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Effect of dietary administration of kappa carrageenan extracted from *Hypnea musciformis* on innate immune response, growth, and survival of Nile tilapia (*Oreochromis niloticus*)

L. Villamil[1] · S. Infante Villamil[2] · G. Rozo[3] · J. Rojas[2]

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Abstract
Immune stimulants are an alternative to antibiotic use and contribute to disease prevention in aquaculture. The effect of dietary administration of kappa carrageenan (Kc), extracted from the red algae *Hypnea musciformis,* in Nile tilapia (*Oreochromis niloticus*) was assessed by monitoring weight gain after a 15-day feeding trial. Immunostimulation was inferred by the relative expression of transferrin, interleukin 1β (IL-1β), and growth hormone (GH) in the spleen after 24 h and 15 days of daily administration. The toxic activity of Kc was evaluated in brine shrimp (*Artemia salina)* nauplii. No significant toxic effects of Kc were observed in *A. salina* at any dose studied. A positive tendency in growth rate and fish survival values was observed when Kc was administered. Correspondingly, GH, transferrin and IL-1 β levels at day 15 post-treatment were higher in the spleens of fish fed with Kc at 5 g kg^{-1} relative to non-Kc-treated control fish. Feeding Kc extract from *H. musciformis* to the fish improved nonspecific immunity parameters and increased survival and growth, but further research, including longer-termed studies, should be conducted before recommendation of Kc supplementation in tilapia diets at commercial scale.

Keywords Immune-stimulant · *Oreochromis niloticus* · *Hypnea musciformis* · Kappa carrageenan · *Edwardsiella tarda* · GH · IL1β · Transferrin

Introduction

Tilapia has become the second most important cultured fish in the world, and global production is expected to increase from 4.3 to 7.3 million tons between 2010 and 2030 as a result of

Highlights
• Kappa carrageenan extracted from *H. musciformis* has immunomodulatory activity in tilapia.
• Dietary supplementation of Kappa carrageenan improves tilapia survival during a challenge with *E. tarda.*

✉ L. Villamil
luisa.villamil@unisabana.edu.co

Back Affiliation

rapid aquaculture expansion (Food & Agriculture Organization of the United Nations (FAO 2014)). Nevertheless, tilapia farming is jeopardized by economical losses related to poor environmental conditions and fish mortalities associated with various pathogens (Dong et al. 2017; Osman et al. 2017).

Inappropriate use of antibiotics in aquaculture has been previously reported as a cause of bacterial antibiotic resistance; this fact could also represent a potential risk to consumer health (Cabello et al. 2016; Zhao et al. 2017; Liu et al. 2017). Strategies oriented toward the improvement of management practices and alternative methods to control pathogenic bacteria have been proposed. Examples of these strategies include preventive approaches such as vaccine use (Zhang et al. 2017) and functional feeds including probiotics, prebiotics, and immune-stimulant feed supplementation (Hai 2015; Huynh et al. 2017; Villamil and Esguerra 2017). Vaccines have been used in tilapia culture, albeit protection could be promoted only toward specific pathogens (Brudeseth et al. 2013). In some countries such as Colombia, vaccination is not a common practice in aquaculture, since commercial vaccines are not licensed. In the same manner, probiotic use requires extensive biohazard studies, if selected bacteria are not in GRAS (generally recognized as safe) status.

Immune stimulants from natural sources are biocompatible, biodegradable, and safe for the environment and human health; among the most commonly used stimulants in fish culture are vitamins (Ibrahem et al. 2010), chitosan (da Silva Santos et al. 2017) and beta-glucans (Salah et al. 2017).

