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Hepatoprotective Potential of Methanolic and Aqueous Extract of *Chenopodium botrys* against Lead-induced Toxicity

Nidhi Gupta[1], Rakesh Sagar[2], Mohan Lal Kori[3,*]
[1] Department of Pharmacology, Sri Sathya Sai Institute of Pharmaceutical Sciences, RKDF University, Bhopal, Madhya Pradesh, INDIA.
[2] Department of Pharmacognosy, Shri G.S. Institute of Technology and Science, Indore, Madhya Pradesh, INDIA.
[3] Department of Pharmacognosy, Vedica College of B Pharmacy, RKDF University, Bhopal, Madhya Pradesh, INDIA.

ABSTRACT

Background: *Chenopodium botrys* L. is local to Europe and Asia and established in North America. The plant commonly used for the treatment of disease. The medicinal use of *Chenopodium botrys* is mainly due to mythology rather than scientific proof. **Objectives:** To evaluate the hepatoprotective potential of methanolic and aqueous extract of *Chenopodium botrys* against lead-induced toxicity. **Materials and Methods:** The aerial parts of *Chenopodium botrys* were extracted by the continuous hot extraction process using acetone and methanol as a solvent and the aqueous extract of the plants were obtained by the cold maceration process. Liver tissue was treated with 5 ppm Lead Acetate and 5 mg/ml of acetone methanol and aqueous extract of *Chenopodium botrys*. During the study, biochemical indices like lipid peroxidation (LPO), Protein levels and enzymatic activities of alkaline phosphatase (ALPase), acid phosphatase (ACPase) and succinate dehydrogenase (SDH) were measured. **Results:** The current study report that protein levels and enzymatic parameters of alkaline phosphatase as well as succinate dehydrogenase declined significantly while levels of lipid peroxidation and acid phosphatase increased significantly in lead acetate exposed goat liver homogenates as compared to control groups. Co-administration of herbal methanol and aqueous extract of *Chenopodium botrys* (5 mg/ml) along with 5 ppm lead acetate to liver homogenate exerted an ameliorative effect and maintained the studied parameters closed to control group. **Conclusion:** *Chenopodium botrys* is endowed with hepatoprotective activity. It can be taken as one candidate for the development of hepatoprotective agents because of its good safety profile.

Key words: *Chenopodium botrys* L., Traditional uses, Lead Toxicity, Hepatoprotective, Goat.

Correspondence

Dr. Mohan Lal Kori,

Vedica College of Pharmacy, RKDF University, Bhopal, Madhya Pradesh, INDIA.

ORCID- orcid.org/0000-0003-2899-7781

Email id: nidhigupta25may@gmail.com;

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INTRODUCTION

The genus *Chenopodium* comprises numerous members of perennial and annual species, which occur everywhere in the world. They could grow as aromatic or non-aromatic herbaceous plants or as shrubs and small trees.[1] *C. botrys* L. (syn. *Dysphania botrys* (L.) Mosyakin and Clemants), known as Jerusalem Oak Goosefoot or Feathered Geranium, commonly grows in Europe and is native to Mediterranean region, but it also could be found in Asia, India, Himalayas, Turkey, Cyprus, Africa, Australia and North and South America.[2] The plant is known as traditional medicine for different ailments in respiratory tract, especially for the treatment of acute rhinitis and respiratory disorder. and it is used as an alternative of C. *ambrosioides*.[3] On the basis of a literature survey it is conclude that *C. botrys* contains flavonoids, alkaloids, terpenes and essential oil.[4] *C. botrys* oil contains distinct number of isomers of monoterpene, ascaridole, were found in the *C. botrys* oil which was used in the treatment of tumor cell lines *in vitro*.[5] Additionally, in the aerial parts of *C. botrys*, the flavon chrysoeriol as well as flavonoids: salvigenin, sinensetin, hispidulin, quercetin and their derivatives were identified, which were related to a potential antioxidant activity.[4]

In the flora of the Republic of Macedonia (RM), 15 species of the genus *Chenopodium* occur naturally, including *C. botrys*.[6] Dried over ground flowering parts of the plant (*herba*) are utilized by local people for preparing infusions or liquid extracts with diuretic antispasmodic, carminative and antidiarrheal properties.[7] Despite its usage, chemical composition and biological activity of this plant are poorly known.

