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ORIGINAL ARTICLE

EVALUATION OF *SYZYGIUM ALTERNIFOLIUM* EXTRACT IN RESTORING ANTIOXIDANT ENZYMES AND PREVENTING LEAD-INDUCED HEPATOTOXICITY IN RATS

D. Veera Nagendra Kumar[1], K. Manimekalai[2], V. Madan Mohan Rao[3], Kanchan Chatterjee[4], Obaiah Jamakala[5] and Sanjay Dey[6]*

[1]Division of Animal Physiology and Ethnopharmacology, Department of Zoology, Government College for Men (Autonomous), Kadapa - 516 004, India.
[2]PG and Research Department of Biotechnology, Kongunadu Arts and Science College, Coimbatore - 641 029, India.
[3]Department of Botany, Government Degree College, Chintalapudi - 534 460, India.
[4]Department of Zoology, Devbhoomi Uttarakhand University - 248 007, India.
[5]Division of Environmental Toxicology and Animal Physiology, Department of Zoology, Sri Venkateswara College, University of Delhi, New Delhi – 110 021, India.
[6]Department of Zoology, Ananda Mohan College, Kolkata - 700 009, India.
*Corresponding author e-mail : sanjay.zoology@anandamohancollege.ac.in; ORCID: https://orcid.org/0000-0003-3874-7188

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ABSTRACT : Lead is a toxic metal that induces a wide range of behavioral, biochemical and physiological effects in humans. Oxidative damage has been proposed as a possible mechanism involved in lead toxicity. The current study was carried out to evaluate the antioxidant activities of *Syzygium alternifolium* supplement against lead acetate -induced hepatic injury in rats. A total of 24 male Wistar albino rats (n=6) were split into four groups at random. To create oxidative stress, Group II was exposed to lead acetate (50 mg/kg b.wt.) for 28 days, while Group I acted as the control. Group III received a 14-day pretreatment with *Syzygium alternifolium* leaf extract (SA. T, 200 mg/kg b.wt.) and then 14 days of lead exposure. Group IV received SA. T and lead acetate at the same time for 28 days. Following treatment, liver samples were taken for histopathological analysis and biochemical assessment of SOD, CAT, GPx, MDA and MDA. In this study, we observed antioxidant enzymes activity decreased in lead induced rats and raised hepatic MDA levels. Compared to the lead-treated group, SALE pretreatment and concurrent treatment successfully restored the antioxidant enzyme activities and decreased MDA levels. Histopathological findings showed that SALE reduced necrotic and degenerative alterations while maintaining the cellular architecture of the liver. SALE's phytoconstituents, which have strong antioxidant and free radical scavenging properties, may be responsible for the hepatoprotective effects that have been observed. SALE supported endogenous defense mechanisms and mitigated the harmful effects of lead on hepatic tissue by regulating oxidative balance and preserving redox homeostasis. Rats exposed to lead-induced oxidative stress show notable hepatoprotective and antioxidant potential when using leaf extract from *Syzygium alternifolium*. It showed promise as a natural therapeutic agent for heavy metal-induced liver toxicity by restoring enzymatic activities, preventing lipid peroxidation and maintaining liver histoarchitecture.

Key words : *Syzygium alternifolium*, lead acetate, oxidative stress, antioxidants, hepatoprotection.

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INTRODUCTION

The liver is an essential organ that is crucial for maintaining biochemical homeostasis, metabolizing fats and carbohydrates and detoxifying xenobiotics (Dai *et al*, 2015). Its vital role in metabolic and detoxification processes makes it extremely susceptible to harm from drugs, heavy metals, and environmental pollutants. Lead (Pb) is one of the most common environmental contaminants and a serious hazard to the health of people and animals (Eivani *et al*, 2023; Bonfanti *et al*, 2013; El-Saber Batiha *et al,* 2020). Prolonged exposure to lead causes oxidative stress by encouraging the overproduction of reactive oxygen species (ROS), which harm proteins, membrane lipids and DNA, impairing liver function and causing hepatocellular damage (Ekhator *et al*, 2022). One of the main mechanisms underlying lead-induced hepatic

toxicity is the imbalance between oxidant generation and antioxidant defense (El-Desoky *et al*, 2022). Lead tends to build up in metabolically active organs like the brain, liver and kidneys (Elgazar *et al,* 2023; Abdelmuhsin *et al,* 2025). There, it interferes with the regular functions of important antioxidant enzymes like glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD). Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP), three hepatic marker enzymes that indicate liver cell damage and functional decline, are released into the bloodstream as a result of this enzymatic inhibition, which also raises lipid peroxidation (El-Rahman, *et al*, 2019).

