ISSN 1996-3351

Asian Journal of Biological Sciences

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OPEN ACCESS Asian Journal of Biological Sciences

ISSN 1996-3351
DOI: 10.3923/ajbs.2019.565.571

Research Article
Toxicological and Histopathological Effects of *Cleistopholis patens* Benth Root Bark Powder Used as Cowpea Protectant and Medicine

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Abstract

Background and Objective: The effects of root bark powder of *Cleistopholis patens* Benth on toxicological and histopathological properties of albino rats was investigated using standard method. **Materials and Methods:** A total of 30 Wistar rats were grouped into 6 (A-F) of 5 rats each. The rats in group (A-E) received 2-10% of the powder while the rats in group F were given only the animal feeds, this group served as the control. **Results:** The results revealed that the alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total protein, urea and creatinine levels in the control group were not significantly different from the experimental animals. **Conclusion:** The results obtained in this research work suggested that *C. patens* root bark powder can be consumed by human being along the protected cowpea seeds since it caused no toxicity to the liver and kidney at the highest dose of 10% to albino rats.

Key words: *Cleistopholis patens*, toxicology, histopathology, powder, liver

Received: December 26, 2018 Accepted: March 31, 2019 Published: June 15, 2019

Citation: Durojaye Olanrewaju Ojo, Olumuyiwa Temitope Omotoso, Olusola Michael Obembe and Adefunke Adedayo Odetoye, 2019. Toxicological and histopathological effects of *Cleistopholis patens* Benth root bark powder used as cowpea protectant and medicine. Asian J. Biol. Sci., 12: 565-571.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The paired kidneys are the excretory organs of humans. They remove unwanted nitrogenous substances like urea and other ammonium compounds from the blood[1]. They also maintained the osmotic pressure of the blood by controlling the excretion of water and salts. Damage to the kidney will prevent the organ from excreting both urea and creatinine leading to accumulation in the blood[2]. The liver is the largest gland in the body of mammals after the skin and it is involved in many metabolic activities which are detoxification of toxic substances, glycogen storage and bile secretion[3,4]. It aids metabolism of carbohydrates, protein and fats, detoxification, secretion of bile and storage of vitamins[5]. A normal liver performs its functions adequately. However, if the liver is damaged, it can no longer carry out its normal functions. Damage to the liver can be caused by toxins, drugs, alcohol and insecticides and all these lower the ability of the liver to perform optimally[4].

Cleistopholis patens Benth (Family: Annonaceae) is a sun-loving of bout 20-30 m tall found in many parts of African countries. It is a fast growing, commonly seen in forest and rapidly colonizing abandoned forests. *Cleistopholis patens* are commonly known as 'salt and oil tree' and its local Nigeria name is Apako or Oke (Yoruba). The sap is reddish and looks like palm oil and has a salty taste, hence the name salt and oil tree. It is a medicinal plant used in the treatment of headache, malaria, measles and anti-fertility[6]. In Nigeria and other parts of African countries, the root bark and leaves are used in the treatment of typhoid fever and urogenital infections[7]. It can also be used for treatment of infectious diseases caused by *Staphylococus aureus*[7]. In addition, alkaloids and 3-methoxy champangine from the ethanolic extracts of *C. patens* are potent anti-fungal agents[7]. The major phytochemicals in the stem bark of *C. patens* are saponins, alkaloids, flavonoids and cardiac glycosides[8]. In addition to the phytochemicals present in the stem bark extract of *C. patens*, it has also been suggested that it contains macro elements such as calcium, magnesium, sodium, potassium, phosphorus, iron, zinc, manganese, copper and cobalt to varying degrees[9]. Alkaloids are medicinally useful, possessing analgesic, anti-spasmodic and bacterial effects. Higher level of five alkaloids and two sesquiterpenes has been reported in the root bark of *C. patens*[7]. The toxicity and anti-feedant effect of alkaloids towards stored products insects has earlier been reported[10]. Many members of the family Annonaceae are known to possess various chemical compounds that act as anti-feedants, repellants and growth or development inhibitors against many insect species[11]. The insecticidal activity of *C. patens* has been reported recently[12,13]. Powders of both stem bark and root bark of *C. patens* significantly reduced emergence of *Sitotroga cerealella*[12]. From the above background, it is evident that *C. patens* could be used as botanical insecticides in the control of stored product insects and medicine. It is therefore necessary to ascertain the safety margin of a botanical insecticide for the benefit of humans and their environment. There is a public campaign against the use of synthetic chemical insecticides due to its high cost of procurement, pest resurgence, poor knowledge of application, poisonous residue accumulation in foods and effect on both human's health and the environmental risk they pose to user's health[14]. All these problems have led to the search for an alternative humanly safe, ecologically tolerant and relatively cheap control measures so as to reduce dependence on synthetic chemical insecticides to a minimum. This research work was carried out to assess the toxicological and histopathological effects of *C. patens* root bark powder on the kidney and liver of albino rats which are scarce in literature.

