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Comparative efficiency of the dietary addition of synbiotic "curazol-M" and norfloxacin on the growth performance, body composition, and histological alteration of the Nile tilapia

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ABSTRACT

The current study was carried out to assess the effect of synbiotic (Curazole-M; CM) and/or antibiotic Norfloxacin (NFLX) as feed additives on growth performance and body composition of the Nile tilapia, *Oreochromis niloticus*. Healthy fish (n=120, average initial weight 15±0.2 g) were randomly divided into four groups in triplicates; the first group (G_1) was fed on a control basal diet, while the second group (G_2) was fed on a basal diet supplemented with 0.1 g.kg $^{-1}$diets of NFLX, the third group (G_3) was fed on a basal diet fortified with 1 ml.kg $^{-1}$ diet of CM, and the fourth group (G_4) was fed on a basal diet supplemented with a mixture of NFLX and CM for 8 weeks. Results showed a significant increase ($P < 0.05$) in growth parameters including body gain (BG), body gain percent (BG %), average daily weight gain (ADWG), and specific growth rate (SGR), with a significant decrease in feed conversion rate (FCR), recorded in G_3, G_4, and G_2 treatments, respectively compared with the G_1 (control). The dry matter contents were assessed as crude protein content increased ($P < 0.05$) in the body of fish in G_4. The body fat content was increased ($P < 0.05$) in fish of G_3, G_2, G_1, and G_4 respectively. The results emphasize that; curazole-M supplemented diet could enhance the health of the Nile tilapia.

INTRODUCTION

Fish diseases are one of the major problems in the fish farm industry especially the bacterial pathogen (**Saikia *et al*., 2017**). For the prevention and control of fish diseases, antibiotics were commonly used in aquaculture for prophylaxis (**Susmita *et al*., 2017**). Fluoroquinolones are used to control bacterial infections that cause pulmonary, urinary, and digestive-tract diseases in farmed animals (**Papich and Riviere, 2001**). NFLX is the third generation of fluoroquinolones; and because it is cheap and has broad-spectrum activity against aerobic Gram-negative bacteria with few side effects on fish, it is generally used for management and controls various fish diseases (**Holmes *et al*., 1985**). Chemotherapy including antibiotics decrease the normal flora of fish and biological filters and must be used as emergency measures. It may also decrease or prevent the

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incidence of bacterial pathogens and represents a hazard for aquatic animals (**Susmita *et al*., 2017**) and may lead to many problems as their cumulative residues may affect human health (**Dawood *et al*., 2018**). So, there are other successful alternatives in aquaculture like probiotics, prebiotics, and synbiotics that could rely on preventing the entrance of the pathogen, enhancing water quality, reducing the different stressors in the fish environment, good nutrition, and immunization (**Susmita *et al*., 2017**).

There is a global interest to use the feed additives as eco-friendly alternatives to chemotherapy for enhancing fish growth, digestive enzyme activities, immunity, and to prevent the occurrence of the disease (**Wang *et al*., 2019**). Synbiotic is formed from a combination of non-digestible food ingredients (prebiotic) and living organisms (probiotic) to compose a symbiotic relationship or synergism and it has been assured to improve the growth, health, and immunity status of various aquaculture species (**Zhang *et al*., 2013; De *et al*., 2014; Putra *et al*., 2015; Kumar *et al*., 2017; Putra and Romdhonah, 2018**). Synbiotic provided more beneficial effects for fish in comparison to the addition of only probiotics or prebiotics (**Dawood *et al*., 2018**) as it promotes the implantation of live microbes in the gastrointestinal tract and prolongs their surveillance, stimulates the metabolism of beneficial bacteria in the gut, and enhanced the secretion of digestive enzymes and nutrients absorption, which undergo improving the fish growth (**Dawood *et al*., 2018; Maftei, 2019**).

Nile tilapia, *Oreochromis niloticus*, is one of the most important tilapia species, which is widely cultured in the tropical, subtropical, and temperate regions (**El-Sayed, 2019**). Improving fish growth during their intensive culture are the most substantial targets in the aquaculture industry. So, the current study aimed to assess the comparative efficiency of dietary supplementation of synbiotic (Curazole-M) and/or Norfloxacin (NFLX) on growth performance, body composition and histological features of Nile tilapia.