Chenopodium botrys (Cb) is a strongly aromatic medicinal plant growing in Jaunsar-Bawar, a hilly tribal inhabited area in Uttar Pradesh, India and in dry sandy areas in the temperate Himalayas from Kashmir to Sikkim.[8] *Chenopodium botrys (*Cb) finds use in multiple therapeutic applications such as expectorant, anticonvulsant, antibacterial, and tonic.[9] In Kashmir Himalayas, an ethnomedicinal survey indicates that the seed decoction of the plant is used relieves a headache due to gallbladder troubles, for treating tapeworm infestation in children[10] anthelmintic, diuretic, liver diseases, and laxative.[11] In Tibetan medicine, Cb is used to treat stomach and liver problems.[12] During an ethnomedicobotanical survey of Jaunsar-Bawar, a hilly tribal inhabited area in Uttar Pradesh, India; it was observed that about 100 plants are being used by the local Jaunsari tribe for the treatment of various ailments.

Keeping this perspective in mind, investigation of the possible therapeutic role of *Chenopodium botrys* as a protective agent against lead-induced hepatic toxicity is necessary. The objective of study was to understand the mechanism of lead toxicity on various biochemical changes such as alterations in lipid peroxidation, protein content and enzyme activities in goat liver homogenate in order to avoid the ethical concern of involving experimental animals. Another objective of the current study was to

explore a substance which will help in the treatment of lead toxicity with maximum beneficial effect and less adverse effect.

MATERIALS AND METHODS

Collection of Plant materials

The aerial parts of *Chenopodium botrys* were collected in the month of August from Jaunsar-Bawar, hills, Uttar Pradesh and were Identified and authenticated by taxonomists.

Chemicals

The analytical reagent (AR) grade lead acetate trihydrate having 99% purity was obtained from HIMEDIA Laboratory Pvt. Ltd., Mumbai, India. All the other chemicals of AR grade used in the present study were procured from Sigma and Merck Laboratory Pvt. Ltd., India. The acetone and methanol extract of the plants were obtained by the continuous hot extraction process. And the aqueous extract of the plants were obtained by the cold maceration process.

Experimental design[13]

In the present study, experimental protocol was designed into two separate phases. During the first phase, goat liver homogenate cultures were exposed for the specific period of time to different concentrations of lead acetate selected on the basis of LD_{50} value and reported literature in order to evaluate the lead-induced alterations in selected biochemical parameters like lipid peroxidation, protein content and enzymatic activities of alkaline phosphatase, acid phosphatase as well as succinate dehydrogenase *in vitro*. The second phase involves co-administration of acetone, methanol and aqueous extract of *Chenopodium botrys* to lead acetate exposed homogenate for specific time duration to investigate an ameliorative effect of the antidote against lead toxicity.

Preparation of plant extract

10 ml of distilled water was used to dissolve 100 mg of crude acetone, methanol and aqueous extract of *Chenopodium botrys*.

Preparation of lead acetate solutions

The 100 ppm of stock solution of lead acetate was prepared by adding 0.010 gm of lead acetate in 100 ml of distilled water. Final concentration used in the experiment are 1 ppm, 3ppm and 5 ppm concentrations of lead acetate.

Sample collection

After sacrificing the goat Capra hircus. The liver sample of 250-350 gm was collected from the local market. The fresh liver tissue was brought to the lab under frozen condition and used immediately. The appearance of fresh tissue was dark reddish-brown color. Liver tissue was washed in normal saline, blotted dry by pressing between 2-3 folds of filter paper and divided into different experimental groups.

