Islamic Azad University
Urmia Branch

Journal of Basic and Clinical Veterinary Medicine

2023; 4(2): 62-73

Official Journal of Veterinary Faculty of Islamic Azad University
Urmia Branch

Journal Homepage: https://sanad.iau.ir/journal/jbcvm/

Original Article

Protective effect of nanocurcumin on renal histological damage in salinomycin-induced toxicity of broiler chickens

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ARTICLE INFO

Received: 15 August 2023

Accepted: 16 January 2024

DOI:10.30495/jbcvm.2024.1993994.1047

KEYWORDS:

Nanocurcumin
Salinomycin
Kidney
Antioxidant
Broiler chickens

ABSTRACT

Salinomycin (SLM) is an ionophore antibiotic used extensively in the poultry industry for the control and prevention of coccidiosis. The toxicity of the ionophore is thought to be due to oxidative damage caused by the production of free radicals. Curcumin is a major component of turmeric, which has a wide range of antioxidant, anti-inflammatory and anticancer activities. The aim of this study was to evaluate the effect of nanocurcumin (NC) as a natural antioxidant on broiler chickens poisoned with a toxic dose of SLM. In this study, 60 broilers were randomly divided into 5 groups. The first group was considered as control. The second group received SLM at a dose of 300 mg/kg bw per day for 14 days. Groups 3, 4 and 5 received oral doses of NC at 50, 100 and 200 mg/kg bw per day for 14 days in addition to SLM. After 14 days, blood and kidney tissue samples were collected for biochemical and histopathological evaluation. It was observed that NC reduced the incidence and severity of renal histopathological lesions. The highest levels of inflammatory cells were observed in the cortex and medulla of the SLM group and it appeared that treatment with NC improved the condition and reduced the presence of inflammatory cells. It also significantly improved renal histomorphometric parameters ($P<0.05$). It seemed that SLM-induced adverse conditions can be reversed by oral administration of NC.

اثر محافظتی نانوکورکومین بر آسیب بافتی کلیوی در مسمومیت ناشی از سالینومایسین جوجه های گوشتی

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چکیده

سالینومایسین یک آنتی بیوتیک یونوفوره بوده که به طور گسترده در صنعت طیور برای کنترل و پیشگیری از کوکسیدیوز استفاده می شود. سمیت یونوفور احتمالاً به دلیل آسیب اکسیداتیو ناشی از تولید رادیکال های آزاد است. کورکومین جزء اصلی زردچوبه بوده که دارای طیف وسیعی از فعالیت آنتی اکسیدانی، ضد التهابی و ضد سرطانی است. هدف از این مطالعه بررسی اثر نانو کورکومین به عنوان یک آنتی اکسیدان طبیعی بر جوجه های گوشتی مسموم شده با دوز سمی سالینومایسین بود. در این مطالعه ۶۰ قطعه جوجه گوشتی به طور تصادفی به ۵ گروه تقسیم شدند. گروه اول به عنوان شاهد در نظر گرفته شد. گروه دوم سالینومایسین را با دوز ۳۰۰ میلی گرم بر کیلوگرم وزن بدن، روزانه به مدت ۱۴ روز دریافت کردند. گروه های ۳، ۴ و ۵ علاوه بر سالینومایسین، به ترتیب روزانه ۵۰، ۱۰۰ و ۲۰۰ میلی گرم بر کیلوگرم وزن بدن نانوکورکومین را به مدت ۱۴ روز دریافت کردند. سپس، نمونه های خون و بافت برای ارزیابی بیوشیمیایی و هیستوپاتولوژی جمع آوری شد. مشاهده شد که نانوکورکومین بروز و شدت ضایعات هیستوپاتولوژیک کلیه را کاهش داده و به نظر می رسد که درمان با نانوکورکومین باعث بهبود وضعیت و کاهش تعداد سلول های التهابی می شود. همچنین پارامترهای هیستومورفومتری را به طور معنی داری بهبود بخشید ($p<۰/۰۵$). به نظر می رسد شرایط نامطلوب ناشی از مسمومیت با سالینومایسین با تجویز خوراکی نانوکورکومین قابل بهبود باشد.

