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Protective Effects of Cinnamon on oxidative stress and nephron toxicity induced by Lead Acetate in Male Albino *(Rattus rattus)*

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Abstract

Cinnamon the eternal tree of tropical medicine is one of the most important and spices used daily by people all over the world for preparing delicious foods. This plant considers as a rich source of antioxidants. Therefore, the current research was aimed to study the protective effects of cinnamon against oxidative stress and, nephron-toxicity induced by Lead acetate in male rats. For this purpose, 35 male rats have been used, they were randomly allotted to five groups each with seven rats; The first group was used as a control negative and was fed on the standard diet and tap water. The second group was injected intraperitoneally (IP) (20 mg/kg BW) with lead acetate. The third group was treated with 10% cinnamon dissolved drinking water and injected with 20 mg/kg BW lead acetate. The fourth group was treated with 20% cinnamon dissolved in drinking water and injected with lead acetate (20 mg/kg BW). The fifth group was treated with 40% cinnamon dissolved in drinking water and injected with lead acetate (20 mg/kg.bw). After 10 weeks of the experiment, blood collected for estimation of superoxide dismutase (SOD), levels of total glutathione (GSH), malonaldehyde (MDA), serum creatinine and blood urea. The second group results revealed that lead acetate has a negative effect on rats by significantly decreasing the level of SOD, total GSH, blood urea and creatinine and significantly increasing the level of MDA in the serum of rats. The protective activity of cinnamon against oxidative stress and nephrotoxicity was dose-dependent because the best result has been obtained from third group Pb+10% cinnamon by improving levels of SOD, GSH, blood urea, serum creatinine concentration. Positive impacts of cinnamon decreased at a higher concentration 20% cinnamon and 40% cinnamon. As a result, cinnamon at low concentration has a great impact on oxidative stress and nephron-toxicity.

Introduction

Heavy metals have abundant deleterious health effects and lead acetate is one of the most dangerous contaminants on the earth with serious impact on human and even animals in several ways and in general, lead associated with environmental pollution because of their toxicity and bioaccumulation [1]. Environmental levels of lead have increased over the past three centuries as a result of human activity, so most of the high levels found throughout the environment come from human activities that is continually increased. As increasing worldwide use of leaded gasoline, paints, and toys [2]. Lead acetate impaired the physiological functions of several organs by causing oxidative stress and induce free radical production such as superoxide radicals, hydrogen peroxide, hydroxyl radicals and lipid peroxides [3]. The serious damages in several organs like liver, kidney, reproductive and central nervous systems in mammals induced by lead were the result of oxidative stress by enhancement of lipid peroxidation [4-6]. Oxidative stress is the outcome of a negative shift of the balance between the production of reactive oxygen species (ROS) and the

ability of the biological systems to remove the ROS mediated damage or repair of it rapidly causing damage to membranes, DNA, and proteins [7]. Recently, proved that the long-term lead exposure inhibits antioxidants activity such as superoxide dismutase (SOD) and catalase (CAT) and it decreases total glutathione (GSH) concentration [8]. There has been increased demand among researchers to use plant products with antioxidant activity for protection against heavy metal toxicity [6,9].

One of these plants is cinnamon which is a medicinal tropical plant belongs to Lauraceae family and is obtained from the inner bark of the cinnamon tree. The used species in this study is the commercial cinnamon that has several bioactive features and widely used in herbal medicines [10]. It was indicated that cinnamon may serve as the potential dietary source of natural antioxidants for improving human nutrition and health. It is rich in natural polyphenol compound [11]. Previous studies reported that cinnamon stimulates the increase of antioxidant enzymes activities, including SOD and CAT in rat's liver and heart [12]. The present study was designed to assess the potential protective effect of cinnamon against lead acetate-induced oxidative stress by evaluating the activity of SOD, level of total GSH, MAD and kidney function tests of male albino rats.

