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Potential Effect of Fisetin and Curcumin Combination in Alleviating Arsenic Trioxide–Mediated Oxidative Stress and Hepatotoxicity

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ABSTRACT

Arsenic trioxide (As_2O_3) exposure remains a major public health concern due to its hepatotoxic effects, which are largely mediated by oxidative stress, inflammation, and apoptosis. Natural bioactive compounds such as Fisetin, a flavonoid found in strawberries, apples, onions, and cucumbers, and curcumin, the principal curcuminoid in turmeric *(Curcuma longa)*, are known for their antioxidant and anti-inflammatory properties. However, their combined protective role against arsenic-induced liver injury has not been well established. This study evaluated the combined effects of Fisetin and curcumin on As_2O_3-induced hepatotoxicity in Wistar rats. Thirty male rats (150–200 g) were divided into six groups (n = 5): control, As_2O_3 only (20 mg/kg), Fisetin only (100 mg/kg), curcumin only (100 mg/kg), Fisetin + curcumin (100 mg/kg each), and As_2O_3 (20 mg/kg) + Fisetin (100 mg/kg) + curcumin (100 mg/kg). Treatments were administered orally. Liver weight, oxidative stress markers and inflammatory marker were measured and liver histology. Arsenic trioxide exposure significantly increased Malondialdehyde and C-reactive protein levels, while decreasing liver weight, superoxide dismutase and catalase ($p < 0.05$). Histological examination revealed extensive hepatic alterations, characterized by hepatocyte abnormalities, sinusoidal dilation, vascular congestion, and steatosis resulting from arsenic trioxide exposure. Treatment with the combination of Fisetin and curcumin after arsenic trioxide exposure significantly improved antioxidant status, reduced inflammation, and restored hepatic architecture. Overall, the findings demonstrate that Fisetin and curcumin in combination exert strong restorative effects against As_2O_3-induced oxidative stress and hepatotoxicity, suggesting their potential as complementary agents for preventing arsenic-related liver injury.

Keywords: arsenic-trioxide, hepatic injury, oxidative stress, fisetin, curcumin hepatoprotection

INTRODUCTION

Arsenic exposure is considered a major global health concern, with approximately 200 million people worldwide at risk of potentially toxic levels [1]. Arsenic (As) is a naturally occurring yet highly toxic metalloid that causes serious health dangers to the general population in many countries around the world because of its proliferation in contaminated groundwater and industrial wastes [2]. Prolonged exposure to arsenic has various health effects, which include hepatotoxicity, skin lesions, vascular damage, neurological damage, and increased susceptibility to cancer in many body organs[3,4]. Arsenic trioxide is used both as a therapy in medicine and as a source of environmental pollution. It is significant in the treatment of acute promyelocytic Leukemia (APL) and significantly extends the survival of patients by inducing the destruction of PML/RARalpha fusion protein, resulting in cell differentiation and apoptosis[5].

The major sources of overexposure to arsenic trioxide can be mainly through contaminated drinking water, food, and occupational practice [2,6]. The issue of arsenic in drinking water is a health emergency worldwide, and it is predominantly a burden in the southern parts of Europe, Southeast Asia, and Africa[7,8]. Arsenic can influence health immensely in both organic and inorganic forms, causing issues like various kinds of cancer, systemic disorders[8.9].

Exposure to arsenic may cause injury to the hepatic tissue because the liver is a major detoxification organ and is highly sensitive to reactive oxygen species (ROS)[10]. Arsenic induces oxidative stress, lipid peroxidation, abnormal mitochondrial function, and production of the inflammatory cytokines, and all these result in hepatocellular injury[2-4]. Another biochemical parameter of arsenic-induced hepatic damage is the depletion of antioxidant enzymes, including superoxide dismutase (SOD) and catalase (CAT), and a rise in levels of malondialdehyde (MDA) along with C-reactive protein (CRP)[11,12]. Consequently, protein pathways implicated in apoptosis (AKT-PKB, MAPK), fibrosis, and inflammation (TNF-α, NF-kB) are finally activated with the subsequent hepatotoxicity triggering through the process of arsenic toxicity [11-12].