واژه های کلیدی: نانوکورکومین، سالینومایسین، کلیه، آنتی اکسیدان، جوجه گوشتی

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INTRODUCTION

Coccidiosis is a parasitic disease of the intestinal tract of animals caused by coccidial protozoa. The disease is spread from one animal to another by contact with infected faces or ingestion of infected tissues [1]. Diarrhea, which may be bloody in severe cases, is the main symptom. Most animals infected with coccidia are asymptomatic, but young or immunocompromised animals may suffer severe symptoms and die. Coccidiosis in poultry is one of the most important and prevalent parasitic diseases and is a major economic burden for producers [2]. The annual cost of the disease is estimated at $60-120 million worldwide and experts estimate that 5-10% of all poultry mortality worldwide is due to coccidiosis [3]. Coccidiosis can be found in poultry of all species, breeds and ages. The disease is found in all different breeding categories of poultry, including broilers, layers, mothers and ancestors, causing mortality, reduced production and disturbance of feed conversion and growth in industrial poultry farms [4]. However, some sources suggest that the disease is more prevalent in young poultry [5]. The extent of damage caused by this disease depends on the time of year it occurs in the breeding season. Pathogenicity depends on many factors including: diet, environmental factors, stress and management. Infection of poultry during the critical period, i.e. the third, fourth and fifth weeks and then up to the time of slaughter, causes irreparable damage to broiler and laying flocks [5]. Ionophore anticoagulants, including SLM, azalide, maduracin, monensin, and narasin, are commonly used to prevent and treat coccidiosis [6]. SLM, which is produced by the fermentation of Streptomyces albus, is a sodium salt of a polyether monocarboxylic acid and belongs to the ionophore group [7]. SLM and its derivatives are ionophore coccidiostats that exhibit high antimicrobial activity against Gram-positive bacteria. They are effective against merozoites, sporozoites, and adult forms of all species of avian poultry pathogens [6]. However, the use of this drug can cause severe functional and morphological disorders in cells, and its use is limited in some animal species and developmental stages. Additionally, the abuse of this drug can induce intoxication [8]. One factor that has received much attention in the literature as a cause of poisoning resulting from the abuse of this drug is oxidative stress [9, 10]. Turmeric (*Curcuma longa*) is a member of the ginger family (*Zingiberaceae*) and is commonly used as an herbal supplement, food flavoring, and food coloring in various communities [11]. The plant species produces three main secondary metabolites: curcumin, dimethoxy curcumin, and bis-demethoxy curcumin. Curcumin, also known as diferuloylmethane, is a bright yellow chemical with various pharmacological properties. These properties include anti-inflammatory, antibiotic, antioxidant, anticancer, and antiangiogenic activities [12, 13]. Numerous clinical studies have demonstrated the therapeutic effects of curcumin on various human and animal diseases, including cancer, cardiovascular disease, diabetes, osteoarthritis, neurological diseases, and Crohn's disease [14-16]. However, it is widely acknowledged that curcumin's therapeutic usage is limited due to its poor bioavailability, water solubility, and pharmacokinetic profiles [17]. The low plasma and tissue levels of curcumin are mainly due to poor absorption, rapid metabolism, and rapid systemic elimination. To improve these effects, several curcumin formulations have been recommended, including the use of adjuvants such as piperine, combination with liposomes, formation of phospholipid complexes, use of structural analogues of

curcumin, and formation of curcumin nanoparticles [16-19]. However, it is important to note that each method has its own set of advantages and disadvantages. Curcumin nanoparticles have garnered significant attention due to their improved bioavailability, absorption, and biodistribution. Additionally, nano-particulate drug delivery systems are widely used to enhance the water solubility of hydrophobic drugs, including curcumin [17, 20, 21]. Numerous studies have demonstrated that curcumin nanoparticles can improve various biochemical abnormalities and imbalances in cellular signaling pathways, such as oxidative stress and inflammatory pathways [9, 22-24]. Therefore, the enhanced performance of curcumin nanoparticles in these cases may be attributed to improved bioavailability. The objective of this study was to assess the impact of NC on SLM toxicity in broilers.