Materials and Methods

a. Animals

A total of 35 healthy male albino rats weighing (160 - 170) g aged 8-10 weeks were used in this study. The cages were cleaned and sterilized weekly with 70% ethanol. Each cage was embedded with wooden shelve and maintained for at least 2 weeks before initiation of the experiments [13]. Rats were acclimatized for 2 weeks for standard condition before the beginning of an experiment.

b. Lead acetate(PbA)

PbA obtained from the Faculty of Science and Educational Science /Sulaimani University for the preparation of the stock solution of 20g/L.

c. Preparation of cinnamon aqueous solution

The cinnamon aqueous solution was freshly prepared from the powdered cinnamon bark by soaking the ground bark in distilled water at 90°C for 2 h for 3 concentrations 10%, 20%, and 40% followed by filtration.

d. Standard diet

The standard diet for rats was prepared for 1.0 kg as follows: wheat 665.5g, soya 256.2g, sunflower oil 43.5g, Ca2(PO4) 6.42, limestone 14.9g, salt 6.34g, methionine 1.56g, lysine 2.44g, vitamins 0.8g, choline 0.58g, chloride 0.62g, enzymes and trace elements 0.5g [14].

e. Experimental design and animal grouping

Thirty-five adult male rats (160-180 g) were housed in temperature-controlled rooms (25°C) with constant humidity (40-70%) and a 12 h light: dark cycle. All animals were treated in accordance with the principles of laboratory animal care. The animals were divided into five groups of seven rats each as follow: 1-Group C: The animals served as the control group. 2-Group Pb: The animals were injected (IP) with 20mg/Kg body weight of PBA, once each a week for 10 weeks. 3-Group Pb+10% Ci: The animals were injected (I.P) with 20mg/Kg body weight of PbA once weekly, and orally treated with 10% cinnamon in drinking water, for 10 weeks. 4-Group Pb+20% Ci: The animals were injected (I.P) with 20mg/Kg body weight of PbA once weekly, and orally treated with 20% cinnamon in drinking water, for 10 weeks. 5-Group Pb+40% Ci: The animals were injected (I.P) with 20mg/Kg body weight of PbA once weekly, and orally treated with 40% cinnamon in drinking water, for 10 weeks.

f. Blood collection

At the end of each experiment, the animals were fasted overnight and sacrificed after chloroform anesthesia. Blood samples have been taken by heart puncture without anticoagulant and allowed to clot for

serum separation.

g. Biochemical assays

1. **Assay for SOD activity**: SOD in serum was measured by using SOD Assay Kit-WST (Dojindo), monitoring the decrease in the rate of superoxide mediated reduction of nitroblue tetrazolium at 450 nm using a spectrophotometer.

2. Determination of serum GSH: The content of reduced GSH and oxidized GSSH in the serum were determined by using OxiSelect^{TM} Total Glutathione Assay Kit (Cell BIOLABS, INC.). Glutathione reductase reduces oxidized glutathione (GSSG) to reduced glutathione (GSH) in the presence of NADPH. Subsequently, the chromogen reacts with the thiol group of GSH to produce a colored compound that absorbs at 405 nm. The total GSH content in unknown samples is determined by comparison with the predetermined GSH standard curve.

3. Determination of serum MDA: In the presence of heat and acid, MDA reacts with TBA to produce a pink colored end product. The intensity of color at 532 nm corresponds to the level of lipid peroxidation in the sample the level of serum MDA was determined spectrophotometrically.

4. Kidney function tests: Serum urea and creatinine levels were determined by enzymatic colorimetric methods using commercial laboratory kit purchased from BIOLABS-FRANCE and by using Cobas instrument**.**

h. Statistical Analysis

Results were expressed as mean ±S.E. Statistical differences were determined by Duncan Post Hoc test for multiple comparisons after ANOVA, The criterion for statistical significance was set at $P < 0.05$ by using SPSS (version15).

