.001$ (compared to the acetaminophen group).

Рис. 4. Результаты определения уровня малонового диальдегида в печени в различных группах: * – $p < 0,05$, ** – $p < 0,01$, *** – $p < 0,001$ (по сравнению с контрольной группой); # – $p < 0,05$, ## – $p < 0,01$, ### – $p < 0,001$ (по сравнению с группой, принимавшей ацетаминофен)

Figure 5 shows the results of CAT enzyme activity in the liver tissue homogenate in different groups. As can be seen, in the acetaminophen group, a significant decrease in the activity of the enzyme was obtained compared with the control group ($P < 0.001$). The same significant decrease in catalase enzyme activity was seen in acetaminophen groups treated with carbon tetrachloride, and chloroform ($P < 0.001$) extracts compared to the control group. On the other hand, a significant rise in catalase enzyme activity was obtained only in the acetaminophen groups treated with hydroethanol extracts and ethereal oil ($P < 0.01$) compared to the acetaminophen group.

Figure 6 shows the results of serum BUN in different groups. As can be seen, in the acetaminophen group, a clear and significant increase in BUN was obtained compared to the control group ($p < 0.001$). A similar significant rise in BUN was obtained to a lesser extent in acetaminophen groups treated with hydroethanol ($p < 0.05$), carbon tetrachloride ($p < 0.001$), and chloroform ($p < 0.05$) extracts compared with the control group. On the other hand, a significant decrease in BUN was obtained

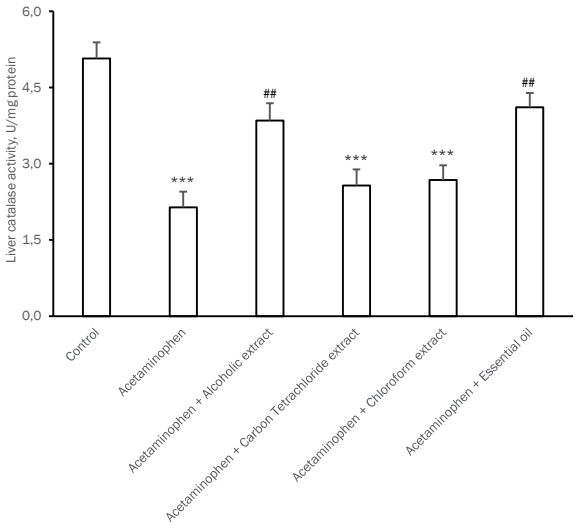

Fig. 5. Catalase enzyme activity in various groups: * – $p < 0.05$, ** – $p < 0.01$, *** – $p < 0.001$ (compared to the control group); # – $p < 0.05$, ## – $p < 0.01$, ### – $p < 0.001$ (compared to the acetaminophen group).

Рис. 5. Результаты активности каталазы в различных группах: * – $p < 0,05$, ** – $p < 0,01$, *** – $p < 0,001$ (по сравнению с контрольной группой); # – $p < 0,05$, ## – $p < 0,01$, ### – $p < 0,001$ (по сравнению с группой, принимавшей ацетаминофен)

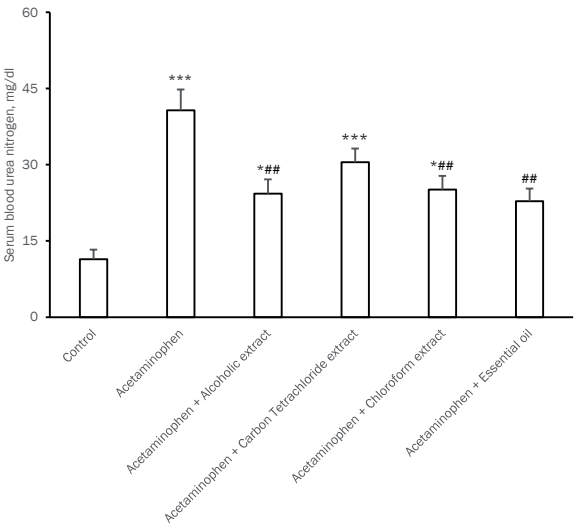

Fig. 6. Serum blood urea nitrogen in various groups: * – $p < 0.05$, ** – $p < 0.01$, *** – $p < 0.001$ (compared to the control group); # – $p < 0.05$, ## – $p < 0.01$, ### – $p < 0.001$ (compared to the acetaminophen group).