MATERIALS AND METHODS

Animals and groups

60-day-old broiler chicks (Ross 308 strain) were obtained from a commercial hatchery. The chicks were fed a diet based on corn and soybean meal, and food and water were provided ad libitum. The basic food ration did not contain any additives such as coccidiostats, growth promoters, or antioxidants. The experimental chicks were placed in cages in five groups of 12. Until the 14th day of rearing, all groups were fed the same basic diet. During the 14-to-28-day experimental period, the diets of the subjects were supplemented with SLM and NC.

Group 1 served as the control group and was fed a basic diet. Group 2 received a dose of 300 mg/kg of SLM powder added to the basic diet. Group 3 received a dose of 300 mg/kg of SLM powder and 50 mg/kg of NC added to the basic diet. Group 4 received a dose of 300 mg/kg of SLM powder and 100 mg/kg of NC in their basic diet. Group 5 received a dose of 300 mg/kg of SLM powder and 200 mg/kg of NC in their basic diet. The breeding period lasted 28 days, followed by a 14-day experimental period. The experimental units were selected randomly, and the chickens were distributed randomly in the cages.

Preparation of NC

In this study, the NC drug from Exir Nano Sina Company (SinaCurcumin®) was administered orally to the chickens at the prescribed dose. The drug was first extracted from the capsule using a syringe due to its encapsulated form. To do this, the NC was dissolved in distilled water.

Blood sampling and measurement of kidney health indicators

At 28 days, 3 ml of blood was collected from the Alar vein of the birds. The blood samples were then centrifuged at 10 rpm for 10 minutes to isolate the serum, which was immediately stored at -20°C until testing. The blood serum samples were analyzed using Pars Azmoun Company kits for each of the blood parameters, including creatinine, blood urea nitrogen, calcium, and phosphorus.

Histomorphological examination

For the histomorphometric study, 25 glomeruli were randomly selected and measured from each section (five sections per group). The diameter of the glomeruli was measured, and vacuolar degeneration was scored from mild to severe (mild = <25% vacuolated cells;

moderate = 26-50% vacuolated cells; severe = >50% vacuolated cells) using a scale of 0 to 3 (0 indicating no vacuolar degeneration and 3 indicating the most severe vacuolar degeneration) [25]. Photographs were taken from 10 randomly selected focal points at ×10 and ×40 magnifications to better illustrate the obtained results [26].

Histopathological examination

After the chickens were slaughtered at the end of the experiment, the kidneys were removed and placed in sample containers with 10% formalin. The fixed tissues were embedded in paraffin after at least 48 hours. Eight sections, each with a thickness of 5 microns, were prepared from each sample and stained with hematoxylin and eosin. The histological characteristics of the kidney tissues were examined under a light microscope at ×10 and ×40 magnifications. To count the number of glomeruli, we studied five randomly selected foci from each tissue section at ×40 magnification [27-29].

Statistical analysis

The study utilized Kruskal-Wallis and Mann-Whitney U tests to compare histopathological scores between the groups. Each tissue was scored from 0 to 3 for edema, necrosis, atrophy, inflammation, and hyperemia (0 indicating none and 3 indicating the maximum score) [30, 31]. Descriptive histological examination and biochemical data were analyzed using one-way analysis of variance (ANOVA) and Duncan post hoc test with SPSS software version 26 [32]. A significant difference was considered when $p<0.05$ [33, 34].

RESULTS

Renal histopathology

Table 1 lists the histopathological changes observed in kidney tissue. The control group's histopathological examination revealed normal tissue conditions without any lesions (Figure 1). The results of the study showed that in the SLM and SLM groups receiving doses of 50 and 100 (mg/kg) of NC, there was glomerular shrinkage, infiltration of inflammatory cells, hyperemia, and vacuolar degeneration (Table 1). However, in the SLM group treated with 200 mg/kg NC, the severity of the lesions was lower, and no vacuolar degeneration was observed (Table 1).

Renal histomorphometry

Number of glomeruli

The group that received SLM had the lowest number of glomeruli, followed by the groups that received 50, 100, and 200 mg/kg, and finally the control group. It appears that SLM had a negative impact on the number of glomeruli, and different doses of NC could improve this condition. Additionally, NC at the doses of 100 and 200 mg/kg could significantly exacerbate the damage caused by SLM compared to the NC group that received 50 mg/kg. There was a significant difference ($p<0.05$) between the control group and the groups receiving 100 and 200 mg/kg, as shown in Table 2.