Results

Table 1 revealed that PbA has the negative effect on the level of SOD in the serum of rats by decreasing to (72.26 ± 0.09) significantly $P<0.05$ by comparing with the control group (85.32 ± 0.23). While drinking 10% cinnamon lead to increase the SOD (85.05 ± 0.19) significantly $P<0.05$ comparing with the pb group (72.26 ± 0.09), so, close to the level of the control group. On the other hand, SOD decreased significantly in both groups that drank 20% and 40% cinnamon (84.49 ± 0.15) and (32.71 ± 0.11) respectively, compared to control group (85.32 ± 0.23).

Table -1: The effect of drinking 10%, 20% and 40% cinnamon after injection of 20mg/Kg body weight of lead acetate on SOD (Mean ± S.E.) in the serum of rats.

Groups	SOD%
Co	85.32±0.23 [a]
Pb	72.26±0.09[b]
Pb+10%Ci	85.05±0.19[a]
Pb+20%Ci	84.49±0.15[c]
PB+40%Ci	32.71±0.11[d]

Table 2 reveal that the mean of total GSH µmol/ml in the serum of the Pb group decrease significantly $P<0.05$ (0.082 ± 0.002) comparing with Co group (0.248 ± 0.003). There are no significant differences between Co and Pb+10% Ci. Also, the same table shows that the level of total GSH increased significantly in the group that drank 10% Cinnamon (0.248 ± 0.005) comparing with Pb group (0.082 ± 0.002). But the level of total GSH decreased significantly in both groups Pb+20% Ci and Pb+40% Ci (0.133 ± 0.001) and (0.318 ± 0.005) respectively, comparing to the Co (0.248 ± 0.003) group.

Table -2: The effect of drinking 10%, 20% and 40% cinnamon after injection of 20mg/Kg body weight of lead acetate on Mean of GSH µmol/ml ±SE in the serum of rats.

Groups	T.Glutathione µmol/ml
Co	0.248±0.003[a]
Pb	0.082 ±0.002[b]
Pb+10%Ci	0.248±0.005[a]
Pb+20%Ci	0.133±0.001[c]

Table 3 shows significant differences among all groups. As apparent from the table, the mean concentration of MDA µmol/ml has been changed significantly in all groups. The level of MDA increased significantly in Pb group (1.379 ± 0.002) comparing to Co group (0.083 ± 0.001). But decreased significantly in all three groups that have been drinking cinnamon at concentrations of 10%, 20% and 40% (0.248 ± 0.005), (0.387 ± 0.002) and (0.172 ± 0.003) respectively, comparing with Pb group (1.379 ± 0.002). But these levels still higher significantly than Co group level (0.083 ± 0.001).

Table -3: The effect of drinking 10%, 20% and 40% cinnamon after injection of 20mg/Kg body weight of lead acetate on MDA activity µmol/ml (Mean ± SE) in the serum of rats.

Groups	MDA µmol/ml
Co	0.083±0.001[a]
Pb	1.379±0.002[b]
Pb+10%Ci	0.188±0.003[c]
Pb+20%Ci	0.387±0.002[d]
PB+40%Ci	0.172±0.003[e]

Table 4 reveal that the mean of the concentration of urea mg/ml has been increased significantly in Pb group (35.74 ± 0.03) after comparing with Co group (29.74 ± 0.030). Also, the table shows that mean of urea mg/ml of group Pb+10% Ci decreased significantly (31.45 ± 0.05) comparing with Pb group (35.74 ± 0.03) and increased non significantly after comparing with CO group (29.74 ± 0.030). On another hand, the mean of urea mg/ml increased significantly in both groups of Pb+20% Ci and Pb+40% Ci (37.80 ± 1.40) (42.77 ± 0.02) respectively after compared with Co group (29.74 ± 0.030).

Table4: The effect of drinking 10%,20% and 40% cinnamon after injection with 20mg/Kg body weight of lead acetate on urea concentration mg/ml (Mean ± SE) in serum the of rats.