Although lead poisoning can be treated with a variety of chelating agents, their therapeutic uses are frequently constrained by side effects and their inability to effectively restore oxidative balance (Swami *et al,* 2012; Al-Mzaien *et al,* 2015). In order to effectively scavenge free radicals, strengthen endogenous antioxidant systems and shield hepatic tissue from oxidative damage, there is increasing interest in investigating natural antioxidants derived from medicinal plants (Thuong *et al,* 2023).

Bioactive phytochemicals with strong antioxidant and hepatoprotective properties, including polyphenols, flavonoids, tannins and terpenoids, are abundant in medicinal plants (Uthra *et al,* 2022; Ruan *et al*, 2008). *Syzygium cumini*, *Syzygium aromaticum* and *Syzygium alternifolium* are among the species in the genus Syzygium (family Myrtaceae) that are well-known for their pharmacological characteristics (Aldahmash *et al,* 2014; Obidike *et al*, 2010). Folk medicine has long utilized Syzygium alternifolium, an endemic tree species of India's Eastern Ghats, to treat conditions like diabetes, inflammation and microbial infections (Pratap and Indira, 2014; Mesure *et al,* 2015). Phenolic compounds, flavonoids and anthocyanins—phytochemicals known for their potent antioxidant and free radical-scavenging properties—are especially abundant in its fruits (Afify *et al*, 2011).

The hepatoprotective and antioxidant potential of *Syzygium alternifolium* fruit extract against oxidative damage caused by heavy metals is still not fully investigated, despite its rich phytochemical composition (Banerjee *et al,* 2009; Alsirhani *et al*, 2024). Thus, the current study intends to assess the protective effect of Syzygium alternifolium extract (SALE) on oxidative stress and the regulation of antioxidant enzyme activities in the liver of albino rats that have been exposed to lead. The study's main objectives are to evaluate histopathological changes in hepatic tissue, changes in antioxidant enzyme status and changes in oxidative stress markers (Suradkar *et al*, 2010). The results should shed important light on Syzygium alternifolium's potential as a natural antioxidant and hepatoprotective agent to treat lead-induced liver damage (Aziz, 2012; Zhang *et al,* 2016; Pandey *et al,* 2025).

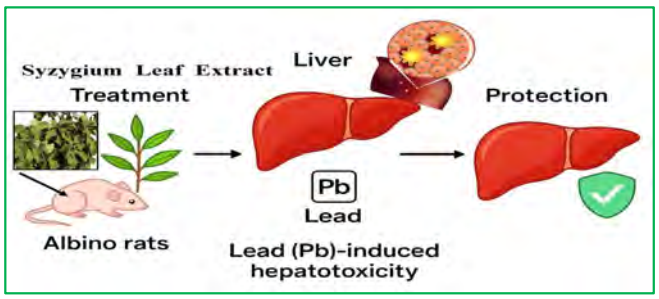


Fig. 1 : Graphical representation of Syzygium leaf extract against Pb induced in liver toxicity.

MATERIALS AND METHODS

Chemicals

All chemicals utilized in the current study were of analar grade (AR) and sourced from reputable companies including Sigma (St. Louis, MO, USA), Fisher (Pittsburgh, PA, USA), Merck (Mumbai, India), Ranbaxy (New Delhi, India) and Qualigens (Mumbai, India).

Collection and preparation of Plant material

Fresh *Syzygium alternifolium* leaves had been collected from Yogi Vemana University's Botanical Garden in Kadapa and the Herbarium Officer of the Department of Botany at S.V. University in Tirupati identified them. After being cleaned and allowed to dry in the shade at room temperature, the leaves were ground into a fine powder. Four iterations of the extraction procedure were conducted using 100 g of the powder and cold water for duration of 24 hours. Using a rotary evaporator, the combined extracts were concentrated at lower pressure after being filtered through muslin cloth. About 12.09 ± 1.59 g (n = 6) was the final extract after air drying.

Experimental animals

An approved animal breeding facility provided the healthy adult male albino rats (*Rattus norvegicus*), weighing 180±20 g. Under standard laboratory conditions, the animals were kept in polypropylene cages with a 12-hour light/dark cycle, a temperature of 25 ± 2°C, and a relative humidity of 60 ± 5%. They were given unlimited water and a typical pellet diet. In compliance with the regulations set forth by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA, 2003), Government of India, all experimental protocols were authorized by the Institutional Animal

Ethics Committee (IAEC). The Institutional Animal Ethics Committee approved the protocol.