MATERIALS AND METHODS

1. Raw materials

1.1. Synbiotic

Commercial product purchased from Memphis for pharmaceuticals and chemical industries, Cairo, Egypt named (curazole-M) which composed of *Saccharomyces cerevisiae* (60g/L), Echinacea (115g/L), Mannanoligosaccharides (35g/L), Beta-Glucan (25g/L), Vitamin E (100g/L), DL-Methionine (30g/L), L-Lysine (10g/L), Choline Chloride (100g/L), Minerals (30g/L) and Propylene Glycol (75g/L).

1.2. Antibiotic

Noracin (norfloxacin 400mg) purchased from Algomhoreha for pharmaceuticals and chemical industries. Cairo, Egypt.

2. Diet preparation and fish cultural conditions

Diet preparation and formulation were done according to the standard requirements of Nile tilapia (**NRC, 2011**) to the control diet, 1 ml of CM and/or 0.1 g of NFLX was added to one kg diet. The ingredients of each diet were well-mixed together, pelletized, dehydrated for 24 h at room temperature, and then kept in a refrigerator until used. Healthy Nile tilapia *(O. niloticus*) fingerlings (n=120) with an average initial weight of 15 ± 0.4 g were obtained from Abbassa fish farm, Sharkia governorate, Egypt. Fish were adapted for 15 days before the beginning of the experiment during which they fed the basal diet (**Table 1**) until the start of the experiment. Before the onset of the experiment, fish health check was done according to **CCAC (2005)**. The aquaria were filled with tap water free from chlorine, aerated by a central air compressor. The fish were then randomly distributed into 12 96-L glass aquaria at a density of 10 fish for each aquarium and assigned to four treatments with three replicates per each. The first group (G_1) was fed on the basal diet only and kept as a control group. The second (G_2) and third groups (G_3) were fed on basal diets supplemented with CM and NFLX at 0.1 g. kg^{-1} and 1 ml. kg^{-1}, respectively. The fourth group (G4) was a mixture of CM and NFLX. The fish were fed twice daily, by hand till satiation, at 9:00 a.m. and 2:00 p.m. for 8 weeks. The dissolved oxygen, water temperature, and pH were measured daily and their values were 6.55 $mg.L^{-1}$, 25±0.5ºC, and 7.8±0.4, respectively. Ammonia-N, nitrite-N, and water hardness were measured weekly according to **APHA (1998)**. The photoperiod was controlled automatically12 h light: 12 h darkness in the laboratory using fluorescent tubes. The protocol of the experiment was carried out according to the guidelines of the care and use of animals for scientific purposes research committee, and ethical approval was obtained from Zagazig University.

3. Growth performance

The initial body weight (IBW) was attained at the onset of the feeding experiment by weighing the fish from each group, and then fish body weights and feed intake were recorded every two weeks. The growth performance parameters were calculated according to **Castell and Tiews (1980).**

4. Proximate chemical composition of the whole fish body

At the end of the feeding trial (8 weeks), three fish were randomly collected from each aquarium. Fish samples were analyzed in triplicates for moisture, crude protein, crude fat, and total ash according to **AOAC (2000)**. Fish samples were frozen at -20 °C till analyzed. The frozen whole fish were thawed, dried in the hot air oven, grounded into powder, and analyzed. Moisture content was estimated by drying the samples to constant weight at 85 °C in a drying oven (GCA, model 18EM, Precision Scientific Group, Chicago, IL, USA). The crude protein (N×6.25) was determined using the Kjeldahl distillation unit (UDK 129, VELP Scientifica, UsmateVelate, Italy), and crude lipids were measured using Soxhlet extractor glassware with petroleum ether (60 – 80 °C). The ash content was measured by muffle furnaces (Barnstead/Thermolyne Benchtop 47900, Thermo Scientific, MA, US).

5. Histopathological examination

Tissue specimens from liver and spleen were dissected out from the control and treatment groups, fixed in 10% neutral buffer formalin for 24 h, and then rinsed with water, dehydrated serially in ethyl alcohol, cleared by xylol and rehydrated with decreased ethanol concentrations. The fixed tissues were embedded in paraffin wax and sectioned at 3- 5 microns then stained with hematoxylin and eosin (H&E) according to **Roberts (2001)** and then, examined microscopically.

6. Statistical analysis

The data were statistically analyzed by one-way Analysis of Variance (ANOVA) using SPSS version 24. Duncan's Multiple Range Test was utilized for detecting statistical differences among groups at a significance level of 0.05 (**Dytham, 2011**).

