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# Hepatoprotective Effects of Piperine on Thioacetamide-Induced Hepatotoxicity in Rats: A Lipid Profile Analysis

**Bhaskar Debbarma [a*], M Usha Rani [b], P. Shivakumar [c], D. Madhuri [d], K. Satish Kumar [e], D D V Hanuman [a], K. Vanitha Sree [a] and Ramavtar [a]**

*[a] Department of Veterinary Pharmacology and Toxicology, CVSc-Rajendranagar, Hyderabad, Telangana, India.*
*[b] Department of Veterinary Pharmacology and Toxicology, CVSc, Mamnoor, Warangal, Telangana, India.*
*[c] Department of Veterinary Pharmacology and Toxicology, AHP, Mamnoor, Warangal, Telangana, India.*
*[d] Department of Veterinary Pathology, CVSc, Rajendranagar, Hyderabad, Telangana, India.*
*[e] Department of Veterinary Medicine, CVSc, Rajendranagar, Hyderabad, Telangana, India.*

***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

Piperine is an alkaloid primarily found in the fruits of *Piper nigrum* L. (black pepper) and *Piper longum* L. (long pepper), which belong to the Piperaceae family. It is also present in smaller amounts in the roots of these plants. They possesses bio-enhancing properties, has a long history

**Corresponding author: E-mail: bhaskardebbarma2019@gmail.com;*

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of traditional use in revitalizing the liver and treating various hepatic ailments. Therefore, the current investigation aimed to determine the hepatoprotective potential of Piperine following oral administration in albino rats with liver damage induced by thioacetamide. In this study, thirty rats were divided into five equal groups, each groups containing 6 rats and experimented for eighth weeks. Group I (control): received normal saline @ 0.9 % p.o daily. Group II (diseased): received a single dose of Thioacetamide (TAA@ 150 mg/kg), twice per week. Group III: received Piperine (PIP @ 50 mg/kg b.d wt p.o daily) orally. Group IV: received TAA (@ 150 mg/kg i.p. twice/week) + PIP (@ 50 mg/kg b.d wt p.o daily). Group V (standard group): TAA (@ 150 mg/kg i.p. twice/week) +standard drug (Silymarin @ 50 mg/kg p.o daily). At the end of the experiment (57$^{th}$ day) all rats were sacrificed. The thioacetamide-treated group (group II) exhibited severe changes in the lipid profile parameters (total cholesterol, triglyceride, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol and glucose level. Based on the observed results in piperine-treated groups (IV) compared to the thioacetamide group (II), the study suggests piperine's potential for hepatoprotection against thioacetamide-induced hepatotoxicity.

*Keywords: Piperine; thioacetamide; lipid profile; hepatoprotection; silymarin.*

## 1. INTRODUCTION

Liver fibrosis is a major health concern with no standard treatment due to its complex causes with significant morbidity and mortality [1]. This chronic condition is characterized by the excessive deposition of extracellular matrix (ECM) by activated hepatic stellate cells (HSCs), leading to a progressive distortion of the normal liver architecture and impaired function [2]. Inflammation, often triggered by oxidative stress, is a key driver of HSC activation [3]. Pro-inflammatory cytokines, chemokines, and adhesion molecules further contribute to this process, creating a complex web of signaling pathways that promote fibrosis [4]. The absence of effective treatment options underscores the urgent need for novel therapeutic strategies to target liver fibrosis. Medicinal plants have been used for centuries as a source of food, spices, and remedies for many diseases. Black pepper (*Piper nigrum*), a member of the *Piperaceae* family, is one of the most commonly used spices in the world. It has a distinct sharp flavor due to the presence of Piperine, a phytochemical. Piperine (1-piperoyl piperidine) is a major alkaloid of *Piper nigrum* Linn. (Piperaceae) and *Piper longum* Linn. (*Piperaceae*) and has been reported to possess bioavailability enhancing activity by increasing absorption various drug molecule [5, 6]. This might be achieved due to alteration in membrane lipid dynamics and change in the conformation of enzymes in the intestine. Piperine was also reported to possess numerous benefits including antioxidant [7], antimicrobial [8], neuroprotective [9], antiparasitic [10], anticancer [11], analgesic [12], anti-inflammatory [13] anti-apoptotic [14], hepatoprotective [15], antitumor [16], immunomodulatory [16], antimutagenic [17] and antimetastatic [18].