Experimental design

Four groups (n = 6 each) of 24 rats were randomly assigned to the following groups: Group I (Control), Group II (Pb-I), Group III (SA-T) and Group IV (Pb-I + SA-T, Protective group). Group II rats were given drinking water containing lead acetate (50 mg/kg/day), while control rats were given unlimited access to regular tap water. According to Reshma Anjum and Reddy's (2013) protocol, Group IV received both Pb and extract treatments, while Group III received *Syzygium alternifolium* extract orally at a dose of 200 mg/kg/day. Every animal was given unlimited access to food and water, and daily behavioral evaluations were conducted at 8:00 a.m.

Biochemical analyses

After undergoing a 28 days treatment, the animals were euthanized by cervical dislocation. The liver tissue was then extracted at a temperature of 4°C. Subsequently, the tissue was rinsed with ice-cold saline solution. It was then submerged in liquid nitrogen and promptly stored in a deep freezer at a temperature of -80°C in order to facilitate subsequent biochemical analysis. The activity of superoxide dismutase (SOD) was measured in tissue homogenates using the method of Misra and Fridovich (1972) on a Hitachi U-2000 spectrophotometer. The absorbance was measured at 480 nm for 4 minutes. The activity of SOD was expressed as the amount of enzyme needed to inhibit the oxidation of epinephrine by 50%, which is equal to 1 unit (U) per milligram of protein. The activity of catalase (CAT) was determined at room temperature using the method of Aebi (1984). The absorbance of the sample was measured at 240 nm for 1 minute using a spectrophotometer. The glutathione peroxidase (GPx) activity was determined using the method of Flohe and Gunzler (1984). NADPH was used in the presence of cumene hydrogen peroxide, and the absorbance was measured at 340 nm. The concentration of reduced glutathione (GSH) in liver homogenates was measured using the method described by Aker boom and Sies (1981). The MDA levels measured by Ohkawa *et al* (1979). All enzyme activities were expressed as per milligram of protein, and the tissue protein concentration was estimated using the method of Lowry, Rosebrough, Farr and Randall (1951) with bovine serum albumin (BSA) as a standard.

Histopathological examination

After being preserved for 48 hours in 10% neutral buffered formalin, the liver tissues were dehydrated in graded ethanol, cleaned in xylene, and then embedded in paraffin wax. Hematoxylin and eosin (H&E) was used to stain the 5 ìm-thick sections, which were then viewed under a light microscope to check for histopathological changes like vacuolation, inflammatory infiltration, and hepatocellular necrosis.

Statistical analysis

All results were expressed as mean ± standard error of mean (SEM). Statistical comparisons between groups were performed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. Differences were considered statistically significant at $p < 0.05$. Data analysis was performed using Graph Pad Prism software (version 9.0).

RESULTS

Effect of *Syzygium alternifolium* Ethanolic extract on antioxidant enzyme status in lead induced rats

Significant decreases in SOD, CAT, GPx, activities and GSH content were observed in the lead induced rats compared with normal control rats. Lead induced rats with *Syzygium alternifolium* Extract treatment, showed significant ($p < 0.05$) increases antioxidant enzymes which reflects restoration of the antioxidant enzyme systems to near-normal values. The extract's time-dependent protective efficacy against lead-induced oxidative stress in hepatic tissues was confirmed by the

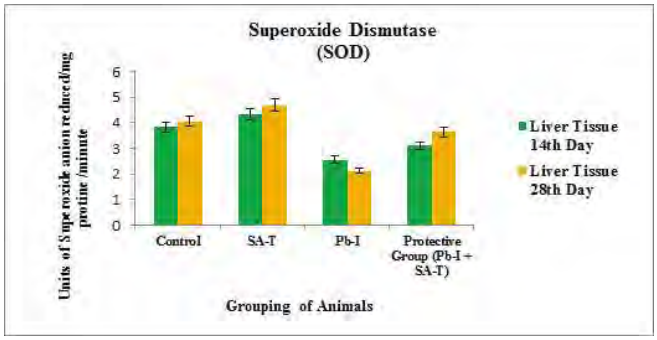


Fig. 2 : Effect of *Syzygium alternifolium* extract on Superoxide Dismutase (SOD) activity in Lead-treated rat liver.

