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Evaluation of The Growth Promoting, Economic Impact and Possible Ameliorative Effect of Hawthorn *(Crataegus Spp)* against Salinomycin Toxicity in Broiler Chicks

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Abstract

THIS STUDY was conducted to evaluate the growth promoting, economic impact and possible ameliorative effect of Hawthorn (HT) (*crataegus spp*) against salinomycin (SM) toxicity in broiler chicks. Therefore, 32 seven day old unsexed Ross broiler chicks were completely randomized design divided into four Groups (3 of them are treatable. Control group, SM-intoxicated group (100 mg/kg feed), HT-treated group (10 g/kg feed) and SM+HT-combination group (SM 100 mg/kg feed plus HT 10 g/kg feed). Results revealed that HT promotes a significant improvement in final body weight (FBW), body weight gain (BWG) and feed intake (FI) while, a decreased final body weight in SM-intoxicated group was recorded. Co-administration of HT with SM did not significantly improve growth performance parameters in comparing with SM-intoxicated group except for feed conversion rate. Total variable costs were increased in HT-treated and SM-intoxicated groups. Total return, net profit, benefit cost ratio and economic efficiency were improved in HT-treated group compared with other groups. Regarding to biochemical analysis, there was significant elevation of serum activity of CK-MB, AST, ALT and in the concentration of cardiac and muscular NO and MDA in SM-intoxicated group and SM+HT-combination group. GSH didn't significantly change in cardiac tissue, but it was reduced in in muscle tissue of SM+ HT-combination group as compared to control group. Our findings concluded that HT could be used as an acceptable growth promoting agent with a satisfying economic impact. Unfortunately, HT fails to ameliorate the deleterious effect of SM in the cardiac and skeletal muscles of broiler chicks.

Keywords: Biochemical, Broiler, Economic Impact, Hawthorn, Salinomycin.

Introduction

Salinomycin is one of a group known as ionophores antibiotics, which extensively used as anticoccidial drugs and for the improvement of feed conversion in broiler chicks [1]. Under certain circumstances as misuse, overdose and the prolonged administration, these compounds could induce severe toxic manifestations in cardiac and skeletal muscles of the chicks [2]. The main toxic mechanism of ionophores is related to the facilitation of transmembrane Na^+ and Ca^{2+} ion influxes leading to degeneration and necrosis of cardiac and skeletal muscle cells. Other minor toxic effects include the enhancement of catecholamines release and the promotion of lipid peroxidation [3].

The novelty of our research based upon salinomycin poisoning occurs frequently in broiler farms, preventive and therapeutic trials are still of limited success. The main aim of this work is the evaluation of protective efficacy of Hawthorn *(Crataegus spp)* against salinomycin-induced cardiac and muscular damage. Furthermore, possible growth promoting and economic impact of addition of Hawthorn to the broiler ration were evaluated. Our choice for Hawthorn (HT) was based on the presence of a range of bioactive constituents such as bioflavonoids and proanthocyanidins which proved significant cardioprotective effects via antioxidant activity, hypotensive properties, down-regulation of capsase-3 gene expression, chronotrophic and antiarrhythmic actions [4].

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Material and Methods

The Ethical Approval

The procedures and experimental design are approved by the Institutional Animal Care and Use Committee of Alexandria University (Approval number: 2024/02/300).

Source of additives which utilized in this experiment

Salinomycin sodium (SM) was purchased commercially from (ATCO Pharm. Co. Egypt) each 100 gm sodium (99.6 % salinomycin base). Hawthorn (HT) was obtained from Agriculture Research Center of Giza (Egypt). Leaves were identified and authenticated by the Botany Department, Faculty of Science Alexandria University. The harvested leaves of Hawthorn (HT) were purified, washed with tape water, dried under shade for 3 weeks and milled in a hammer mill fitted with 2mm sieve.