Table 1. Ingredients and proximate chemical composition of the basal diet on air dry basis (g/kg):

Ingredients	g/kg diet
Yellow corn	213
Wheat flour	100
Soy bean meal 44% CP	280
Corn gluten 60% CP	100
Fish meal 60% CP	180
Wheat bran	60
Fish oil	60
Methionine	4.0
Vitamins and minerals mixture [1]	3.0
Chemical analysis (g/kg)[2]	
DM	947.6
Crude protein	338.2
Fat	96.7
Crude fiber	38.9
NFE[3]	392.8
GE (kcal/kg)	4590.29
Lysine	18.7
Methionine	10.9
Calcium	10.4
AP [4]	8.9

[1] Composition of vitamins and minerals premix kg^{-1}: vitamin A580,000 IU; vitamin D_3 8,600 IU; vitamin E 720 mg; vitamin K_3 142 mg; vitamin C 0.1 mg; vitamin B_1 58 mg; vitamin B_2 34 mg; vitamin B_6 34 mg; vitamin B_{12} 58 mg; biotin 50 mg; folic acid 86 mg; pantothenic acid 8 mg; manganese sulfate 65 mg; zinc methionine 3,000 mg; iron sulfate 2000 mg; copper sulfate 3,400 mg; cobalt sulfate 572 mg; sodium selenite 25 mg; calcium iodide 25 mg; calcium carbonate as carrier up to till 1 kg.

[2] According to NRC (2011)

[3]Nitrogen free extract = 100 % – (% EE + % CP + % Ash + % CF)

EE: Ether extract. CP: Crude protein. CF: Crude fiber.

[4] Available phosphorus.

RESULTS

Growth performance

As illustrated in **Table 2**, the growth performance parameters such as final body weight (FBW) body gain (BG), average daily gain (DBWG) and relative growth rate (SGR) were significantly (P <0.05) enhanced in the group G_3 followed by G_4 and G_2 compared with G_1 (control group). Meanwhile, a significant decrease (P <0.05) in the feed conversion ratio (FCR) in experimental groups was recorded when compared with the control.

Table 2. Growth performance of Nile tilapia, *O. niloticus* fed diets containing antibiotic (Norfloxacin NFLX) and/or synbiotic (Curazol-M CM) for 8 weeks

Groups	IBW/g	FBW/g	WG /g	DBWG	RGR	FCR
G1	15.40±.05	46.69 ± 0.79 [c]	26.56 ± 0.37 [c]	0.38 ± 0.01 [c]	1.43 ± 0.01 [c]	1.82 ± 0.45 [a]
G2	15.47±.06	47.47 ± 0.69 [bc]	29.16 ± 0.24 [b]	0.42 ± 0.003 [b]	1.51 ± 0.01 [b]	1.76 ± 0.14 [ab]
G3	15.42±.06	53.00 ± 0.89 [a]	31.38 ± 0.57 [a]	0.45 ± 0.01 [a]	1.59 ± 0.02 [a]	1.60 ± 0.72 [b]
G4	15.42±.05	50.29 ± 1.52 [ab]	29.93 ± 1.02 [ab]	0.43 ± 0.01 [ab]	1.54 ± 0.03 [ab]	1.59 ± 0.58 [b]

[abc]Means with different superscript are statistically different $P< 0.05$ according to Duncan's multiple range test.
IBW: Initial body weight. FBW: Final body weight. Wg: Weight gain. DBWG: Daily body weight gain. RGR: Relative growth rate. FCR: Feed conversion ratio. G_1: The control group. G_2: Fish fed on a basal diet supplemented with 0.1 $g.kg^{-1}$ diets of NFLX. G_3: Fish fed on a basal diet supplemented with 1 $ml.kg^{-1}$ diet of CM. G_4: Fish fed on a basal diet supplemented with a mixture of NFLX and CM

Proximate composition of the whole-fish body

Table 3 highlights the proximate composition of the whole- fish body. The fish body contents from the crude protein, fat, and ash were evaluated. The crude protein content was significantly increased ($P <0.05$) by 63.69% in G_4 followed by other groups. The crude fat content was increased by 18.97, 14.32, 14.08, and 11.31 % for G_3, G_2, G_1, and G_4 respectively. The ash content was significantly increased by 18.97, 14.32, 14.08, and 11.31% for G_1, G_2, G_4, and G_3 respectively.

