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CURCUMIN ADMINISTRATION ATTENUATES ACCUMULATION OF MERCURIC CHLORIDE IN VITAL ORGANS OF EXPERIMENTAL RATS AND LEADS TO PREVENT HEPATIC AND RENAL TOXICITY

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ABSTRACT: Mercury is a hazardous, environmental and industrial pollutant, and causes several health issues related to various organs such as brain, kidney, gut, liver. In 2013, Environmental Protection Agency, USA, reported a higher concentration of mercury (5.8 µg/L) in approximately 1.4 million women (2.3% of total USA population) of reproductive age. Based on this prevalence, it was estimated that more than 75,000 newborns would have increased risk of learning disabilities associated with *in-utero* exposure to methylmercury annually. Curcumin, an active compound of turmeric, is well known for its antioxidant property and used in various diseases including inflammation and cancer. Here, we have shown that curcumin administration decreases mercury accumulation in liver and kidneys, and which leads to suppression of mercury toxicity. For the purpose, experimental rats were administered mercury chloride with and without curcumin treatment in time dependent manner. At the end of the study, we observed that the accumulation of mercury was higher into liver than kidneys measured using ICP-AES. Curcumin treatment significantly reduces mercury accumulation up to 58 - 59% in these organs in time dependent manner. The statistical analysis shows a positive correlation between liver and kidney, justified by one-way analysis of variance. In addition to attenuation of the mercury accumulation, curcumin administration also improves the liver / kidney functions as assessing through alteration in the levels of their serum biomarkers. Our findings indicate that curcumin has potential to inhibit mercury accumulation in various tissue and may provide new strategies for the prevention of mercury toxicity.

INTRODUCTION: Mercury exists globally in the environment that derives from both natural geological processes such as volatilization of rocks, dissolution, and volcanic eruption as well as due to some anthropogenic activities like combustion of fossil fuels, incineration of waste, mining and industrial discharge [1].

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Human civilization and other men made activities increase the amount of mercury almost triple times in the atmosphere, and its burden is rising at the rate of 1.5% per year.

The release of processed mercury can lead to a progressive increase in the amount of atmospheric mercury, which enters the atmospheric soil water distribution cycles by different ways and undergoes a process of methylation and remains in circulation system for several years. It is ranked third by the US government agency with regard to toxic substances and disease registry of the most toxic element on the planet with arsenic and lead, continuously dumped into our water ways and soil,

spilled into our biosphere and consumed in our food and water [2, 3]. Mercury can exist in several isoforms: elemental, inorganic and organic, and have their profile of toxicity and target pathways [4]. Ionic or inorganic mercury formed in the atmosphere in the form of elemental mercury vapours and returns to earth's surface with rain and snow and gets converted to organic mercury by bacteria and fungi, to be more potent neurotoxic, hepatotoxic and nephrotoxic agent.

Due to solubility, inorganic mercury has deleterious effects. Although, Mercury poorly absorbed through the gastrointestinal tract, completely absorbed in lungs about > 90% in vapour form [5, 6]. Once mercury introduced into the body through food or some other way, is rapidly absorbed and accumulates in several tissues leading to oxidative damage, mitochondrial dysfunction and cell death [7, 8]. It has mainly devastating effects on the brain, kidney, liver, and blood. Mercury primarily metabolized in the liver. Due to its accumulation in the liver, resultant severe hepatic damages [9], including histopathological and ultra-structural lesions evidenced by periportal fatty degeneration and cell necrosis [10], whereas, the kidney is the primary organ of elimination. Being recognized mercury as a hazardous environmental pollutant[11], and has efficacy to produce several adverse effects on human health, achieve considerable attention and need to investigate through about the toxicity.

Phytochemicals have shown and proved for their effectiveness against oxidative stress, inflammation, cancers of several organs, *etc.* Curcumin, an active compound, obtained from turmeric, belongs to the group of curcuminoids, and responsible for yellow color in turmeric has been considered to be a potent antioxidant. Curcumin has been used for the treatment of several diseases including inflammatory disorders, cancer prevention, and various metal toxicities. In the present study, we evaluate the effect of curcumin on the accumulation of mercury chloride in vital organs and mercuric chloride induced hepatic and renal toxicity.