Experimental design, management and treatment protocol

This research was carried out during the period from March to May 2023 at Faculty of Veterinary Medicine, Alexandria University, Egypt. Unsexed Ross broiler chicks (n=32), seven days old, obtained commercially from EL-Wataniya Company, with initial body weight (IBW) 161.25 gm. Chicks were divided in a completely randomized design among four groups (eight chicks/treatment). Control group (T1) received basal diet and clean water without any medications. The second group (T2) (SM-intoxicated group) received basal diet plus Salinomycin sodium (SM) at dose of 100 mg/kg feed [5]**.** The third group (T3) (HT-treated group) received basal diet plus HT at dose of 10 g/kg feed [6] and clean water. The fourth group (T4) (SM+HT-protected group) received basal diet plus SM at dose of 100 mg/kg feed SM and HT at dose of 10 g/kg feed. The experiment continued for 28 consecutive days during which all groups received daily treatments without rest.

Data

Body weight gain (BWG) (g), feed intake (FI), and feed conversion rate (FCR) were calculated at 7, 14, 21, 28, and 35 days of age According to [7] as follow: BWG, The chicks were individually weighted at the first day of the experiment, then chicks were weighted weekly and the live body weight change was recorded. BWG was calculated as differences between two successive weights (BWG = W2-W1). Feed intake was calculated by differences between the offered feed weight per week and the remained part, and then divided by the number of chicks in each group to measure the weekly feed intake/bird. FCR was calculated by dividing the amount of feed consumed (g) during the week by the gain in weight (g) during the same week. Also, blood samples were collected from wing vein, centrifuged at 3000 rpm/15 minutes for serum separation and stored at -20 $^{\circ}$C until the assessment of biochemical markers. Chicks were sacrificed and samples from heart and skeletal muscles were transected for the further evaluation of oxidative damage and inflammatory response.

Economic Evaluation (LE/chick)

Partial budget for economic evaluation of the current study through calculation of chick cost, total feed costs/chick, price of kg ration, fixed cost/chick, feed additives (FA) cost, total costs /chick, broiler meat per kg at end of the trial, total return (TR) per chick, net profit margin calculated by (NP)=(NP/TR)*100, (BCR) benefit cost ratio = (TR/TC)*100, economic efficiency (EE) = (NP/TC) *100.

Biochemical Assessment

Serum samples were used for determination of total cholesterol (T. cholesterol) [8], alanine aminotransferase (ALT, EC 2.6.1.2), aspartate aminotransferase (AST, EC 2.6.1.1) [9], total protein [10], creatinine [11], urea [12], and creatine kinase isoenzyme (CK MB, EC 2.7.3.2) [13]. Biochemical tests measured using ready kits (Diamond Diagnostics, Egypt). Troponin T (TnT, Sunred, Product code: 201- 16-0007, China) ELISA kits, which were commercially available for measurement of Tnt levels in serum samples.

Assessment of the oxidative Stress and the antioxidant Status

The oxidative stress and the antioxidant biomarkers analyzed in heart and muscle homogenates 20% (w/v) using cooled 0.1 M phosphate buffer saline and subjected to determination of malondialdehyde (MDA) [14], nitric oxide (NO) [15] and glutathione reduced (GSH) [16] levels and the activities of superoxide dismutase (SOD; EC 1.15.1.1) [17] using commercial Randox Co. kits (U.K.).

Statistical Analysis

One-way ANOVA of SPSS/PC+ version25, were used for statistically analysis of data according to the following model, Xij=M +Ti + Eij where, Xij= the observations, M=treatment average, Ti= treatment effect, Eij=error. A difference among means was tested by Duncan's multiple range technique at 5% probability. GraphPad Prism v.5 (https:// www. graph pad. com/), (GraphPad, San Diego, CA, USA).