Groups	Urea mg/ml
Co	29.74± 0.030[a]
Pb	35.74± 0.03[b]
Pb+10%Ci	31.45± 0.05[a]
Pb+20%Ci	37.80± 1.40[b]
PB+40%Ci	42.77± 0.02[c]

Table 5 shows that the mean of serum creatinine mg/ml increased significantly in Pb group (0.640 ± 0.008) comparing to Co group (0.298 ± 0.003). While the levels of serum creatinine decreased significantly in both groups Pb+10% Ci and Pb+20% Ci (0.298 ± 0.004) (0.291 ± 0.003) respectively comparing to Pb group (0.640 ± 0.008) and became very close to the level of creatinine of control group. But the level of serum creatinine increased significantly in the group of Pb+40% Ci (0.4 ± 0.003) compared to Co group (0.298 ± 0.003) and decreased significantly when compared to Pb group (0.640 ± 0.008).

Table -5: The effect of drinking 10%,20% and 40% cinnamon after injection with 20mg/Kg body weight of lead acetate on creatinine mg/mml (Mean ±SE) in the serum of rats.

Groups	Creatinin mg/mml
Co	0.298± 0.003[a]
Pb	0.640± 0.008[b]
Pb+10%Ci	0.298± 0.004[a]
Pb+20%Ci	0.291± 0.003[a]
PB+40%Ci	0.400± 0.003[c]

Discussion

The current study was aimed to investigate whether 10%, 20% or 40% cinnamon has protective effects against oxidative stress and nephrotoxicity induced by lead acetate in male rats. The findings of this study have shown in the Tables (1-5) that the injection of 20mg/kg BW PbA inhibited the antioxidant defense mechanisms and caused oxidative stress by decreasing the SOD and GSH concentration. Also, lead enhanced lipid peroxidation that causes elevation MDA level. Lead caused nephrotoxicity by inducing oxidative damage and peroxidation of the lipids in the cell membranes and then renal cellular dysfunction and this reflected by elevation of both of serum urea and creatinine levels. There are several mechanisms to explain how lead cause oxidative stress, one of them is disrupted pro-oxidant/antioxidant balance by formation of reactive oxygen species and decreasing the scavenging capacity of antioxidants mechanisms that lead to accumulation of toxic and harmful free radicals and then cause oxidative damage to critical enzymes, proteins, membrane lipids and DNA [15]. These finding supported by other studies on the renal toxicity of lead. Lead causes nephropathy and impairment of renal tubules leading to the serious disorder called Fanconi syndrome also inhibits uric acid excretion and causes predisposition in animals [16,17]. Literature data on the effects of acute PbA exposure triggering oxidative stress in the kidney of animals are rare. The present results are in agreement with findings of Salim that showed the concentration of urea and creatinine have been increased significantly in the serum of lead acetate treated rats [18]. Sharma and Singh [19] have recently reported that exposure to 10 and 150 mg/kg BW of Pb caused lipid peroxidation in the kidney of Balb-c mice. Several recently researchers have also confirmed that there were increased in lipid peroxidation in the kidneys as well as another organ of Pb-exposed animals. Our results are in agreement with Moneim [20] and Lakshmi [21] as they indicated that intraperitoneal injection of 20 mg/kg BW of PbA could induce increased in renal lipid peroxidation. Oxidative stress is presently accepted as the main factor in the development of many serious diseases and syndromes. On the other hand, antioxidant dietary intakes could be a possible method to reduce the incidence of these diseases and disorders. Antioxidants have the great impact on the progress and existence of humans as they fight free radicals in metabolic diseases and considered as anti- age-related syndromes of humans [22]. The present results regarding the effect of cinnamon show that treatment with 10% cinnamon shows improvement of physiological parameters in lead acetate intraperitoneally injected rats indicated by increasing the levels of SOD, GSH concentration and decreasing level of MDA. These improvements may be due to its antioxidants activity [23]. Cinnamon is used as the spice that gives a delicious taste to foods and plays important role in improving and protecting human health and healing several diseases because it is the very rich source of antioxidants. Our results confirmed by several studies like Kim *et al.* [24] they reported that cinnamon oil potentially exhibits SOD-like activity. Also, the aqueous and alcoholic extract (1: 1) of cinnamon could significantly inhibit fatty acid oxidation and lipid peroxidation [25]. The free radical scavenging activity of the flavonoids that separated from cinnamon with antioxidant features was confirmed [26]. Cinnamon extracts exhibit a protective capacity against irradiation that induced lipid peroxidation in liposomes and inhibit hydroxyl radicals and hydrogen peroxide [27]. These properties of cinnamon reduce the renal toxicity, and the results supported that by decreasing the concentration of urea and creatinine in the serum of lead acetate injected rats, these findings are in agreement with Mohammad *et al.* [28] and Khan *et al.* [29] that they observed normal histological structures of kidney and normal serum levels of urea and creatinine in rats treated with cinnamon extract. Also cinnamon has the ability to increase glomerular filtration rates, improve renal function and control some physiological complication in diabetes mellitus patients [30]. Tanomand and Najafian [31] reported that the concentration of urea and creatinine decreased in gentamicin-induced nephrotoxicity male rats after administration of cinnamon extract. The nephroprotective effects of cinnamon were recorded by El-Yamani [32] who observed decreased serum creatinine and urea levels in diabetic rats treated with cinnamon extract. Mishra *et al.* [33] studied the effect of cinnamon oil against diabetic nephropathy, their histological studies of the kidney revealed the protective effect of cinnamon oil by reducing the glomerular expansion, decreasing the tubular dilatations, and eradicating hyaline casts. Ullah *et al.* [34] observed that cinnamon