MATERIALS AND METHODS

Preparation of *C. patens* powder: Root bark of *C. patens* used in this study was collected fresh from a local farmland in Ikole Ekiti in Ikole Local Government Area of Ekiti state, Nigeria. The collected root bark was first of all rinsed in clean water to remove sand and other impurities and then cut into smaller pieces before air-dried in the laboratory. The root bark was later pulverized into fine powder using JTC OmniBlender V (Model TM-800). The powder was later sieved to pass through 1 mm^2 perforations. The powder was packed in plastic containers with tight lid and stored in a refrigerator at 4°C prior to use. This research was carried out between April and June, 2018 at the Biochemistry Research Lab., Federal University of Technology, Akure, Ondo state, Nigeria.

Experimental animals: Adult males and females albino rats weighing (130-140 g) were purchased from the breeding colony of the Department of Biochemistry, Federal University of Technology, Akure, Ondo state, Nigeria. The rats were maintained at 25°C in a 12 h light/ dark cycle with free access to food and water.

Feed formulation and treatment groups: Feed used was standard basal diet (Animal feeds) product by United Africa Company, Nigeria. Animals were divided into 6 groups:

Group 1 : Rats fed with basal diet plus 2% *C. patens* root bark powder for 28 days
Group 2 : Rats fed with basal diet plus 4% *C. patens* root bark powder for 28 days
Group 3 : Rats fed with basal diet plus 6% *C. patens* root bark powder for 28 days
Group 4 : Rats fed with basal diet plus 8% *C. patens* root bark powder for 28 days
Group 5 : Rats fed with basal diet plus 10% *C. patens* root bark powder for 28 days
Group 6 : Rats fed with basal diet (control)

Determination of biochemical parameters: Control and treated animals were decapitated after an overnight fast by cervical dislocation. The blood was rapidly collected by direct heart puncture and plasma was prepared using standard method. Also, the plasma AST, ALT, ALP, total protein, urea and creatinine were determined using commercially-available kits (Randox Laboratories, UK).

Histopathological examination: Histopathological examination was carried out using the method of Adonu *et al.*[7]. After blood collection, the liver and kidney were carefully collected from the abdominal region and fixed in 10% formalin to prevent decay. The tissues were dehydrated with alcohol of graded concentrations. After dehydration, they were cleared with 100% xylene and were left for 2 h to remove any remnant alcohol and then embedded in paraffin wax and cast into blocks. Sections of the tissues were then cut on a microtome to 6 µm. These sections were later spread on a slide and allow to dry. The slides were subsequently stained with hematoxylin-eosin[1]. Excess stain was removed with tap water. After clearing in xylene, Canada balsam was added and cover slips placed on the slides. The preparations were left in the oven for 40°C and then placed under the microtome equipped with a digital camera connected to a computer system to be examined by a Histopathologist and the photographs were taken.

Data analysis: Data were subjected to one way analysis of variance (ANOVA) and the acceptance level of significant was $p>0.05$ for all results. Treatment means were separated using the New Duncan's Multiple Range test. The ANOVA was performed with SPSS 16.0 software (SPSS, Inc., 2007).