In vitro study

The experimental protocol for *in vitro* study on hepatoprotective effect of *Chenopodium botrys* against lead-induced toxicity includes ten experimental groups:

(I) Control Group

(II) Acetone extract of *Chenopodium botrys* (5 mg/ml) Exposed Group

(III) Methanol extract of *Chenopodium botrys* (5 mg/ml) Exposed Group

(IV) Aqueous extract of *Chenopodium botrys* (5 mg/ml) Exposed Group

(V) Low Dosage 1ppm Lead Acetate Group

(VI) Mid Dosage 3 ppm Lead Acetate Group

(VII) High Dosage 5 ppm Lead Acetate Group

(VIII) 5 ppm Lead Acetate + 5 mg/ml acetone extract of *Chenopodium botrys*

(IX) 5 ppm Lead Acetate + 5 mg/ml methanol extract of *Chenopodium botrys*

(X) 5 ppm Lead Acetate + 5 mg/ml aqueous extract of *Chenopodium botrys*

The sample of various lead and extract group was proceed to the process of homogenization with constant speed and temperature of 4°C in mortar pestles made up of glass. The color of the tissue changes to whitish red after haemolysis. All the group containing lead and extract together homogenate for time interval of 30 min. The other group as well as exposed group were maintained at same conditions in 5% CO_2 containing BOD incubator at 37°C and subjected to study of various biochemical indices for investigating ameliorative effect of the antidote against lead-induced hepatotoxicity.

Biochemical analysis

To analyze free radical induced cell injury by lead acetate, the levels of lipid peroxides were determined in liver homogenates. The measurement of lipid peroxidation (LPO) in the liver homogenates of control and exposed groups were done by the method of Ohkawa.[14] A 10% of tissue homogenate of liver was prepared in ice cold 0.1M phosphate buffer solution (pH=7.4) for the estimation of lipid peroxidation levels. For investigation of toxic effect of lead acetate on the protein metabolism, levels of soluble proteins were estimated in goat liver homogenates by the method of Lowery.[15] At the end of the lead acetate treatment as well as *Chenopodium botrys* exposure, certain specific parameters of goat liver, including enzyme activities of alkaline phosphatase, acid phosphatase and succinate dehydrogenase were also investigated. The alkaline phosphatase and acid phosphatase activities were analyzed by the method of Bessey[16] while the Beatty[17] method was used to measure the activity of succinate dehydrogenase. 0.1 gm of liver tissue was homogenized in the known amount of double distilled water for the estimation of soluble proteins, alkaline phosphatase, acid phosphatase and succinate dehydrogensase activities.

Statistical analysis

Student's'*t* – test' was used for the statistical analysis of the data. For each parameter (n=5), the data were expressed as mean ± SEM after subjecting to Student's '*t* – test' using GraphPad software for the interpretation of results. The significance difference was statistically considered at the level of $p < 0.05$.

RESULTS

Hepatoprotective effect of *Chenopodium botrys*

Lipid peroxidation

Results of the LPO in the goat liver homogenate exposed to different concentrations of lead acetate, *Chenopodium botrys* extracts and related control *in vitro* are given in Table 1. Their percentage of difference, due to the lead acetate and extracts exposure with respect to their control, is given in Table 2. As the concentration of lead increases the lipid peroxidation also increases due to the formation of thiobarbituric acid substance. Lipid peroxidation at low dosage (1 ppm) and medium dosage (3 ppm) and high dose of 5ppm exposure was represented as 6.74% ($p < 0.05$), 20.92% ($p < 0.01$) and 35.10% ($p < 0.001$) respectively. However,

the lead acetate (5 ppm) along with the acetone, methanol and aqueous extract (5 mg/ml) in goat liver homogenate significantly reduced to 24.34 %, 25.84%, and 25.71% respectively. Supplementation of methanol and aqueous extract of *Chenopodium botrys* as an ameliorative agent resulted in significant reduction in elevated MDA (Malondialdehyde) levels in lead exposed group.

Protein levels

Lead acetate exposure caused the significant decline in the protein levels in goat liver homogenates compared to control (Table 1). The decrease in the protein content at 1 ppm and 3 ppm exposure was represented as 17.53 % ($p < 0.02$) and 26.66% ($p < 0.001$), respectively. Maximum reduction of protein content 35.49% in the liver homogenate was observed at 5 ppm concentration of lead acetate ($p < 0.001$). Administration of acetone methanol and aqueous extract of *Chenopodium botrys* (5 mg/ml) to homogenate did not cause any significant effect. However, simultaneous supplementation of lead acetate (5 ppm) and *Chenopodium botrys* acetone methanol and aqueous extract (5 mg/ml) in liver homogenate significantly increased 43.19 %, 54.28% and 51.00% respectively protein level compared to lead acetate (5 ppm) exposed group (Table 2). Supplementation of methanol and aqueous extract of *Chenopodium botrys* as a therapeutic agent resulted in significant maintenance of protein levels against lead intoxication.