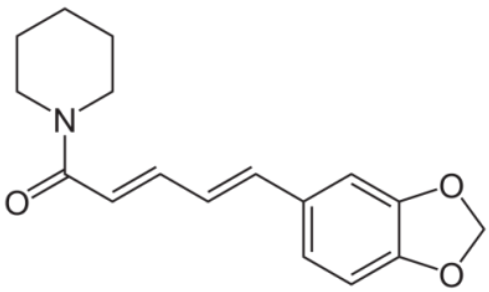


**Fig. 1. Structure of Piperine [19]**

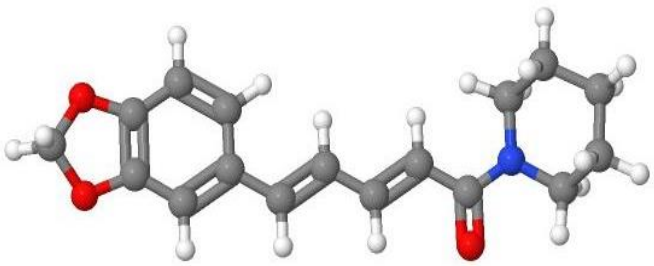

**Fig. 2. Structure of Piperine 3D Model (Ball and Stick) [20]**

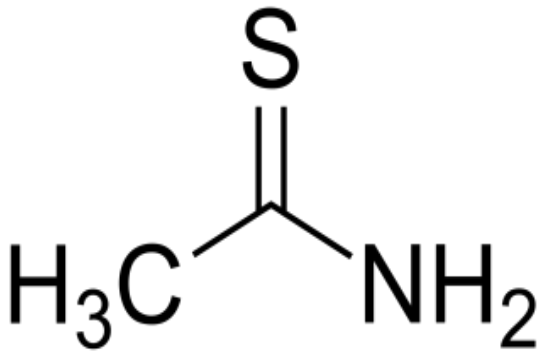


**Fig. 3. Chemical Structure of thioacetamide [21]**

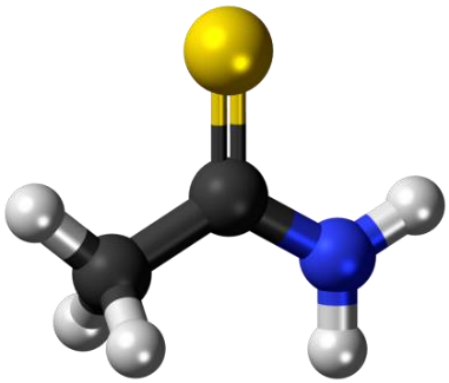

**Fig. 4. Interactive Chemical Structure 3D Model of thioacetamide [22]**

## 2. MATERIALS AND METHODS

This study was conducted at the Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science, P.V. Narsimha Rao Telangana Veterinary University, Hyderabad, Telangana.

Adult, inbred albino rats of either sex, weighing 150–200 g, were used in this study. The rats were housed in clean polycarbonate cages at the College of Veterinary Science, Hyderabad, Telangana, with ad libitum access to water and a regular pellet diet. Following a two-week acclimation period under close veterinary supervision to ensure good health, the animals were subjected to the experiment. All procedures were conducted in accordance with ethical guidelines to minimize stress. The study was approved by the Institutional Animal Ethics Committee (IAEC) with approval number (02/26/C.V.Sc, Hyd. IAEC). All procedures adhered to the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines for animal care and use. Table demonstrates the experimental design of the research work.