MATERIALS AND METHODS:

Animals: The female albino rats (4 - 6 weeks of age) were purchased from the commercial supplier of experimental animals. Before conducting experiments, the animal protocol was approved (APN: SLS/DZ/PNS/2014-AA02) by the institutional animal ethical committee, Dr. Bhimrao Ambedkar University, Agra. The colony of experimental rats was maintained under standard conditions of a 12 hour dark and 12 hour light cycle, a temperature of 24 ± 2 °C, and relative humidity of 50 ± 10%. The rats were provided standard pellet diet as food (Golden feed, New Delhi) and water *ad libitum*.

Chemicals and Reagents: $HgCl_2$ and curcumin were purchased from Merck India Ltd., (Mumbai, India) and formulated in oil and water suspension. All other chemical and reagents were of analytical grade.

Induction of Mercury Toxicity and Treatment Protocol: To determine the effect of curcumin on mercury ($HgCl_2$) toxicity, experimental female rats were divided into four groups (20 rats per group) in following time dependent studies: acute toxicity (1 day) and sub-acute toxicity (7, 14 and 21 days). Each group was further divided into another four sub-groups (5 rats per group) as follows. Group I: Control (vehicle alone), Group II: Curcumin alone (50 mg/kg body weight/day, through oral gavage suspended in pea nut oil), Group III: $HgCl_2$ alone (through oral gavage), and Group IV: $HgCl_2$ + curcumin

The single dose of $HgCl_2$ in acute study (10.0 mg/kg body weight) and multiple doses of $HgCl_2$ in sub-acute studies (1.47 mg/kg body weight, 7 days; 0.735 mg/kg body weight, 14 days, and in 0.49 mg/kg body weight, 21 days) were administered throughout the experiments with and without curcumin treatment. At the end of each study, experimental rats were euthanized using cervical dislocation and vital organs such as liver and kidneys were collected and stored at - 80 °C until further use. Samples obtained at various time points were assayed and analyzed altogether.

Biochemical Analysis: To evaluate the effect of curcumin treatment on mercury toxicity in liver and kidneys, the blood was drawn from the eye vein (retro-orbital) of rats, and allowed to clot for 15 min at room temperature. Serum was separated by centrifugation at 1500 × g for 10 minutes and used for the analysis of biochemical changes.

Serum samples were stored at -20 °C until further analysis. The levels of Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were estimated using diagnostic kits based on the methods described by Prasad *et al*., [12] and the enzyme activity was determined by measuring the absorbance of the colored complex at 505 nm.

Alkaline phosphatase (ALP) was measured in serum samples followed by the protocol described by Prasad *et al*., [13] In brief, a reaction mixture consisting of 0.1 ml of serum was incubated at room temperature for 30 min with 1.0 ml of the alkaline buffered substrate (equal volume of 0.1M glycine buffer and 0.4% p-nitrophenyl phosphate), pH 10.4. The absorbance after 30 min was recorded at 410 nm before and after the addition of 50 µl of 1 M HCl. Enzyme activity was expressed as equivalent unit/ml, where one unit is defined as one µmol of p-nitrophenol (PNP) formed under defined conditions per ml of serum.

The serum creatinine level was measured using colorimetric kits in accordance with the manufacturer's protocol.

Measurement of Mercury Concentration in Vital Organs by Inductively Coupled Plasma-Atomic Emission Spectroscopy (ICP-AES): To determine the concentration of mercury accumulation in vital organs with and without curcumin treatment, the experimental rats were euthanized *via* cervical dislocation. The vital organs (liver / kidney) were immediately removed, washed in ice - cold saline solution and blotted. Accurately weighed pieces of tissue were minced and digested with sulphuric-potassium permanganate for Hg analysis.

The mercuric chloride concentration in vital organs was determined using inductively coupled plasma-atomic emission spectroscopy (ICP - AES). Accumulation and elimination kinetics of inorganic mercury were determined using one compartment open model with water as the source and the organism as the recipient. The model describes the changes in metal concentration in animals over time.

Statistical Analysis: The statistical analysis of the data was carried out one-way analysis of variance (ANOVA) using Graph Pad Prism software (Online version: www.graphpad.com). The results were expressed as mean ± S.E. $p < 0.05$ was considered statistically significant to measure toxicokinetics of $HgCl_2$.