Alkaline phosphatase (E.C.3.1.3.1) [E.C. - Enzyme Commission Number]

Lead acetate exposure to goat liver homogenate for 30 min brought about a significant reduction in the alkaline phosphatase activity. Results revealed that alkaline phosphatase activity markedly decreased as the dose of lead acetate was increased in goat liver homogenate, and it remained less than control always (Table 1). The decline in the enzyme activity at 1 ppm and 3 ppm exposure was represented as 57.19% ($p < 0.01$) and 59.42% ($p < 0.01$), respectively. Maximum retardation of enzyme activity 63.58% in liver homogenate was noted at 5 ppm exposure of lead acetate ($p < 0.001$). Addition of 5 mg/ml acetone methanol and aqueous extract of *Chenopodium botrys* to homogenate did not cause any significant effect. However, simultaneous addition of the lead acetate (5 ppm) and acetone methanol and aqueous extract of *Chenopodium botrys* (5 mg/ml) in goat liver homogenate significantly maintained 4.79%, 0.96% and 1.60 % reduction in enzyme activity as compared to control (Table 2). Supplementation of methanol and aqueous extract of *Chenopodium botrys* significantly maintained alkaline phosphatase activity closest to control group and exerted protective effect against lead toxicity.

Acid phosphatase (E.C.3.1.3.2)

Results revealed that acid phosphatase activity significantly increased as the dose of lead acetate was increased in goat liver homogenate (Table 1). The increase in the enzyme activity at 1 ppm and 3 ppm lead exposure in homogenate cultures was represented as 2.21% ($p < 0.0001$) and 10.87 % ($p < 0.0001$), respectively. Statistically extremely significant elevation of $p < 0.0001$ 29.83% of enzyme activity in liver homogenate was observed at 5 ppm concentration of lead acetate. Addition of 5 mg/ml acetone methanol and aqueous extract of *Chenopodium botrys* to homogenate did not cause any significant effect. However, simultaneous addition of lead acetate (5 ppm) and acetone methanol and aqueous extract of *Chenopodium botrys* (5 mg/ml) in goat liver homogenate significantly ameliorated 8.09 %, 22.70 % and 18.16 % respectively the enzyme activity (Table 2). Addition of methanol and aqueous extract of *Chenopodium botrys* as the therapeutic agent significantly maintained acid phosphatase activity in lead exposed liver homogenate nearest to control group.

Table 1: Biochemical parameters of control and exposed liver homogenates *in vitro* study of *Chenopodium botrys* (*n*=5, mean ± SEM) against lead-induced toxicity.

Biochemical Parameters	Group I Control	Group II Acetone CB (5mg/ml)	Group III Methanol CB (5mg/ml)	Group IV Aqueous CB (5mg/ml)	Group V LA (LD) (1ppm)	Group VI LA (MD) (3ppm)	Group VII LA (HD) (5ppm)	Group VIII LA (HD) + Acetone CB (5mg/ml)	Group IX LA (HD) + Methanol CB (5mg/ml)	Group X LA (HD) + Aqueous CB (5mg/ml)
LPO[a]	5017.21± 18.12	5009.21 ±20.36	5012.23±25.36	5011.09±19.36	5355.39±14.35	6066.92±23.96	6777.86±41.11	5128.36± 21.03	5026.15±19.38	5035.53± 24.10
Protein[b]	20.82 ±0.251	20.27± 0.312	20.81± 0.121	20.82±.363	17.17± 0.151	15.27± 0.144	13.43± 0.344	19.23± 0.243	20.72± 0.152	20.28± 0.382
ALPase[c]	3.13± 0.321	3.05± 0.124	3.13± 0.342	3.10± 0.321	1.34± 0.125	1.27± 0.025	1.14± 0.064	2.98± 0.124	3.10± 0.112	3.08± 0.154
ACPase[d]	5.43±	5.25±	5.39±	5.35±	5.55±	6.02±	7.05±	6.48±	5.45±	5.77±
SDH[e]	410.03±4.021	407.00± 2.015	410.01± 3.265	408.32±1.254	351.18± 2.018	316.74±3.065	255.78± 2.154	378.26± 1.354	405.23± 1.235	390.22± 3.241

