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Protective effects of the dietary supplementation of turmeric (*Curcuma longa* L.) on sodium arsenite-induced biochemical perturbation in mice

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Abstract

The present study was undertaken to evaluate the protective effect of turmeric powder on arsenic toxicity through mice model. Swiss albino male mice were divided into four groups. The first group was used as control, while groups 2, 3, and 4 were treated with turmeric powder (T, 50mg/kg body weight/day), sodium arsenite (Sa, 10mg/kg body weight/day) and turmeric plus Sa (T+Sa), respectively. Results showed that oral administration of Sa reduced the weight gain of the mice compared to the control group and food supplementation of turmeric prevented the reduction of weight gain. Turmeric abrogated the Sa-induced elevation of serum urea, glucose, triglyceride (TG) level and alanine aminotransferase (ALT) activity except the activity of alkaline phosphatase (ALP). Turmeric also prevented the Sa-induced perturbation of serum butyryl cholinesterase activity (BChE). Therefore, ameliorating effect of turmeric on Sa-treated mice suggested the future application of turmeric to reduce or to prevent arsenic toxicity in human.

Introduction

Arsenic is a ubiquitous element present in food, soil, water and airborne particles. The general population is exposed to inorganic and organic arsenic through water, food, occupation and other environmental sources. Arsenic toxicity is a global health problem affecting many millions of people in many countries. Arsenic toxicity has caused an environmental tragedy in Bangladesh and West Bengal of India where millions of peoples have been affected due to the drinking of arsenic contaminated ground water[1-3]. A huge numbers of toxicity cases have already been reported in the north-west region of Bangladesh and it is becoming alarming day by day as the new cases of toxicity are being found. Around 35-77 millions of peoples are at risk for arsenicosis in Bangladesh. In Bangladesh the number of toxicity cases have exceeded over the number of Chernobyl catastrophe[4]. Although arsenic is a well established human carcinogen, paradoxically, arsenic is also used to treat acute promyelocytic leukemia (APL) for its potentiality to induce apoptosis in cancer cells. Due to its dual roles in therapeutic application and in acute toxicity, arsenic has created a renewed attention.

Arsenic toxicity induces dermatitis, multi site cancers, cardiovascular diseases, diabetes mellitus, peripheral neuropathy, liver damage, renal failure, and many other pathogenesis[5-11]. The major metabolic pathway of inorganic arsenic in humans is its methylation in liver. This methylation of arsenic is proved by the presence of monomethylarsonic acid (MMA) and dimethylarsinic acid in urine and bile[12,13]. Generally toxicity of arsenic is thought to cause largely by its reaction with free sulfhydryl groups of enzymes and proteins followed by their cross linking[14,15]. The cross linking of enzymes or proteins activate the multiple intracellular signaling pathways inside the cells that may be responsible for arsenic-mediated pathogenesis. Moreover, arsenic-induced intracellular signals are largely mediated through redox-linked mechanism since reactive oxygen species (ROS) produced by arsenic act as second messengers[15,16].

Attempt to apply nutritional antioxidant to prevent or to treat the diseases caused by oxidative stress have been getting attention in recent years. Many plant products exert their protective effects against oxidative stress-mediated diseases by scavenging free radicals. Although arsenic as an oxidative

stress causes serious human sufferings, few reports on the beneficial effects of plant products against arsenic-toxicity are available. Turmeric is used as a popular cosmetic for the women in India, Nepal and Bangladesh. It is believed that it brightens the skin. The most important feature of turmeric is that its powder or pest forms are used as important natural coloring/flavoring agents in the Indian subcontinent for the preparation of curry and foods. Turmeric (*Curcuma longa linn)* exhibits antioxidant properties. Rhizome of Turmeric (family *Zingiberaceae*) is composed of yellow colored phenolic pigment called curcumin which has been reported as a potent antioxidant. It has been reported that curcumin can potentially inhibit the generation of reactive oxygen species (ROS) both *in vitro* and *in vivo*[17]. To heal many health disorders like liver problems, inflammation, digestive disorders and skin disease, turmeric has long been used as medicine. There are multiple beneficial roles of turmeric but no side effects have been reported yet. The present study has been undertaken to evaluate the effect of turmeric on arsenic-induced growth retardation and biochemical alterations in the serum of mice.