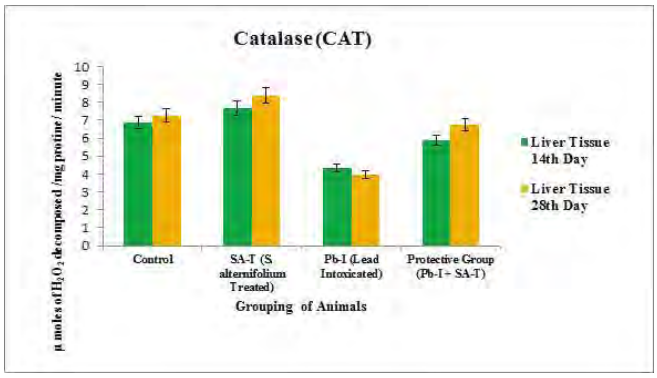


Fig. 3 : Effect of *Syzygium alternifolium* Extract on Catalase (CAT) activity in Lead-treated rat liver.

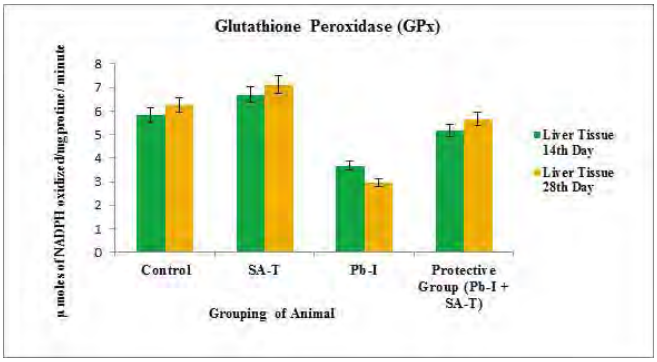


Fig. 4 : Effect of *Syzygium alternifolium* extract on Glutathione Peroxidase (GPx) activity in Lead-treated rat liver.

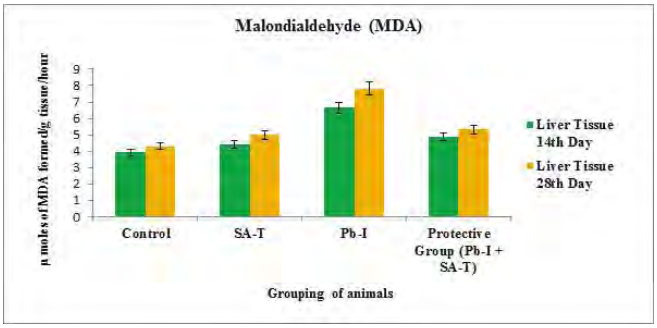


Fig. 6 : Effect of *Syzygium alternifolium* on Hepatic MDA levels in Lead-exposed rats.

notable recovery effects seen in the 28th-day measurements compared to the 14th-day observations. (Figs. 2-5).

Effect of *Syzygium alternifolium* Ethanolic extract on MDA levels in lead induced rats

In this study, we observed MDA levels were

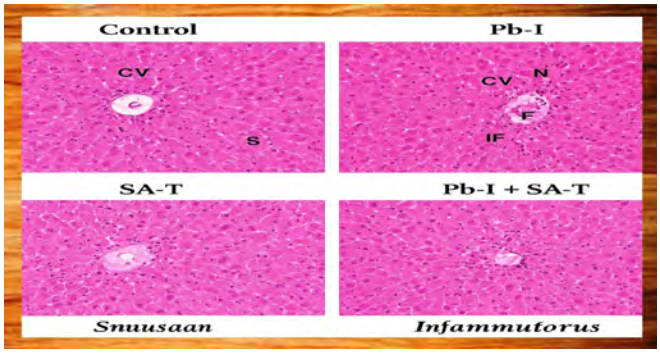


Fig. 7 : Histopathological observations of liver tissue from control and experimental rats (H&E stain, 40×).(A) Control group: Shows normal hepatic architecture with well-organized hepatocytes (H) radiating from the central vein (CV) and intact sinusoids (S). (B) Lead-intoxicated (Pb-I) group: Exhibits hepatic degeneration with necrotic cells (N), cytoplasmic vacuolation, and inflammatory foci (IF) around the central vein. (C) *Syzygium alternifolium*-treated (SA-T) group: Displays nearly normal hepatocytes with mild vacuolar changes and preserved sinusoidal structure. (D) Protective (Pb-I + SA-T) group: Shows almost normal hepatic architecture with restored sinusoids (S), active Kupffer cells (K) and reduced necrosis, indicating the hepatoprotective efficacy of *S. alternifolium* extract.