Рис. 6. Результаты определения азота мочевины в сыворотке крови в различных группах: * – $p < 0,05$, ** – $p < 0,01$, *** – $p < 0,001$ (по сравнению с контрольной группой); # – $p < 0,05$, ## – $p < 0,01$, ### – $p < 0,001$ (по сравнению с группой, принимавшей ацетаминофен)

in the acetaminophen groups treated with hydroethanol, chloroform extracts, and aetherolea oil ($p < 0.01$) compared to the acetaminophen group.

Figure 7 shows the results of serum creatinine levels in various groups. As can be seen, in the acetaminophen group, a statistically significant increase in serum creatinine was obtained compared to the control group ($p < 0.01$). A similar significant rise in creatinine was not obtained in the acetaminophen group treated with extracts and essential oil compared with the control group ($p \geq 0.05$). On the other hand, a significant decrease in creatinine was not obtained in the acetaminophen groups treated with extracts and volatile oil ($P > 0.05$) compared to the acetaminophen group.

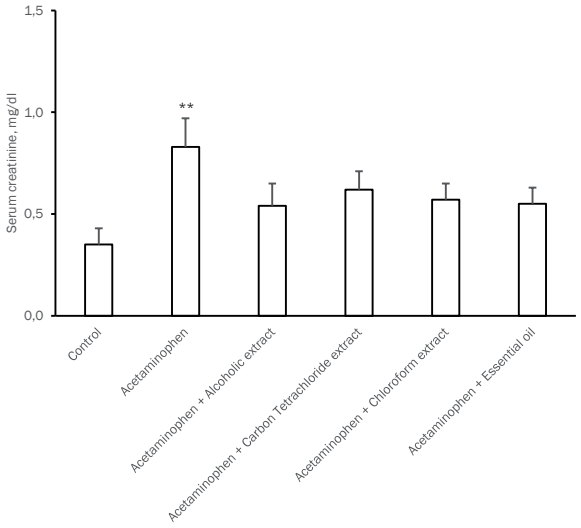

Fig. 7. Serum creatinine in various groups: * – $p < 0.05$, ** – $p < 0.01$, *** – $p < 0.001$ (compared to the control group); # – $p < 0.05$, ## – $p < 0.01$, ### – $p < 0.001$ (compared to the acetaminophen group).

Рис. 7. Результаты определения сывороточного креатинина в различных группах: * – $p < 0,05$, ** – $p < 0,01$, *** – $p < 0,001$ (по сравнению с контрольной группой); # – $p < 0,05$, ## – $p < 0,01$, ### – $p < 0,001$ (по сравнению с группой, принимавшей ацетаминофен)

Figure 8 shows the outcomes related to the tissue level of MDA as an index of lipid peroxidation in kidney tissue in different groups. As can be seen, in the acetaminophen group, a strong and significant increase in malondialdehyde was observed compared to the control group ($p < 0.01$). A similar significant rise in malondialdehyde was not obtained in acetaminophen groups treated with extracts and essential oil ($P > 0.05$) compared to the control group. Also, there was a significant fall in malondialdehyde in the acetaminophen groups treated with hydroethanol extracts and aetheroleum oil ($p < 0.05$) compared to the acetaminophen group.

Figure 9 shows the results related to the kidney level of catalase enzyme in different groups. By measuring the level of catalase enzyme activity in the kidney, it was found that in the acetaminophen group, there was a significant fall in this parameter compared with the control group ($p < 0.001$). This significant fall in catalase enzyme activity was obtained in acetaminophen groups treated with carbon tetrachloride ($p < 0.001$) and chloroform ($P < 0.01$) extracts compared

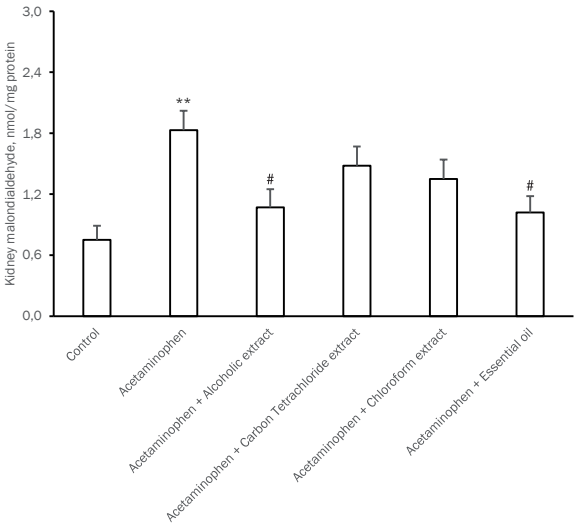

Fig. 8. Kidney malondialdehyde levels in various groups: * – $p < 0.05$, ** – $p < 0.01$, *** – $p < 0.001$ (compared to the control group); # – $p < 0.05$, ## – $p < 0.01$, ### – $p < 0.001$ (compared to the acetaminophen group).