Despite the serious impact of arsenic-induced hepatotoxicity, effective treatment options remain limited, particularly in regions with restricted access to healthcare, shifting scientific attention toward natural bioactive compounds as preventive or adjunctive therapies. The use of medicinal plants and their bioactive compounds has become of great interest in the world due to their possible usage as therapeutic agents [6,13-16]. These natural products are now being investigated in connection with their ability to prevent and treat various health conditions, and in terms of being complementary or alternative medicine to conventional medicine. Certain medicinal plants and their bioactive compounds have a significant potential in this regard and thus they can be considered useful in the development of new therapeutic agents and nutritional supplements since they are widely available, exhibit a broad range of biological activity and reasonably good safety. Fisetin is a natural bioflavonoid that can be found in strawberries, apples, onions, and cucumbers, showing numerous pharmacological advantages[6,17]. Fisetin possesses antioxidant and anti-inflammatory properties, with its strongest anticancer effects observed in strawberries[18]. Fisetin has neuroprotective, anti-oxidative, cardioprotective, and antimicrobial properties, making it a promising bioactive compound to improve health in general [19]. Curcumin, the primary curcuminoid in turmeric, is a potent antioxidant and anti-inflammatory agent and can protect the liver against a wide range of hepatotoxic agents[20]. Studies have shown that curcumin is effective in inhibiting oxidative stress and inflammation. Also, it inhibits cellular toxicity through neutralizing detrimental reactive oxygen species and improving antioxidant defenses, thus protecting tissues against oxidative damage [20,21].

Curcumin has liver-protective effects against heavy metals, drugs, and alcohol-induced toxicity[21-23]. These actions are achieved by preventing oxidative damage, mediating inflammation, and manipulating pathways related to the drug. Although Fisetin and curcumin have each been studied for their individual hepatoprotective effects, limited research has examined their combined use, especially regarding their synergistic potential in protecting the liver from arsenic-induced toxicity. Their combined therapeutic efficacy remains largely unexplored, highlighting a gap in understanding how these compounds may work together to enhance liver protection. Since their mechanisms of action are complementary, this study hypothesizes that Fisetin and curcumin may offer synergistic protection against arsenic-induced hepatotoxicity. Thus, the purpose of this study is to determine the individual and combined effects of Fisetin and curcumin on oxidative stress indicators (SOD, CAT, MDA), to determine their effect on inflammation through CRP levels, and to analyze histological recovery of the liver tissue after arsenic exposure in Wistar rats. The study seeks to explore the effectiveness of these natural compounds in protecting against arsenic-related hepatotoxicity, highlighting their possible role in developing safer, plant-based therapeutic strategies.

MATERIALS AND METHODS

Experimental animals and ethical considerations

Thirty healthy male Wistar rats, aged 8–10 weeks and weighing 150–200 g, were obtained and housed in standard polypropylene cages at the animal facility of the Department of Anatomy, Ambrose Alli University, Ekpoma. The rats were maintained in a controlled environmental condition (temperature 24 ±1 °C, relative humidity 55±5 %, light/dark period of 12 hours). The rats were freely provided with standard rodent meal and clean water. This work was approved by the Anatomy Department of Ambrose Alli University, Ekpoma. The rats were accustomed to climate two weeks before the experiment. All experimental procedures were performed under the care and use of laboratory animals and the ARRIVE guideline on the use of experimental animals.

Reagents and chemicals used

- Arsenic trioxide (As_2O_3) – source of arsenic-induced hepatotoxicity
- Fisetin and curcumin – purified phytochemicals (procured from Sigma Aldrich, USA)
- Biochemical assay kits - for MDA, SOD, CAT, and CRP (from Randox Laboratories)
- Histological reagents – Formalin, paraffin wax, Hematoxylin and eosin (H&E), Buffer Phosphate-buffered saline (PBS), Triz-HCl buffer (pH 7.6)

Grouping and treatment protocol

The rats were randomly divided into six experimental groups (n = 5 per group). The study design is shown in Figure 1 below.

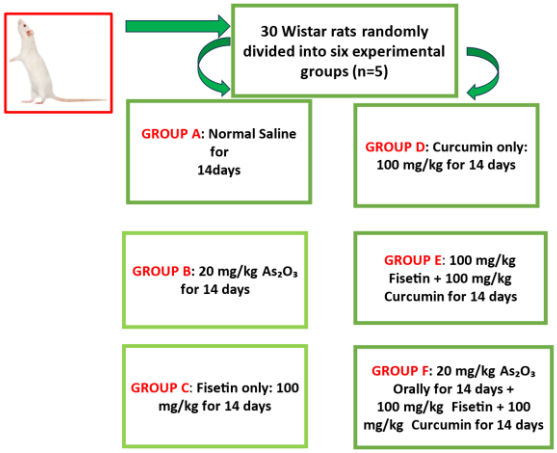

Figure 1: Showing Animal Grouping and Experimental Protocol

The dose of Fisetin and curcumin was dependent on the literature published, which shows efficacy as an antioxidant [24-26]. A daily dose of Fisetin, curcumin, and arsenic trioxide was dissolved in normal saline solution and administered orally.

