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Ameliorative Role of Curcumin and Ascorbic Acid on Alterations in Marker Enzymes and Oxidative Stress in the Liver of Albino Rats Caused due to Heavy Metals in Water

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Abstract

The male albino rats were exposed to a combination of variable doses of arsenic, cadmium, and lead through drinking water, with or without pre-treatment with a combination of curcumin and ascorbic acid in variable doses for 90 days. The activity of liver marker enzymes, i.e., acid phosphatases, alkaline phosphatases, alanine aminotransferases, and aspartate aminotransferases in plasma was observed to be significantly high in heavy metals-treated rats. However, groups receiving curcumin and ascorbic acid showed non-significant variations in enzyme activities, with the most notable improvement observed in rats exposed to low doses of heavy metals and high doses of the antioxidants. The oxidative stress markers revealed that malondialdehyde levels were significantly increased in heavy metal-treated rats, while the activities of antioxidant enzymes, such as superoxide dismutase and catalase, were significantly decreased. The rats treated with a combination of low doses of heavy metals and high doses of curcumin and ascorbic acid exhibited non-significant variations in oxidative stress parameters compared to the control group. These findings suggest that the combination of curcumin and ascorbic acid provides protection up to some extent against liver alterations caused by a combination of heavy metals above permissible limits in drinking water.

Key words: Ascorbic acid, Curcumin, Drinking water, Heavy metals, Human health, Oxidative stress, Reactive oxygen species (ROS), Albino Rats

Introduction

Heavy metals are well recognized for their toxicity and pose human health risks depending on their concentration, period of exposure, and route of exposure. The various heavy metals such as arsenic (As), cadmium (Cd), chromium (Cr), cobalt (Co), copper (Cu), iron (Fe), lead (Pb), manganese (Mn), mercury (Hg), nickel (Ni), selenium (Se), and zinc (Zn) result in chronic and acute toxicities and the humans are exposed to these heavy metals through various sources including drinking water (Lubal, 2024). The excessive use of fertilizers in agriculture and rapid industrialization are responsible for causing heavy metal pollution of the aquatic environment around the world. The concentrations of different heavy metals in drinking water are higher than international guideline values in many parts of the world (Kumar *et al.*, 2019). Drinking water contaminated with heavy metals increases illnesses, skin disorders, cancer, and even deaths (Maria *et al.,* 2012). Heavy metals such as Arsenic lead to reproductive issues, chromosomal as well as DNA damage, and cause cancers of the renal, respiratory, and digestive systems. Cadmium affects kidneys and foetal development. Lead causes anaemia, infertility, and organ damage and is particularly harmful to children, causing developmental issues and learning disabilities (Sharma and Sharma, 2022).

The major role of the liver is to detoxify the body by the clearance and transformation of harmful chemicals. The various chemicals, like heavy metals as well as their metabolites, cause injuries to the liver and result in hepatotoxicity (Navarro and Senior, 2006). The effect of long-term exposure to a mixture of As, Cd, and Pb at low doses produced hepatotoxic effects in albino rats (Bhattacharjee *et al.,* 2016). Liver enzymes, such as aspartate aminotransferase (AST), alanine

aminotransferase (ALT), Alkaline phosphatase (ALP), and Acid phosphatase (ACP) are the most sensitive indicators of hepatocyte injury and are normally present in low concentrations. However, with cellular injury or changes in cell membrane permeability, these enzymes leak into circulation and the level of these enzymes is raised in blood (Jeschke, 2009). The heavy metals are causing the overproduction of free radicals in the form of reactive oxygen species (ROS) which are the end-products of many degenerative reactions in various tissues resulting in oxidative stress and cellular damage as these are highly reactive to membrane lipids, proteins, DNA and consequently enhancing lipid peroxidation, decreasing the saturated fatty acids, increasing the unsaturated fatty acid contents of membranes suppressing activities of antioxidant enzymes.