### 2.1 Experimental Design

Thirty healthy, inbred albino rats (150-200 g) were randomly divided into five groups (n=6/group). The chemicals used were Piperine (PIP, 50 mg/kg body weight/day, oral), thioacetamide (TAA, 150 mg/kg body weight, intraperitoneal injection twice/week), and normal saline (0.9 %, oral). The groups were as follows:

**Body weight:** The body weight changes were recorded weekly for 8 weeks. Individual body weights of all rats were recorded on $0^{th}$, $7^{th}$ day, $14^{th}$ day, $21^{st}$ day, $28^{th}$ day, $35^{th}$ day, $42^{nd}$ day, $49^{th}$ day and $56^{th}$ day of the total 8 weeks of experiment.

**Organ weight:** On the $56^{th}$ day of the study, rats were euthanized with a $CO_2$ chamber, and liver and kidney weights were measured. The relative organ weight was calculated as organ weight (mg) per body weight (g).

**Table 1. Different experimental groups and their treatment**

| Groups | Treatments | No. of animals |
|---|---|---|
| I | Control (Normal Saline @ 0.9 % p.o daily) | 6 |
| II | Disease control Thioacetamide (TAA @ 150 mg/kg i.p. twice/week) | 6 |
| III | Piperine (PIP @50 mg/kg b.d wt p.o daily) | 6 |
| IV | TAA (@ 150 mg/kg i.p. twice/week) + PIP (@ 50 mg/kg b.d wt p.o daily) | 6 |
| V | TAA (@ 150 mg/kg i.p. twice/week) +Standard drug (Silymarin @ 50 mg/ kg p.o daily) | 6 |

**Lipid profile parameters:** This study investigated the potential of Piperine, a nutraceutical from black pepper (Piper nigrum), against thioacetamide (TAA)-induced liver fibrosis in mice. Silymarin served as a reference antifibrotic drug. Piperine @ 50 mg/kg significantly improved liver function by reducing total cholesterol, triglyceride, HDL and LDL cholesterol and glucose These improvements were confirmed by body weight and liver index (%) changes in rats.

**Statistical Analysis:** For group wise comparisons of means was analyzed in Statistical Package for Social Sciences (SPSS, version 29.0.2.0). The data between the groups over the weeks were statistically analyzed using one-way ANOVA followed by LSD (least significant difference) test.

## 3. RESULTS AND DISCUSSION

The present study employed prolonged (8 weeks) TAA administration in wistar rats, resulting in observable visual and quantifiable changes in body weight (Table 1) and body weight gain (Table 2), TAA administration in the toxic group resulted in a significantly reduced body weight gain compared to the normal control group. The observed decrease in body weight suggests a state of sustained catabolism. However, it remains to be elucidated whether this reduction is a direct consequence of TAA-induced hepatotoxicity or an indirect effect mediated by liver injury. Thioacetamide (TAA) administration induced marked toxicity in rats, as evidenced by their impaired body weight gain. The body weight in Group II (TAA) animals was observed to be significantly lower than in all other groups on 56$^{th}$ day of experiment, this finding aligns with previous studies suggesting that TAA exposure reduces nutrient absorption and metabolic efficiency, thereby hindering growth rate [23-25]. Interestingly, the body weight measurements in group IV (TAA+PIP) demonstrated a significant recovery compared to group II (TAA) exposed only to thioacetamide (TAA). This finding suggests that piperine treatment (PIP) may mitigate the body weight loss associated with TAA-induced hepatic toxicity. The combine affrect of curcuming and piperine against thioacetamide induced hepatotoxicity found to have increase body weight in rats demostrated by Shivhare et al. [26]. The treatment groups receiving TAA combined with PIP (Group IV) exhibited a statistically significant increase in body weight gain relative to the TAA group alone, corroborating findings by Zaidi and Masood [27]. As previously demonstrated by Álvarez-Mercado et al. [28], they observed hepatomegaly in TAA-treated rats is a well-established indicator of hepatic lesions and associated liver damage resulting from the well-documented toxicological effects of TAA. Hsieh et al. (2008) reported a significant increase in liver weight in rats following thioacetamide administration, a well-established model of hepatotoxicity [29]. Furthermore, the formation of ECM in fibrotic livers offers the higher liver-to-body weight ratio (liver index). This explains the elevated liver index observed in the TAA group [30].