Sample collection

Blood samples were obtained at the end of the treatment period through the retro-orbital plexus. The rats were mildly anaesthetized with ketamine and sacrificed through cervical dislocation. Serum was obtained through centrifugation of the collected blood sample at 3000 rpm for 15 minutes to analyze the biochemical parameters. The liver tissues were removed, weighed, and separated into two equal parts; one was fixed in 10% neutral buffered formalin and used to determine the histopathological findings.

Biochemical assays

Determination of lipid peroxidation level

The thiobarbituric acid reactive substances (TBARS) assay was used to measure the liver's level of malondialdehyde (MDA), a marker of lipid peroxidation, in accordance with the procedure of Tsikas[27]. In this procedure, MDA was reacted in acidic and heated conditions with thiobarbituric acid (TBA) to produce a pink MDA-TBA complex, which was measured spectrophotometrically at 532 nm. Results were given as nmol/mL.

Evaluation of superoxide dismutase activity

Activity of superoxide dismutase (SOD) was determined according to the procedure of Marklund and Marklund[28]. This is determined by the fact that SOD can prevent the autoxidation of pyrogallol in an alkaline solution. The autoxidation of pyrogallol to reach a colored product was measured by following the absorbance at 440 nm as the test progressed through time (180s). The unit (U) of SOD activity was the quantity of the enzyme that produced a 50% inhibition of the pyrogallol autoxidation under the test condition, and the results were measured as (U/mL).

Evaluation of catalase activity

The Aebi method was used in measuring the catalase (CAT) activity. Triton X-100 was used, and the spectrophotometric determination of the enzyme action liability was attained by measuring the hydrogen peroxide degradation rate at 240 nm [40]. The expression of catalase was in as U/mL

Determination of C-reactive protein level

The serum concentrations of the inflammatory marker C-reactive protein (CRP) were analytically measured using a commercially available ELISA kit (Abcam, USA). The assay was performed according to the manufacturer's instructions to measure CRP as a marker of systemic inflammation adequately.[29]

Histopathological examination

The liver fixed in formalin was subjected to histological processing by the standard protocol procedure of dehydration in a sequence of ethanol grades, clearing in xylene, and embedding in paraffin wax [15]. The microtome was used to cut sections at 5 μm thickness and place them on glass slides. They were then stained using Hematoxylin-Eosin stain (H&E) to view the general morphology of the liver. Histological evaluation was done to evaluate hepatocyte pattern, dilation of the sinusoids, and the central vein, as well as the occurrence of pathological characteristics of hepatocellular necrosis, inflammation, local fibrosis, etc. Photomicrographs of the liver were taken using an Olympus microscope that was fitted with a digital camera.

Statistical analysis

Data was expressed as mean ±standard error of the mean (SEM). One-way ANOVA was used to perform the statistical comparison between groups, followed by the Tukey post hoc test to determine the significant difference. A p-value less than 0.05 was defined as statistically significant. All the analyses were carried out using GraphPad Prism version 10.0 (GraphPad Software LLC, San Diego, CA, USA).

RESULTS

Effects of *Fisetin* and *curcumin* on the weight of the Liver

Figure 2 indicates that the weight of the liver was significantly reduced in the group administered with Arsenic trioxide compared to the control group. However, in groups treated with 100 mg/kg of Fisetin only, 100 mg/kg of curcumin only, 100 mg/kg of Fisetin or 100 mg/kg of curcumin only and in the group treated with 20 mg/kg of Arsenic trioxide before receiving 100 mg/kg of Fisetin or 100 mg/kg of curcumin, the liver weights were found to be significantly higher than those of group B.