Material and Methods

Animal maintenance: Adult healthy (4 weeks of age) Swiss albino male mice with average body weight were purchased from ICDDR,B (International Centre for Diarrhoeal Disease Research, Bangladesh). The animals were randomly selected and housed in polycarbonate cages with steel wire tops and wood-cobe bedding (six mice per cage). After one weeks of acclimation, animals were divided into four equal groups named control (C), turmeric (T), sodium arsenite (Sa) and turmeric plus sodium arsenite (T+Sa). They were maintained with 12h:12h dark light cycle with available supply of distilled water and feed. Sa was given to the mice with water (10 mg/kg body weight/day) and turmeric powder (50 mg/Kg body weight/day) was added to the normal diet (as supplement). The amounts of water and food consumed were recoded every day.

Preparation of turmeric powder: First rhizomes of turmeric plant were collected from farmer and then cleaned and washed. The rhizomes were then sliced and sun dried. Finally turmeric powder were obtained by grinding the sun dried slice and kept at 4°C with sealed plastic packet to avoid the microbial contamination.

Sample collection and assessment of serum: Blood specimens were collected from the thoracic artery of the mice after anaesthetization with diethyl ether. For coagulation, blood was kept about 20 minutes at room temperature. After centrifugation at 1600g for 15 minutes at 4°C, serum were drawn off and stored at-80°C until the experiments were performed.

Laboratory examination: The analyzer (CHEM-5 V3, Erba, Mannheim, Germany) were used for the measurement of serum indices by using commercially available kits according to the manufacture's protocol. Serum urea, glucose, TG level and the activity of ALT were measured by the kits from Human, Germany. ALP activity was determined by the kit from BioSystems, SA. Spain. BChE activity was measured by using butyryl cholinesterase (CHE) kit (RANDOX, UK). All serum samples were analyzed in duplicate and then mean values were taken.

Statistical analysis: Statistical analyses were performed with SPSS for windows, version 15.0 (SPSS, Chicago, IL). Data are expressed as mean ± SD or mean ± SE. Differences between the body weights and serum indices of different groups of mice were analyzed by using t-test.

Results

Protective effect of turmeric on the Sa-induced inhibition of body weight gain: Previous study demonstrated that arsenic inhibited the body weight gain of the experimental animals[18,19]. We investigated whether turmeric could prevent the loss of body weight of the growing mice caused by Sa. The initial average weights (mean±SD) of the experimental mice were 18.89±0.525, 18.06±0.672, 18.97±0.838, and 19.126±0.743 gms for control, turmeric, Sa, and turmeric plus Sa groups, respectively. Body weight of the mice in each groups were taken on 2, 4, 6, 8 and 10 weeks from the starting day of the experiment. The body weight was plotted against weeks and a curve for each group of mice was obtained (Fig. 1). Body weight gain of Sa-treated mice comparing with the control group was found to be lower. The average body weight (mean±SD) of the control, turmeric, Sa, and turmeric plus Sa groups were 40.038±0.966, 39.58±1.003, 33.044±0.933 and 36.142±0.73 gms respectively, at 10 weeks which indicated that turmeric supplemented food prevented the Sa-induced inhibition of growth of mice. Only turmeric did not show any apparent effects on the growth of the mice as the pattern of growth of this group was almost similar to control group. There were no significant differences in water intake volume and in amount of food consumption

between animals in four different groups (data not shown).