Antioxidants have the potential to scavenge free radicals and are thus capable of providing a defence mechanism in the body. The antioxidants protect the membranes from oxidative damage by influencing characteristics like fluidity, stability, and susceptibility. Curcumin is a perennial herb of the ginger family and a natural polyphenol found in the rhizome of *Curcuma longa* (turmeric), which is cultivated in India, China, Indonesia, and other tropical countries (Lim, 2016). Curcumin is a dietary element, easily available, a well-known herb for its therapeutic uses, which has antioxidant, anti-inflammatory, and anti-tumorous potential. Ascorbic acid, also known as vitamin C, has the therapeutic role as an antioxidant that provides protection against oxidative stress caused due to heavy metals by maintaining the level of antioxidant enzymes (Shaukat *et al.,* 2018). Recently, Kaur *et al.* (2024) reported that curcumin and ascorbic acid showed restoration of histological damage and content of biochemical components in the liver of albino rats exposed to a mixture of heavy metals (As, Cd, and Pb) in drinking water.

The objective of the present study was to access the ameliorative potential of curcumin and ascorbic acid combination in variable doses on liver marker enzyme abnormalities and oxidative stress in male albino rats caused by a combination of heavy metals (As, Cd, Pb) at higher and variable doses than the Maximum Permissible Limit of Bureau of Indian Standards (BIS) in drinking water.

Materials and Methods

Treatment of rats

The sexually mature male albino rats weighing 100-150 g were procured from the Disease-Free Small Animal House, Lala Lajpat Rai University of Veterinary and Animal Sciences (LUVAS), Hisar, after clearing the proposal through the Institutional Animal Ethics Committee (IAEC) vide letter no IAEC/2019/104- 123 dated 15/07/2019. The rats were given 5-fold and 10-fold concentrations of the maximum permissible limit of heavy metals as recommended by BIS in the mixture through drinking water for 90 days. The rats were provided with As in the form of Sodium Arsenite, Cd in the form of cadmium chloride, and Pb in the form of lead acetate. The curcumin and ascorbic acid were given to rats by oral gavage one hour before exposure to heavy metals. The rats were divided into seven groups with six rats in each group and treatment was given as: Group I: 0.25 mg L^{-1} of As + 0.015 mg L^{-1} of Cd + 0.05 mg L^{-1} of Pb (LDHM/5-fold); Group II: 0.50 mg L^{-1} of As + 0.03 mg L^{-1} of Cd + 0.10 mg L^{-1} of Pb (HDHM/ 10-fold); Group III: 0.25 mg L^{-1} of As + 0.015 mg L^{-1} of Cd + 0.05 mg L^{-1} of Pb 200 mg of curcumin and 100 mg of ascorbic acid kg^{-1} of body weight (LDHM + high dose C + A); Group IV: 0.25 mg L^{-1} of As + 0.015 mg L^{-1} of Cd + 0.05 mg L^{-1} of Pb + 100 mg of curcumin and 50 mg of ascorbic acid kg^{-1} of body weight (LDHM + Low dose C + A); Group V: 0.50 mg L^{-1} of As+0. 03 mg L^{-1} of Cd+0.10 mg L^{-1} of Pb +200 mg of curcumin and100 mg of ascorbic acid kg^{-1} of body weight (HDHM+ high dose C +A); Group VI:0.50 mg L^{-1} of As + 0.03 mg L^{-1} of Cd+0.10 mg L^{-1} of Pb + 100 mg of curcumin and 50 mg of ascorbic acid kg^{-1} of body weight (HDHM + low dose C +A) and Group VII: Control.

Collection of blood plasma and preparation of liver tissue homogenate

At the end of treatment, the rats were dissected with cervical dislocation. The blood was collected from the rats by cardiac puncture in heparinised vials and then centrifuged at 2300 r.p.m. for 15 minutes. The supernatant was collected as plasma

and used for the estimation of liver marker enzymes. The liver tissue was homogenised in 50 mM phosphate buffer (pH 7.4), which was centrifuged at 5000 r.p.m. for 20 minutes. The supernatant was collected, stored at -20°C in deep freezer, and used for the analysis of oxidative stress parameters.