There is evidence that polysaccharides extracted from seaweed are able to exert positive immunomodulatory effects in cultured aquatic species. For example, sodium alginate extracted from brown algae *Undaria pinnatifida* and *Macrocystis pyritera* increased fish survival in an experimental infection with *Edwardsiella tarda* (Fujiki and Yano 1997). In the tiger grouper, *Epinephelus fuscoguttatus*, dietary supplementation with sodium alginate extracted from *Lessonia nigrescens* enhanced the expression of an antiviral gene (Cheng et al. 2012). Furthermore, iota-carrageenan and sodium alginate injection caused a significant increase in the alternative complement, respiratory burst, phagocytic activity, and higher resistance of grouper *Epinephelus coicoides* against *Vibrio alginolyticus* (Cheng et al. 2007). Commercial products containing alginates (Aquavac, Ergosan, Merk) extracted from *Laminaria digitata* and *Ascofillum nodosum* increased the non-specific defense response of rainbow trout *Oncorhynchus mykiss* and sea bass *Dicentrarchus labrax* (Bagni et al. 2005).

In the present study, kappa carrageenan (Kc) was obtained from red algae, *Hypnea musciformis*, a common specie in the Colombian Caribbean, which is cultivable and produces high-quality carrageenan yields (Camacho dan Montaña 2012). Kappa carrageenan toxicity was evaluated in brine shrimp (*Artemia salina*) nauplii. After confirming safety, feeding trials were conducted to investigate the effect of 15 days of dietary administration of Kc on tilapia weight gain and survival after a *E. tarda* challenge. Expression of transferrin, interleukin 1β (IL-1 β), and growth hormone (GH) in the spleen was studied after 24 h and 15 days of daily administration.

Materials and methods

Kappa carrageenan toxicity assay in *Artemia salina*

Purified Kappa carrageenan (Kc) was provided by Gladys Rozo (Jorge Tadeo Lozano University) after extraction from the red seaweed *Hypnea musciformis* following

Colombian Patent titled: "Procedure for extracting and purifying kappa carrageenan obtained from *H. musciformis*". Patent number 08043691, Certificate number 29475, Gazette No 597.

The carrageenan obtained is a pure compound, consisting in a linear chain of repeated subunits of D-galactose with 3,6-anhydro-galactose (3,6-AG) and linked by glycosidic bonds of type α-1,3 and β-1,4. It is a strongly anionic polymer of molecular weight 287 KD, with gelation temperature of 40 C and melting point of 71.05 °C.

Artemia salina cysts (Artemia International LLC, Houston, TX, USA) were hatched in seawater filtered through 30-μm Millipore cellulose filters. Briefly, cysts were first hydrated in distilled water at 4 °C for 12 h and washed to separate the floating cysts from those that sink. Approximately 3 g of the pre-cleaned cysts were incubated in 1.5 L of seawater in a conical plastic container at 28–30 °C with stone aeration and constant illumination for 24 h.

The potential toxicity of Kc was evaluated in brine shrimp *A. salina* nauplii by adding Kc to the culture water at final doses of 0, 2.5, 5, and 10 mg L^{-1}. Each treatment was replicated four times. Falcon tubes (Fisher Scientific, Waltham, MA, USA), containing 3 mL of sterile-filtered water at 30 UPS were used to expose 20 nauplii to each treatment ($n = 80$ per treatment). Living nauplii were counted after 24 and 48 h of exposure. The toxic activity of Kc was determined according to the previous report of Harwig and Scott (1971).

Nile tilapia

Healthy tilapia juveniles were obtained from a commercial farm (SENA, Centro Agropecuario de Gaira, Santa Marta, Colombia). Fishes were acclimatized for 15 days in rectangular tanks with dechlorinated water at 28 °C, constant aeration, and 12-h photoperiods before experiments. Tilapia were fed three times a day with commercial food, and daily water exchange (75%) was performed half an hour after feeding.

Experimental design and diet preparation

A total of 360 healthy tilapia (0.61 ± 0.031 g) were randomly selected from the stock and split into 12 20-L aquaria (30 fish per aquarium). Animals were fed with a commercial diet (Italcol S.A., Bogota, Colombia), containing 24% of protein, three times a day for 30 days at a biomass rate of 5%.

Four treatments consisting of Kc at 0, 2.5, 5, and 10 g kg^{-1} were evaluated in triplicate (three aquaria per treatment). Kc was dissolved in sterile phosphate-buffered saline (PBS), and then thoroughly mixed with the commercial feed (Italcol, Colombia) to assure uniform distribution of Kc. The feed was dried in an oven at 45 °C to avoid mold growth and kept dry until use (Villamil et al. 2014).