Our results of lipid profile test demonstrated a significant decrease in HDL cholesterol levels within the TAA-exposed group compared to the control group. Conversely, groups IV (TAA + PIP) exhibited a significant increase in HDL (high-density lipoprotein cholesterol) cholesterol and total cholesterol levels compared to the TAA-exposed group. These observations suggest that TAA toxicity induces significant alterations in plasma and hepatic metabolism. Plasma analysis reveals hypoglycemia (decreased blood glucose), decreased HDL cholesterol (the “good” cholesterol), and a reduction in total protein. Conversely, plasma levels of triglycerides, total cholesterol, and LDL (low-density lipoprotein cholesterol) cholesterol (the “bad” cholesterol) and total cholesterol are elevated. Hepatic analysis demonstrates disrupted metabolic protein profiles alongside dysregulation of both carbohydrate and lipid metabolism [31-33].

The liver serves as a central metabolic hub, act as the regulator of carbohydrate, protein, and lipid metabolism. A critical function of the liver is the storage and metabolism of glycogen as a readily available energy source. This process ensures glucose homeostasis during fasting periods, particularly for tissues with a preferential or obligate reliance on glucose, such as neurons and erythrocytes [34]. In our findings the glucose level was reduced (on both 28th and 56th day of experiment) as compare to the TAA induced rats as compare to the normal control group, but the treatment group TAA+PIP (Group IV) showed significantly higher in glucose level as compare to the TAA toxic group. TAA toxicity likely induces a biphasic response in blood glucose regulation. Initially, TAA may promote glycogenolysis (breakdown of liver glycogen), leading to a temporary increase in blood glucose.

**Table 2. Mean ± body weight (g) in different groups of rats in different weeks**

| Groups | Weeks | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **0** | **1st** | **2nd** | **3rd** | **4th** | **5th** | **6th** | **7th** | **8th** |
| I | 167.33 ± 6.96$^{a}$ | 175.17 ± 3.22$^{a}$ | 213.67 ± 3.27$^{a}$ | 242.50 ± 9.50$^{a}$ | 267.83 ± 3.58$^{a}$ | 282.83 ± 6.00$^{a}$ | 298.00 ± 5.75$^{a}$ | 329.33 ± 7.07$^{a}$ | 357.17 ± 3.82$^{a}$ |
| II | 166.83 ± 6.15$^{a}$ | 168.00 ± 7.84$^{a}$ | **185.67 ± 3.77$^{*c}$** | 206.50 ± 5.53$^{b}$ | **225.17 ± 5.13$^{*c}$** | **234.50 ± 12.38$^{*b}$** | **241.50 ± 12.26$^{*b}$** | **253.50 ± 5.32$^{**c}$** | **265.50 ± 10.00$^{*b}$** |
| III | 163.00 ± 9.38$^{a}$ | 174.33 ± 8.87$^{a}$ | 204.83 ± 5.60$^{ab}$ | 229.50 ± 6.87$^{ab}$ | 244.00 ± 5.97$^{bc}$ | 265.67 ± 6.62$^{a}$ | 274.17 ± 7.45$^{a}$ | 322.00 ± 2.86$^{a}$ | 343.00 ± 14.73$^{a}$ |
| IV | 166.33 ± 8.98$^{a}$ | 173.00 ± 7.37$^{a}$ | **187.17 ± 7.63$^{*bc}$** | 222.67 ± 12.88$^{ab}$ | **231.33 ± 7.36$^{*bc}$** | 262.33 ± 12.31$^{a}$ | 271.50 ± 11.53$^{a}$ | **274.83 ± 11.54$^{*bc}$** | 311.17 ± 17.66$^{a}$ |
| V | 165.50 ± 7.17$^{a}$ | 175.50 ± 8.64$^{a}$ | 197.17 ± 7.26$^{abc}$ | 223.50 ± 8.50$^{ab}$ | 249.17 ± 5.16$^{ab}$ | 278.33 ± 8.09$^{a}$ | 290.67 ± 11.35$^{a}$ | 303.50 ± 18.07$^{ab}$ | 320.83 ± 16.54$^{a}$ |