RESULTS:

Mercury Chloride Distribution in Vital Organs: Mercury has been recognized as a toxic heavy metal and causes several deleterious effects after environmental or occupational exposure. First, to understand the accumulation of mercury, we checked the mercury concentration in important vital organs such as liver and kidneys in dose and time dependent manner. As shown in **Table 1**, the accumulations of mercury in sub-acute studies were higher in liver (6.44, 15.7 and 18.4 ppm) and kidneys (0.55, 0.83 and 2.23 ppm) than acute intoxication. The accumulation of mercury in liver was higher upto 6 folds as compared with the concentration of mercury in kidneys. These results demonstrate that the liver is more susceptible to mercury accumulation than kidneys and this may indicate that liver is primary target site of mercury-induced toxicity.

TABLE 1: EFFECT OF CURCUMIN ON MERCURY ACCUMULATION IN LIVER AND KIDNEY OF EXPERIMENTAL RATS IN ACUTE AND SUB-ACUTE STUDIES

Treatment	Accumulation of $HgCl_2$ (ppm)	
	$HgCl_2$ alone	$HgCl_2$ + Curcumin
Acute (1 day)		
Liver	1.48 ± 0.24	0.82 ± 0.13 (45)*
Kidney	1.43 ± 0.08	0.59 ± 0.02 (59)*
Sub-acute (7 days)		
Liver	6.44 ± 0.55	3.15 ± 0.56 (52)*
Kidney	0.55 ± 0.03	0.53 ± 0.10 (4)^{NS}
Sub-acute (14 days)		
Liver	15.70 ± 0.92	7.60 ± 0.58 (52)*
Kidney	0.83 ± 0.28	0.36 ± 0.009 (57)*
Sub-acute (21 days)		
Liver	18.40 ± 0.35	7.74 ± 0.29 (58)*
Kidney	2.23 ± 2.4	0.93 ± 0.26 (59)*

Data represents mean ± S.E of mercury concentration in liver and kidney (ppm). The values indicated in brackets showed percent decrease of mercury accumulation in the vital organs with curcumin treatment compared with $HgCl_2$ alone group. The values of each $HgCl_2$ alone group were assigned as 100%. *$p < 0.01$, which was statistically significant compare to the $HgCl_2$ alone group. NS: not significant, n = 5

Effect of Curcumin on Mercury Chloride Accumulation in Vital Organs: Next, we checked the effect of curcumin administration on mercury accumulation in liver and kidneys in dose and time

dependent manner. As shown in **Table 1**, Oral administration of curcumin significantly inhibits mercury accumulation upto 45% in liver and 59% in kidneys in acute studies. The inhibition of mercury accumulation in sub-acute studies was higher upto 52 - 58% in the liver in time dependent manner.

Inhibitory Effect of Curcumin on Mercury Concentration in Liver and Kidneys: Toxico-kinetics: In the pharmacology, first order kinetics is considered as a linear process, because the rate of elimination is proportional to the drug concentration. As shown in **Fig. 1**, the accumulation of mercury was less in the acute study in liver (upper panel) and kidney (lower panel), while significantly higher in the sub-acute study (21 days). Curcumin administration inhibited mercury accumulation upto 42 - 58% in sub-acute studies but did not affect mercury deposition in acute studies.

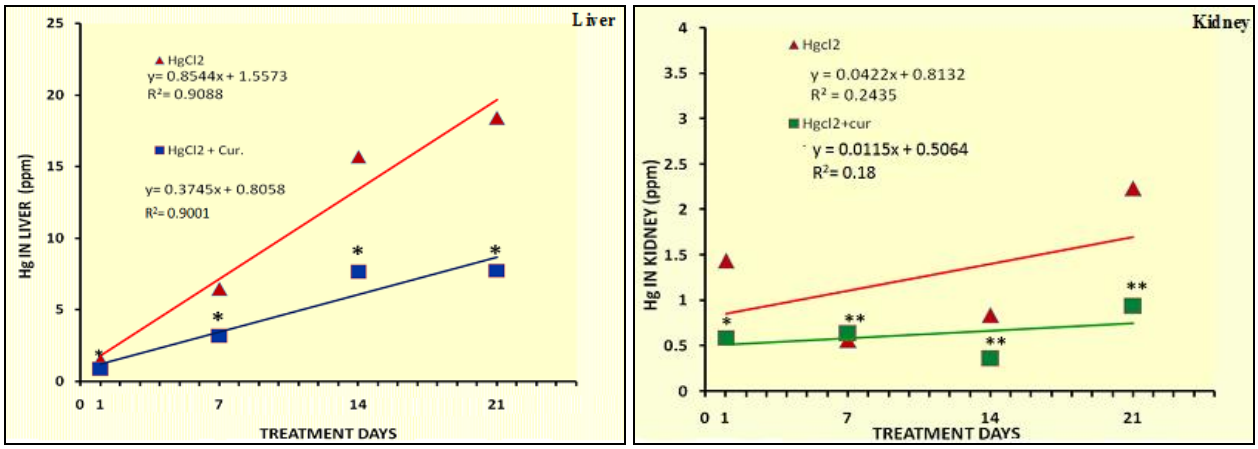

FIG. 1: EFFECT OF CURCUMIN ADMINISTRATION ON FIRST ORDER TOXICOKINETIC REACTION OF MERCURIC CHLORIDE ACCUMULATION AND ELIMINATION