Results

Effect of HT and/or SM on Growth Performance Parameters

Table (1) showed that, HT-treated group showed a significant improvement in FBW (final body weight), BWG (body weight gain) and FI (feed intake) in comparison with control group and SM-intoxicated group. Feed conversion rate (FCR) was improved in HT-treated group, SM+HT group and control group compared with SM-intoxicated group. While there were no significant differences in all other growth parameters between HT+SM group and SM–intoxicated group.

Effect of HT and/or SM on Economic Indicators and Economic Efficiency

Total variable costs (LE/bird) were significantly ($P<0.05$) increased in HT-treated and SM-intoxicated groups compared with other groups. Total return (LE/bird), net profit, benefit cost ratio and economic efficiency were significantly increased in HT-treated group followed by control group. The lowest values were recorded in SM-intoxicated group as showed in table (2).

Effect of HT and / or SM on Serum Biochemical Profile

Serum of SM-intoxicated chicks and SM+HT-combination group showed significant elevation in the level of serum CK-MB, ALT and AST in comparison with control group and HT-treated group, while the concentrations of total protein, urea, creatinine and troponin T were relatively similar to control values. The observed increase in the level of cholesterol in chicks treated by HT and/or SM than control was non-significant. (Table. 3). As shown in Figures 1 and 2, compared to control chicks, SM-intoxicated group and SM+HT-combination group showed significant increments in the concentration of cardiac and muscular NO and MDA. Results also revealed absence of any significant deviation in the content of SOD in both heart and muscle tissue in between all experimental groups. However, GSH didn't significantly change in cardiac tissue, but it was reduced in in muscle tissue of SM+HT-combination group as compared to control group.

Discussion

Salinomycin functions as a highly selective potassium ionophore and is a monocarboxylic polyether antibiotic developed from the *Streptomyces albus* strain [18]. Salinomycin is effective against a variety of Gram-positive bacteria and the common forms of *Eimeria* seen in chicken and turkeys. Also, It is frequently used to increase feeding efficiency in ruminants and as an anticoccidial agent in chicken feed [19]. Clinically, feed refusal, muscle weakness, sternal recumbency, diarrhea, weight decline, and mortality are symptoms of salinomycin poisoning in birds [20]. Salinomycin causes significant skeletal muscle and cardiac lesions that are histopathologically associated with myocardial hyperemia, myocardial fiber degeneration, and myocardial mitochondrial damage. Skeletal muscle histology revealed significant muscular degeneration and necrosis with myocardial fragmentation and oedema in those with increased mortality suggesting cardiac failure is probably related to animal death [21, 22].

Our results related to SM-intoxicated chicks are compatible with Gao *et al.* [23] and Ekinci *et al.* [24] who recorded that salinomycin has the potential to induce severe deleterious effect on the cardiac and skeletal muscles of broiler chicks. This study aims to evaluate the growth promoting, economic impact and the possible ameliorative effect of Hawthorn *(Crataegus Spp)* against salinomycin toxicity in broiler chicks. In accordance with the results of this study, HT promotes growth rate through the improvement of appetite (increase FI) and body weight gain (BWG). Our results are consistent with what Tan *et al.* [25] recorded in golden pompano, where they recorded an improvement in the growth promoting activity after HT supplementation. On the other hand, SM administration (dose under study) decreases final body weight of chicks. Matching with our result in rabbit, salinomycin at dose of 40 mg/kg ration showed the same deleterious effect on weight gain [26]. The co-administration of HT with SM did not improve growth performance parameters in comparison with SM-intoxicated group except an improvement of FCR. Total variable costs showed a significant increase ($P<0.05$) in HT-group and SM-intoxicated chicks compared with other groups. This result clearly highlights that co-administration of HT with SM improves the feed conversion saving more costs of feed intake that reflected on improvement of total return, net profit, benefit cost ratio and economic efficiency which were significantly increased in HT-treated group then control group.