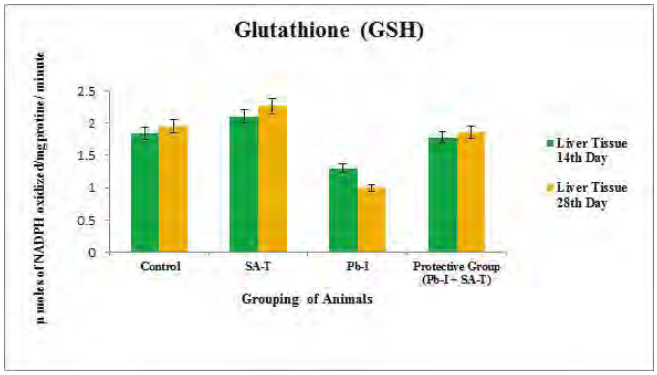


Fig. 5 : Effect of *Syzygium alternifolium* extract on Reduced Glutathione (GSH) levels in Lead-treated rat liver.

Significant ($p < 0.05$) increase in lead induced rats. When *Syzygium alternifolium* was administered to lead toxicity rats, MDA levels significantly decreased indicating that the MDA levels has been restored that are close to normal (Figs. 6).

DISCUSSION

The liver is considered one of the target organs affected by lead toxicity owing to its storage in the liver after lead exposure. Also, the liver being one of the major organs involved in the storage, biotransformation and detoxification of toxic substances, is of interest in heavy metal poisoning (Ohkawa *et al*, 1979). The present study was planned to investigate the hepatoprotective effects of *Syzygium alternifolium* supplement against lead-induced hepatic injury in rats.

The current study found that the lead-exposed group (Pb-I) had significantly lower hepatic SOD activity ($p < 0.05$) than the controls, confirming that lead-induced oxidative stress suppresses the enzymatic antioxidant defense system. Lead acetate is known to cause free radical damage in tissues by two mechanisms: Increased generation of ROS, including hydroperoxides, singlet oxygen and hydrogen peroxides and by causing direct depletion of antioxidant reserves (Ercal *et al*, 2001). While the extract-alone group (SA-T) demonstrated somewhat higher activity than controls, indicating intrinsic antioxidant potential, treatment with *Syzygium alternifolium* extract (Pb-I + SA-T) significantly restored SOD activity toward normal levels. Day 28 saw a greater recovery, suggesting a time-dependent protective response. These results are consistent with past research demonstrating that heavy metals, such as lead, damage SOD by attaching to its metal cofactors or preventing the synthesis of new enzymes (Patra *et al,* 2011; Abd Elghaffar *et al*, 2015). Thus, the current results significant SOD suppression in Pb-I rats and its time-dependent restoration by *Syzygium alternifolium* strongly imply that the extract provides hepatoprotective antioxidant effects by increasing or

stabilizing SOD activity. The phenolic compounds present in different parts of a plant contain hydroxyls that are responsible for the radical scavenging redox properties (Ratnam *et al*, 2015).

The study found that the lead-exposed group (Pb-I) had significantly lower hepatic catalase (CAT) activity ($p < 0.05$), confirming that oxidative stress impairs hydrogen peroxide detoxification. Lead is known to decrease CAT activity by interfering with iron utilization and heme biosynthesis (Wang *et al*, 2013). Conde de la Rosa *et al* (2022) reported similar CAT suppression in oxidative liver injury. *Syzygium alternifolium* (SA-T) treatment significantly increased CAT activity, with the improvement being more pronounced on day 28, suggesting a time-dependent effect. Furthermore, Melekh *et al* (2017) showed that phytochemicals such as phenolic compounds and flavonoids can improve CAT in stressful situations, bolstering hepatoprotective function of *Syzygium alternifolium*.