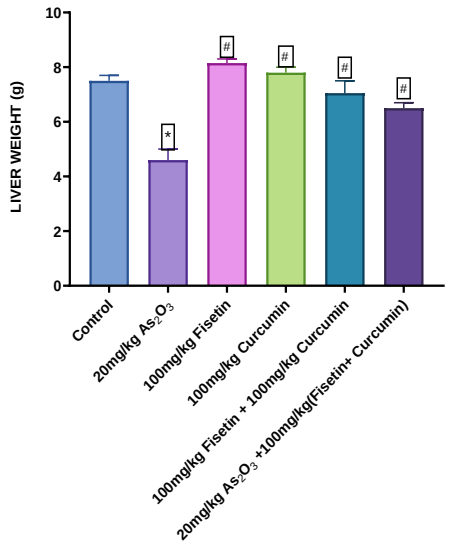

Figure 2: Bar chart showing the effect of Fisetin and curcumin on the weight of the liver in arsenic trioxide-treated animals. The weight of the liver (g) was measured in various experimental groups, namely control, As_2O_3 (20 mg/kg), Fisetin (100 mg/kg), curcumin (100 mg/kg), Fisetin + curcumin (100 mg/kg each), and combination treatment (As_2O_3+ Fisetin + curcumin). (n = 5) Data are expressed as mean +/- SEM (*p < 0.05 vs. control group; #p < 0.05 vs. As_2O_3 group)

Effect of Fisetin and curcumin on antioxidant markers, lipid peroxidation and inflammatory marker

The results in Table 1 show the outcomes of Fisetin and curcumin effects on oxidative Stress and inflammation in Wistar rats. Arsenic trioxide (As_2O_3) exposure had a pronounced effect in increasing the levels of malondialdehyde (MDA) along with reduced activities of superoxide dismutase (SOD) and catalase (CAT), which represented increased lipid peroxidation and diminished antioxidant defense. These changes were abated by the combined treatment with Fisetin and curcumin after arsenic exposure. The groups exposed to curcumin alone, Fisetin alone, and a combination of Fisetin and curcumin showed similar restorative effects to the control group, with reduced levels of MDA and increasing activity of SOD/CAT. These parameters were enhanced with the combination of Fisetin and curcumin, which also indicated the synergistic effect of relieving oxidative stress. Also, C-reactive protein (CRP) concentrations were significantly higher ($P < 0.05$) in the arsenic-treated group and lower after the treatment with Fisetin, curcumin, and in combination. It suggests a decrease in inflammation.

Table 1: Effects of fisetin and curcumin on oxidative stress and inflammation. Values expressed as Mean ± SEM.

GROUPING	MDA (nmol/mL)	SOD (U/mL)	CAT (U/mL)	CRP (mg/L)
A-Control	3.0± 0.16	3.5±0.10	60.0 ±2.50	0.41 ±0.09
B-20 mg/kg (As_2O_3)	5.4 ±0.27*	1.0±0.04*	27.0 ±0.90*	3.8 ±0.77*
C-100 mg/kg Fisetin	2.3± 0.04#	3.0±0.010#	52.5 ± 1.15#	0.75± 0.07#
D-100 mg/kg Curcumin	2.2 ±0.10#	2.8±0.07#	59.6 ±1.40#	0.56±0.23#
E- 100 mg/kg Fisetin +100 mg/kg Curcumin	2.0±0.11#	4.8±0.02#	68.0 ±0.80#	0.64±0.33#
F- 20 mg/kg (As_2O_3) +100 mg/kg Fisetin +100 mg/kg Curcumin	3.2±0.03#	2.1±0.11#	58.03±0.90#	1.4 ±0.02#

MDA = malondialdehyde (µmol/mg protein); SOD = Superoxide Dismutase (U/mL); CAT = Catalase (U/mL); CRP = C-Reactive Protein (mg/L). *indicates significant difference ($P < 0.05$) vs. control group; "#" indicates significant difference ($P < 0.05$) vs. arsenic trioxide-treated group.

Liver histology observation

The control group showed regular hepatic architecture, well-preserved hepatocytes, and the central vein. The livers of rats treated with arsenic trioxide only were characterized by a high level of disorganization, with disorganized hepatocytes, enlargement of sinusoids, and congestion of veins. Fisetin only, curcumin only, or both maintained normal architecture in a similar manner as the controls. Incomplete recovery was observed in the group administered initially with arsenic trioxide and treated with Fisetin and curcumin group; they experienced partial recovery with streamlined lobulation, although hepatocyte necrosis and minimal steatohepatitis were observed.