Tissue injury and necrosis occur in various organs, in animals intoxicated with salinomycin, particularly the myocardium and liver [27]. The liver enzymes were increased in SM intoxicated groups and results of our research paper match what was mentioned by Kamashi *et al.* [28]**.** Increased AST activity may be related to hepatocellular injury from oxidative damage brought on by salinomycin produced free radicals. Furthermore, Kamashi *et al.* [28] linked the production of degenerative changes in liver and the effect of a toxic salinomycin dose on hepatocytes as the causes of liver damage. Salinomycin caused muscle damage and AST was sensitive for this damage.

CK-MB is an isoenzyme of creatine kinase catalyzes exchange of a phosphate moiety between creatine phosphate and ATP in myocardial and skeletal muscles. In domestic species, CK activity is used as a skeletal muscle injury marker [29]. As expected, SM markedly increases the activity of CK-MB indicating muscular damage. Unfortunately, the administration of HT with SM did not elevate the

activity of CK-MB toward normal control value. AST is a cytosolic enzyme present in various tissues and considered to be a non-specific but it is highly sensitive marker of muscle damage; even though CK is a more specific for muscle damage, AST often used to confirm changes in CK. In the current study, a significant increase in the activity of AST after exposure to salinomycin, confirming the sensitivity of this enzyme to the muscular damage.

Regarding the oxidative stress biomarkers, our finding revealed that SM caused marked oxidative effect which indicated by the elevation of NO and lipid peroxidation product (MDA) levels in both cardiac and muscle tissue. These results were completely consistent with results of Ghonaim *et al.* [26] who mentioned that SM intoxication caused obvious increase in MDA concentration and significant decline in GSH, SOD, and the catalase activities in rabbits**.** On the other hand, HT showed unsatisfied antioxidant activity either alone or when combined with SM.

The imbalance between oxidants and antioxidants within cells causes the oxidative damage. This process includes structural tissue damage, apoptosis or necrosis-induced cell death, and oxidative modification of cellular macromolecules [30]. In comparison to the control group, salinomycin causes a notable rise in MDA levels but a notable decrease in GSH. Hajimohammadi *et al.* [31] noted noteworthy decrease in glutathione level in rats given salinomycin. Our results demonstrated that lipid peroxidation products are elevated in salinomycin intoxication. According to Cinar *et al.* [32], MDA examination is typically utilized to uncover lipid peroxidation. Kargin *et al.* [33] reported increased levels of the lipid peroxidation (MDA) in various diseases, as kidney diseases. Hajimohammadi *et al.* [31] showed an increase in MDA (lipid peroxidation) in salinomycin-treated sheep than control group.

Our findings were the same with those of Rajaian *et al.* [34], who reported that salinomycin did not significantly change the total protein ,lipid, urea and creatinine concentration. Opposite, when rabbits were administered with salinomycin, their serum creatinine levels were significantly higher. According to Huczyński [35] and Kamashi *et al.* [28], oxidative damage is likely the cause of ionophores' toxicity. Besides, when chickens were given the salinomycin, Arun *et al.* [36] found a substantial drop in total protein, albumin, and globulin.

Conclusion

Salinomycin induced obvious damage of myocardial cells also promoted the release of AST and the release of CK-MB. Salinomycin also triggered the apoptosis of myocardial cells which contributed to its cytotoxicity. Our results concluded that Hawthorn could be used as an acceptable growth promoting agent with a satisfying economic impact. Unfortunately, it fails to ameliorate the deleterious effect of salinomycin on the cardiac and skeletal muscles of broiler chicks.

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Not applicable.

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Conflicts of interest

The authors declared no competing interests.

Ethical of approval

The procedures and experimental design are approved by the Institutional Animal Care and Use Committee of Alexandria University (Approval number: 2024/02/300).