Рис. 8. Результаты определения уровня малонового диальдегида в почках в различных группах: * – $p < 0,05$, ** – $p < 0,01$, *** – $p < 0,001$ (по сравнению с контрольной группой); # – $p < 0,05$, ## – $p < 0,01$, ### – $p < 0,001$ (по сравнению с группой, принимавшей ацетаминофен)

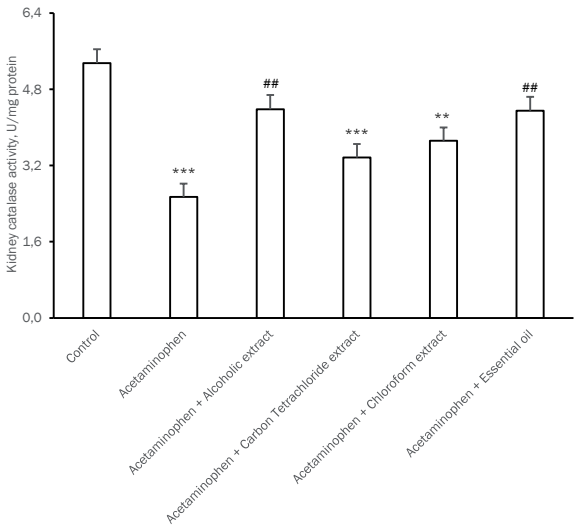

Fig. 9. Kidney catalase enzyme activity in various groups: * – $p < 0.05$, ** – $p < 0.01$, *** – $p < 0.001$ (compared to the control group); # – $p < 0.05$, ## – $p < 0.01$, ### – $p < 0.001$ (compared to the acetaminophen group)

Рис. 9. Результаты определения активности каталазы в почках в различных группах: * – $p < 0,05$, ** – $p < 0,01$, *** – $p < 0,001$ (по сравнению с контрольной группой); # – $p < 0,05$, ## – $p < 0,01$, ### – $p < 0,001$ (по сравнению с группой, принимавшей ацетаминофен)

to the control group. Also, a significant rise in the renal activity of catalase enzyme was seen in the acetaminophen groups treated with hydroethanol extracts and volatile oil ($p < 0.01$) compared to the acetaminophen group.

Figure 10 shows the results related to the kidney level of SOD enzyme in different groups. By measuring the level of SOD enzyme activity in the kidney, it was found that in the acetaminophen group, there is a significant fall in this parameter compared to the control group ($p < 0.01$). This decrease in superoxide dismutase enzyme activity was obtained in acetaminophen groups treated with hydroethanol, carbon tetrachloride, chloroform extracts, and essential oil compared to the control group but was not significant ($p < 0.05$). Also, a significant rise in the renal activity of this enzyme was observed only in the acetaminophen group treated with essential oil ($p < 0.05$) compared to the acetaminophen group.

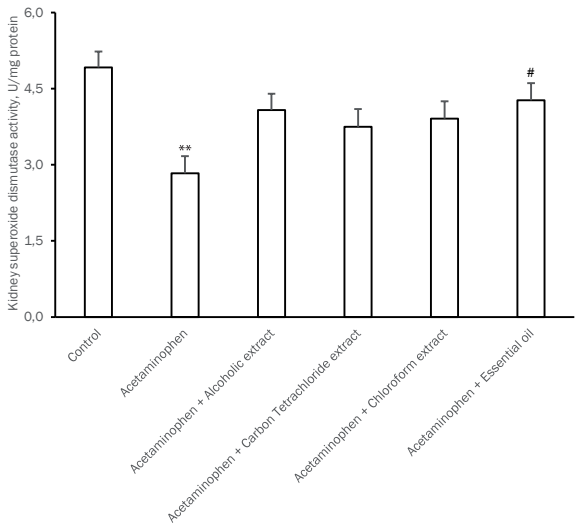

Fig. 10. Kidney superoxide dismutase enzyme activity in various groups: * – $p < 0.05$, ** – $p < 0.01$, *** – $p < 0.001$ (compared to the control group); # – $p < 0.05$, ## – $p < 0.01$, ### – $p < 0.001$ (compared to the acetaminophen group).

Рис. 10. Результаты определения активности супероксиддисмутазы в почках в различных группах: * – $p < 0,05$, ** – $p < 0,01$, *** – $p < 0,001$ (по сравнению с контрольной группой); # – $p < 0,05$, ## – $p < 0,01$, ### – $p < 0,001$ (по сравнению с группой, принимавшей ацетаминофен)

The liver is particularly vulnerable to drug toxicity because it metabolizes and eliminates chemicals. Drug-induced liver disorders are common and can be life-threatening, often resembling various liver diseases. However, liver injury usually resolves after stopping the medication, with rare exceptions like drug-induced chronic hepatitis [1].