A significant decrease in curcumin administered followed by mercuric chloride intoxication vs. mercuric chloride alone (non-curcumin administration) (*p < 0.01; **p < 0.05) n = 5

Effect of Curcumin on Gross Elimination / Retention of Mercury Concentration in Experimental Rats: Based on first order kinetic reaction, data for total elimination / retention of intoxicated mercury are summarized in **Table 2** and **3**. As shown in **Table 2**, curcumin administration enhances mercury elimination upto 42% from the body of experimental rats when compared with mercury alone intoxicated groups in sub-acute (21 days) study.

TABLE 2: EFFECT OF CURCUMIN ON GROSS ELIMINATION OF MERCURY FROM EXPERIMENTAL RATS

Studies	Total administration of $HgCl_2$/rat	Elimination of mercury in experimental groups	
		$HgCl_2$ alone	$HgCl_2$ + Curcumin
Acute (1 day)	1030 ppm	1026.9	1028.5 (0.15)^{NS}
Sub-acute (7 days)	147 ppm	139.95	143.18 (2.30)^{NS}
Sub-acute (14 days)	73 ppm	56.41	65.01 (15.24)^{NS}
Sub-acute (21 days)	49 ppm	28.32	40.32 (42.37)*

Data represents total mercury concentration in experimental rat (ppm). The values indicated in brackets showed percent decrease of mercury accumulation in rats after curcumin treatment compared with $HgCl_2$ alone group. The values of each $HgCl_2$ alone group were assigned as 100%. *p < 0.01, which was statistically significant compare to the $HgCl_2$ alone group. NS; not significant, n = 5

Table 3 shows that curcumin administration decreases retention of mercury concentration upto 57.82% in the body of experimental rats compared with mercury alone intoxicated groups.

Effect of Curcumin Administration on Serum Markers of Liver and Kidney Injury: Serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) are considered as most important marker enzymes of liver injury and used to measures the liver functions. In accordance of higher accumulation of mercury in liver tissues after 21 days, next, we measured the levels of ALT, AST,

and ALP in serum samples obtained from experimental rats with and without curcumin administration and compared with healthy control group. As shown in **Fig. 2a**, **2b**, and **2c**, the levels of ALT (56.47%), AST (45.48%), and ALP (99.53%) were significantly elevated ($p < 0.01$) in mercury intoxicated group as compared with healthy control group (without mercury intoxication). Curcumin administration significantly blocks ($p < 0.001$) this elevation in the levels of ALT (63.46%), AST (71.47%), and ALP (46.16%) as compared with the mercury alone intoxicated group. These results suggest that curcumin administration mediated changes in serum markers of liver injury reduces the risk of mercury-induced hepatotoxicity.

TABLE 3: EFFECT OF CURCUMIN ON GROSS RETENTION OF MERCURY IN EXPERIMENTAL RATS

Studies	Total administration of $HgCl_2$/rat	Retention of mercury in experimental groups	
		$HgCl_2$ alone	$HgCl_2$ + Curcumin
Acute (1 day)	1030 ppm	2.98	1.45 (51.35)*
Sub-acute (7 days)	147 ppm	7.06	3.81 (46.04)*
Sub-acute (14 days)	73 ppm	16.59	7.99 (51.84)*
Sub-acute (21 days)	49 ppm	20.6	8.69 (57.82)*

Data represents total mercury concentration in experimental rat (ppm). The values indicated in brackets showed percent decrease of mercury accumulation in rats after curcumin treatment compared with $HgCl_2$ alone group. The values of each $HgCl_2$ alone group were assigned as 100%. *$p < 0.01$, which was statistically significant compare to the $HgCl_2$ alone group n = 5