TABLE 1. Effect of HT and/or SM on growth performance parameters indicators of broiler chicks

Growth indicators	Control	SM- intoxicated group	HT-treated group	SM+HT combination group
IBW	161.25±6.53 [a]	161.25±9.62 [a]	160.63±9.75 [a]	164.38±9.84 [a]
FBW	2232.50±81.43 [b]	2140.35±93.19 [c]	2492.59±99.69 [a]	2165.62±72.96 [c]
BWG	2071.25±80.9 [b]	1979.10±94.15 [c]	2331.96±99.72 [a]	2001.24±71.33 [c]
FI	3032.88±1.36 [b]	3159.13±1.01 [b]	3372.50±0.87 [a]	2995.25±0.98 [d]
FCR	1.46±0.06 [b]	1.59±0.07 [a]	1.44±0.07 [b]	1.49±0.05 [b]

Data presented as (Mean ± S.E). Means within same row bearing different superscripts are significantly different (P<0.05). SM= salinomycin sodium, HT=Hawthorn, IBW=initial body weight (gm), FBW=final body weight (gm), BWG= Body weight gain (gm), FI= Feed intake (gm), FCR= Feed Conversion Ratio (g feed/g body wt. gain).

TABLE 2. Effect of HT and/or SM on Economic Indicators and Economic Efficiency

Economic indicators	Control Group	SM-intoxicated Group	HT-treated group	HT+SM combination Group
Chick cost (LE)	16	16	16	16
Ration cost (LE/kg)	26	26	26	26
Total feed cost (LE)	78.85±0.04 [d]	84.71±0.03 [b]	87.69±0.02 [a]	77.85±0.03 [c]
Additive cost (LE/bird)1	0	0.07	3.37	3.44
Management cost (LE/bird)	2.35	2.35	2.35	2.35
Total variable costs (LE/bir	97.20±0.04 [c]	103.13±0.03 [b]	109.41±0.02 [a]	99.64±0.03 [c]
Sale price (LE/kg)	70	70	70	70
Total return (LE/bird)	156.28±5.70 [b]	151.94±7.08 [d]	174.48±7.05 [a]	153.69±5.03 [c]
Net profit (LE/bird)	59.08±5.72 [b]	48.81±7.11 [d]	65.07±7.06 [a]	54.05±5.11 [c]
Benefit cost ratio	1.61±0.06 [a]	1.47±0.07 [c]	1.60±0.06 [a]	1.54±0.05 [b]
Economic efficiency	0.61±0.06 [a]	0.47±0.07 [c]	0.60±0.06 [a]	0.54±0.07 [b]

Data presented as (Mean ± S.E). Means within same row bearing different superscripts are significantly different (P<0.05). SM= salinomycin sodium, HT=Hawthorn.

TABLE 3. Effect of HT and/or SM on Serum Biochemical Profile

	Control group	SM-intoxicated group	HT-treated group	SM+HT combination group
CK-MB (U/L)	591.36±59.6 [b]	686.30±46.2 [a]	605.57±44.1 [b]	741.79±39.8 [a]
ALT (U/ml)	6.14±0.34 [b]	7.37±0.88 [a]	5.83±0.47 [b]	7.13±0.18 [a]
AST (U/ml)	438.3±23.66 [b]	521.1±4.74 [a]	425.5±14.74 [b]	540.9±5.59 [a]
Total protein(g/dl)	3.49±0.2 [a]	3.28±0.1 [a]	3.31±0.1 [a]	3.54±0.0 [a]
Urea (mg/dl)	23.14±1.1 [a]	21.91±0.7 [a]	19.97±2.2 [a]	22.21±0.9 [a]
Creatinine (mg/dl)	0.74±0.03 [a]	0.75±0.0 [a]	0.77±0.0 [a]	0.80.0.0 [a]
Cholesterol(mg/dl)	92.28±6.7 [a]	100.10±11.1 [a]	106.25±7.9 [a]	107.19±5.8 [a]
TnT (ng/ml)	0.16±0.02 [a]	0.16±0.01 [a]	0.15±0.01 [a]	0.17±0.03 [a]

Data represented as (means ±SE). Means with different superscripts in same raw differ significantly (P≤0.05). CK-MB=Creatine kinase-MB, ALT=Alanine amino transferase, AST=Aspartate amino transferase, TnT=Troponin T.