significantly reduced aminoglycosides-kidney toxicity by improving the urea, creatinine, uric acid, urinary protein levels and histopathological alterations of the kidneys. Furthermore, Sakr and Albarakai [35] proved that cinnamon has protective ability against cypermethrin-nephrotoxicity by an improvement in renal tubules and glomeruli, with decreasing urea and creatinine of rats. Cinnamon consists of a variety of essential oils including linalool, limonene, a-terpineol, terpinen-4-ol, c-terpinene, a- terpinene, and 1,8-cineole, and methyl eugenol, so there is high total phenolic content with good antioxidant activity [36]. In another study, it was reported that cinnamon bark contains flavonoids, steroids, terpenoids, coumarins, glycosides, anthraquinone, tannins and alkaloids [37]. Numerous studies have suggested that flavonoids function as antioxidants [38]. The ROS scavenging ability of hydroxyl substituent, with the number of OH-groups on the B-ring, gave the antioxidant capacity to cinnamon bark [39]. In the current study, we also reported that intake at high concentration, exactly 20% and 40% cinnamon, had no beneficial effects on MDA, SOD, and GSH. The findings of limited data in this context are rare and conflicting. Some studies showed that there is no significant effect of cinnamon on some physiological parameters like, in human study proved that the intakes of cinnamon for six weeks showed no significant change in MDA levels of women athletes [40]. Recently, Talaei [41] revealed that an 8-week intervention of 3.0g of cinnamon supplement per day had no beneficial effects on total antioxidant capacity, MDA levels and some other physiological parameters. Whereas, current study showed that intake of 20% cinnamon can reduce the creatinine level close to control level but elevate the level of serum urea. While intake of 40% cinnamon cause elevation of urea and creatinine levels. That mean high concentration cinnamon has toxic effect on kidney may be due to coumarin that is one of the cinnamon constitutes that has toxicity on kidney at high concentration [42].

Conclusion

The present results showed that the cinnamon at low concentration has a protective effect against nephrotoxicity induced by PbA. These positive effects can be related to the antioxidant effects of cinnamon due to inhibition of free radical production induced by PbA or by reactivation of the antioxidant enzymes. On another hand, there were no nephroprotective effects of cinnamon at high concentration against PbA. Further studies are needed to better evaluate the impact of cinnamon intake on renal function and antioxidant system in rats.