Growth performance and fish survival

Fish weight was collected at the beginning and at the end of the experiment and specific growth rate (SGR) was calculated as (Ln Final Weight − Ln Initial Weight) / time (days) * 100. The percentage survival rate was obtained with the formula: (fish / total fish) * 100.

Tilapia survival after *E. tarda* challenge

Edwardsiella tarda was obtained from the Universidad Nacional de Colombia and was originally isolated from mass mortalities at a commercial farm. The bacterium was grown on blood-enriched brain heart agar (Difco; Fisher Scientific, Hampton, New Jersey, USA) at 27 °C for 24 h. Next, the bacterium was suspended in PBS (1×) and adjusted to 1×10^6 CFU mL^{-1}. Following the 30-day feeding period supplemented with Kc at 0, 2.5, 5, and 10 g kg^{-1}, the fish were challenged with 100 μL of the pathogenic bacteria via intraperitoneal injection (i.p.) at 5×10^5 CFU mL^{-1}. The control group was injected i.p. with 100 μL of PBS (1×) to account for the stress induced by the injection or incidental bacterial contamination. Mortality was recorded three times per day, and *E. tarda* was isolated from diseased fish to full Koch's postulates.

Kappa carrageenan dietary administration effects on gene expression

After a 15-day acclimation period, 96 fish (mean weight 1.48 ± 0.10 g) were split into 8 20-L aquaria: 4 replicates for the treatment group given commercial feed (Italcol) containing Kc at 5 g kg^{-1} for 15 days and 4 replicates of the control group given non-Kc-supplemented commercial feed. Five fish from each group were euthanized with eugenol in water (20 μg L^{-1} for 15 min) at 24 h and at 15 days post-treatment. Spleen samples were aseptically collected and stored at − 80 °C in RNAlater (Thermo Fisher Waltham, MA, USA) for RNA extraction. Relative expression of growth hormone (GH), IL-1β, transferring, and β-actin as the house-keeping gene was determined using primers previously optimized (Villamil et al. 2014).

Statistical analysis

Results are expressed as mean ± standard error. For the toxicity, cytotoxicity, and dietary supplementation experiments, differences between control and treatments were established using a Kruskal-Wallis test at a $p \leq 0.05$ level of significance. This test was chosen due to lack of normality and/or homogeneity of variances. Differences in gene expression were determined by statistical analysis of the band intensity data via a Mann-Whitney *U* test after verification of normality and homogeneity of variances. The Stat graphics (Centurion XV.I) was used to perform all statistical analysis.

Results

Kappa carrageenan toxicity assay in *Artemia salina*

Incubation of *A. salina* with Kc resulted in a survival rate between 90 and 98.75% in all treatments at 24 h, in comparison to 97.50 ± 2.50 in the control group, with Kc at 10 g kg^{-1} giving the relatively lowest value at 90% at 48 h of incubation, and survival was above 87% in all treatments, with the exception of 10 mg L^{-1} with a survival of 78.75%. (Table 1). No statistical significant differences ($p > 0.05$) in nauplii survival were found between Kc treatments and the control.

Table 1 Toxicity evaluation of kappa carrageenan obtained from *H. musciformis*, according to the survival of *Artemia salina* incubated with Kappa carrageenan concentrations of 0, 2.5, 5.0, and 10 mg L^{-1} for 24 and 48 h

Kappa carrageenan (mg L^{-1})	*A. salina* survival (%)	
	24 h	48 h
10	90.00 ± 2.04	78.75 ± 3.75
5	98.75 ± 1.25	87.50 ± 4.79
2.5	95.00 ± 2.04	88.75 ± 1.25
0	97.50 ± 2.50	92.50 ± 4.79

Values are expressed as means of four replicates ± standard error ($n = 80$) at the same sampling time; $p > 0.05$

Tilapia survival and growth performance

After 30 days of kappa carrageenan feed supplementation, the Kc 10 g kg^{-1} group had a survival of 96.00 ± 0.072, while the control group 88.00 ± 0.337, Kc diet supplementation favor tilapia survival during feeding supplementation (Table 2). Even though Kc treatment positively influenced survival, no significant differences ($p > 0.05$) were found.