Analysis of the activity of liver marker enzymes

The activities of Acid phosphatase (ACP) as well as Alkaline phosphatase (ALP) in the plasma were estimated by the method of Bessey *et al.* (1946). The activities of Aspartate aminotransferase (AST) as well as Alanine aminotransferase (ALT) in the plasma were analysed by the colorimetric method of Reitman and Frankel as described by Bergmeyer (1974) in the plasma of rats. The activities of liver marker enzymes in plasma were expressed as Units Litre^{-1}(UL^{-1}).

Analysis of oxidative stress parameters

Lipid peroxidation was analysed in the liver tissue homogenate by estimating the level of malondialdehyde (MDA) following the method of Stocks and Dormandy (1971), and values of lipid peroxidation level were expressed as nmol MDA produced g^{-1} tissue. The molar extinction coefficient of pure MDA as 1.56×10^5 was used for calculations (Esterbauer *et al.,*1982). The activity of superoxide dismutase was determined in liver tissue homogenates by the method of Marklund and Marklund, (1974) and values were expressed as units mg protein^{-1} and activity of catalase was determined by method of Aebi, (1983) and the obtained results were expressed as µmol H_2O_2 decomposed min^{-1} mg protein^{-1} using 36 as the molar extinction coefficient of H_2O_2.

Statistical analysis

The comparisons were made between the treated rats and control rats using SPSS one-way ANOVA. A "P" value of 0.05 was selected as a criterion for statistically significant differences.

Results and Discussion

Liver marker enzymes

The activity of ACP in plasma was observed to be significantly high in LDHM, HDHM, LDHM + low dose C+A, HDHM + high dose C+A and HDHM + low dose C+A treated rats as compared to control rats and the amelioration of ACP level occurred in LDHM + high dose C+A group only (Fig.1). The activity of ALP in plasma was observed to be significantly increased in LDHM, HDHM, HDHM + high dose C+A and HDHM + low dose C+A treated rats as compared to control rats which indicated that amelioration occurred in LDHM + high dose C+A and LDHM + low dose C+A treated rats only.

ACP and ALP are enzymes found in various tissues throughout the body, including the liver, and their elevated level in the plasma indicate liver damage. Singh *et al.* (2012) reported that groundwater containing As significantly increased the ACP and ALP levels in plasma. Chronic As poisoning caused significant elevation of inorganic phosphatase in plasma, as well as due to leakage of ACP and ALP enzymes from liver cytosol to the bloodstreams. Kenston *et al.* (2018) observed mixture of heavy metals significantly reduced the ALP activity in the plasma of rats. The levels of ACP were significantly reduced only in the LDHM + high dose of C+A, while ALP levels were significantly reduced in both LDHM groups treated with high and low doses of curcumin and ascorbic acid. Yousef *et al.* (2008) reported that curcumin reduced the level of ACP and ALP enzymes in the plasma of rats, which were increased due to As toxicity. Badr *et al.* (2016) reported that ALP activity was maintained, and Pb-induced liver toxicity was reduced with ascorbic acid.

The activity of ALT in plasma was found to be high in LDHM and HDHM-treated rats as compared to control rats. There was non-significant variation in ALT level in LDHM + low dose C+A, LDHM + high dose C+A, HDHM + low dose C+A, and HDHM + high dose C+A treated rats as compared to control rats indicating the hepatoprotective effect of curcumin and ascorbic acid against heavy metal toxicity. The activity of AST in plasma was found to be significantly high in LDHM, HDHM, and HDHM + low-dose C+A as compared to control rats. The amelioration of AST level was recorded in LDHM + low dose C+A, LDHM + high dose