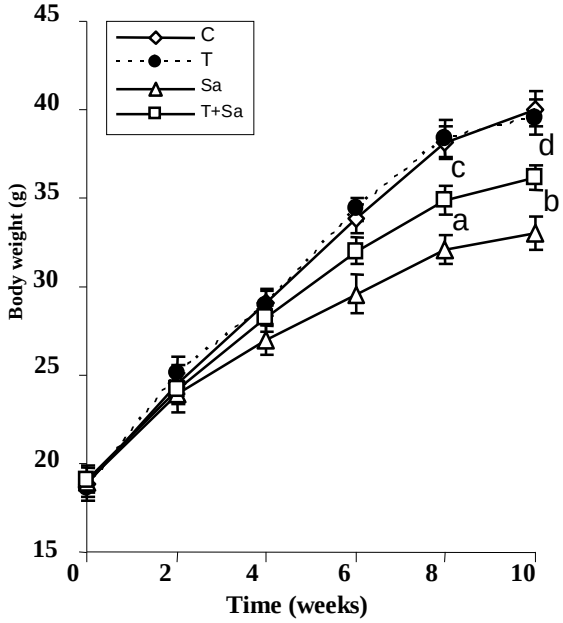

Fig. 1. Prevention of Sa-induced body weight loss by turmeric. Body weight (mean ± SD) were taken at every two weeks up to 10 weeks from the starting date of the experiment (0 week) of control (c), turmeric (T), sodium arsenite (Sa) and turmeric plus sodium arsenite (T+Sa) groups of mice. *X*- and *Y*-axis represented the duration (weeks) with in study and body weight (g), respectively. [a]Significantly different from control at the same time point at $p<0.05$. [b]Significantly different from control at the same time point at $p<0.05$. [c]Significantly different from the group of Sa-treatment at the same time point at $p<0.05$. [d]Significantly different from the group of Sa-treatment at the same time point at $p<0.05$.

Protective effect of turmeric on the Sa-induced alteration of serum biochemical indices: Elevated serum urea level is very often associated with renal dysfunction and excessive amount of protein catabolism. Therefore, we measured the serum urea level in all groups of our experimental mice and evaluated the effect of turmeric on this phenomenon. As shown in Table I, the serum urea level (mean±SE) of four groups of mice were 74.26±4.454, 51.07±6.32, 100.67±4.88 and 67.16±2.305 mg/dl in control, turmeric, Sa, and turmeric plus Sa groups of mice, respectively. The results showed that Sa treatment significantly ($p<0.05$) increased serum urea level compared to the control group and turmeric supplementation inhibited the Sa-induced elevation of serum urea level which was also statistically significant ($p<0.05$). Turmeric alone also decreased the baseline serum urea level as the level of turmeric treated mice is lower than that of control group of mice. Tseng et al. (2004) found that arsenic induced diabetes mellitus in the chronically exposed subjects[20]. Therefore, we investigated the serum glucose level in the four groups of experimental mice to see the effect of turmeric on arsenic-induced hyperglycemia and we found that arsenic treatment significantly ($p<0.05$) increased the serum glucose level and supplementation of turmeric with food prevented the Sa-induced increase of blood glucose level (Table I). Intriguingly, turmeric alone also decreased the baseline blood glucose level comparing with the control group. It has been reported that chronic arsenic exposure alters the several blood lipid parameters associated with cardiovascular diseases[21]. In this study, we also evaluated the serum TG level and we found that Sa treatment significantly ($p<0.05$) increase serum TG level (Table I). Addition of turmeric to the food showed the significant ($p<0.05$) protection against the elevation of TG level caused by Sa. The TG level (mean ± SE) of the control, turmeric, Sa and turmeric plus Sa groups were 72.85±3.1, 69.21±5.87, 112.59±4.7 and 97.22±3.05 mg/dl, respectively. Thus these results suggested that turmeric might have protective effect on the alteration of serum parameters that have been associated arsenic-induced cardiovascular diseases.

Table I: Serum urea, glucose and TG level of the groups of experimental mice

Serum indices (mg/dl)	Experimental groups			
	Control(C)	Turmeric (T)	Sodium arsenite (Sa)	Turmeric+ Sodium arsenite (T+Sa)
Urea	74.26±4.454	51.07±6.32[a]	100.67±4.88[a]	67.16±2.305[b]
Glucose	123.4±4.24	66.6±8.46[a]	183.1±14.8[a]	143.67±16.86[b]
TG	72.85±3.1	69.21±5.87	112.59±4.7[a]	97.22±3.05[b]

Values are expressed as mean ± SE, n=6 for each group of mice.
[a]Significantly different from control at $p<0.05$. [b]Significantly different from the Sa-treated group at $p<0.05$

Table II: Activities of liver enzymes in serum of the groups of experimental mice

Serum indices (U/L)	Experimental groups			
	Control (C)	Turmeric (T)	Sodium arsenite (Sa)	Turmeric+ Sodium arsenite (T+Sa)
ALT	61.99±6.39	61.4±3.65	71.79±4.21[a]	66.54±8.73
ALP	119.3±10.35	120.35±3.6	178.82±24.75[a]	179.8±21.36
BChE	13247±343.93	13102.33±427.07	9905.33±806.36[a]	13212.67±1463.41[b]

Values are expressed as mean ± SE, n=6 for each group of mice.
[a] Significantly different from control at $p<0.05$. [b] Significantly different from the Sa-treated group at $p<0.05$.