Table 3. Proximate chemical composition of the whole body of Nile tilapia, *O. niloticus* fed diets containing antibiotic (Norfloxacin NFLX) and/or synbiotic (Curazol-M CM) for 8 weeks

Groups	Crude protein	Total lipids	Ash
G1	55.83 ± 0.87 **[b]**	14.08 ± 0.39 **[b]**	22.31 ± 0.16 **[c]**
G2	57.66 ± 0.69 **[b]**	14.32 ± 0.43 **[b]**	26.11 ± 0.21 **[b]**
G3	57.59 ± 0.48 **[b]**	18.97 ± 0.13 **[a]**	28.78 ± 0.38 **[a]**
G4	63.69 ± 0.89 **[a]**	11.31 ± 0.23 **[c]**	19.04 ± 0.15 **[d]**

[abcd] Means with different superscript are statistically different $P< 0.05$ according to Duncan's multiple range test.
G_1: The control group. G_2: Fish fed on a basal diet supplemented with 0.1 $g.kg^{-1}$ diets of NFLX. G_3: Fish fed on a basal diet supplemented with 1 $ml.kg^{-1}$ diet of CM. G_4: Fish fed on a basal diet supplemented with a mixture of NFLX and CM.

Histopathological investigation

The examined sections of the fish liver in the control group (G_1) revealed normal hepatocytes, central vein, and hepatopancreas (**Fig.1A**). Histopathological alterations were detected in the liver among fish of G_2 fed on NFLX supplemented diet, such as:

congestion of the hepatic blood vessels with hyperplasia of hemopoietic tissue around blood vessels with hyperplasia of hemopoietic tissue around blood Vessels and vacuolation of the hepatic cells (**Fig.1B**). The liver of fish in G_3 fed on CM in the diet showed hydropic degeneration of the hepatic cells with leucocytic cells infiltration (**Fig. 1C**) and congestion with perivascular edema and hyperplasia of hemopoietic tissue around blood vessels of the liver of fish in G_4 feeding on NFLX and CM supplemented diet (**Fig. 1D**).