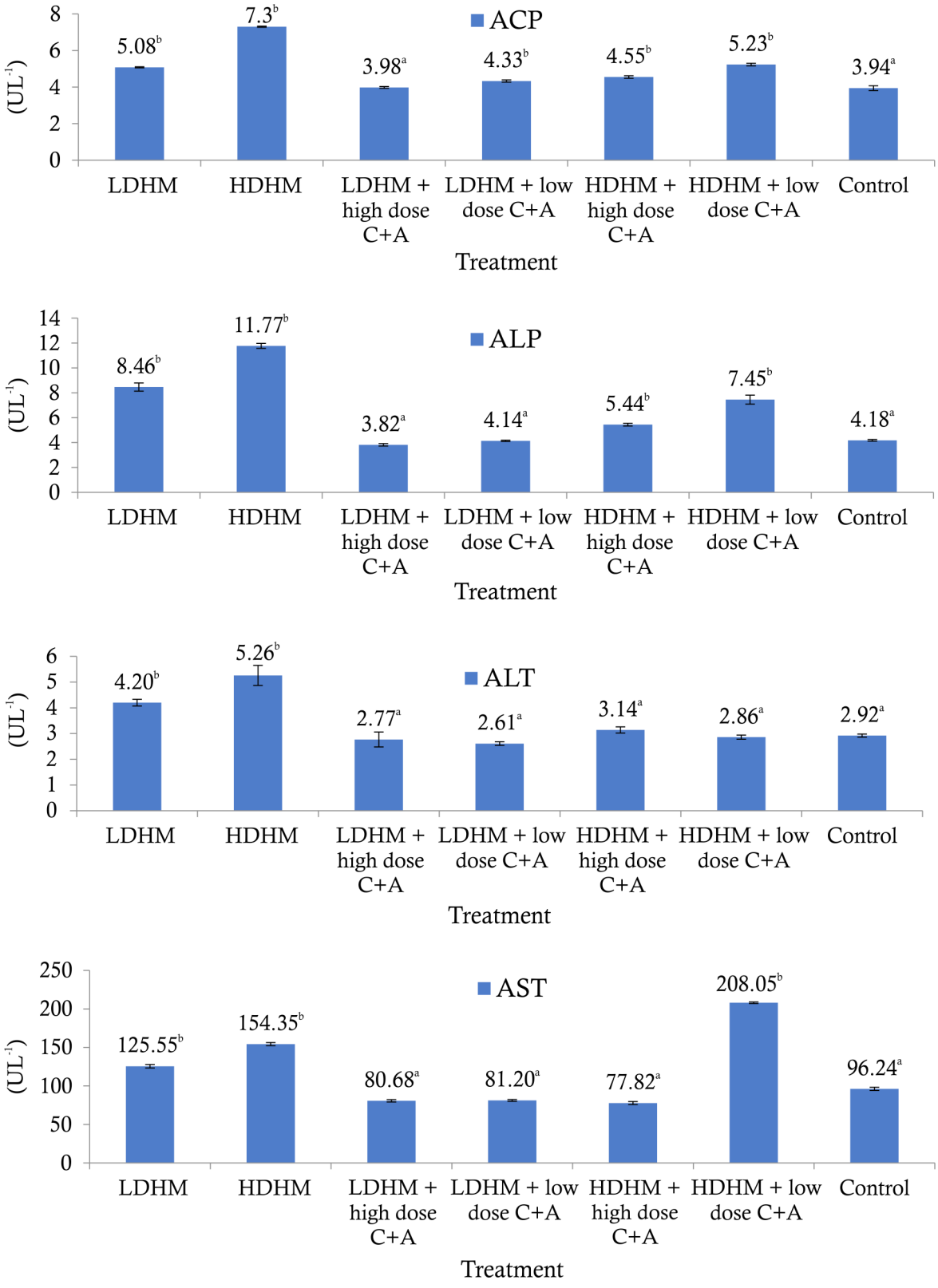

Fig. 1 Activity of liver marker enzymes in plasma of rats treated with heavy metals, curcumin, and ascorbic acid. Values are expressed as Mean±SE. Values with different superscripts (a,b) above the bars represent significant differences ($p \leq 0.05$). LDHM: 0.25 mg L^{-1} of As+ 0.015 mg L^{-1} of Cd+0.05 mg L^{-1} of Pb; HDHM: 0.50 mg L^{-1} of As+ 0.03 mg L^{-1} of Cd+0.10 mg L^{-1} of Pb; high dose C +A: 200 mg of curcumin and 100 mg of ascorbic acid kg^{-1} of body weight; Low dose C +A: 100 mg of curcumin and 50 mg of ascorbic acid kg^{-1} of body weight.