p – Values: *$p < 0.05$, **$p < 0.01$, *** $p < 0.001$; CB - *Chenopodium botrys* extract, LA - Lead Acetate, LD - Low Dose, MD - Mid Dose, HD - High Dose NS - Non significant v/s control group; a = nano moles of MDA / 100 mg tissue weight / 60 min; b = mg Protein / 100 mg fresh tissue weight; c, d = µ moles of p– nitrophenol released / 30 min / 100 mg tissue weight; e = µg formazan formed / 15 min / 100 mg tissue weight

Table 2: Gross effect of lead and *Chenopodium botrys* (CB) on biochemical parameters of goat liver homogenates *in vitro* (% of difference with respect to their control as well as lead exposed homogenate cultures).

Biochemical Parameters	Group V LA (LD) (1ppm)	Group VI LA (MD) (3ppm)	Group VII LA (HD) (5ppm)	Group VIII LA (HD) + Acetone CB (5mg/ml) (a)	Group IX LA (HD) + Methanol CB (5mg/ml) (a)	Group X LA (HD) + Aqueous CB (5mg/ml) (a)	Group VIII LA (HD) + Acetone CB (5mg/ml) (b)	Group IX LA (HD) + Methanol CB (5mg/ml) (b)	Group X LA (HD) + Aqueous CB (5mg/ml) (b)
LPO[a]	6.74	20.92	35.10	2.22	0.18	0.37	24.34	25.84	25.71
Protein[b]	17.53	26.66	35.49	7.64	0.48	2.59	43.19	54.28	51.00
ALPase[c]	57.19	59.42	63.58	4.79	0.96	1.60	161.40	171.93	170.18
ACPase[d]	2.21	10.87	29.83	19.33	0.37	6.26	8.09	22.70	18.16
SDH[e]	14.35	22.75	37.62	7.75	1.17	4.83	47.88	58.43	52.56

All values are expressed in % of decrease or increase; a – compared to control group; b – compared to Group VII

Succinate dehydrogenase (E.C.1.3.99.1)

A significant decline was observed in the activity of succinate dehydrogenase in lead exposed homogenate cultures compared to control (Table 1). Reduction in enzyme activity at low dosage (1 ppm), medium dosage (3 ppm), and high dosage (5 ppm) exposure was represented as 14.35 % ($p < 0.001$), 22.75 % ($p < 0.001$) and 37.62 % ($p < 0.001$), respectively. Administration of acetone methanol and aqueous extract of *Chenopodium botrys* to homogenate did not cause any significant effect. However, co-administration of lead (5 ppm) and acetone methanol and aqueous extract of *Chenopodium botrys* (5 mg/ml) in liver homogenate significantly ameliorated 47.88 %, 58.43 % and 52.56% respectively succinate dehydrogenase activity as compared to lead (5 ppm) exposed group (Table 2) and methanol and aqueous extract of *Chenopodium botrys* exerted protection against lead-induced hepatotoxicity.

DISCUSSION

During the *in vitro* study the Malondialdehyde level was found to be elevated in the lead group and the level in control group was normal as compared to lead group. The rise in the level of MDA was due to the formation of reactive oxygen called as free radicals. The imbalance between antioxidant system and free radicals leads to oxidative stress. According to the previous literature the mechanism behind the increase in the formation of free radicals are hydroxyl radicals, hydrogen peroxide and superoxide ions are responsible for the decrease of scavenger glutathione.

The *in vitro* investigation shows that the addition of methanol and aqueous extract of *Chenopodium botrys* to the lead group of various concentrations shows a tremendous decrease in the lipid peroxides and protein content level in the goat liver homogenates. The active phytoconstituents present in the methanol and aqueous extract of *Chenopodium botrys* shows a beneficial effect in decreasing the free radicals.