*Values are mean±SEM, one-way ANOVA with Duncan's post hoc test (SPSS), means bearing different alphabets in the column indicates significant difference (p<0.05). *- Significant at p < 0.05, **- Highly significant at p < 0.01*

**Table 3. Relative body weight (%), liver weight and liver index (%)**

| Groups | Treatment | Relative body weight (%) | Mean liver weight (g) | Relative liver weight or liver index (%) |
|---|---|---|---|---|
| I | Control | 115.71 ± 10.98$^{a}$ | 11.52 ± 0.42$^{ab}$ | 3.22 ± 0.11$^{b}$ |
| II | Thioacetamide control | **61.02 ± 10.78$^{**b}$** | 10.75 ± 0.21$^{b}$ | **4.09 ± 0.24$^{a*}$** |
| III | Piperine *per se* | 112.04 ± 8.80$^{a}$ | 11.44 ± 0.75$^{ab}$ | 3.33 ± 0.17$^{b}$ |
| IV | Thioacetamide + Piperine | 90.45 ± 17.12$^{ab}$ | 10.43 ± 0.37$^{b}$ | 3.41 ± 0.23$^{ab}$ |
| V | Thioacetamide + Standard (Silymarin) | 94.14 ± 7.15$^{ab}$ | 10.94 ± 0.37$^{ab}$ | 3.45 ± 0.17$^{ab}$ |

*Values are mean±SEM, (n=6) in one-way ANOVA with Duncan's post hoc test (SPSS), means bearing different alphabets in the column indicates significant difference (p<0.05). *- Significant at p < 0.05, **- Highly significant at p < 0.01*

**Table 4. Triglycerides concentration (mg/dL) in different groups of rats**

| Groups | Treatment | 28th day | 56th day |
|---|---|---|---|
| I | Control | 69.19 ± 3.46$^{b}$ | 72.50 ± 3.60$^{b}$ |
| II | Thioacetamide control | **145.83 ± 13.33$^{**a}$** | **177.03 ± 7.60$^{a**}$** |
| IV | Piperine *per se* | 73.38 ± 3.60$^{b}$ | 74.41 ± 2.67$^{b}$ |
| VI | Thioacetamide + Piperine | 86.50 ± 9.97$^{b}$ | 86.17 ± 9.57$^{b}$ |
| VII | Thioacetamide + Standard (Silymarin) | 89.67 ± 9.20$^{b}$ | 85.00 ± 6.86$^{b}$ |

*Values are mean±SEM, (n=6) in one-way ANOVA with Duncan's post hoc test (SPSS), means bearing different alphabets in the column indicates significant difference (p<0.05).* ***- Highly significant at p < 0.01*

**Table 5. HDL Cholesterol concentration (mg/dL) in different groups of rats**

| Groups | Treatment | 28th day | 56th day |
|---|---|---|---|
| I | Control | 33.17 ± 1.30$^{a}$ | 37.93 ± 4.78$^{a}$ |
| II | Thioacetamide control | **15.50 ± 1.71$^{*b}$** | **14.27 ± 2.11$^{b**}$** |
| III | Piperine *per se* | 40.00 ± 5.21$^{a}$ | 39.33 ± 4.53$^{a}$ |
| IV | Thioacetamide + Piperine | 32.83 ± 5.64$^{a}$ | 30.67 ± 3.09$^{a}$ |
| V | Thioacetamide + Standard (Silymarin) | 38.67 ± 8.22$^{a}$ | 37.67 ± 3.24$^{a}$ |

*Values are mean±SEM, (n=6) in one-way ANOVA with Duncan's post hoc test (SPSS), means bearing different alphabets in the column indicates significant difference (p<0.05). *- Significant at p < 0.05, **- Highly significant at p < 0.01*

**Table 6. LDL Cholesterol concentration (mg/dl) in different groups of rats**

| Groups | Treatment | 28th day | 56th day |
|---|---|---|---|
| I | Control | 58.75 ± 4.86$^{ab}$ | 58.67 ± 4.84$^{b}$ |
| II | Thioacetamide control | 75.50 ± 5.36$^{a}$ | **82.33 ± 5.40$^{a**}$** |
| IV | Piperine *per se* | 52.00 ± 6.85$^{b}$ | 48.17 ± 2.44$^{b}$ |
| VI | Thioacetamide + Piperine | 63.67 ± 9.61$^{ab}$ | 54.50 ± 7.54$^{b}$ |
| VII | Thioacetamide + Standard (Silymarin) | 54.33 ± 7.72$^{b}$ | 57.17 ± 7.94$^{b}$ |