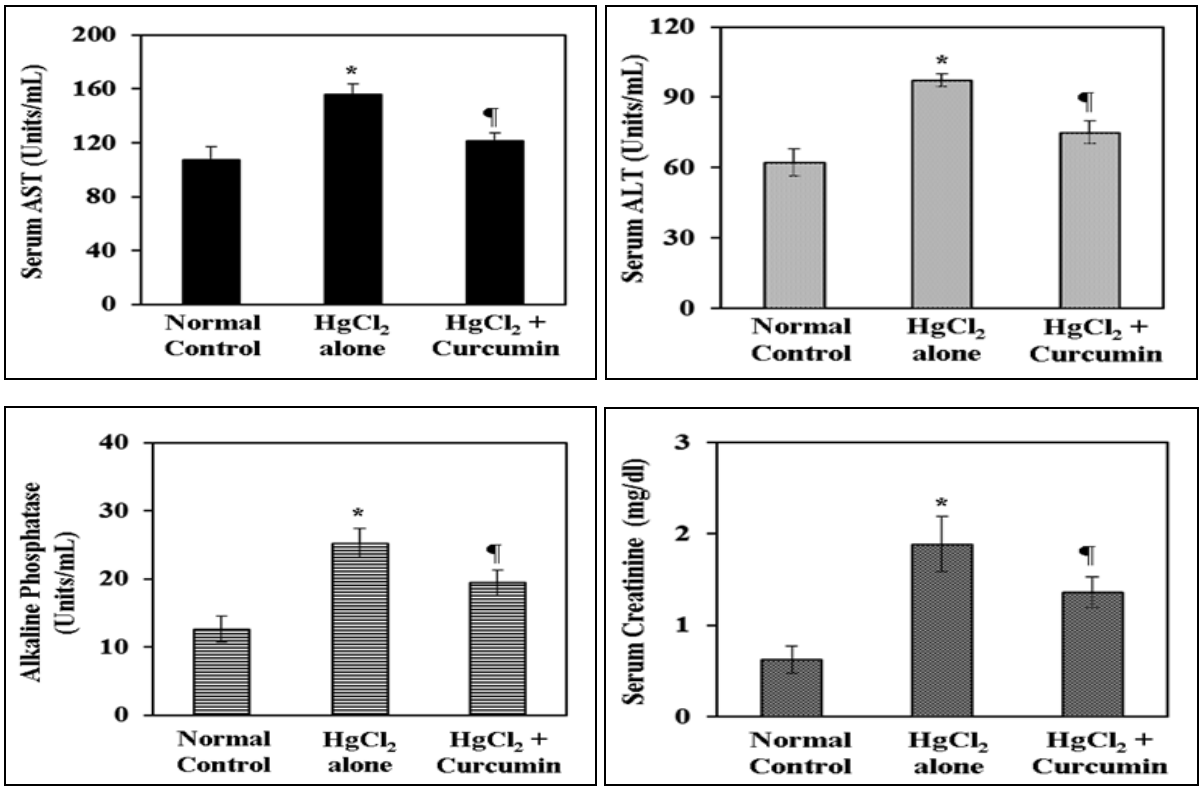

FIG. 2: EFFECT OF THE CURCUMIN ADMINISTRATION ON SERUM BIOMARKER OF LIVER AND KIDNEY FUNCTIONS. EXPERIMENTAL RATS WERE ORALLY ADMINISTERED WITH CURCUMIN FOLLOWED BY MERCURIC CHLORIDE (49 ppm / DAY) UPTO 21 DAYS. AT THE END OF THE STUDY, BLOOD WAS DROWNING FROM RETRO-ORBITAL AND SUBJECTED TO SERUM SEPARATION FOR BIOCHEMICAL ANALYSIS (A) AST, (B) ALT, (C) ALP, AND (D) CREATININE LEVELS.

Data were presented mean ± S.D and compared with heathy control. Significant increase in mercuric chloride alone *vs.* normal control (*$p < 0.001$). A significant decrease in curcumin administered followed by mercuric chloride intoxication *vs.* mercuric chloride alone (non-curcumin administration) (¶$p < 0.01$) n = 5

Kidney injury is characterized by abrupt deterioration in kidney function and manifested by an increase in serum creatinine level with or without reduced urine output. Next, in sequence, we measured the levels of creatinine in serum samples obtained from experimental rats with and without curcumin administration and compared with healthy control group. As shown in **Fig. 2d**,

the serum creatinine level was significantly higher ($p < 0.01$) upto 3 folds in mercury intoxicated group as compared with healthy control group (without mercury intoxication). While curcumin administration significantly blocks ($p < 0.001$) the elevation of creatinine level compared with the mercury alone intoxicated group. These results suggest that curcumin administration prevents the risk of mercury induced renal toxicity.