Drugs or their metabolites can disrupt biochemical functions, increase the liver's sensitivity to cytokines, or trigger an immune response. Symptoms may mimic acute hepatitis or cholestasis and can vary based on factors such as environment, age, sex, and genetics [3].

Drug-induced kidney disorders are also serious complications that can impair kidney function and lead to high mortality and morbidity rates. These issues can arise from medications used for diagnosis or treatment, like chemotherapeutic agents, antimicrobials, immunosuppressants, NSAIDs, and radiocontrast agents [8, 21, 22]. Drug-induced kidney disorders are currently a leading cause of renal damage. Therefore, developing strategies to mitigate these disorders is urgently needed [23].

APAP, also known as paracetamol, is one of the widely used medications for reducing fever and relieving pain. However, excessive intake of APAP can lead to severe toxicity in the liver and kidneys, potentially resulting in acute liver failure (ALF) and acute kidney injury (AKI). Although the exact molecular mechanisms underlying the liver and kidney toxicity associated with APAP are complex, several studies have suggested that this toxicity is linked to elevated levels of Fe^{2+} in models of liver and kidney damage [24–27].

Multiple studies have demonstrated that excessive consumption of APAP can lead to decreased glutathione levels and increased production of N-acetyl-p-benzoquinone imine (NAPQI). This process results in oxidative stress, DNA damage, and cell necrosis in the liver, ultimately leading to liver damage [28].

Research has shown that natural products can activate the liver's antioxidant defense system, primarily through a key component called Nrf2. These natural substances help decrease oxidative stress damage and protect the liver. Furthermore, cytochrome P450 enzymes, which play a crucial role in metabolizing APAP into its toxic form, NAPQI, are viewed as promising targets for treating liver injury induced by APAP [29].

The accurate molecular mechanism behind APAP-induced liver injury is not yet fully understood. At therapeutic concentrations, approximately 60 to 90% of APAP is metabolized in the liver through glucuronidation and sulfation. A smaller portion, around 5 to 15%, is metabolized via the cytochrome pathway [30, 31].

Many phytochemicals are known for their properties that protect the liver. Natural substances that safeguard liver health often demonstrate a variety of effects, like antioxidant, anti-inflammatory, immunomodulatory, and antiviral activities. These compounds may help reduce liver damage made by APAP and hold the potential for further development as antioxidants or liver-protective agents [32].

Understanding the hepatoprotective effects of natural products can inform future drug development. Two promising strategies for treating APAP induced acute liver injury are inhibiting a specific enzyme (CYP450) and activating the Nrf2 signaling pathway to enhance glutathione (GSH) synthesis. Nevertheless, challenges remain, including improving the therapeutic window, developing optimal drug carriers, and minimizing toxicity [9].

On the other hand, natural products are recognized for their kidney protective effects and are often used to treat kidney diseases. Research indicates that these products, including phytochemicals and herbal formulas, offer protection against DIN [33].

Nephrotoxicity is less common than hepatotoxicity in APAP overdose, with different metabolites causing these effects. In the liver, the metabolite NAPQI binds to proteins, leading to oxidative stress and hepatocyte necrosis. Conversely, both NAPQI and metabolites from acetaminophen-glutathione (APAP-GSH) contribute to nephrotoxicity in mice [5].

Previous studies have shown that certain phytochemicals in medicinal plants have antioxidant and anti-inflammatory properties, which can protect against hepatotoxicity and renal toxicity caused by APAP [17–22].

The study aims to evaluate the hepatoprotective and nephroprotective effects of *Alpinia officinarum* (Galangal, I) by analyzing liver parameters (ALT, AST, ALP, MDA, and CAT) and kidney parameters (BUN, creatinine, CAT, MDA, and SOD).

GC-MS analysis shows that various extracts and essential oils of I are rich in compounds such as flavonoids (like galangin), alkaloids (including capsaicin and dihydrocapsaicin), terpenes, fatty acids, phytosterols, and phenols. These compounds are noted for their antioxidant, anti-inflammatory, and oxidative stress-reducing properties, which may enhance kidney and liver functions [13–20].

For example, flavonoids have antioxidant, anti-inflammatory, anti-mutagenic, and anti-carcinogenic properties, and they regulate important cellular enzymes. They also inhibit several enzymes, like xanthine oxidase (XO), cyclooxygenase (COX), and lipoxygenase [34].