Number of cells per glomerulus

The group that received SLM had the lowest number of cells per glomerulus, while the control group had the highest. The toxic effects of SLM were downregulated in a dose-dependent manner by NC. The 100 and 200 mg/kg groups were closer to the control group, and this group was significantly different from the other groups ($p<0.05$) (Table 2).

Glomerulus area

The group with the lowest glomerulus area was the SLM group, while the control group had the highest. The 200 mg/kg group had better conditions and showed a significant difference compared to the other groups ($p<0.05$) (Table 2).

Diameter of the medulla and cortex

The control group had the largest cortex diameter, while the SLM group had the smallest. The treatment group that received 200 mg/kg NC showed a significant difference compared to the other groups ($p<0.05$). The use of NC appeared to significantly improve the adverse conditions induced by SLM (see Table 2). The group that received SLM had the lowest medulla diameter, while the control group had the highest. The 200 mg/kg group showed significant improvement compared to the control and other groups ($p <0.05$). The use of therapeutic doses of NC appears to alleviate the toxic conditions induced by SLM (Table 2).

Table 1. Evaluation of histopathological changes of kidney tissue between the experimental groups. CTR: control; SLM: salinomycin; NC: nanocurcumin. Values are presented as Mean ± SE. A statistically significant difference in kidney lesions between the treated groups was observed ($p<0.05$; Kruskal-Wallis test). Statistically significant differences were observed between the control group and the SLM-treated group ($p<0.05$; Mann-Whitney U test), as well as between the control group and the SLM + NC 50 mg/kg-treated group ($p<0.05$; Mann-Whitney U test). Statistically significant differences were observed between SLM + NC 100 mg/kg-treated ($p<0.05$; Mann-Whitney U test), SLM + NC 200 mg/kg-treated ($p<0.05$; Mann-Whitney U test), and NC-treated ($p<0.05$; Mann-Whitney U test).

Groups	CTR	SLM	SLM +NC 50 mg/kg	SLM +NC 100 mg/kg	SLM +NC 200 mg/kg	P value*
Vacuolar Degeneration	0.2±0.13	1.7±0.26$^{a, d}$	1.3±0.21^{e}	1±026^{e}	0.6±0.22	0.001
Hyperemia	0.3±0.15	1.3±0.21$^{a, d}$	0.9±0.23	0.7±0.21	0.4±0.16	0.013
Inflammatory cells infiltration	0.1±0.10	2.3±0.26$^{a, b, c, d}$	1.2±0.20^{e}	0.9±0.23^{e}	0.6±0.22	0.000
Glomerular atrophy	0.1±0.10	1.8±0.29$^{a, c, d}$	1.3±0.26^{e}	0.9±0.23^{e}	0.7±0.21^{e}	0.001
necrosis	0.4±0.16	2±0.21$^{a, b, c, d}$	1.3±0.15^{e}	1.1±0.23^{e}	0.8±0.25	0.000

Table 2. Mean ± SEM of histological changes of kidney tissue between the experimental groups. CTR: control; SLM: salinomycin; NC: nanocurcumin.

Groups	CTR	SLM	SLM +NC 50 mg/kg	SLM +NC 100 mg/kg	SLM +NC 200 mg/kg
Glomeruli (N)	7.50±0.15^{c}	5.53±0.15^{a}	5.63±0.19^{a}	6.40±0.17^{b}	6.60±0.16^{b}
Glomeruli cells (N)	91.06±3.91^{d}	49.56±1.69^{a}	58.53±2.36^{b}	65.43±1.54^{c}	68.70±1.08^{c}
Glomeruli area(µm2)	1810.78±44.33^{d}	1277.02±27.02^{a}	1354.72±33.37^{ab}	1448.14±22.41^{b}	1678.40±49.65^{c}
Cortex diameter(µm)	2146.03±28.15^{d}	1669.10±19.09^{a}	1759.71±34.54^{b}	1782.91±34.18^{b}	1932.38±29.15^{c}
Medulla diameter (µm)	2970.99±66.20^{d}	1756.84±27.19^{a}	2223.63±76.06^{b}	2268.02±43.13^{b}	2723.46±71.44^{c}
Medulla inflammatory cells (N)	3.43±0.34^{a}	6.46±0.17^{c}	4.66±0.28^{b}	4.46±0.19^{b}	4.03±0.36^{ab}
Cortex inflammatory cells (N)	3.42±0.22^{a}	6.80±0.30^{c}	4.86±0.15^{b}	4.50±0.32^{b}	4.36±0.40^{b}