Regarding fish growth performance, the Kc 5.0 g kg^{-1} treatment resulted in 0.63% SGR increase compared to the control group. The other Kc treatments tended to increase SGR, but not significantly ($p > 0.05$) (Fig. 1).

Tilapia survival after *E. tarda* challenge

After 30 days of Kc supplementation at 10 g kg^{-1}, mortality was at 50% while the control group given no Kc exhibited 75% mortality at 5 days post-challenge with *E. tarda*. The fish group injected with PBS and not exposed to *E. tarda* had 5% mortality. Even though fish survival was improved in the treatment group, no significant difference ($p > 0.05$) between treatments was determined (Fig. 2).

Kappa carrageenan dietary administration effects on gene expression

Transferrin, GH, and IL-1β relative expression to the house-keeping gene β-actin did not show significant differences in spleens of the control and 5 g kg^{-1} Kc treatment groups after 24 h of feed supplementation. After 15 days of Kc dietary administration, transferrin, GH, and IL-1β relative expression was significantly ($p < 0.05$) enhanced in comparison to control fish; GH and transferrin and IL-1β relative expression increased in more than 2.5 times in Kc-

Table 2 Survival rate of *O. niloticus* during dietary administration of kappa carrageenan at concentrations of 0, 2.5, 5, and 10 g kg^{-1} for 30 days

Kappa carrageenan (g kg^{-1})	Survival (%)
0.0	88.00 ± 0.337
2.5	92.00 ± 0.129
5	94.00 ± 0.179
10	96.00 ± 0.072

Values are expressed as means of four replicates ± standard error (total 90 fish); $p > 0.05$

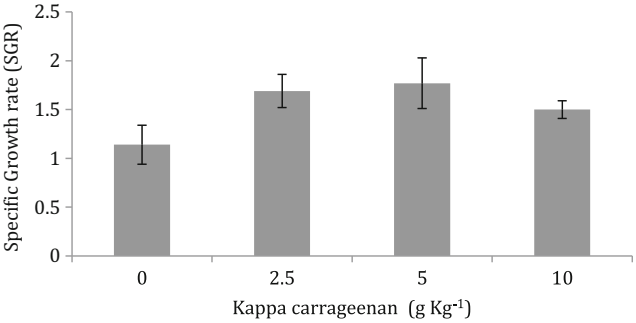

Fig. 1 Growth performance measured as specific growth rate (SGR) of *O. niloticus* with dietary supplementation with kappa carrageenan at concentrations of 0, 2.5, 5, and 10 g kg^{-1} for 30 days. Values are expressed as means of four replicates ± standard error (total 90 fish), $p > 0.05$

treated fish, in comparison to control group, although the overall relative expression of IL-1b was lower than the expression observed in GH and transferrin (Fig. 3a–c).

Discussion

Seaweed may represent a natural source of immunostimulants that could be used as feed additives to promote fish health, to limit the use of antibiotics in aquaculture (Reverter et al. 2014; Safari et al. 2016). The present study, to our knowledge, is the first to evaluate the potential use of kappa carrageenan obtained from *H. musciformis* as an immune stimulant for tilapia. The biosafety of Kc extracts, at the doses used, was confirmed by the cytotoxic activity assays using *A. salina* nauplii and *L. variegatus* embryos, as well as in an in vivo trial, where high survival was observed in Kc-supplemented groups. Accordingly, found that dietary administration of carrageenan extracted from *H. musciformis* to mice, at concentrations of 1 and 5%, for 1 year did not have adverse effects nor caused histological alterations in the intestines or liver. Recently, Gomaa and Elshoubaky (2016) showed that Kc extracted from the brown seaweed *Hydroclathrus clathratus* had limited cytotoxicity in Vero cells while inhibiting replication of the Herpes simplex virus type 1 and the Rift valley fever virus.