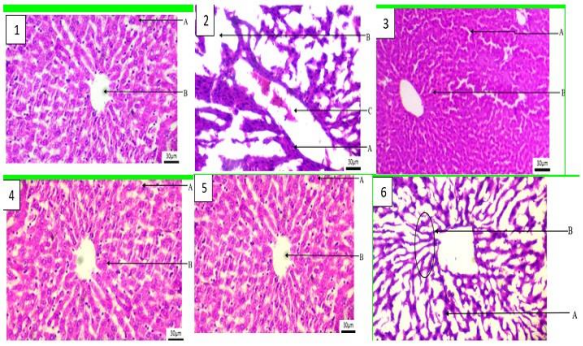

Figure 3 (Plates 1-6): H&E-stained liver histology at magnifications of X400. Plate 1-Control group showing normal liver histoarchitecture, with centrally located veins and evenly distributed hepatocytes indicated as A and B. Plate 2: Distorted liver histology with hepatocytes appearing as disorganized cord-like arrays (A), sinusoidal spaces are enlarged and irregular (B), and congestion in the hepatic veins (C). Plates 3–5: show normal liver architecture, featuring well-distributed

hepatocytes around the central vein (B) and preserved lobular organization (A). Plate 6: shows partial recovery, hepatocytes are radially aligned around the central vein, indicating some restoration of liver architecture; fragmented hepatocytes with mild necrosis are present (B), alongside vacuolated hepatocytes suggestive of fatty changes (A).

DISCUSSION

This study aimed to evaluate the ameliorative role of a combination of Fisetin and curcumin on arsenic trioxide-induced hepatotoxicity by examining oxidative stress markers, inflammatory mediators, liver histopathology, and organ weight. The findings confirm the hepatotoxic effects of arsenic trioxide and underscore the therapeutic potential of Fisetin and curcumin.

The overproduction of reactive oxygen species (ROS), lipid peroxidation, endogenous antioxidant depletion, mitochondrial dysfunction, and pro-inflammatory signaling have been widely attributed to arsenic-induced hepatotoxicity[31]. The combination of these mechanisms results in hepatocellular degeneration, congestion, and inflammatory cell infiltration as observed in earlier research[2,11,12,30,31]. This paradigm is supported by our data, which illustrates that arsenic exposure facilitated oxidative imbalance and structural liver damage, thus validating the multi-faceted toxicity of As_2O_3. Fisetin only, curcumin only, and Fisetin and curcumin in combination groups showed hepatic tissue architecture similar to the control group. This synergistic activity could be due to their complementary antioxidant activity. Our results indicated that exposure to As_2O_3 had significant toxic effects in raising oxidative stress biomarkers like malondialdehyde (MDA), while markedly reducing the activities of key antioxidant enzymes, namely, superoxide dismutase (SOD) and catalase (CAT). The liver weight was significantly reduced in the As_2O_3-treated group compared to the control group, the Fisetin and curcumin-only treated groups. The As_2O_3-exposed group treated with a combination of Fisetin and curcumin also showed improved liver weight and histoarchitecture compared to the As_2O_3-only induced group. This aligns with prior occurrences that arsenic intoxication leads to hepatic swelling and cellular infiltration, which is probably caused by inflammation, congestion, and hepatocellular degeneration[2,11,12,30,31].

Curcumin has been demonstrated to suppress oxidative stress by activating the Nrf2 pathway and subsequent induction of antioxidant enzymes, and Fisetin has powerful free radical scavenging abilities and prevents lipid peroxidation in animal models [6, 32, 33]. Together, these processes might explain the normalization of the activities of superoxide dismutase (SOD) and catalase (CAT), as well as the decreased malondialdehyde (MDA) in the treated groups. Mechanistically, Fisetin and curcumin improve the cellular antioxidant defense system through scavenging free radicals, stimulating endogenous antioxidant enzymes, and inhibiting lipid peroxidation. This redox restoration reduces oxidative stress, which in turn maintains membrane integrity and total hepatocellular performance[17,21].

The increased levels of C-reactive protein (CRP) after arsenic exposure are a biomarker of systemic inflammation, which is an indicator of the acute-phase response in the body. This CRP increase also indicates hepatocellular damage, as the liver is the major site of CRP production and is affected directly by the toxicity of arsenic[6]. Interestingly, the combination of Fisetin and curcumin significantly decreased CRP levels, which aligns with their observed capability to block major inflammatory pathways[19,34]. These phytochemicals suppress inflammatory signaling and, in addition to reducing oxidative damage, disrupt the cascade of tissue injury, thus improving hepatocyte survival.