*Values are mean±SEM, (n=6) in one-way ANOVA with Duncan's post hoc test (SPSS), means bearing different alphabets in the column indicates significant difference (p<0.05).* ***- Highly significant at p < 0.01*

**Table 7. Total Cholesterol concentration (mg/dl) in different groups of rats**

| Groups | Treatment | 28th day | 56th day |
|---|---|---|---|
| I | Control | 77.00 ± 2.90$^{bc}$ | 74.95 ± 8.03$^{a}$ |
| II | Thioacetamide control | **97.67 ± 3.26$^{a*}$** | **127.33 ± 13.54$^{b**}$** |
| IV | Piperine *per se* | 70.20 ± 5.32$^{c}$ | 72.22 ± 5.53$^{a}$ |
| VI | Thioacetamide + Piperine | 76.33 ± 4.72$^{c}$ | 82.00 ± 8.45$^{a}$ |
| VII | Thioacetamide + Standard (Silymarin) | 77.83 ± 8.96$^{bc}$ | 85.50 ± 8.84$^{a}$ |

*Values are mean±SEM, (n=6) in one-way ANOVA with Duncan's post hoc test (SPSS), means bearing different alphabets in the column indicates significant difference (p<0.05). *- Significant at p < 0.05, **- Highly significant at p < 0.01*

**Table 8. Glucose concentration (mg/dl) in rats of different groups**

| Groups | Treatment | 28th day | 56th day |
|---|---|---|---|
| I | Control | 103.42 ± 4.85$^{a}$ | 125.98 ± 3.30$^{a}$ |
| II | Thioacetamide control | **64.83 ± 9.80$^{b**}$** | **71.83 ± 11.36$^{c**}$** |
| III | Piperine *per se* | 88.80 ± 10.72$^{ab}$ | 111.88 ± 8.42$^{a}$ |
| IV | Thioacetamide + Piperine | 88.17 ± 12.43$^{ab}$ | **87.50 ± 8.98$^{bc**}$** |
| V | Thioacetamide + Standard (Silymarin) | 93.67 ± 9.83$^{ab}$ | 112.17 ± 7.16$^{a}$ |

*Values are mean±SEM, (n=6) in one-way ANOVA with Duncan's post hoc test (SPSS), means bearing different alphabets in the column indicates significant difference (p<0.05).* ***- Highly significant at p < 0.01*

This could potentially stimulate pancreatic β-cells and subsequent insulin secretion. However, with prolonged exposure (e.g., by the 8th week observed by Ebrahim et al. [35], TAA-induced hepatotoxicity may deplete hepatic glycogen stores, resulting in hypoglycemia despite elevated serum insulin levels.

## 4. CONCLUSION

Piperine may effect the production of total cholesterol, triglycerides, LDL, HDL, glucose level and may improve the function of hepatocytes, which are responsible for many important tasks, such as detoxification. Experimentally proven pharmacological effects are aimed at stabilising the functional state of the liver. The analysis of the obtained experimental data may be the basis for further in-depth studies of the functioning of the liver and the hepatobiliary system as a whole, to identify biomarkers of enzymatic nature to prove the presence of membrane-stabilising, antioxidant, anti-inflammatory activity of Piperine and its probable mechanisms of pharmacological action.