Our results showed a tendency to improve the growth and survival of tilapia after 30 days of Kc dietary supplementation, although not significantly. Carrageenan supplemented at 1% in

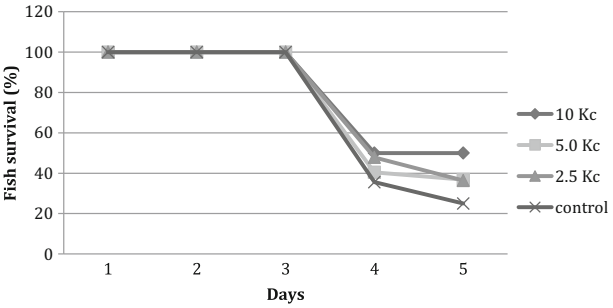

Fig. 2 Survival rate of *O. niloticus* fed with dietary supplementation with kappa carrageenan at concentrations of 0, 2.5, 5, and 10 g kg^{-1} for 30 days after a challenge with *E. tarda* (5×10^5 UFC mL^{-1}), $p > 0.05$

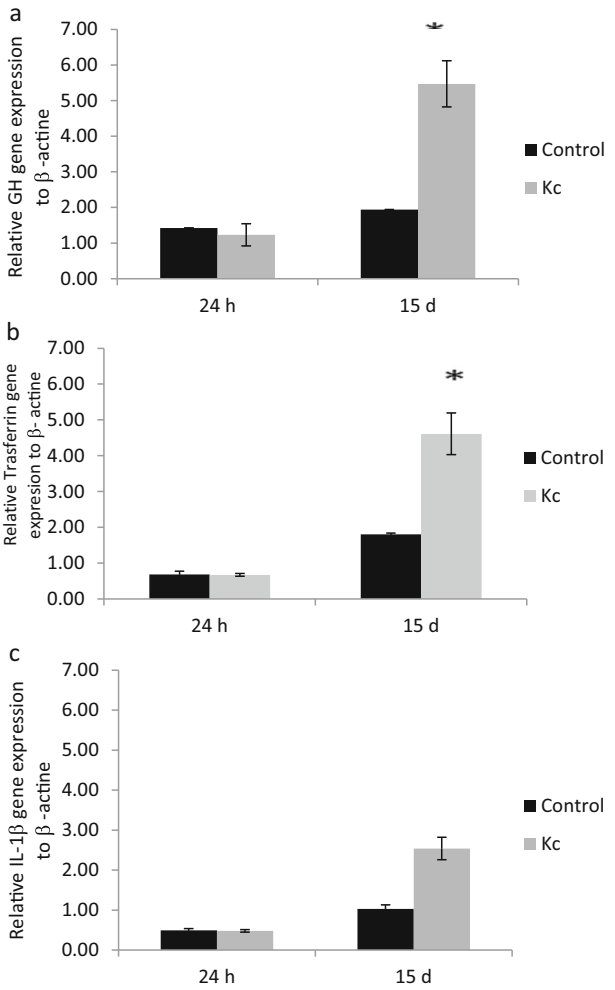

Fig. 3 Relative gene expression of growth hormone (GH) (**a**), transferrin (**b**), and IL1-β (**c**) to β-actin in spleen of the control and Kc treated *O. niloticus* after 24 h and 15 days of dietary administration. Values are means ± SE of independent RT-PCR reactions ($n = 5$). Significant difference at an alpha level of 0.05 $*p < 0.05$; Mann-Whitney *U* test of control vs Kc. 24h 24 h, 15d 15 days

the carp (*C. carpio*) diet enhanced the specific growth rate, protein efficiency, and food conversion rate in fingerlings (Murthy 2017). The observed beneficial effect of Kc on fish growth and survival may be related to alteration of intestinal microbiota by the oligosaccharide, as previously reported (Li dan Gatlin 2004); however, this observation remains to be clarified. Other studies dealing with the inclusion of dietary seaweeds did not lead to major differences in growth performance (Valente et al. 2006; Peixoto et al. 2016; Palstra et al. 2018); however, the varieties of fish and seaweed species, their inclusion levels, and time of administration are diverse, which makes it difficult to generalize.