References

[1] Mohammed, S.M.. *"Effect of Broccoli (Brassica oleracea) on Some Physiological Variables and Reproductive System on Lead Acetate Exposed Adult Male Albino (Rattus rattus)".* Tikrit University College of Science. (2015).

[2] Agency for Toxic Substances and Disease Registry (ATSDR), *"Toxicological Profile for Lead, U.S. Department of Health and Human Services*", Public Health Service, Atlanta, GA. (2007).

[3] Mohammed, S.M, Mohammed, M.J., Al Aboosi, E. *"Effects of Broccoli on Oxidative Stress Produced by Lead Acetate in Male Albino Rats Rattus Rattus".* IJSRSET,Vol. 1, No. 4, pp. 153-158. (2015).

[4] Mohammed, M.M. *"Physiological and histological effects of lead acetate in the kidney of Mus Musculus", Journal of the University of Anbar for pure science.* Vol. 4, No.2, pp. 1-7. (2010).

[5] Farrag, R.H., Mahdy, K.A., AbdelRahman, G.H. & Osfor, M.M. *"Protective effect of Nigella Sativa seeds against lead-induced hepatorenal damage in male rats,"* Pakistan Journal of Biological Sciences. Vol. 10, No. 17, pp. 2809–2816. (2007).

[6] El-Nekeety, A.A., El-Kady, A.A., Soliman, M.S., Hassan, N.S. & Abdel-Wahhab, M.A. *"Protective effect of Aquilegia vulgaris (L.) against lead acetate-induced oxidative stress in rats".* Food Chem. Toxicol., Vol. 47, No. 9, pp. 2209–2215. (2009).

[7] Sharma, B., Singh, S., & Siddiqi, N. J. *"Biomedical Implications of Heavy Metals Induced Imbalances in Redox Systems".* BioMed Research International, Vol. 26. (2014).

[8] Abdou, H. M. & Hassan, M. A. *"Protective Role of Omega-3 Polyunsaturated Fatty Acid against Lead Acetate-Induced Toxicity in Liver and Kidney of Female Rats"*. BioMed Research International, 435857. (2014).

[9] Skerget, M., Kotnik, P., Hadolin, M., Hras, A.R., Simonic, M., Knez, Z. *"Phenols, proanthocyanidins, flavones and flavonols in some plant materials and their antioxidant activities"*. Food Chem. Vol. 89, pp. 191–198. (2005).

[10] Su, L., Yin, J.J., Charles, D., Zhou, K., Moore, J., Yu, L. *"Total phenolic contents, chelating capacities, and radical-scavenging properties of black peppercorn, nutmeg, rosehip, cinnamon and oregano leaf"*. Food Chem. Vol. 100, pp. 990–997. (2007).

[11] Morgana, A.M., El-Ballal, S.S., El-Bialy, B.E. & EL-Borai, N.B. *"Studies on the potential protective effect of cinnamon against bisphenol A- and octylphenol-induced oxidative stress in male albino rats"*. Toxicology Reports Vol. 1, pp. 92–101. (2014).

[12] Kim, S.H. Hyun, S.Y. Choung, J. *"Antioxidative effects of Cinnamon cassia and Rhodiola rosea extracts in the liver of diabetic mice"*. Biofactor Vol. 26, pp. 209–219. (2006).

[13] Subramanian, P., Sivabalan, S., Menon, V.P., and Vasudevan, K. "*Influence of chronic zinc supplementation on biochemical variables and circadian rhythms in Wistar rats"*. J. Nutr. Res., Vol. 20, pp. 413-425. (2000).

[14] National Research Council. *"Nutrient requirements of Laboratory Animals, Fourth Revised Edition",* Washington, DC: The National Academies Press. (1995).