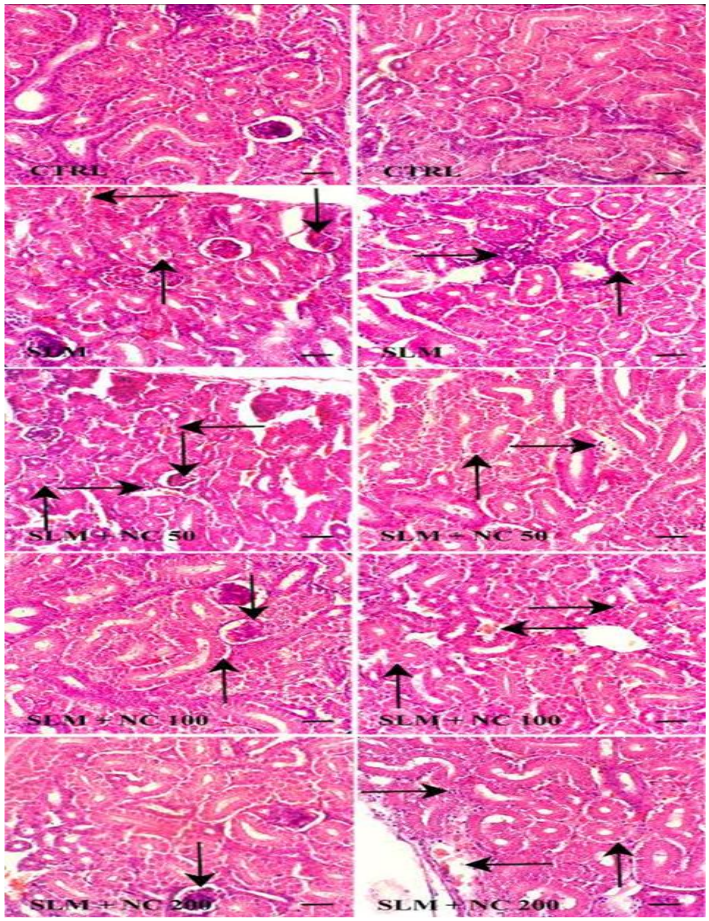

Figure 1. kidney tissue under different conditions. The control group (CTR) had normal tissue conditions, while the SLM group and other treated groups showed hyperemia (indicated by the left arrow), infiltration of inflammatory cells (indicated by the right arrow),

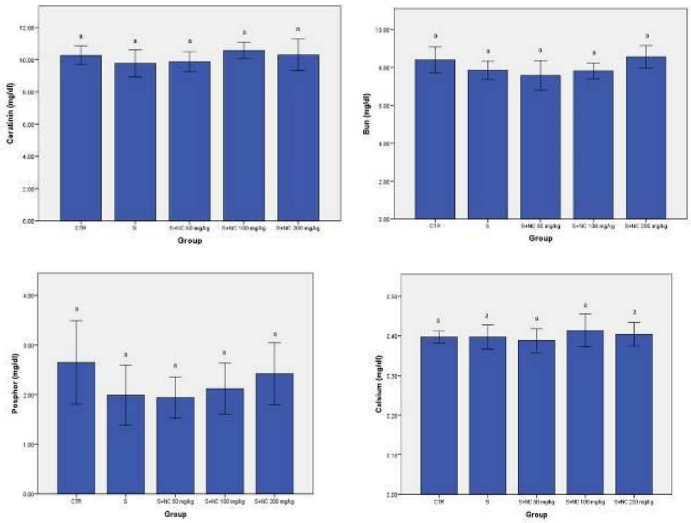

Figure 2. a comparison between the control and treated animals in terms of calcium, phosphorus, blood urea nitrogen, and creatinine (mg/dl) levels in the experimental groups. The values represent the Mean ± SEM of the mean. Different small alphabetic letters indicate significant differences with other groups at $p<0.05$.