DISCUSSION: Mercury is a toxic heavy metal and has been shown to induce various diseases associated with the nervous system, kidneys, liver and other organs. It has several resources to come in contact with consumers such as environmental and occupational. Environmental mercury is present in each tropical level of the food chain, while occupational exposure to mercury has been strengthened by industrial discharge, extensive agriculture practices, vaccines preservatives, dental amalgams and by many other sources [14]. The gastrointestinal tract, lung, and skin are the main routes, through which heavy metals get absorbed.

In the present study, mercury was orally administered to experimental rats in the form of mercuric chloride. Skip *et al*., reported that some part of mercury gets detoxified while remaining un-detoxified gets distributed to other vital organs including kidney [15]. The liver is the primary site of biotransformation and detoxification, so maximum metabolism and detoxification take place in the liver. The concentration of heavy metals in vital organs of animal body relies on the binding capability of toxicant. The higher binding results in a higher concentration in that tissue, and which subsequently exert more severe effects. Our data indicate that liver and kidney have a higher binding capacity with mercury.

As shown in **Table 1** and **Fig. 1**, the liver and kidney showed the highest levels of mercury, which could be responsible for the abnormal functions of these organs. Accumulation of mercury was maximum on day 21 in liver and kidneys, in comparison with acute (single higher dose; 1030 ppm/day). These findings suggest that slower and continuous exposure at low doses have severe detrimental effects that acute exposure. Curcumin administration significantly blocks the accumulation of mercury in the vital organs.

Mercury did not metabolize by phase I or II reactions; however, its excretion is possible through oxidation by which it gets transformed to water soluble divalent form. The primary pathway of excretion of inorganic Hg is through urine and feces. Renal excretion has earlier been considered a major route of elimination of oxidized mercury, which perhaps could be accounted for its affinity with proteins and epithelium of the nephron in particular [5]. After absorption and distribution in an organism, mercuric chloride excreted rapidly or slowly. A commonly well-accepted indicator of the rate of elimination of a toxicant is its "half-life" ($t_{1/2}$), which is the time required to remove 50% of it from the bloodstream. The toxicants are excreted as the parent chemicals, as their metabolites, and as conjugates of them.

The principal route of excretion is the urine, but the liver is a vital excretory organ for particular types of chemicals. The elimination rate of administered mercury was approximate 99.69% in acute studies (**Table 2**), which has been declined by 4.8%, 22.72%, and 42.22% in sub-acute studies. Curcumin administration enhances the elimination rate of mercury upto 42% in sub-acute studies. This could have been possible due to modulation by the post-treatment of curcumin on account of its anti-inflammatory and antioxidant properties.

Approximately 85% of an oral dose is excreted in feces within a couple of days. Most of the absorbed ionic Hg is excreted in urine. Smaller amounts are excreted in saliva, bile, sweat, exhalation and breast milk. Hg^{+2} induced serum biochemical changes responsible for oxidative stress. Therefore, in addition to investigating the accumulation, absorption, and elimination, we also measured biochemical parameters associated with liver and kidney functions. Serum biomarkers ALT, AST, ALP, and creatinine have been reported abnormally elevated.

As shown in **Fig. 2**, the elevated levels of these biomarkers were significantly decreased following curcumin administration. The absorbed mercury can cause various digestive disturbances as it has inhibited the production of digestive enzymes such as trypsin, chymotrypsin, and pepsin resulting in abdominal pain, bowel disease, ulcers and bloody diarrhea [2].

It is thus evident that mercury is distributed in different tissues and organs creating metabolic disturbances leading to deleterious effects. The concentration of mercury deposits is differential in various organs, and the extent of damage induced by it depends on its concentration, as well as its acceptability by the organ itself.

CONCLUSION: The present study investigated the effect of curcumin on mercury accumulation in liver and kidney tissues, and mercury induced hepatotoxicity and renal toxicity in albino rats. It suggests that curcumin administration not only enhances the elimination of mercury and reduces mercury accumulation but also improves liver and kidney functions through regulating their biomarkers. Our present investigation also provides new insights that use of curcumin may have potential to subside the effect heavy metal toxicity.

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CONFLICT OF INTERESTS: The authors declare that they have no conflict of interests.

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