The lead-exposed group (Pb-I) in this study had significantly lower hepatic glutathione peroxidase (GPx) activity ($p < 0.05$), suggesting oxidative stress and depletion of this selenium-dependent enzyme. Hydroperoxide detoxification is hampered by lead exposure, which is known to counteract selenium uptake and inhibit GPx synthesis (Wang *et al,* 2013). Several hepatotoxicity models involving drugs and heavy metals have shown similar GPx suppression (Patra *et al,* 2011; Ali Riza *et al,* 2006). While co-treatment (Pb-I + SA-T) significantly restored activity toward normal, with stronger effects by day 28, treatment with *Syzygium alternifolium* extract (SA-T) alone increased GPx levels. *S. alternifolium* extract thus seems to strengthen hepatic redox defense mechanisms and improve GPx restoration. Significant oxidative stress and thiol reserve depletion were indicated by the Pb-I group's significantly lower hepatic reduced glutathione (GSH) levels. The intrinsic antioxidant capacity of SA-T was demonstrated by the increased GSH levels in the SA-T alone group. GSH was considerably brought back to normal levels by co-treatment (Pb-I + SA-T), especially on day 28, indicating hepatoprotective action through improved redox balance. According to similar research, lipid peroxidation and enzyme suppression are highly correlated with GSH depletion (Park *et al,* 2023; Allameh *et al*, 2023).

In the present study, there was significant increase of MDA levels indicating that lead toxicity causes oxidative membrane damage and lipid peroxidation. Our results are in agreement with other previous studies (Newairy *et al*, 2009). Lead is known to produce oxidative damage by enhancing peroxidation of membrane lipids, and LPO is a deleterious process carried out solely by free radicals. In fact, LPO is an outcome of the chain of events involving initiation, propagation, and termination reactions (Halliwell., 1996). Lipid peroxidation, a reactive oxygen species mediated mechanism, has been implicated in the pathogenesis of various liver injuries and subsequent liver fibrogenesis in experimental animals and humans. Unchecked peroxidative decomposition of membrane lipids is catastrophic for living systems. The lipid peroxides produced are degraded into a variety of products, including alkanals, hydroxyl alkanals, ketones and alkenes. All these products inactivate cell constituents by oxidation or cause oxidative stress by undergoing radical chain reactions ultimately leading to loss of membrane integrity. LPO can also adversely affect the function of membrane bound proteins, such as enzymes and receptors (Niemela *et al*, 1994). However, in our study, we found that administering *Syzygium alternifolium* extract to the lead-exposed rats resulted in a reduction of MDA levels in liver homogenates. A previous study demonstrated that the *Syzygium alternifolium* extract decrease oxidative stress in lead treated rats, as shown by the decrease in levels of TBARS (Pratap Mannem, 2014).

Lead exposure resulted in significant cellular changes, such as hepatocellular necrosis, cytoplasmic vacuolation, sinusoidal dilatation, and inflammatory infiltration—all of which are indicative of oxidative hepatotoxicity, according to histopathological analysis of liver tissues. Lead-intoxicated rodents have also been shown to exhibit similar hepatic lesions, confirming structural disruption brought on by lipid peroxidation and ROS production (Sivakumar *et al*, 2020; Al-Ghamdi *et al*, 2022). *Syzygium alternifolium*-treated groups, on the other hand, showed reduced necrosis and near-normal hepatic architecture with well-preserved hepatocytes, demonstrating the extract's histoprotective and antioxidant effectiveness (Rao *et al*, 2023).

To the best of our knowledge, this study is the first report of *Syzygium alternifolium* effectiveness against lead-induced toxicity. A possible mechanism could be due to the effect of various phytochemicals found within *Syzygium alternifolium* (Ratnam *et al*, 2015). For example, flavonoids could retain their heavy-metal binding activity and act as chelating agents that neutralize the lead toxicity. (Adhikari *et al*, 2018). This fact could reduce ROS and other free-radical-induced oxidative stress and inflammation during lead exposure in the cells. Flavonoids also retain their antioxidant and anti-inflammation properties after lead chelation resulting in even more health benefits. Since significant oxidative stress is generated due to cellular lead exposure, an exogenously

supplied chelator with sustainable antioxidant activity and a low cost, like *Syzygium alternifolium* could be a promising agent for treating lead-induced diseases

CONCLUSION

This study clearly shows that exposure to lead results in severe oxidative stress and damage to liver cells, as evidenced by decreased antioxidant enzyme activity and elevated lipid peroxidation. While *Syzygium alternifolium* extract alone demonstrated strong inherent antioxidant potential, treatment with the extract significantly restored antioxidant levels and decreased oxidative injury in a time-dependent manner. These findings were corroborated by histopathological analysis, which showed that the groups treated with extract had liver structures that were almost normal and showed less inflammation and necrosis. In general Strong hepatoprotective and antioxidant properties of *Syzygium alternifolium* point to its potential as a natural treatment for liver damage brought on by heavy metals.

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