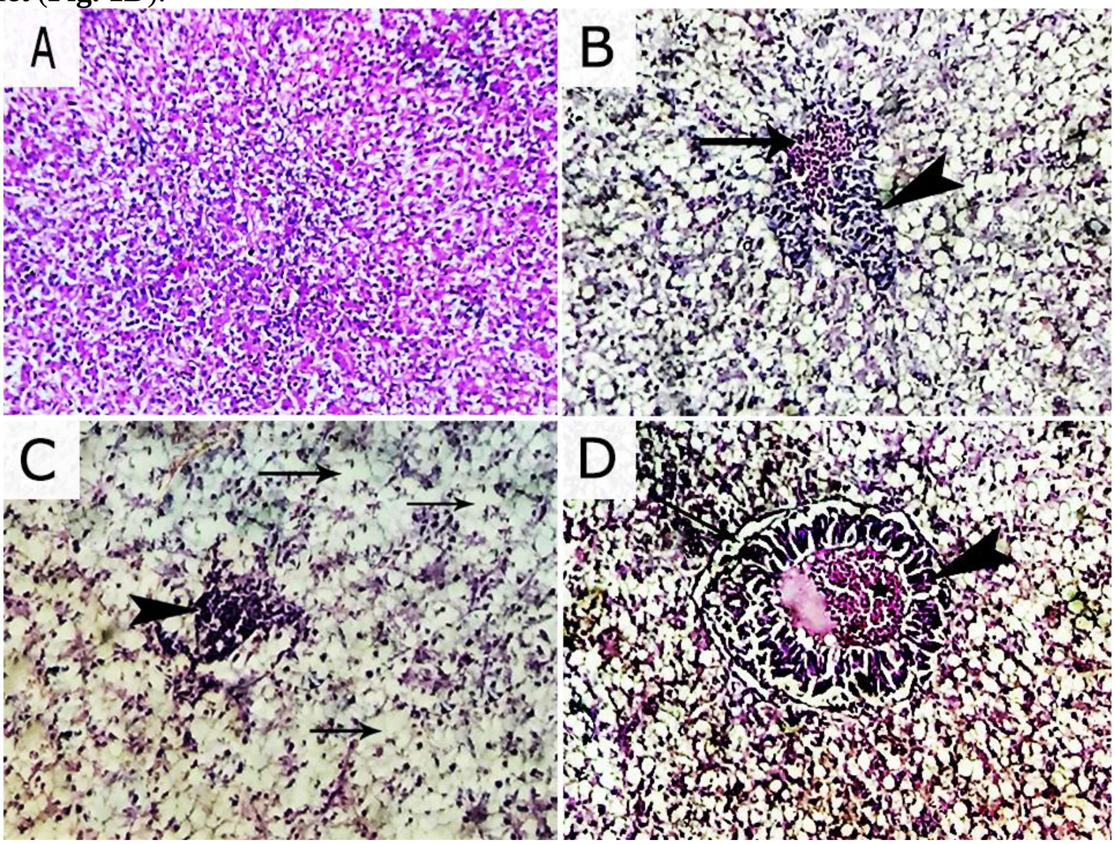

Fig.1. (A) Photomicrograph of Liver (G_1) feeding on basal diet showing apparently normal tissue, architecture and cellular details (H&E x 400). (B)Photomicrograph of liver (G_2) feeding on antibiotic supplemented diet showing congestion of the hepatic blood vessels (arrow) with hyperplasia of hemopioetic tissue (arrow head) around blood Vessels and vacuolation of the hepatic cells (H&E x 400). (C) Photomicrograph of liver of (G_3) feeding on CM supplemented diet showing hydropic degeneration of the hepatic cells (arrow) with leucocytic cells infiltration (arrow head) (H&E x 400). (D) Photomicrograph of Liver (G_4) feeding on NFLX and CM supplemented diet showing congestion with perivascular edema (arrow) and hyperplasia of hemopioetic tissue around blood vessels (arrow head) (H&E x 400).

The histological examination of the spleen in the control group showed normal tissue, architecture and cellular details with mild diffuse hemosiderosis (**Fig.2A**). Spleen from fish in G_2 showed focal hemosiderosis with depletion of lymphocytes from the white pulp (**Fig.2B**). The spleen of fish in G_3 showed interstitial edema with severe perivascular hemosiderosis (**Fig.2C**) and congestion and severe perivascular hemosiderosis of fish spleen in G_4 feeding on NFLX and CM supplemented diet (**Fig. 2D**).