RESULTS

Effect of *C. patens* root bark powder on body weight of rats: Mean values for rats body weight fed with basal diet and basal diet plus *C. patens* root bark powder at various doses for 28 days are presented in Table 1. Body weight determination after 28 days was used to evaluate the health status of the rats during the experimental period. There was no significant difference ($p>0.05$) in the body weight of rats from the start until the end of the experimental period in all groups when compared with the normal control rats (basal diet only). Weight gain in albino rats fed with basal diet plus 2, 4, 6, 8 and 10% *C. patens* root bark powder were 6.02, 5.13, 4.06, 3.26 and 3.18% and were not significantly different ($p>0.05$) from the control rats with 3.47% weight gain (Table 1).

Effect of *C. patens* root bark powder on liver functions of albino rats: Table 2 presents the effects of *C. patens* root bark powder on liver biochemical parameters of albino rats. The liver activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and total protein (TP) of the animals fed were not significantly different ($p>0.05$) in serum levels when compared with the control rats (Group 6).

Effect of *C. patens* root bark powder on kidney functions of albino rats: The effects of *C. patens* root bark powder on kidney biochemical parameters of albino rats were presented in Table 3. The kidney activities of urea and creatinine were not significantly different ($p>0.05$) when compared with the control group.

Effects of *C. patens* root bark on the histopathology of albino rat kidney: The results of the kidney histopathology of rats fed with *C. patens* root bark powder showed that the

Table 1: Change in body weight (g/rat) of rats fed with basal diet and treated diet

Groups	Initial weight (g)	Final weight (g)	Weight gain/loss (%)
1	135.38±1.53^a	143.53±1.14^a	6.02^a
2	133.50±2.50^a	140.35±1.01^a	5.13^a
3	134.99±1.28^a	140.46±1.73^a	4.06^a
4	136.75±0.80^a	141.21±0.90^a	3.26^a
5	136.75±1.49^a	141.09±0.58^a	3.18^a
9	135.98±1.62^a	140.70±0.58^a	3.47^a

Each value is a mean±standard error of four replicates, Means followed by the same letter(s) in the same column are not significantly different ($p>0.05$) from each other by Duncan's New Multiple Range Test (DNMRT)

Table 2: Biochemical parameters of liver of albino rats fed with *C. patens* root bark powder

Groups	AST (U L^{-1})	ALT (U L^{-1})	ALP (U L^{-1})	Total protein (g dL^{-1})
1	18.30±0.04^a	34.68±0.34^a	101.80±0.23^a	5.58±0.00^b
2	19.79±0.21^a	29.11±0.72^a	104.40±3.18^a	5.68±0.09b
3	20.01±0.05^a	26.76±1.76^a	105.40±2.94^a	5.89±0.02^b
4	20.65±0.21^a	28.18±0.94^a	105.60±5.74^a	5.94±0.02^b
5	21.52±0.22^a	29.17±1.06^a	108.40±4.92^a	6.02±0.01^b
6	22.05±0.32^a	32.47±2.75^a	104.40±2.61	6.11±0.03^b

Each value is a Mean±standard error of four replicates, Means followed by the same letter(s) in the same column are not significantly different ($p>0.05$) from each other by Duncan's New Multiple Range Test (DNMRT)