These biochemical observations are also supported by histopathological findings, which

give direct morphological indication that the liver is damaged. In the group treated with arsenic trioxide alone, there was a high level of severe hepatocellular degeneration, with sharp sinusoidal congestion, vascular congestion, and massive steatosis. Such changes are typical of hepatic injury caused by arsenic, which indicates a loss of cellular integrity, the disruption of vascular organization, and changes in lipid metabolism in the liver tissue. The observation concurs with the findings made by other authors and states that exposure to arsenic trioxide causes significant hepatocellular degeneration, sinusoidal dilatation, vascular congestion, and fatty changes in experimental models [31,35.]

The curcumin and Fisetin only-treated groups showed mostly intact hepatic architecture with well-organized hepatocytes similar to the control group. There was a significant decrease in foci of necrosis in the group administered with arsenic trioxide and treated with a combination of Fisetin and curcumin. Interestingly, the arsenic trioxide plus Fisetin and curcumin group showed partial recovery, with recovered hepatocellular orientation, the enhancement of the vascular integrity, and the reduction of necrosis, even though mild fatty changes remained. This suggests that, although the combination regimen could be effective in offering therapeutic effect on arsenic-induced injury, it might not be able to completely reverse chronic or severe pathological changes, which underscores the restrictions of antioxidant therapy in later stages of toxicity. These findings align with earlier reports on the curative activity of Fisetin and curcumin, which highlight their antioxidant, anti-inflammatory, and anti-apoptotic properties[23,36-39]. However, the persistence of moderate steatosis in the combination-treated group underscores the need for further studies to optimize dosing strategies, duration of treatment, and the potential use of additional protective compounds. The above observation highlights the necessity of further studies that will help to streamline dosing schedules, define the right durations of treatment, and investigate the possibility of using complementary therapeutic agents that could be used to ensure full protection. Future studies should also aim at clarifying the exact molecular targets of Fisetin and curcumin, their pharmacokinetics, bioavailability, and interactions in combination therapy, and the evaluation of their synergistic actions. Notably, clinical studies should be adequately designed to prove their safety and efficacy in human subjects, thus converting preclinical results into actual therapeutic use.

CONCLUSION

This study demonstrates that the combination of curcumin and Fisetin mitigates against arsenic trioxide–induced hepatotoxicity in Wistar rats by improving liver architecture, oxidative stress, inflammation, and liver weight. Co-administration of both Fisetin and curcumin showed synergistic effects, warranting further research to clarify underlying molecular mechanisms and potential clinical relevance.

Conflict of interest: The authors declare that there is no conflict of interest

Author Credit: ECO: conceptualization, methodology, investigation, validation, resources, supervision, manuscript writing, review & editing; **AO**: conceptualization, validation, formal analysis, data curation, manuscript writing, review & editing; **EOS**: method, investigation, manuscript writing, review & editing; **KEN:** manuscript writing; **NMO, OFU**: methodology, investigation, resources, manuscript writing

REFERENCES

1. Chen QY, Costa M. Arsenic: A Global Environmental Challenge. Annu Rev Pharmacol Toxicol. 2021;61:47–63.
2. Fatoki JO, Badmus JA. Arsenic as an environmental and human health antagonist: A review of its toxicity and disease initiation. J Hazard Mater Adv 2022;5 https://doi.org/10.1016/j.hazadv.2022.100052