## DISCLAIMER

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 manuscripts.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES


1. Altamirano-Barrera A, Barranco-Fragoso B, Méndez-Sánchez N. Management strategies for liver fibrosis. Annals of Hepatology. 2017;16(1):48-56.
2. Reeves HL, Friedman SL. Activation of hepatic stellate cells—a key issue in liver fibrosis. Front Biosci. 2002;7(4):808-26.
3. Greenwel P, Domínguez-Rosales JA, Mavi G, Rivas-Estilla AM, Rojkind M. Hydrogen peroxide: A link between acetaldehyde-elicited α1 (i) collagen gene up-regulation and oxidative stress in mouse hepatic stellate cells. Hepatology. 2000;31(1):109-16.
4. Pinzani M, Macias-Barragan J. Update on the pathophysiology of liver fibrosis. Expert review of gastroenterology & hepatology. 2010;4(4):459-72.
5. Lee SA, Hong SS, Han XH, Hwang JS, Oh GJ, Lee KS, Lee MK, Hwang BY, Ro JS. Piperine from the fruits of Piper longum with inhibitory effect on monoamine oxidase and Antidepressant-like activity. Chemical and Pharmaceutical Bulletin. 2005;53(7):832-5.
6. Khatri S, Awasthi R. Piperine containing floating microspheres: An approach for drug targeting to the upper gastrointestinal tract. Drug Delivery and Translational Research. 2016;6:299-307.
7. Vijayakumar R, Surya D, Nalini N. Antioxidant efficacy of black pepper (*Piper nigrum* L.) and piperine in rats with high fat diet induced oxidative stress. Redox Report. 2004;9(2):105-10.
8. Mirza ZM, Kumar A, Kalia NP, Zargar A, Khan IA. Piperine as an inhibitor of the MdeA efflux pump of Staphylococcus aureus. Journal of Medical Microbiology. 2011;60(10):1472-8.
9. Chonpathompikunlert P, Wattanathorn J, Muchimapura S. Piperine, the main alkaloid of Thai black pepper, protects against neurodegeneration and cognitive impairment in animal model of cognitive deficit like condition of Alzheimer's disease. Food and Chemical Toxicology. 2010;48(3): 798-802.
10. Freire-de-Lima L, Ribeiro TS, Rocha GM, Brandão BA, Romeiro A, Mendonça-Previato L, Previato JO, de Lima ME, de Carvalho TM, Heise N. The toxic effects of piperine against Trypanosoma cruzi: ultrastructural alterations and reversible blockage of cytokinesis in epimastigote forms. Parasitology Research. 2008;102: 1059-67.
11. Bezerra DP, Castro FO, Alves AP, Pessoa C, Moraes MO, Silveira ER, Lima MA, Elmiro FJ, Alencar NM, Mesquita RO, Lima MW. In vitro and *In vivo* antitumor effect of 5-FU combined with piplartine and piperine. Journal of Applied Toxicology: An International Journal. 2008;28(2):156-63.
12. Yasir A, Ishtiaq S, Jahangir M, Ajaib M, Salar U, Khan KM. Biology-oriented synthesis (BIOS) of piperine derivatives and their comparative analgesic and antiinflammatory activities. Medicinal Chemistry. 2018;14(3):269-80.