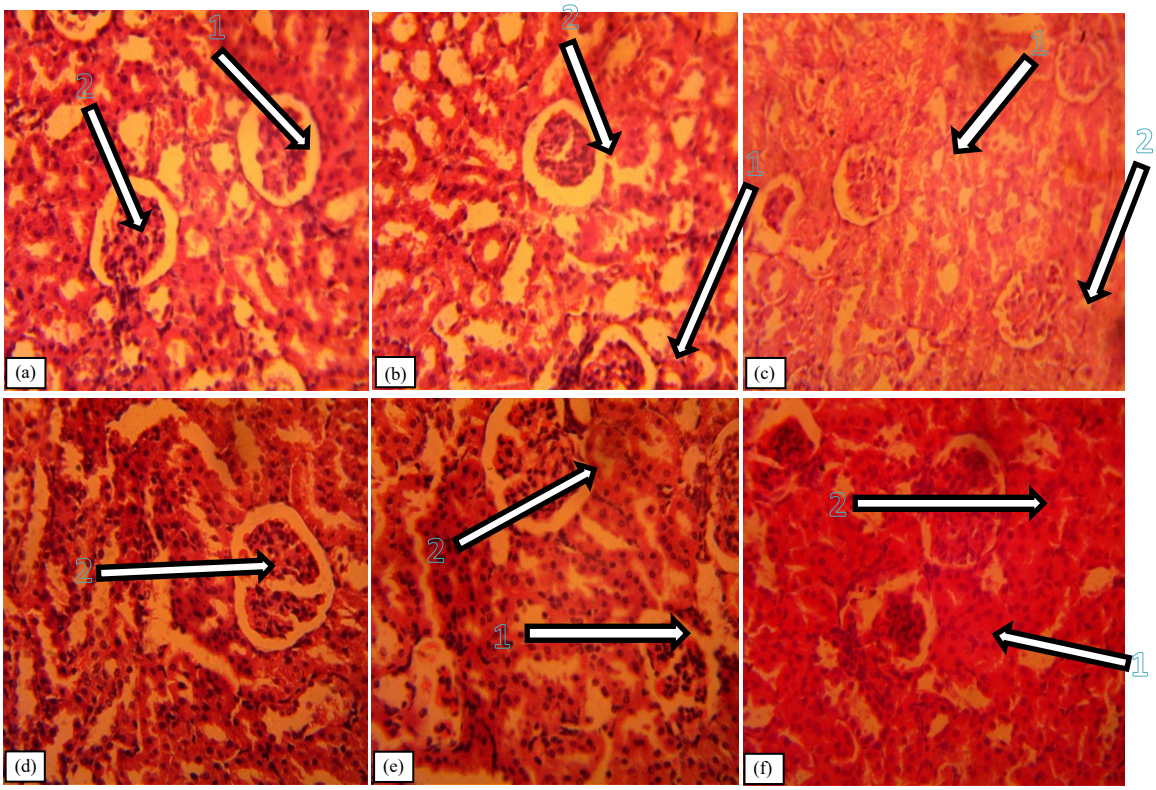

Fig. 1(a-f): Effects of *C. patens* root bark powder on the histopathology of the kidneys of albino rat (×400), (a) 2%-Normal kidney nephrons without necrosis or haemorrhage. The Bowman's capsule is well- formed. No necrosis or heamorrhage observed, (b) 4%-Kidney nephrons is well-formed as well as the Bowman's capsule. There is no necrosis and haemorrhage, (c) 6%-Kidney nephrons showed no negative pathological features. There is no necrosis and haemorrhage observed, (d) 8%-Well-formed kidney nephrons and Bowman's capsule. There is prominent renal corpuscle. No necrosis and heamorrhage, (e) 10%-Kidney nephrons are well-formed. No sign of necrosis and haemorrhage and (f) Basal Diet (control): Normal kidney nephron with prominent interstitial cells and well-formed separated loop of henle. There is presence of cell infiltrations. No necrosis or haemorrhage observed
Arrow 1: Bowman's capsule, Arrow 2: Glomerular capsule

Table 3: Biochemical parameters of kidney of rats fed with *C. patens* root bark powder

Groups	Urea (mg dL^{-1})	Creatinine (mg dL^{-1})
1	30.74±0.50^{b}	0.90±0.01^{a}
2	31.35±12.09^{b}	0.60±0.05^{a}
3	32.98±4.27^{b}	0.67±0.09^{a}
4	31.93±8.51^{b}	0.65±0.02^{a}
5	32.86±6.61^{b}	0.71±0.09^{a}
6	32.26±8.07^{b}	0.63±0.11^{a}

Each value is a mean±standard error of four replicates, Means followed by the same letter(s) in the same column are not significantly different (p>0.05) from each other by Duncan's New Multiple Range Test (DNMRT)

animal fed with basal diet (control) have normal kidney structure without any pathological alteration. The animals fed with 2-10% concentrations of *C. patens* root bark powder showed normal kidney structure with presence of normal nephrons as well as normal cell infiltration. No sign of necrosis, karyolysis and haemorrhage (Fig. 1).

Effects of *C. patens* root bark on albino rat liver: The results of the liver histopathology of rats fed with *C. patens* root bark powder showed that the animal fed with basal diet (control) have normal liver structure in which the hepatocytes are well formed, no necrosis or haemorrhage. All the treated animals fed with 2-10% concentrations of *C. patens* root bark powder showed normal liver structure, the hepatocytes are well-formed, sinusoids are distinct and well formed (Fig. 2).