3. Garkal A, Sarode L, Bangar P, Mehta T, Pratap D, Rawal R. Journal of Hazardous Materials Letters Understanding arsenic toxicity: Implications for environmental exposure and human health. J Hazard Mater Lett. 2024;5. https://doi.org/10.1016/j.hazl.2023.100090
4. Ganie SY, Javaid D, Hajam YA, Reshi MS. Arsenic toxicity: sources, pathophysiology, and mechanism. 2024;1–20.
5. Yang Y, Li Y, Li R, Wang Z. Research progress on arsenic, arsenic-containing medicinal materials, and arsenic-containing preparations: clinical application, pharmacological effects, and toxicity. Frontiers in Pharmacology. 2024:1;15:1338725.
6. Oviosun E. C., Oviosun A., Shelu E. O., Olugbenga M. A., Abiodun B. O. Antioxidative and Anti-inflammatory Effects of Fisetin and Curcumin on Sodium Arsenite-Induced Pancreatic Toxicity. J Exp Clin Anat 2025;22(2):402-411. https://dx.doi.org/10.4314/jeca.v22i2.28
7. Shaji E, Santosh M, Sarath KV, Prakash P, Deepch V, Divya BV. Arsenic contamination of groundwater: A global synopsis with focus on the Indian Peninsula. Geosci Front. 2021;12(3):101079. https://doi.org/10.1016/j.gsf.2020.08.015
8. Verma SK, Chaurasia S. Implicating the effects of consuming water with a high level of arsenic content: highlighting the cause and consequences of arsenic contamination in drinking water. Water Pract Technol. 2024;19(4):1071–83.
9. Chaudhary MM, Hussain S, Du C, Conway BR, Ghori MU. Arsenic in Water: Understanding the Chemistry, Health Implications, Quantification and Removal Strategies. ChemEngineering. 2024;8(4).
10. Ramadan O, Abuamara T, Taha R, Awad M, Mohammed M, Omar N, *et al*. Alleviation of the arsenic-induced hepatotoxicity in rats by ginger or omega-3: a histological and biochemical study. Bioact Compd Heal Dis. 2024;7(4):221–32.
11. Oyagbemi AA, Omobowale TO, Asenuga ER, Afolabi JM, Adejumobi OA, Adedapo AA, *et al*. Effect of arsenic acid withdrawal on hepatotoxicity and disruption of erythrocyte antioxidant defense system. Toxicol Reports. 2017;4:521–9. https://doi.org/10.1016/j.toxrep.2017.09.006
12. Ijaz MU, Ahmed A, Al-Ghanim KA, Al-Misned F, Riaz MN, Kaimkhani ZA, Mahboob S. Evaluation of the possible protective role of nobiletin against arsenic-induced liver damage in male albino rats. Toxics. 2023;24;11(2):110.
13. Oviosun A, Oviosun EC, Nto NJ, Memudu AE, Anyanwu EG. Zingerone Attenuates Cadmium-Induced Neuroinflammation, Oxidative Stress, and Cognitive Deficit on the Prefrontal Cortex of Adult Wistar Rats. Journal of Experimental Pharmacology. 2025; 31:323-41.
14. Oviosun EC, Oviosun A, Nto NJ, Okwara BO, Anyanwu EG. Hesperidin Protects Against Bisphenol-A-Induced Renal Damage in Adult Male Wistar Rats. Tropical Journal of Natural Product Research. 2025;1;9(6).
15. Emeka AG, Augustine O, Chidinma OE, Nto NJ. Zingerone improves memory impairment in Wistar rats exposed to cadmium via modulation of redox imbalance. J Krishna Inst Med Sci Univ. 2023;12(1):3–16.
16. Kim DU, Kweon B, Oh JY, Noh GR, Lim Y, Yu J, *et al*. Curcumin ameliorates cerulein-induced chronic pancreatitis through Nrf2-2/HO-1 signaling. Molecular Medicine Reports. 2025;26;31(5):136.
17 Jiang K, Yang J, Xue G, Dai A, Wu H. Fisetin ameliorates the inflammation and oxidative stress in lipopolysaccharide-induced endometritis. Journal of Inflammation Research. 2021;5:2963-78.