Liver is the primary organ for arsenic intoxication. Elevated activity of liver enzymes represents the liver dysfunction. So we next measured the activities of liver enzymes, ALT and ALP in serum and found that treatment of Sa significantly ($p<0.05$) increased the activities of these enzymes (Table II). However, turmeric was found to inhibit the Sa-induced elevation of ALT activity although this inhibition was not so much statistically significant ($p>0.05$). We did not found any protective effect of turmeric on the arsenic-induced elevation of ALP activity. Previously Anita K Patlolla et al. (2005) showed that acute arsenic exposure decreased the cholinesterase activity in rats[22]. Decreased butyryl cholinesterase (BChE) activity has been reported to be observed in liver dysfunction[23-26]. In this study we therefore, investigated whether turmeric could prevent the Sa-induced serum BChE (Table II). Serum BChE activity (Mean ± SE) was measured in the control, turmeric, Sa and Turmeric plus Sa groups were 13247±343.93, 13102.33±427.07, 9905.33±806.36 and 13212.67±1463.41 U/L, respectively. The enzyme activity was significantly ($p<0.05$) decreased in the group exposed to Sa compared to the control and turmeric groups. Intriguingly, we observed that supplementation of turmeric with food significantly ($p<0.05$) prevented the Sa-induced perturbation of cholinesterase activity.

Discussion

Arsenicals are potent environmental pollutants and human exposure occurred mainly through drinking water, foods and air. The main cause of arsenic toxicity in Bangladesh, India, Taiwan and Mongolia is the drinking of ground water which has heavily been contaminated with arsenic and recently alarming level of arsenic has been found in food grains, vegetables, milk and other food chains[27]. The main purpose of the study was to investigate the ameliorating effect of turmeric on the Sa-induced biochemical alterations in the serum of mice. Several soluble enzymes/molecules of serum have been considered as indicators of the cardiovascular diseases, hepatic and kidney dysfunction. Arsenic affects almost all organs including liver, kidney and cardiovascular system. Arsenic has been reported to be associated with diabetes mellitus**,** cardiovascular diseases, hepatic and renal dysfunction, neurotoxicity and multi-site cancers[21,28-32]. Moreover, growth retardation and disturbance of the metabolism are also associated with arsenic toxicity[33,34]. In this study, Sa-induced loss of weight gain in Sa-treated mice (Fig. 1) was compatible with the previous results demonstrated by Verma et al. (2004) and Yang et al. (2007)[18,19]. Interestingly, food supplementation of turmeric prevented the growth retardation indicating that turmeric might have the potentiality to reduce the intensity of toxicity induced by Sa. Pathogenic condition as well as organ dysfunction can be diagnosed by the alteration of several serum indices[35]. The elevation of serum urea level in Sa-treated mice is considered as a significant marker of renal dysfunction. The blood urea becomes raised when the kidney tubules are prevented from removing the urea and other waste products from the blood. Elevated blood urea is correlated with an increased protein catabolism in mammalian body or from more efficient conversion of ammonia to urea as a result of increased synthesis of enzyme involved in urea production. Also, the high levels of blood urea results from either increased breakdown of tissue, dietary or impaired excretion[36]. Moreover, the increase in urea concentrations in serum of animals treated with Sa might be due to its effect on liver function, as urea is the end-product of protein catabolism[37]. The present study indicated that turmeric potentially inhibited the elevation of serum urea by Sa (Table I). Sa-induced elevation of blood glucose level observed in this study was an agreement with the result of Tseng (2004), who showed that chronic arsenic exposure increased blood glucose level in human population[20]. Oxidative stress like arsenic destroy β cells of the pancreatic islets that leads to the insufficient production of insulin required for the utilization of blood glucose[38]. Inhibitory effect of turmeric powder on Sa-induced elevation of blood glucose level was probably due to the anti-oxidant properties of turmeric. Moreover, curcumin and its structurally related compounds (curcuminoids) of turmeric decreased total cholesterol and triglyceride level in blood[39]. So food supplementation of turmeric powder abrogated the elevation of serum TG level in the Sa-treated mice. We also tried to evaluate the effect of turmeric on the alteration of total cholesterol level (TC) or other blood lipid parameters such as low density lipoprotein (LDL) and high density lipoprotein (HDL); however, we were unable to include those results in this study because the results were not strongly conclusive. We need more investigations to evaluate the effect of turmeric on the arsenic-induced alteration of TC, LDL and HDL.