Previous studies showed that galangin significantly protects against APAP-induced acute liver (ALI) and AKI by reducing oxidative stress and increasing hepatic glutathione levels [35].

Galangin is a natural flavanol with antioxidant, anti-inflammatory, and anticancer properties. It can scavenge free radicals, regulate enzymes, and lower lipid levels, potentially inhibiting liver fibrosis by reducing lipid peroxidation and blocking the activation of hepatic stellate cells [36]. It has also been studied for its effects on acute kidney injury (AKI). It reduces oxidative stress by lowering renal MDA levels and enhances the activity of antioxidant enzymes, like SOD and CAT [37]. Galangin may protect against APAP-induced acute kidney injury by reducing oxidative stress levels, similar to its effects on liver injury. However, the exact protective mechanisms in the kidneys are not fully understood [37]. It has been shown to protect kidney tissue from injury and decrease excess reactive oxygen species (ROS), lipid peroxidation, and inflammatory mediators in rats exposed to CPF intoxication. It also upregulates Nrf2 and FXR and boosts enzymatic antioxidant activity [38].

It has been widely shown that phytochemicals extracted from I have significant antioxidant and anti-inflammatory effects [13–20]. For this reason, they are potential molecules for the development of new drugs that could be specially applied for the treatment and/or control of liver and kidney diseases.

In the present study, mice that received a toxic dose of acetaminophen exhibited elevated levels of liver enzymes (ALT, AST, and ALP) in their blood. Additionally, there was an increase in the amount of MDA, which serves as an indicator of lipid peroxidation and oxidative stress. Furthermore, a decrease in the levels of catalase, one of the most important antioxidant enzymes responsible for the direct reduction of reactive oxygen species, suggests the presence of liver disease. Also, after receiving a toxic dose of acetaminophen, the serum levels of BUN and creatinine increased, while the amount of MDA also rose. In contrast, the activity of the catalase enzyme in kidney tissue showed a significant decrease.

The results indicated that Galangal essential oil, along with hydroethanolic and chloroform extracts, played a significant role in protecting the livers of mice that had been induced with acetaminophen toxicity. Notably, the levels of the liver enzymes (ALT and AST) showed a substantial decrease across all extracts, whereas ALP exhibited a significant decrease only with the essential oil. Additionally, there was a marked decrease in MDA levels, and catalase enzyme activity significantly increased with both the essential oil and the hydroethanolic extract.

Similarly, the findings also demonstrated that the essential oil and the aforementioned extracts were effective in protecting the kidneys from paracetamol poisoning. Serum levels of BUN and creatinine decreased with the use of essential oil and extracts; however, the fall in serum creatinine was not statistically significant. Moreover, there was a significant fall in MDA levels and a notable rise in catalase enzyme activity in the essential oil and hydroethanolic extract, while the chloroform extract did not yield significant changes. Finally, the kidney levels of SOD enzyme increased significantly with the essential oil, but this increase was not observed with the hydroethanolic and chloroform extracts.

The observed effects are likely because of the presence of various phytochemicals in the extracts and essence derived from the rhizome of this plant. These phytochemicals possess antioxidant and anti-inflammatory properties, which have been illustrated to significantly decrease inflammation in kidney and liver tissues.

Based on the results presented in Table, the volatile oil product contains a high concentration of terpenes, along with phenolic and alkaloid compounds that exhibit documented antioxidant and anti-inflammatory activities. This composition enabled the essential oil to demonstrate the most effective protective effects on the liver and kidneys. Following closely, the hydroethanolic and chloroform extracts, which contain galantine as well as fatty acids, alkaloids, and sterols, were also able to improve certain serum markers related to liver and kidney health, attributable to their antioxidant and anti-inflammatory activities.

The diverse pharmacological effects observed in this study were attributed to the use of solvents with varying polarities. These solvents effectively separate and concentrate terpenes, flavonoids, alkaloids, phenols, fatty acids, and sterols in extracts and volatile oil.s

It is hoped that this method could serve as a viable alternative for obtaining specific components, individual compounds, from medicinal plants, such as galangal, to reduce drug-induced toxicity in the liver and kidneys. However, it is important to note that this topic goes beyond the scope of the current study and necessitates a more detailed understanding of the metabolites involved and their mechanisms of action.

CONCLUSION

The solvent plays a key role in the extraction and separation of active medicinal compounds from plants. In this research, the extraction procedure was conducted using different solvents with varying polarities. The results indicated that essential oil, as well as hydroethanolic and chloroformic extracts from *Alpinia officinarum* rhizome, showed the most effective protection against liver and kidney injuries caused by paracetamol.

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Conflict of interest

The authors declare no conflict of interests regarding the publication of this article.

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