[15] Patra, R. C., Rautray, A.K. & Swarup, D. *"Oxidative Stress in Lead and Cadmium Toxicity and Its Amelioration"*. Veterinary Medicine International, Vol. 2011, p: 9 (2011).

[16] Wright, L.F., Saylor, R.P, & Cecere, F.A. *"Occult lead intoxication in patients with gout and kidney disease"*. The Journal of Rheumatology. Vol. 11, No. 4, pp. 517–520. (1984).

[17] kumar, R., Sikary, S.K., Jaiswal, A. K., Millo, T., Singh, N.& Sharma, K. *"Lead Poisoning Analytical Aspects and It's Management"*. International Journal of Biological & Pharmaceutical Research. Vol. 5, No, 12, pp. 893-903. (2014).

[18] Salim, M. *"Evaluation of performance of date palm pollen on urea and creatinine levels in adult female rats exposed to lead acetate intoxication"*. Int. J. Biomed. Adv. Res. Vol. 6, No. 1, pp. 20-24. (2015).

[19] Sharma, S. & Singh, B. *"Effects of acute and chronic lead exposure on kidney lipid peroxidation and antioxidant enzyme activities in BALB-C mice (Mus musculus*)". Int. J. Sci. Res. Vol. 3, pp. 1564-1566. (2014).

[20] Moneim, A.E.A., Dkhil, M.A. & Al-Quraishy, S. *"The protective effect of flaxseed oil on lead acetate-induced renal toxicity in rats"*. J. Hazard. Mater., Vol. 194, pp. 250-255. (2011).

[21] Lakshmi, B.V.S., Sudhakar, M. & Aparna, M. *"Protective potential of Black grapes against lead-induced oxidative stress in rats"*. Environ. Toxicol. Pharmacol. Vol. 35, No. 3, pp. 361-368. (2013).

[22] B. Halliwell, *"Free radicals and antioxidants—quo Vadis?"*. Trends in Pharmacological Sciences, Vol. 32, No. 3, pp. 125–130, (2011).

[23] Rao, P.V. & Gan, S.H. *"Review Article Cinnamon: A Multifaceted Medicinal Plant. Evidence-Based Complementary and Alternative Medicine"*, 12 Articles. (2014).

[24] Kim, S. J., Han, D., Moon, K. D.& Rhee, J. S. *"Measurement of superoxide dismutase-like activity of natural antioxidants. Bioscience"*. Biotechnology, and Biochemistry, Vol. 59, No. 5, pp. 822–826. (1995).

[25] Shobana, S. & Naidu, K.A. *"Antioxidant activity of selected Indian spices"*. Prostaglandins Leukotrienes and Essential Fatty Acids. Vol. 62, No. 2, pp. 107-110. (2000).

[26] Okawa, M., Kinjo, J., Nohara, T. & Ono, M. *"DPPH (1,1-diphenyl-2-Picrylhydrazyl) radical scavenging activity of flavonoids obtained from some medicinal plants"*. Biological and Pharmaceutical Bulletin, Vol. 24, No. 10, pp. 1202–1205. (2001).

[27] Murcia, M., Egea, I., Romojaro, F., Parras, P., Jimenez, A., Martinez-Tome, M. *"Antioxidant evaluation in dessert spices compared with common food additives. Influence of irradiation procedure"*. Journal of Agricultural and Food Chemistry, Vol. 52, pp. 1872-1881. (2004).

[28]Muhammad, H.A., Jubrail, A.M.S.& Najee, M.K. *"Impact of Cinnamon Extract on Liver, Kidneys, and Spleen of Diabetic Rats"*. International Journal of Chemical and Biomolecular Science Vol. 1, No. 4, pp. 248-254. (2015).

[29] Khan, R., Khurshid, A., Zakkia K., Safdar, HS., Nawab, Z., and Mohammad S.K. *"Cinnamon on the Functions of Liver and Kidney in Type 2 Diabetic Individuals"*. Ann. Pak. Inst. Med. Sci., Vol. 8, No. 2, pp. 145-149. (2012).