Hepatic cancer as well as hepatic disorder appears to be a primary cause of arsenic-related mortality[40-42]. Elevated activities of ALP and ALT in the Sa-treated mice were in agreement with the results of Mazumder (2005) who conducted a study on Indian population group exposed to arsenic and showed that prolong drinking of arsenic

contaminated water developed hepatomegaly with the increasing activities of hepatic enzymes that are used for liver function test[43]. BChE present in serum/plasma has a broader range of esterase activity referred to as "pseudo" or "nonspecific" cholinesterase which hydrolyzes both choline and aliphatic esters. Decreased serum/plasma BChE activity is associated with hepatitis, hepatic metastases and heart attack[2,23,24,44]. Usually BChE activity is used to monitor the toxicity of organophosphate and carbamate present in herbicides and pesticides. In the previous study, we reported that BChE activity was decreased in the population exposed to arsenic chronically[26]. In this study, we also observed that Sa decreased the serum BChE activity. All these results suggested that Sa administration induced liver dysfunction. Interestingly, we found that turmeric supplementation prevented the decrease of butyryl cholinesterase activity significantly. Some protective effect of turmeric on the alteration of ALT activity was also observed although this protection was not statistically significant. On the other hand, turmeric did not show any significant protection against the elevation of ALP activity caused by Sa treatment. Preventive action of turmeric on butyryl cholinesterase and ALT activities suggested that turmeric at least in part, provided protection against Sa-mediated liver toxicity.

This study clearly indicated the efficacy of turmeric on the protection of Sa-induced changes of serum indices. However, we did not clarify in this study how turmeric showed the protection against arsenic action. Further study is needed to explain the mechanism of turmeric for the reduction of arsenic toxicity. One possibility is that curcumin and other antioxidant of turmeric inhibit the arsenic action as they act as ROS scavengers[45-47]. ROS plays a pivotal role as a second messenger in arsenic-induced transduction of intracellular signals[15,16]. Previously Hossain et al. (2000) showed that curcumin effectively inhibited the Sa-induced cell death by blocking the c-Jun amino-terminal kinase (JNK) pathway[15]. It has also been reported that antioxidant properties of curcumin protects the several organs including liver and kidney from oxidative damage[5,48,49]. Very recently, ameliorating effect of curcumin on arsenic-induced biochemical perturbations and neuro toxicity in rats has been reported[50,51]. However, application and usefulness of turmeric powder to reduce the level of arsenic toxicity is practically important as turmeric has already been recognized as safe natural coloring and flavoring agents. From the ancient period, turmeric powder and pest forms are being used by the population of Indian subcontinent for the preparation of food and for the brightening of skin without any side effects. Until recently, extremely high doses of curcumin were required to obtain desired blood levels as curcumin has very poor oral bioavailability. Many commercial curcumin products include additives to improve the absorption that have extremely adverse side effects on human body. So application of turmeric powder against arsenic toxicity has more beneficial roles than the active ingredient curcumin. Due to the deleterious action of arsenic on human body, there is increasing interest in the development of preventive or protective therapy for reducing arsenic toxicity in humans. Plants or their extracts have been created a renewed attention as protective therapies against oxidative damage of the several organs in human body. This study demonstrated that Sa could reduce the body weight gain and change the serum indices associated with pathogenesis of liver, kidney and cardiovascular system, and food supplementation of turmeric powder showed the protection against those changes induced by Sa. The results in this study, therefore, suggested that turmeric could be used in future to reduce or to prevent the toxic effect of arsenic in humans.

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