C+A, and HDHM + high dose C+A treated rats, which varied non-significantly from control rats.

The levels of ALT and AST elevated in hepatotoxicity due to heavy metals (both low as well as high doses) and combination of curcumin and ascorbic acid (low as well as high doses) mostly maintained the levels of these enzymes in plasma (except the level of AST in HDHM + low dose C+A). ALT is an enzyme that is predominantly found in liver cells, while enzyme AST is present in the liver and also in skeletal muscle, cardiac muscle, renal tissue, and brain, though in lesser concentrations and there was a disproportionate increase in ALT and AST levels in liver damage (Kalas *et al.,* 2021). Heavy metals destroy the hepatocytes by destroying their tight junction, resulting in a damaged cell membrane that causes an increased permeability to the hepatocyte membrane, due to which both ALT, AST are released into the bloodstream, and thus their levels get elevated in plasma (Renugadevi and Prabu*,* 2009). The activity of ALT and AST in plasma was increased by the mixture of heavy metals as compared to control rats (Bhattacharjee *et al.*, 2016; Kenston *et al.*, 2018). Curcumin prevents liver disorder by decreasing the levels of AST, ALT, and AKP (Mathews *et al.*, 2012; Farzaei *et al.*, 2018). Vitamin C was described to minimize the liver damage caused by various chemical mediators, and it helped to normalize the abnormal levels of ALT, AST, and ALP. ALT and AST activities significantly increased due to As and Pb toxicity, while rats treated with As + ascorbic acid and Pb + ascorbic acid showed significantly reduced ALT and AST activities (Singh and Rana, 2007; Hamadouche *et al.*, 2012).

Oxidative stress parameters

The lipid peroxidation revealed by the level of MDA was found to be significantly high, and the activity of antioxidant enzymes i.e. superoxide dismutase and catalase, in the liver was found to be significantly low in LDHM, HDHM, LDHM + low dose C+A, HDHM + low dose C+A and HDHM + high dose C+A treated rats as compared to control rats (Table 1). The non-significant variation in MDA level, activity of superoxide dismutase and catalase in the liver of LDHM + high dose C+A treated rats as compared to control indicated the antioxidant potential of the combination of curcumin and ascorbic acid in high dose against a mixture of low doses of heavy metals. Heavy metals cause oxidative stress by producing free radicals called reactive oxygen species (ROS) which include hydrogen peroxide, singlet oxygen, hypochlorous acid, superoxide radical, hydroxyl radical, and nitric oxide, which leads to lipid peroxidation and modulate the activities of antioxidant enzymes and causes disturbances in metabolic functions (Ozougwu, 2016). Malondialdehyde (MDA) acts as an oxidative stress marker as it is the final product of lipid peroxidation and is widely used to define oxidative stress. The free radicals are capable of reacting with protein and obstructing a hydrogen atom from polysaccharides, fatty acids in

Table 1. Oxidative stress parameters in liver tissue of rats treated with heavy metals, curcumin, and ascorbic acid

Treatment	Level of MDA (nmol g^{-1})	Activity of Superoxide dismutase (units mg $protein^{-1}$)	Activity of Catalase (µmol min^{-1} mg $protein^{-1}$)
LDHM	5.77 ± 0.09^{b}	5.10 ± 0.27^{b}	7.48 ± 0.53^{b}
HDHM	9.37 ± 1.78^{b}	4.19 ± 0.54^{b}	4.68 ± 0.40^{b}
LDHM+ high dose C+A	1.10 ± 0.46^{a}	8.56 ± 0.43^{a}	14.94 ± 0.26^{a}
LDHM + low dose C+A	2.33 ± 0.15^{b}	6.55 ± 0.54^{b}	11.82 ± 0.49^{b}
HDHM + high dose C+A	4.10 ± 0.16^{b}	6.55 ± 0.58^{b}	9.45 ± 0.40^{b}
HDHM + low dose C+A	5.05 ± 0.12^{b}	5.31 ± 0.31^{b}	8.63 ± 0.44^{b}
Control	0.85 ± 0.17^{a}	9.13 ± 0.50^{a}	16.70 ± 0.35^{a}