Effect of HT and/or SM on Oxidative Stress Biomarkers of Cardiac and Skeletal Muscle

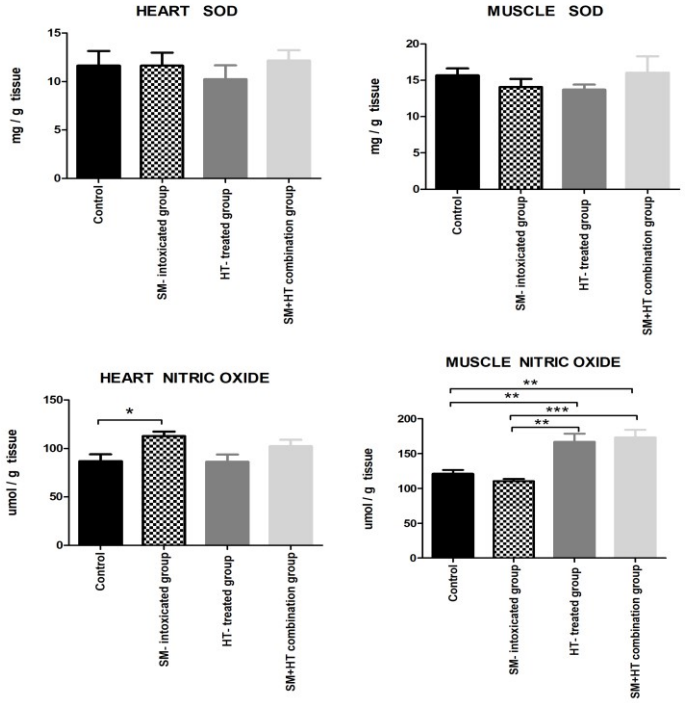

Fig. 1. Oxidative stress and antioxidant status in heart and skeletal muscle superoxide dismutase (SOD) and nitric oxide (NO). *P < 0.05, **P < 0.01, and ***P < 0.001 vs the control.