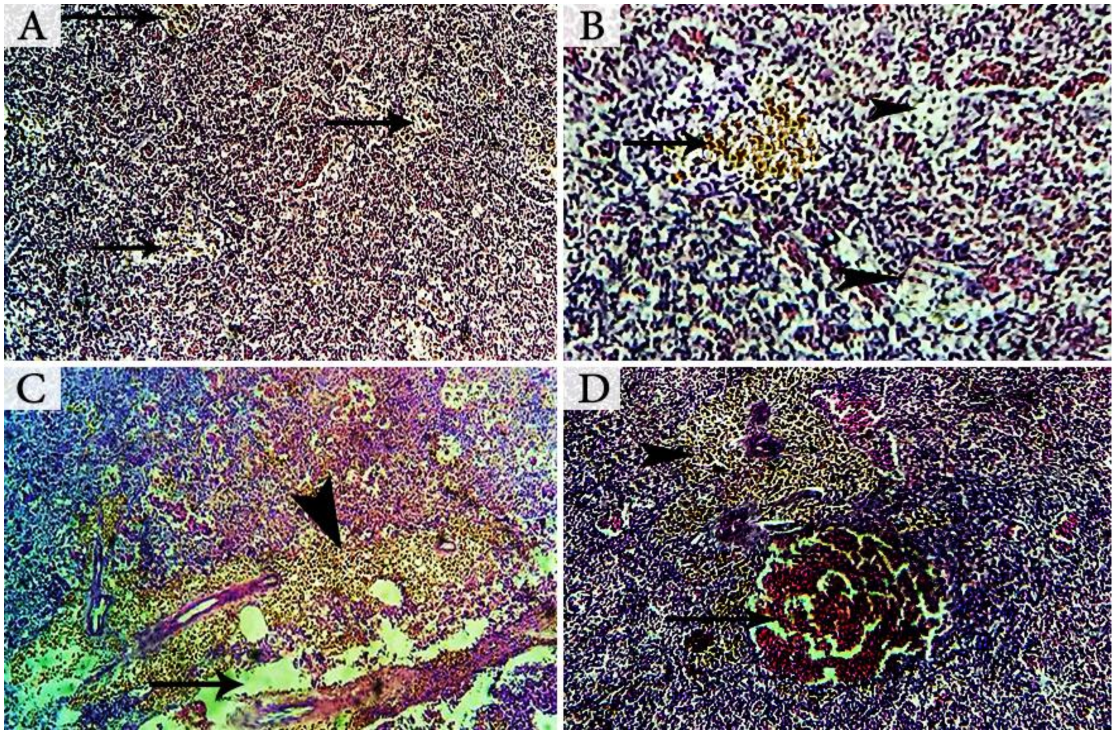

Fig.2. (A) Photomicrograph of spleen (G_1) feeding on basal diet showing apparently normal tissue, architecture and cellular details with mild diffuse hemosidrosis (arrow) (H&E x 200). (B)Photomicrograph of spleen (G_2) feeding on antibiotic supplemented diet showing focal hemosiderosis (arrow) with depletion of lymphocytes from white pulb (arrow head) (H&E x 200). (C) Photomicrograph of spleen of (G_3) feeding on CM supplemented diet showing interstitial edema (arrow) with severe perivascular hemosidrosis (arrow head) (H&E x 200). (D) Photomicrograph of spleen (G_4) feeding on NFLX and CM supplemented diet showing congestion (arrow) and severe perivascular hemosidrosis (arrow head) (H&E x 200).

DISCUSSION

The combination of the probiotic and prebiotic is known as synbiotic, which ameliorates the survival and colonization of live microbial dietary supplements (probiotics) in the gastrointestinal tract enhancing the health status of the fish (**Daniels *et al*., 2010**). In the present study, the growth performance parameters were significantly ($P < 0.05$) enhanced in the experimental groups (G_3. G_4 and G_2) compared with the control group. The obtained data are coordinated with **Mohammadi *et al*. (2016)** and **Okey *et al*. (2018)** who mentioned that synbiotic has beneficial effects on nutrients digestion and absorption by fish enhancing their survival and growth. Also, **Pilarski *et al*. (2017)** reported that the addition of β-glucan with different doses to Nile tilapia diets improved the growth performance of fish and helps in energy conservation, increased feed efficiency, and consequently enhanced growth. Synbiotic supplementation showed the best values of SGR and FCR as documented by **Putra and Romdhonah (2018)**, who attributed these results to the enhanced activity of the digestive enzymes, which promoted nutrients digestibility and absorption, leading to enhanced feed efficiency (**Cerezuela *et al*., 2011**). The significant decrease in FCR in CM treated group could be due to the presence of *Saccharomyces cerevisiae* which increases the enzymatic digestion of a complex polysaccharide including cellulose; organic phosphorous (phytic acid) utilization and fiber digestion (**Mohammadi *et al*., 2016**).

Concerning the effect of dietary supplementation of NFLX on the growth performance of Nile tilapia, the results showed that growth performance parameters of experimented fish significantly decreased when compared with other groups. The long-term exposure (8 weeks) of fish to NFLX, can reduce the gut microbiome that can negatively affect the fish physiological status through enzymatic activity reduction thus exhibit less growth than other groups. The results could be supported by **Carlson *et al*., 2015; Carlson *et al*., 2017; Zhou *et al*., 2018; Kim *et al.*, 2019**). **Dibner and Richards (2005)** and **Reda *et al*. (2013)** who reported significant enhancements in final body weight (g), WG (g), and a significant decrease in FCR of fish fed oxytetracycline in diet when compared to the control.

The current study revealed a significant increase ($P < 0.05$) in the protein and fat contents of the whole-fish body in G_4 and G_3 in comparison with the other groups. The results agreed with **Dawood *et al*. (2020)** who attributed the improved body protein content by fish fed synbiotic to the protease-enzyme which released from aged yeast cells enhancing the protein digestibility. The addition of synbiotic showed higher protease activity as compared to the control and the other treatments as supported by **Putra and Romdhonah (2018)**. A similar result also obtained by **Kumar *et al*. (2017)** who reported that the addition of synbiotic to feed could improve protease activity in *Cirrhinus mrigala* (Ham.) fingerling, leading to improving protein, starch, and fat digestions and subsequently enhanced the growth performance fed synbiotic in diets. Little literature about the effect of antibiotics on proximate composition analysis of fish, in the current study NFLX significantly decreased the protein content; however, there was a relatively significant increase in lipid content of Nile tilapia ensuring the stress effect of antibiotic on fish. It could be explained as the chronic exposure of fish to NFLX leads to genotoxicity which resulted in some physiological alterations such as alterations in the energy metabolism of liver tissue and muscles of fish (**Yang *et al*., 2020**) leading to increase the protein and decrease the lipid contents of Nile tilapia.