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Number of inflammatory cells in the cortex and medulla

The control group had the lowest rate of inflammatory cells in the cortex area, while the SLM group had the highest rate. This difference was statistically significant ($p<0.05$) (Table 2, Figure 2). Similarly, the control group had the lowest rate of inflammatory cells in the medulla region, while the SLM group had the highest rate (Table 2, Figure 1).

Blood biochemical parameters: blood urea nitrogen, creatinine, phosphorus, and calcium levels

Although the creatinine level was the lowest in the SLM group, there was no significant difference with the other groups. The results suggest that renal health indices were not clinically significantly affected by SLM or NC ($p <0.05$) (Figure 2). There were no significant differences in phosphorus and calcium levels and blood urea nitrogen levels between the groups ($p <0.05$) (Figure 2).

DISCUSSION

Coccidiosis is a parasitic disease caused by coccidian protozoa that affects the intestinal tract of animals. It leads to intestinal tissue damage, resulting in malabsorption, dehydration, blood loss, loss of skin pigmentation, and increased susceptibility to other diseases in poultry. Recently, there has been increased attention on the use of medicinal plants, such as turmeric and curcumin, due to their improved bioavailability, absorption, and biodistribution. The aim of this study was to evaluate the effect of NC on SLM toxicity in broilers. The histological findings of this study indicate that SLM causes tissue damage, including glomerular shrinking, infiltration of inflammatory cells, hyperemia, and vascular destruction in the kidneys. However, dose-dependent administration of NC was able to improve these tissue lesions. SLM, as a type of ionophore, can cause severe functional and morphological disturbances in cells and may induce toxic syndromes in cases of overdose or misuse. The risk of poisoning is not only due to overconsumption but also to certain animal species and age groups. Therefore, it is recommended to fully consider their safe use [35]. Several studies have reported accidental or experimental ionophore poisoning in various species, including chicken, poultry, quail, turkey, rabbit, and horse [36-38]. In a study conducted by Sayrafi et al., the protective effects of turmeric and vitamin E against SLM damage in the bursa of Fabricius in broilers were evaluated. The results showed that SLM reduces the thickness of the cortex and increases the central area of the follicles, and causes severe necrosis of lymphocytes in the bursa of Fabricius. Furthermore, studies have shown that SLM causes tissue damage, including the kidneys and bursa, as evidenced by interstitial fibrosis with severe edema in the central region of the follicles in the bursa fabric of chickens [35]. It is important to note that any change in the structure of vital tissues in the body can lead to a change in their function. In contrast to the histological changes observed in this study, the parameters used to evaluate kidney function, such as creatinine, urea, calcium, and phosphorus levels, did not show significant changes with SLM. However, Kamashi et al. (2004) reported a significant increase in the level of renal health index biomarkers, including serum creatinine and BUN, in the group receiving SLM (120 mg/kg) [8]. Ionophore toxicity may result from oxidative damage caused by free radicals. This damage can potentially be prevented by incorporating antioxidant supplements into the diet [39]. The study's most notable histological findings included a reduced number of glomeruli, cells per glomerulus, glomerulus area, and medulla and cortex diameter in the SLM group. Additionally, the SLM group exhibited the highest rate of inflammatory cells in the cortex and medulla regions. The use of NC in a dose-dependent manner appears to significantly improve SLM-induced adverse conditions. This finding is consistent with the Madhavi and Saraswathi study, which showed the therapeutic effects of turmeric against the toxicity of chlorpyrifos (an organophosphate insecticide) in rats [40]. Sayrafi et al. conducted a study to evaluate the protective