DISCUSSION

The measurement of the activities of various enzymes in tissues and body fluids play a significant and well known aid in disease investigation and diagnosis[15,16]. The concentration of liver enzymes in the serum is an indicator of hepatic function[16].

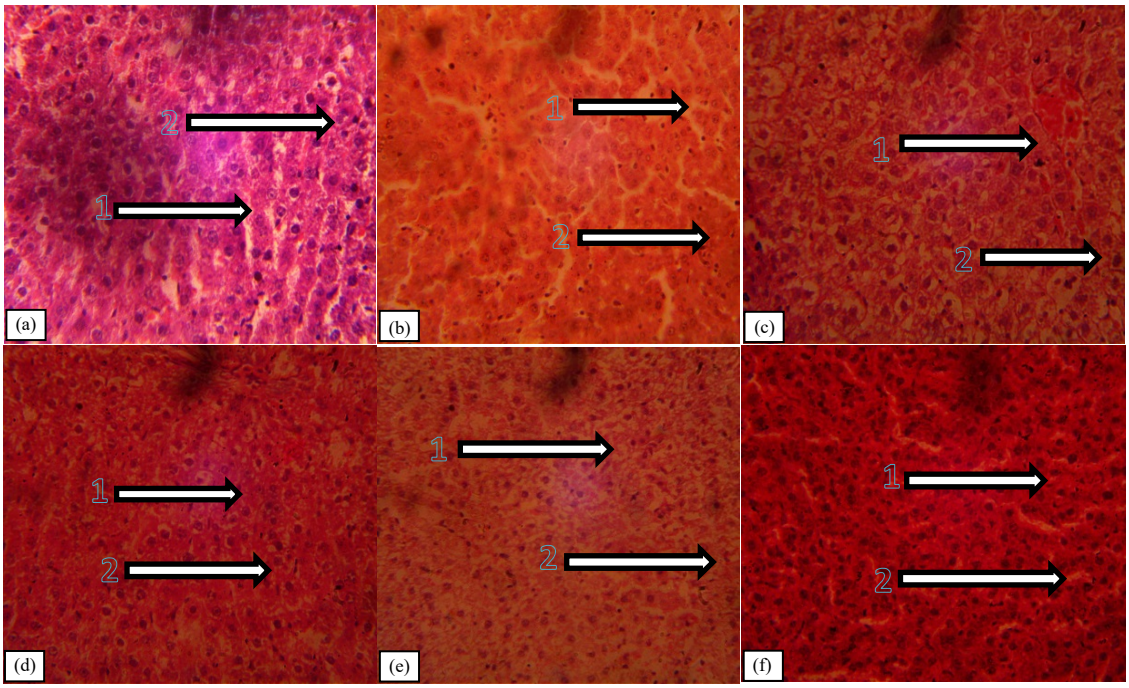

Fig. 2(a-f): Effects of *C. patens* root bark powder on the histopathology of the livers of albino rat (×400), (a) 2%: Well-formed liver hepatocytes without any drainage, necrosis or haemorrhage, (b) 4%: Liver hepatocytes show no necrosis or haemorrhage. The sinusoids are immature but well formed. The inter-hepatocellular drains are dispersed evenly, (c) 6%: Well-formed hepatocytes with cell infiltrations on the sinusoids and dot inflammatory cell infiltrations, (d) 8%: Well-formed liver hepatocyte with distinct interstitial sinusoids that is well distributed across the plate, (e)10%: Liver hepatocytes are well formed with distinct sinusoids. There is no drainage, necrosis or haemorrhage. There is equally no hepatocellular displahia and (f) Basal diet (control): Liver hepatocytes are not prominent but there are cells infiltrations. The sinusoids are dispersed evenly and inter-hepatocellular drains are even
Arrow 1: Sinusoids, Arrow 2: Hepatocytes