[30] Sengsuk, C., Sanguanwong, S., Tangvarasittichai, O.& Tangvarasittichai, S. *"Effect of cinnamon supplementation on glucose, lipids levels, glomerular filtration rate, and blood pressure of subjects with type 2 diabetes mellitus*". Diabetology International, Vol. 7, No. 2, pp. 124–132. (2016).

[31] Tanomand, S. & Najafian, M. *"Inhibitory effects of cinnamon extract on gentamicin-induced nephrotoxicity in male adult Wistar rats"*. Advances in Environmental Biology, Vol. 7, No. 9, pp. 2100-2104. (2013).

[32] El-Yamani, M. *"Cinnamon, cardamom and ginger impacts as evaluated on hyperglycemic rats"*. Research of Specific Education Mansoura University, Vol. 20, pp. 664-679. (2011).

[33] Mishra A., Bhatti R., Singh A. & Singh Ishar M. *"Ameliorative effect of the cinnamon oil from Cinnamomum zeylanicum upon early-stage diabetic nephropathy"*. Planta Med, Vol. 76, No. 5, pp. 412-417. (2010).

[34] Ullah, N., Khan M., Khan T.&Ahmad W. *"Bioactive traditional plant Cinnamomum zeylanicum successfully combat against nephrotoxic effects of aminoglycosides"*. Bangladesh J Pharmacol. Vol. 8, pp. 15–21. (2013).

[35] Sakr1, S.A & Albarakai, A.Y. *"Research Article, Effect of cinnamon on cypermethrin-induced nephrotoxicity in albino rats"*. International Journal of Advanced Research, Vol. 2, No.7, pp. 578-586. (2014).

[36] Abdelwahab, S.I., Mariod, A.A., Elhassan, M.M., Zaman, F.Q., Ahmed, A.H., Khamis, S., Sivasothy, Y. & Awang, K. *"Chemical composition and antioxidant properties of the essential oil of* Cinnamomum altissimum *Kosterm. (Lauraceae)"*. Arabian Journal of Chemistry,Vol. 10, No. 1, pp. 131-135. (2017).

[37] Shihabudeen, M., Priscilla, H., Thirumurugan, K. *"Cinnamon extract inhibits glucosidase activity and dampens postprandial glucose excursion in diabetic rats"*. Nutr Metab, Vol. 8, pp. 1-11. (2011).

[38] Gould, K. & Lister, C. *"Flavonoid functions in plants. In: Andersen OM, Markham KR (Eds.)"*. Flavonoids: chemistry, biochemistry, and applications.London: CRC Press: pp. 397-440. (2006).

[39] Heim, K.E., Tagliaferro, A.R.and Bobilyo, D.J. *"Flavonoid antioxidants: chemistry, metabolism, and structure-activity relationships"*. J. Nutr Biochem., Vol. 13, No. 10, pp. 572-584. (2002).

[40] Mashhadi, N.S., Ghiasvand, R., Hariri, M., Askari, G., Feizi, A., Darvishi, L., Hajishafiee, M.& Barani, A. *"Effect of ginger and cinnamon intake on oxidative stress and exercise performance and body composition in Iranian female athletes"*. Int. J. Prev. Med., Vol. 4, S31–S35. (2013).

[41] Talaei, B., Amouzegar A., Sahranavard S., Hedayati M., Mirmiran P. & Azizi F. *"Article, Effects of Cinnamon Consumption on Glycemic Indicators, Advanced Glycation End Products, and Antioxidant Status in Type 2 Diabetic Patients"*. Nutrients, 9, 991, doi: 10.3390/nu9090991. (2017).

[42] Born, S.L, Api, A.M., R.A., Lefever F.R., and Hawkins, D.R. *"Comparative metabolism and kinetics of coumarin in mice and rats"*. Food and chemical toxicology. Vol. 41, No. 2, pp. 247–58. (2003).