13. Bang JS, Oh DH, Choi HM, Sur BJ, Lim SJ, Kim JY, Yang HI, Yoo MC, Hahm DH, Kim KS. Anti-inflammatory and antiarthritic effects of piperine in human interleukin 1β-stimulated fibroblast-like synoviocytes and in rat arthritis models. Arthritis Research & Therapy. 2009;11:1-9.
14. Shrivastava P, Vaibhav K, Tabassum R, Khan A, Ishrat T, Khan MM, Ahmad A, Islam F, Safhi MM, Islam F. Anti-apoptotic and anti-inflammatory effect of Piperine on 6-OHDA induced Parkinson's rat model. The Journal of Nutritional Biochemistry. 2013;24(4):680-7.
15. Koul IB, Kapil A. Evaluation of the liver protective potential of piperine, an active principle of black and long peppers. *Planta medica*. 1993;59(05):413-7.
16. Sunila ES, Kuttan G. Immunomodulatory and antitumor activity of *Piper longum* Linn. and piperine. Journal of Ethnopharmacology. 2004;90(2-3):339-46.
17. Abo-Zeid MA, Farghaly AA. The anti-mutagenic activity of piperine against mitomycine C induced sister chromatid exchanges and chromosomal aberrations in mice. Nat. Sci. 2009;7:72-8.
18. Smilkov K, Ackova D G, Cvetkovski A, Ruskovska T, Vidovic B and Atalay M. Piperine: old spice and new nutraceutical?. Current Pharmaceutical Design. 2019;25 (15):1729-39.
19. Haq IU, Imran M, Nadeem M, Tufail T, Gondal TA, Mubarak MS. Piperine: A review of its biological effects. Phytotherapy Research. 2021;35(2):680-700.
20. Available:https://pubchem.ncbi.nlm.nih.gov/compound/Piperine#section=3DConformer&fullscreen=true
21. Available:https://en.wikipedia.org/wiki/Thioacetamide#:~:text=Thioacetamide%20is%20an%20organosulfur%20compound,2H5NS.
22. Available:https://pubchem.ncbi.nlm.nih.gov/compound/Thioacetamide#section=3D-Conformer&fullscreen=true
23. Kadir FA, Kassim NM, Abdulla MA, Yehye W A. Hepatoprotective role of ethanolic extract of Vitex negundo in thioacetamide-induced liver fibrosis in male rats. Evidence-based Complementary and Alternative Medicine. 2013(1):739850.
24. Li X, Benjamin IS, Alexander B. Reproducible production of thioacetamide-induced macronodular cirrhosis in the rat with no mortality. Journal of Hepatology. 2002;36(4):488-93.
25. Hessin A, Hegazy R, Hassan A, Yassin N, Kenawy S. Lactoferrin enhanced apoptosis and protected against thioacetamide-induced liver fibrosis in rats. Open access Macedonian Journal of Medical Sciences. 2015;3(2):195.
26. Shivhare S, Shrman K, Gautam V, Dubey S. Histopathological examination of the hepatoprotective effect of curcumin with piperine on thioacetamide induced hepatotoxicity in rats. Emer Life Sci Res. 2023;9(2):51-60
27. Zaidi SN, Masood J. The protective effect of fenugreek seeds extract supplementation on glucose and lipid profile in thioacetamide induced liver damage in rats. Pakistan Journal of Pharmaceutical Sciences. 2020;33 (5).
28. Álvarez-Mercado AI, García-Mediavilla MV, Sánchez-Campos S, Abadía F, Sáez-Lara MJ, Cabello-Donayre M, Gil Á, González-Gallego J, Fontana L. Deleterious effect of human umbilical cord blood mononuclear cell transplantation on thioacetamide-induced chronic liver damage in rats. Cell Transplantation. 2009;18(10-11):1069-79.
29. Hsieh CC, Fang HL, Lina WC. Inhibitory effect of Solanum nigrum on thioacetamide-induced liver fibrosis in mice. Journal of Ethnopharmacology. 2008;119 (1):117-21.
30. Chen IS, Chen YC, Chou CH, Chuang RF, Sheen LY, Chiu CH. Hepatoprotection of silymarin against thioacetamide-induced chronic liver fibrosis. Journal of the Science of Food and Agriculture. 2012; 92(7):1441-7.
31. Trennery PN, Waring RH. Early changes in thioacetamide-induced liver damage. Toxicology letters. 1983;19(3):299-307.
32. Galisteo M, Suárez A, Montilla MP, Fernandez MI, Gil A, Navarro MC. Protective effects of Rosmarinus tomentosus ethanol extract on thioacetamide-induced liver cirrhosis in rats. Phytomedicine. 2006;13(1-2): 101-8.
33. Jain NK, Singhai AK. Protective effects of *Phyllanthus acidus* (L.) Skeels leaf extracts on acetaminophen and thioacetamide induced hepatic injuries in Wistar rats. Asian Pacific Journal of Tropical Medicine. 2011;4(6):470-4.

34. Nelson DL, Cox MM. Princípios de bioquímica de Lehninger. Artmed Editora; 2022.
35. Ebrahim AT, El-Gendy A, El-Zawahry B. Antihepatotoxic potential of ginseng (*Panax ginseng*) in thioacetamide-induced acute hepatocellular injury in rats. The Egyptian Journal of Hospital Medicine. 2004;16(1):55-64.



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