18. Rasal PB, Kasar GN, Punekar AD, Nagare MB, Shinde VS, Gayake AU. Fisetin : From Dietary Source to Therapeutic Possibilities. 2025;9(4):84–103.
19. Telrandhe UB, Hasnain AN, Kothawade SN, Telange DR. Recent advancement of Fisetin-based nanoformulations in the management of psoriasis. Discover Nano. 2025; 7;20(1):105.
20. Cheng M, Ding F, Li L, Dai C, Sun X, Xu J, *et al*. Exploring the role of curcumin in mitigating oxidative stress to alleviate lipid metabolism disorders. Frontiers in Pharmacology. 2025; 30;16:1517174.
21. Alhusaini A, Fadda L, Hasan IH, Zakaria E, Alenazi AM, Mahmoud AM. Curcumin ameliorates lead-induced hepatotoxicity by suppressing oxidative stress and inflammation, and modulating the Akt/gsk-3β signaling pathway. Biomolecules. 2019;9(11).
22. Park JH, Lee BM, Kim HS. Potential protective roles of curcumin against cadmium-induced toxicity and oxidative stress. J Toxicol Environ Heal - Part B Crit Rev 2021;24(3):95–118. Available from: https://doi.org/10.1080/10937404.2020.1860842
23. Gao S, Duan X, Wang X, Dong D, Liu D, Li X, *et al*. Curcumin attenuates arsenic-induced hepatic injuries and oxidative stress in experimental mice through activation of the Nrf2 pathway, promotion of arsenic methylation, and urinary excretion. Food Chem Toxicol 2013;59:739–47. Available from: http://dx.doi.org/10.1016/j.fct.2013.07.032
24. Charles CA. Effect of arsenic trioxide poisoning on hematological parameters, liver marker enzymes, and the kidney of male albino rats. Pinnacle Biological Sciences. 2014;2(2):262-5.
25. Ghelani H, Razmovski-Naumovski V, Chang D, Nammi S. Chronic treatment of curcumin improves hepatic lipid metabolism and alleviates the renal damage in adenine-induced chronic kidney disease in Sprague-Dawley rats. BMC Nephrology. 2019. 21;20(1):431.
26. Kayali A, Bora ES, Acar H, Yilmaz G, Erbaş O. Fisetin ameliorates methotrexate induced liver fibrosis. European Review for Medical & Pharmacological Sciences. 2024;15;28(8).
27. Tsikas D. Assessment of lipid peroxidation by measuring malondialdehyde (MDA) and relatives in biological samples: Analytical and biological challenges. Anal Biochem. 2017;524:13–30. http://dx.doi.org/10.1016/j.ab.2016.10.021
28. Marklund S, Marklund G. Involvement of the Superoxide Anion Radical in the Autoxidation of Pyrogallol and a Convenient Assay for Superoxide Dismutase. 1974; 474:469–74.
29. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. 2003;111(12):1805–12.
30. Zhao JW, Zhao WY, Zhao M, Yu L. Functional foods and bioactive compounds: a comprehensive review on their role in mitigating drug-induced liver injury. Frontiers in Nutrition. 2025; 21;11:1499697.
31. Wen J, Li A, Wang Z, Guo X, Zhang G, Litzow MR, *et al*. Hepatotoxicity induced by arsenic trioxide: clinical features, mechanisms, preventive and potential therapeutic strategies. Front Pharmacol. 2025;16:1–13.
32. Ghafouri-Fard S, Shoorei H, Bahroudi Z, Hussen BM, Talebi SF, Taheri M, *et al*. Nrf2-Related Therapeutic Effects of Curcumin in Different Disorders. Biomolecules. 2022;12(1):1–15.
33. Zhang J, Sun X, Chai X, Jiao Y, Sun J, Wang S, *et al*. Curcumin Mitigates Oxidative Damage in Broiler Liver and Ileum Caused by Aflatoxin B1-Contaminated Feed through Nrf2 Signaling Pathway. Animals. 2024;14(3).

34. Hu P, Li K, Peng X xu, Kan Y, Yao T jia. Curcumin derived from medicinal homologous foods: its main signals in immunoregulation of oxidative stress, inflammation, and apoptosis. 2023;1–7.
35. Ling S, Shan Q, Liu P, Feng T, Zhang X, Xiang P, *et al*. Metformin ameliorates arsenic trioxide hepatotoxicity via inhibiting mitochondrial complex I. Cell death & disease. 2017;8(11):e3159-.
36. El Shaer DF, El Halim HIA. The Possible Ameliorating Role of Fisetin on Hepatic Changes Induced by Fluoxetine in Adult Male Albino Rats: Histological, Immunohistochemical, and Biochemical Study. J Microsc Ultrastruct. 2023;11(3):161–71.
37. Ugan RA, Cadirci E, Un H, Cinar I, Gurbuz MA. Fisetin Attenuates Paracetamol-Induced Hepatotoxicity by Regulating CYP2E1 Enzyme. An Acad Bras Cienc. 2023;95(2):1–11.
38. Vasanthkumar T, Hanumanthappa M, Hanumanthappa SK. Hepatoprotective effect of curcumin and capsaicin against lipopolysaccharide-induced liver damage in mice. Pharmacogn J. 2014;9(6):947–51.
39. Damiano S, Longobardi C, Andretta E, Prisco F, Piegari G, Squillacioti C, *et al*. Antioxidative effects of curcumin on the hepatotoxicity induced by ochratoxin A in rats. Antioxidants. 2021;10(1):1–12.
40. Aebi H. Catalase in vitro. In Methods in Enzymology. Academic Press. 1984 ;(105)121-126).