Values are expressed as Mean±SE

Values with different superscripts (a,b) in a column represents significant difference ($p\leq0.05$)

LDHM: 0.25 mg L^{-1} of As+ 0.015 mg L^{-1} of Cd+0.05 mg L^{-1} of Pb ; HDHM: 0.50 mg L^{-1} of As+ 0.03 mg L^{-1} of Cd+0.10 mg L^{-1} of Pb; high dose C +A: 200 mg of curcumin and 100 mg of ascorbic acid kg^{-1} of body weight; Low dose C +A: 100 mg of curcumin and 50 mg of ascorbic acid kg^{-1} of body weight

membranes in lipids to initiate lipid peroxidation, which increases the MDA level in the liver (Balali-Mood *et al.,* 2021). Superoxide dismutase represents an antioxidant enzyme responsible for converting the superoxide anion radicals to hydrogen peroxide and molecular oxygen, and it is important to control the ROS levels. Catalase is an antioxidant enzyme that catalyses the conversion of ROS, i.e, hydrogen peroxide, to molecular oxygen and two molecules of water (Jomova *et al.*, 2024). The prolonged exposure to a combination of heavy metals (both low and high doses) for 90 days led to a decrease in the activities of superoxide dismutase and catalase due to sustained ROS production and oxidative damage. Bozdag and Eraslan, (2020) observed that the level of MDA and activity of superoxide dismutase and catalase were found to be lowest in the liver of albino rats treated with Pb as compared to control. Ezedom *et al.* (2020) studied that a mixture of Cd and As in rats significantly elevated level of MDA and lowered the activity of superoxide dismutase and catalase in liver tissue as compared to control rats. The oxidative stress due to exposure to heavy metals determines the expression of transcription factor, *Nuclear factor erythroid 2-related factor 2* (*Nrf2*) which cause ROS removal by regulating the expression of antioxidant gene products such as superoxide dismutase and catalase as well as by lowering the level of lipid peroxidation (MDA content) (Hussein *et al.,* 2024). However, the decreased activities of superoxide dismutase and catalase as well as increased MDA contents due to heavy metals exposure in the present studies, indicated an excessive production of ROS leading to disruption of *Nrf2* pathway.

The antioxidants like curcumin and ascorbic acid protect the cellular damage by interfering with the generation of free radicals by heavy metals. Curcumin showed good electron-transfer capability because of its unique structure and different functional groups, including a â-diketone and several ð electrons that can conjugate between two phenyl rings and readily transfer electrons or easily donate H-atoms to scavenge free radicals. Ascorbic acid is a chemical with large resonance-stabilized electron clouds and works as an electron donor for free radicals. Earlier studies reported that curcumin improved activity of activity of superoxide dismutase and catalase in Cd-treated rats (Deevika *et al.,* 2012). However, Naovarat *et al.* (2012) reported that the mixture of curcumin and ascorbic acid had a more protective role than curcumin and ascorbic acid alone against the Pb-induced oxidative stress in the liver. The components such as curcumin and ascorbic acid suppress metal-induced toxicity via modulation of *Nrf2*-dependent cellular defence mechanisms as both these components have been proven as natural activators of the *Nrf2* pathway, thus regulating expression of antioxidant enzymes.

Conclusion

The combination of heavy metals (As, Cd and Pb) above permissible limits recommended by the Bureau of Indian Standards in drinking water induced alterations in the activity of marker enzymes and oxidative stress in liver of albino rats and the combination of curcumin and ascorbic acid, particularly in high doses protect against this damage thus indicating that awareness should be created among human populations that the dietary antioxidants have the potential to mitigate heavy metal-induced liver toxicity in humans.

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