The lowering of protein level is due to combining of lead and sulfhydryl group containing protein and various enzymes interfere in this process which plays a vital role in the cell metabolism. Further, at the time of lipid peroxidation Malondialdehyde was manufacture which attaches to –SH groups of protein and show a harmful effect. Thus inhibiting enzymes requiring –SH groups for their activities.[18] The reduction of protein level is due to proteolysis and the reduced incorporation of amino acids into proteins[19] or increased deamination of amino acids in the liver and kidney. Thus, one of the reasons for liver toxicity in the current study might be the decreased availability of proteins necessary for growth and differentiation of tissues and enzyme systems.

The methanol and aqueous extract of *Chenopodium botrys* is able to prevent cell injury by maintaining sulfhydryl groups of membrane binding proteins. The hepatoprotective and membrane stabilizing properties of the plant can be attributed to its anticholestic action, reduction in free radicals and reduction in cell protein necrosis as well as glutathione depletion reduction potential.

Many products of LPO such as hydro peroxides can inhibit protein synthesis and alter enzyme activity.[20] Results of current study elucidated that lead acetate exposure caused significant depletion in activity of alkaline phosphatase in liver. Alkaline phosphatases are a group of enzymes, which hydrolyze phosphate esters at alkaline pH. Reduced alkaline phosphatase activity might be attributed to the alteration in cell membrane permeability in addition to lead-induced imbalance between synthesis and degradation of enzyme.

The data of current investigation also revealed the increase in acid phosphatase activity in lead acetate exposed liver homogenates. Acid phosphatase, a lysosomal enzyme is involved in a number of activities such as phagocytosis,[21] autolysis, and dissolution of tissue components, fat absorption in intestine; cellular differentiation and keratinization.[22] Alteration in activity might be due to direct inhibitory effect of accumulated lead and fat as well as disturbed balance between synthesis and degradation of enzyme in liver.

Results shows that liver homogenate with lead acetate group lost the SDH. The changes occur due to the change in the metabolism occur during TCA cycle which affect the conversion of succinate to fumarate which block the Kreb's cycle that will result in decrease in the production of ATP. Changes in the SDH activity is also due to changes in mitochondrial structure and functions of mitochondrial enzymes due to accumulation of lead in mitochondria. Lead may uncouple oxidative phosphorylation, which may reflect on the slow rate of TCA cycle. Thus, lowering of SDH activity shows the altered state of oxidation and energy metabolism of a damaged liver.

The methanol and aqueous extract *Chenopodium botrys* also manifested maintenance of alkaline phosphatase, acid phosphatase and succinate dehydrogenase enzyme activities in goat liver homogenate nearest to control.

CONCLUSION

In conclusion, the findings of present study suggest the role of oxidative mechanisms in lead-acetate induced liver damage. From the current *in vitro* study, it can be clearly elucidated that heavy metal lead affects the antioxidative as well as other biochemical indices of goat liver possibly by inducing oxidative stress. Present research study also suggested that

lead metal appears to cause an imbalance in the antioxidant defense system by inhibiting some related enzymes, thereby enhancing the free radical mediated peroxidation of lipids. The study findings also confer that lead adversely affects the protein content as well as energy and oxidative metabolism of goat liver. Thus, from the present *in vitro* study, it can be clearly concluded that lead exposure has a definitely destructive effect on the structural, metabolic and functional status of liver.

The current investigation also emphasized that co–administration of methanol and aqueous extract of *Chenopodium botrys* in liver homogenate significantly exerts protective effects against lead intoxication due to the presence of flavonoids and phenolic compounds. Thus, it is clearly revealed that *Chenopodium botrys* has a significant role in alleviating the lead toxicity. It acts as a therapeutic eliminator of heavy metals. Hence, this antidote could be a very effective and beneficial ameliorating agent against lead-induced hepatic toxicity the world over.

The present investigation has elucidated the mechanism of action of lead-induced hepatotoxicity and also suggested its amelioration, which can be considered as a significant contribution in the field of mitigation of plumbism in endemic regions.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

LPO: Lipid peroxidation; **ALPase:** Alkaline phosphatase; **ACPase:** Acid phosphatase; **SDH:** Succinate dehydrogenase; **TCA cycle:** Tricarboxylic acid cycle.

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