We found that tilapia survival increased when Kc was included in the diet after a challenge with *E. tarda* in comparison to control fish. Accordingly, previous studies with grouper, *Epinephelus fuscoguttatus*, reported higher fish survival after challenge with *V. alginolyticus*

in the Kc-treated group than in the control group (Cheng et al. 2008). In that study, Kc supplementation significantly increased leucocyte count, respiratory burst, phagocytic activity, and phagocytic index (Cheng et al. 2008).

Other studies have confirmed carrageenan to have immunostimulatory properties in cultured fish. Iota-carrageenan, intraperitoneally injected at 10, 20, and 30 mg kg^{-1}, increased the alternative complement activity, respiratory burst, and phagocytic index of *Epinephelus coicoides* (Cheng et al. 2007). Similarly, iota-carrageenan in the diet of *Labeo rohita* at 10 g kg^{-1} for 60 days significantly increased the myeloperoxidase respiratory burst and phagocytic activity and significantly enhanced growth parameters (Kumar et al. 2014). Correspondingly, we found that Kc stimulated tilapia immune response as demonstrated by upregulation of transferrin, IL-1β, and GH gene expression in spleens of Kc-treated groups in comparison to control fish.

Regarding other immune stimulants, powdered herb *Ferula assafoetida* exhibited be antioxidant activity in the common carp (*C. carpio*), increased IL-1β gene expression, and upregulation of the appetite-related gene GH (Safari et al. 2016). Accordingly, here, we describe increased gene expression in Kc-supplemented groups. IL-1 plays an important role in fish defense during bacterial infection, preventing microbial invasion, and also aids in the removal of damaged cells and injured tissues (Corripio-Miyar et al. 2007; Kumar et al. 2014). IL-1 has been a useful marker gene contributing to determination of immune modulation capabilities of immunostimulant diets as reviewed by Vallejos-Vidal et al. (2016). In addition, we saw upregulation of the transferrin gene in response to Kc supplementation. Transferrin is a bactericidal or bacteriostatic protein; it is an iron-binding glycoprotein that participates in different metabolic processes such as immune regulation, antimicrobial and antioxidant activity, DNA synthesis, cytoprotection, and electron transport (Ong et al. 2006; Ganz dan Nemeth 2015). Previous studies have shown that symbiotic (*Shewanella putrefaciens* Pdp11 + alginate) administration to *Solea senegalensis* also caused an increase in transferrin expression in correlation with increased pathogen resistance (Vidal et al. 2016).

Based on our findings, a dietary supplementation of Kc at 5 g kg^{-1} appeared to cause positive effects in tilapia aquaculture. Overall, KC feed supplementation could be an alternative to antibiotic use and increase productivity. Nonetheless, further studies should be carried out on a larger scale to validate results, cost-benefit analysis, and optimal time of administration to assure safety and efficiency. Also, to have a better insight of the effects and possible relation to immune stimulation and survival increase, further nutrigenomic studies need to be carried out, such as transcriptome analysis, to identify activated physiologic pathways following Kc dietary supplementation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statements Experiments were carried out according to the Laboratory Safety Manual of the participating institutions, Law 84 (National Congress of Colombia, 1989) and National Institutes of Health guide for the care and use of laboratory animals (NIH Publications No. 8023, revised 1978).

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Affiliations

L. Villamil [1] · S. Infante Villamil [2] · G. Rozo [3] · J. Rojas [2]

[1] Facultad de Ingeniería, Universidad de La Sabana, Campus Puente del Común, Chia, Colombia

[2] Grupo de Investigación en Cultivo y Manejo de Organismos Acuáticos, Facultad de Ciencias Naturales e Ingeniería, Universidad Jorge Tadeo Lozano, carrera 2ª # 12 – 68, Edificio Mundo Marino, Santa Marta, Colombia

[3] Grupo de Bioprospección y Biotecnología, Facultad de Ciencias Naturales e Ingeniería, Universidad Jorge Tadeo Lozano, carrera 2ª # 12 – 68, Edificio Mundo Marino, Bogotá, Colombia