effects of turmeric and vitamin E against SLM damage in the bursa of Fabricius in broilers. The results showed that both vitamin E and turmeric powder significantly prevented the side effects caused by SLM. There was no significant difference between the effects of vitamin E and turmeric powder [35]. Sefidan and Mohajeri's research, in line with our own findings, demonstrated that turmeric powder significantly reduces functional and tissue damage in the ischemic kidney [41]. However, there have been no reports of the protective effects of NC on ionophore-induced immunity in all SLM-poisoned broilers to date. Our results demonstrate that NC particles improved the prominent SLM-induced tissue changes in a dose-dependent manner. Treatment with doses of 50, 100, and 200 mg/kg NC improved SLM-induced damage. Turmeric's protective effects are primarily due to curcumin's antioxidant activity, which acts as a mechanism against cytotoxicity [42]. The plant has extensive medicinal use [43], and numerous studies have demonstrated its safety and non-toxicity to both animals and humans [44]. Curcumin exhibits antioxidant, anti-inflammatory, anti-tumor, anti-cancer, and immune-boosting properties in biological systems, which have garnered attention from researchers in recent years [43]. Gowda et al. [45] demonstrated that adding turmeric to broiler diets increased total antioxidant activity, as well as superoxide dismutase and catalase concentrations. Additionally, curcumin was found to alleviate kainic acid-induced cell death in the rat hippocampus [46]. Curcumin stimulates enzymes involved in the synthesis and alteration of unsaturated fatty acids. It also acts as a superoxide anion scavenger and removes hydroxyl radicals and nitrogen dioxide. Studies have shown that curcumin prevents tumor cell formation and slows the growth and progression of many cancers by inducing apoptosis. Curcumin has been shown to induce apoptosis in many cancer cells at specific doses. It achieves this by releasing cytochrome C from the mitochondria, producing free radicals, and stabilising p53, thus demonstrating its apoptotic effects [47, 48]. Additionally, curcumin increases the permeability of mitochondrial membranes and, like other proteasome inhibitors, has a stronger effect on proliferating cells than differentiated cells [49]. A recent study demonstrated that dietary supplements containing turmeric or curcumin can provide protective immunity and antioxidant activity against free radicals [50]. Furthermore, another experimental study showed that curcumin exhibits strong antioxidant activity in vital organs such as the liver, kidneys, and heart, and has free antiradical activity [45]. Additionally, curcumin can enhance the antioxidant potential of turmeric-fed chickens by increasing SOD gene expression [51]. These findings suggest that curcumin has a multifaceted role in improving various pathogenic conditions. However, its therapeutic use is limited due to its short retention time, low uptake, relatively low water solubility at physiological pH, and low bioavailability [35, 52]. This study demonstrates, for the first time, that curcumin nanoparticles can improve kidney damage caused by SLM. Several studies have supported the finding that the use of curcumin nanoparticles increases its bioavailability and solubility in water [53, 54]. Furthermore, different formulations of curcumin nanoparticles have an absorption rate 10-14 times higher than the same oral dose of curcumin [54, 55]. Appetite regulation is a crucial factor in controlling food intake. While the factors that reduce appetite and subsequent food intake are not yet fully understood, ionophore complexes may play a role [56]. While the factors that reduce appetite and subsequent food intake are not yet fully understood, ionophore complexes may play a role [56]. Numerous studies have demonstrated that SLM induces weight loss in poultry [57]. Specifically, it has been observed that SLM significantly reduces the body mass volume of broilers. They found that administering SLM at doses of 60, 120, and 180 during weeks 4, 6, and 8, respectively, significantly reduced body mass compared to controls. Danforth et al. (1977) investigated the anticoccidial effects of SLM in broilers. The study also showed that this drug, in small amounts, can have satisfactory effects on reducing oocyst excretion and symptoms of various types of Eimeria [58]. Based on the results of these studies, it can be concluded that the effects

of SLM poisoning are dose-dependent and can be modified.

CONCLUSION

Based on the explanations and findings of this study, it appears that using nanoparticles to enhance certain plant compounds, such as curcumin, could be an effective solution for overcoming their limitations. The study concludes that SLM toxicity alters the structure and function of chickens' kidneys, but the use of NC can mitigate the drug's toxic effects. Therefore, it is recommended that this substance be used as a supplement or as part of the poultry diet to enhance herd performance.

ETHICS

Approved.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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