Alkaline phosphatase (ALP) is a marker enzyme for the plasma membrane and endoplasmic reticulum[17] and often employed to assess the integrity of the plasma membrane[18]. The observed normal alkaline phosphatase (ALP) activities in the liver of the test groups and the control will not hinder the transportation of the required ions on the molecules across the plasma membrane. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are important marker enzymes for assessing damage to organs. They are normally localized within the cells of the liver, kidney and some other organs[1]. They are released into the serum usually when there is damage to the hepatic membrane due to chemical attack[19]. Therefore, serum levels of the enzymes are useful indicators of extent of hepatic damage[16]. The non-significant difference observed in the values of AST and ALT in the test and control is an indication that the livers of the animals were not damaged. Similar observations have been made by Akomolafe *et al.*[20] in the toxicological effects of aqueous extracts from African Walnut (*Tetracarpidium conophorum*) leaves in rats.

The main function of the kidneys is to excrete the waste products of metabolism and to regulate the body concentration of water and salts[1]. One of the objectives of this research was designed to investigate the toxicity of *C. patens* root bark powder on renal function by assessment of the creatinine, blood urea and histopathological changes of kidney. Urea is a byproduct from protein breakdown. They are synthesized in the liver from ammonia, produced as a result of the deamination of amino acids. About 90% of urea produced is excreted through the kidney[21]. Meanwhile, creatinine is a waste product from muscle creatinine, which is used during muscle contraction. Creatinine is commonly measured as an index of glomerular function[22]. It is excreted exclusively through the kidney. Therefore, damage to the kidney will make the kidney inefficient to excrete both urea and creatinine and cause their accumulation in the serum. In this study, the powder of *C. patens* root bark did not change the biochemical parameter of kidney functions, since there was no significant increase ($p>0.05$) in the serum level of the urea and creatinine of the test and control groups. Therefore, the level

of serum urea and creatinine indicate no kidney damage. Similar observations have been made by Bamisaye *et al.*[16], Momoh *et al.*[23] and Dollah *et al.*[24] in normal rats treated with extract of *Morindalucida*, Castor seed oil and powder of Nigella sativa for 7 days, 30 days and 4 weeks, respectively. Weber *et al.*[25] indicated that the normal range of serum creatinine in rats to be 0.2-0.8 mg dL^{-1}. Ileke *et al.*[1] and Treasure[22] stressed that serum creatinine is an index of glomerular function. It was also observed that there were no changes in physical activities between the control and the test groups. Moreover, no mortality cases were recorded up to 24 h post treatment in the test groups. Also, the body weight of the rats in all groups did not decline during the experimental period. These findings indicated that the powder improved the growth performance of the test groups and had no adverse effect on their metabolic activities.

The histopathology of the livers showed that the control and the test groups had normal liver structure with their sinusoids intact. The fact that the liver sinusoids are intact shows that the animals fed with basal diet (control group) and the animals fed with 2, 4, 6, 8 and 10% *C. patens* root bark powder did not have any deleterious effect on the organ[26].

The kidney structure of the control and the test groups was normal with normal kidney nephron and cell infiltration. This is an indication that the kidney is actively performing its function of ultrafiltration and selective reabsorption although few infiltrations of inflammatory cells were observed in animals fed with 6, 8 and 10%.

With the evidence of normal urea and creatinine level in the blood and normal kidney tissue in histopathological examination for rats fed with basal diets and rats fed with basal diet plus 2, 4, 6, 8 and 10% *C. patens* powder, it is suggested that there was no toxic effect on kidney functions of rats fed with 2, 4, 6, 8 and 10% *C. patens* root bark powder for 28 days exposure period. The results of the present study showed the absence of toxic effects of *C. patens* root bark powder at all the doses tested on rat kidney and liver and suggest that the popular consumption of *C. patens* root bark powder by human being to protect cowpea seeds against cowpea bruchid will not cause toxicity effect on the kidney and liver functions.

CONCLUSION

The powder of *C. patens* root bark was tested on albino rats and found to be non- toxic since there were no significant differences between the control and the treated rats, at all the concentrations tested. Thus, popular consumption of *C. patens* root bark powder by human along the protected cowpea seeds will not cause toxicity effect on the liver and kidney functions.

SIGNIFICANCE STATEMENT

This study revealed that the powder of *C. patens* root bark is not toxic to albino rats and this suggest that regular usage of the plant by human will not cause any toxicity effect on the kidney functions.

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