The toxicological consequences of NFLX in the liver of humans and rats have been studied, and include the induction of hepatoxicity (**López-Navidad *et al*., 1990**) and the toxic effect may be of similar metabolic pathways in fish. The observed alterations in the liver of the current study showed hepatocellular damages. Fish in other groups mostly exhibited a normal hepatic architecture; however, some alterations were observed for all experimental groups, but lesser than that of individuals fed NFLX in diet. The results of the liver histological examination are in agreement with that discussed by **Ahmed *et al*. (2013); Rodrigues *et al*. (2019a)** they proposed that hypertrophy of hepatocyte of fish liver exposed to antibiotics may due to denaturation of regulating ATPases, cellular energy transfer processes disruption, and endoplasmic membranes proliferation, that leads to increase the processes of biotransformation. The hepatocytes vaculations may result from lipids and glycogen deposition, which inhibit the protein synthesis and depletion of energy (**Ahmed *et al*., 2013; Rodrigues *et al*., 2019b**). Here-observed hemorrhages of hepatocytes which specially recorded due to the chronic exposure to NFLX (8 weeks) compared to G_1 and G_3. This could be related to that the liver is a highly vascular organ (**Abdel-Hameid, 2007**) thus led to the rupture of sinusoid causing hemorrhages. Herein, in our study, the spleen showed a reduction in lymphocytes and hemosiderin pigments comparing with other groups. The results coordinated with that reported by **Gaikowski *et al*. (2003) and Reda *et al*. (2013)**.

CONCLUSION

The present study elucidates that dietary addition CM as a synbiotic could improve growth performance and body composition of Nile tilapia. The results provide data for the application of synbiotic as a beneficial feed additive in the Nile tilapia aquaculture industry. Also, we do not recommend the use of antibiotics, NFLX as an additive in fish diets, as they have a severe hazardous effect on the health of Nile tilapia.

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الملخص العربي

مقارنه الكفاءة للإضافة الغذائية لكل من "كورازول إم" ونورفلوكساسين على أداء النمو وتكوين الجسم والتغير النسيجي للبلطي النيلي

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أجريت الدراسة الحالية لتقييم تأثير السينبيوتيك (CM) Curazole-M و / أو المضاد الحيوي Norfloxacin (NFLX) كاضافات للعليقه الأسماك على أداء النمو وتكوين الجسم للبلطي النيلي. قسمت الأسماك الصحية (ن = 120 ، متوسط الوزن الأولي (15 ± 0.2 جم) بشكل عشوائي إلى أربع مجموعات في ثلاث تكرارات. تم تغذيه المجموعة الأولى (G1) على نظام غذائي أساسي كمجموعه ضابطه ، بينما تم تغذية المجموعة الثانية (G2) على نظام غذائي أساسي مكمل بـ 0.1 جم كجم $^{-1}$ كجم من النورفلوكساسين ، وتم تغذية المجموعة الثالثة (G3) على نظام غذائي أساسي مدعم ب 1 مجم $^{-1}$ حمية من السنبيوتك ، والمجموعة الرابعة (G4) تمت تغذيتها على العليقه الاساسيه مدعمة بخليط من NFLX و CM لمدة 8 أسابيع. أظهرت النتائج زيادة معنوية (P <0.05) في معدلات النمو بما في ذلك اكتساب الجسم (BG) ونسبة اكتساب الجسم (BG) ومتوسط زيادة الوزن اليومية (ADWG) ومعدل النمو النوعي (SGR) ، مع انخفاض معنوي في التحويل الغذائي. تم تسجيل معدل (FCR) في معاملات G3 و G4 وG2 ، على التوالي مقارنة مع G 1 (المجموعة الضابطه). تم تقييم محتويات المادة الجافة مع زيادة محتوى البروتين الخام (P<0.05) في جسم الأسماك في .G4 تمت زيادة محتوى الدهون في الجسم (P <0.05) في أسماك G3 و G2 و G1و G4 على التوالي. النتائج تؤكد ذلك ؛ النظام الغذائي المكمّل من curazole-M يمكن أن يعزز صحة البلطي النيلي.