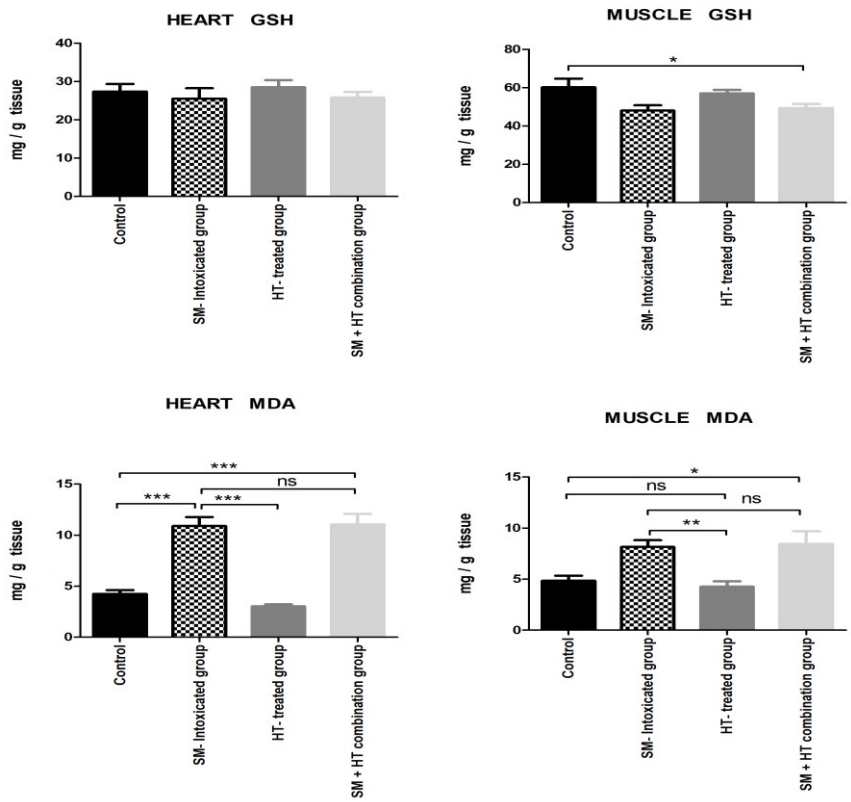

Fig. 2. Oxidative stress and antioxidant status in heart and skeletal muscle glutathione reduced (GSH) and malondialdehyde (MDA). *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ vs the control.

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تقييم التأثير المنشط للنمو والأثر الاقتصادي والتأثير التحسيني المحتمل لنبات الزعرور ضد التسمم بالساليونوميسين في بدارى التسمين

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الملخص

أجريت هذه الدراسة لتقييم التاثيرالمنشط النمو والأثر الاقتصادي والتأثير التحسيني المحتمل لنبات الزعرور ضد التسمم بالساليونوميسين في بدارى التسمين. لذلك، تم توزيع 32 فرخًا غير مجنس بعمر سبعة أيام من سلالة دجاج روس اللاحم بشكل عشوائي تمامًا على أربع مجموعات معالجة. المجموعة الضابطة، المجموعة المسممة بالساليونوميسين (100مجم/كجم علف)، المجموعة المعالجة بـالزعرور (10 جم/كجم علف) والمجموعة المركبة (100 مجم ساليونوميسين/كجم علف بالإضافة إلى 10 جم من نبات الزعرور /كجم علف). كشفت النتائج أن نبات الزعرور يسبب تحسنًا كبيرًا في وزن الجسم النهائي ، ومعدل الزيادة فى وزن الجسم استهلاك العلف ، بينما تم تسجيل انخفاض في وزن الجسم النهائي في المجموعة المسممة بالساليونوميسين . لم تؤدي الاضافة المشتركة لـنبات الزعرور مع الساليونوميسين إلى تحسين معايير أداء النمو بشكل ملحوظ بالمقارنة مع المجموعة المسممة بالساليونوميسين باستثناء التحسن فى نسبة التحويل الغذائى للعلف. بالنظر للاثر الاقتصادى فقد لوحظ زيادة إجمالي التكاليف المتغيرة في المجموعات المعالجة بـنبات الزعرور والمجموعات المسممة بالساليونوميسين . وكذلك تحسن إجمالي العائد وصافي الربح ونسبة تكلفة المنفعة والكفاءة الاقتصادية في المجموعة المعالجة بـنبات الزعرور مقارنة بالمجموعات الأخرى. فيما يتعلق بالتحليل الكيميائي الحيوي، كان هناك ارتفاع كبير في مستوى الكرياتين كيناز إيزوزيم و الاسبرتات أمينوترانسفيراز و ألانين أمينوترانسفيراز فى بلازما الدم وكذلك ارتفاع في تركيز أكسيد النيتريك و مالونديالدهيد القلبي والعضلي في المجموعة المسممة بالساليونوميسين والمجموعة المركبة (الساليونوميسين + نبات الزعرور). لم يتغير مستوى الجلوتاثيون بشكل ملحوظ في أنسجة القلب، ولكن انخفض في الأنسجة العضلية للمجموعة المركبة (الساليونوميسين + نبات الزعرور)مقارنة بالمجموعة الضابطة. خلصت نتائجنا إلى أنه يمكن استخدام نبات الزعرور كمحفزنمو مقبول فى بدارى التسمين وله تأثير اقتصادي مرضي. لكنه ولسوء الحظ ، فشل في تحسين التأثير الضار لـلتسمم بالساليونوميسين في عضلات القلبية والهيكلية لبدارى التسمين.

الكلمات الدالة: الكيمياء الحيوية، بدارى التسمين، التأثير الاقتصادي، نبات الزعرور، الساليونوميسين.