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BIOACTIVITY OF Caulerpa taxifolia (Vahl) Agardh (1817) IN METABOLISM AND VASCULOGENE OF TUMOR CELLS.

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ABSTRACT

Among many mechanisms, stimulation of angiogenesis leads to increased secretion of vaso-inducing factors and decreased inhibitors. The present study evaluated the interference of Caulerpa taxifolia hydroalcoholic (EHA - 50 µg / mL) and methanolic (EM - 50 µg / mL) extracts in energy metabolism and Angiogenesis of embryos of Gallus gallus domestic L. Rhode Island Red Eggs Red of four lots, were incubated at 37º C, with automatic turning, for the study of energy metabolism and angiogenesis. The groups were distributed and divided into control groups, treated EHA (50 µg / mL) and ME (50 µg / mL), and control enriched with ω-3, with and without tumor. In the 288 hour stage, development was halted. The vessels were quantified and characterized morphologically and the embryos photographed, fixed and processed. The results of energetic metabolism indicated that there was no significant difference between control and normal treated groups, however, animals with EHA and ME induced tumors and those with ω-3 enriched presented a significant response when compared to control ($p \leq 0.05$). It was observed that the physical properties and the structural integrity of the bark of the control animals showed formation abnormalities: rough, rough and soft bark. Morphometric parameters were not significant between groups ($p \leq 0.05$). In relation to vasculogenesis and angiogenesis there was a significant reduction between normal and tumorous groups. The vessels showed a slight reduction of the caliber when compared to the control group ($p \leq 0.05$). The microscopic appearance of the amniotic membrane of the organisms treated with EHA and ME from the normal and tumor groups maintained the morphology preserved throughout the treatment. Cardiovascular tissue from tumor-containing embryos had bleeding points and a congestion in the lumen of the vessel, perhaps due to the presence of malignant cells. Microscopy of the medulla was preserved. In the control embryos it was poorly conserved, with congested vessels in the mantle region, possibly due to interference of the tumor in the analyzed tissue. These biocomposites also had an anisculogenic and antiangiogenic effect, without compromising the macroscopic and microscopic anatomy of the organisms treated during the embryonic development. In view of the present, it is concluded that the compounds present in extracts of Caulerpa taxifolia can be considered a potential antitumor agent of marine origin, which may act on the intrinsic mechanisms related to the extracellular matrix, stabilizing and remodeling vascular structure and the capacity of induction of neovasculogenesis.

Keywords: Seaweed.Caulerpa taxifolia Angiogenesis. Vasculogenesis. . Antitumoral.

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INTRODUCTION

The process of progression from a normal cell to malignancy involves among many mechanisms the ability to stimulate angiogenesis by increasing the secretion of vaso-inducing factors and decreasing inhibitors in which hypoxia is an important triggering signal of the release of angiogenic cytokines, influencing tumor progression and metastasis (GRAÇA, 2004).

Angiogenesis is an important mechanism in tumor development, being responsible for the nutritional contribution to proliferating neoplastic cells and establishing favorable conditions for metastatic dissemination. It is a complex process with several stages that involve the remodeling of the extracellular matrix, migration and proliferation of the endothelial cells, capillary differentiation and anastomosis (SOUZA et al., 2007; CAPP et al., 2009, STOCKMANN et al., 2014).

Growth factors are constitutive mediators that modulate tissue repair through the production of proteins, synthesis and renewal of the extracellular matrix (ECM). They bind to receptors (transmembrane glycoproteins) and further activate the intrinsic receptor tyrosine kinase autophosphorylation in the cytosolic domain and intracellular phosphorylative reactions (BROUGHTON et al., 2006; SANT'ANA, 2008).

Vascular Endothelial Growth Factor (VEGF), is one of the most expressive molecules in the stimulation of angiogenesis directly and indirectly, increases the cellular expression of metalloproteinases, degrading the extracellular matrix and facilitating the penetration of neovas in the tissue (HIRATSUKA et al., 2002; TAMMELA et al., 2005;

KOWANETZ; FERRARA, 2006; In the present study, it was found that the inhibitory effect of metalloproteinases on the inhibition of metalloproteinase inhibition (HARATSUKA et al., 2002) neuroprotector (STORKEBAUM; CARMELIET, 2004), and participates in vascular stabilization and remodeling (BENJAMIN, 1998).

The genus Caulerpa is made up of benthic green marine algae present in the Mediterranean Sea. In the present study, a number of species of this genus are found in the Brazilian coast (SZE, 1998; JOLY, 2005), and has biological properties, such as antiviral and anticoagulant (GHOSH et al., 2004; RODRIGUES, FARIAS, 2005).

Among the other chemical compounds present in this genus are: the indolic alkaloid caulerpine, caulerpinic acid, the mixture of amides called caulerpicin, the terpenes caulerpine and trifarine, and the steroids: cholesterol, β-sitosterol and cholestenol (NAPRALERT, 2014).

The Caulerpa taxifolia (Vahl) Agardh (1817) is a native species of tropical waters. The phytochemical approach of the crude methanolic extract of this species has been identified the presence of alkaloids, terpenes, steroids and saponins (MOURA et al., 2012).

This work aimed to study the energetic metabolism in embryos treated with Caulerpa taxifolia (Vahl) Agardh (1817), as well as to show the activity of vasculogenesis and angiogenesis.

Material and Methods

Study of the Energy Metabolism of Caulerpa taxifolia

We used 270 eggs (30 for each treated group and control without tumor and enriched with ω-3 with and without tumor) of fertilizable peel, packed in polyethylene packages, with the same potting date. After identification, they were stored at room temperature (25 ° C) for 120 days. The variables analyzed were egg weight, bark weight and bark thickness (HAMILTON, 1982, STALDEMEN; COTTERILL, 1990).

Experimental Animal Model

EHA and ME - describe the abbreviations Rhode Island Red red eggs of four batches, were incubated at 37º C, with automatic turning, for the study of energy metabolism and Angiogenesis. The groups were distributed in control groups, treated with EHA (50 µg / mL) and ME (50 µg / mL), and control enriched with ω-3, with and without tumor, and tumor treated

with methotrexate (10 mg / mL). At the age of 288 hours, development was discontinued. The vessels were quantified and characterized morphologically and the embryos photographed, fixed and processed.

Antitumor Activity

Ehrlich Carcinoma donated tumor cells (0.2 mL - 25 x 106 cells / mL) were transplanted into the eggs in the control, standard reference drug methotrexate (10 mg / mL) treated, EHA and ME treated and treated with ω-3. Experimental chemotherapy was started 48 hours after tumor transplantation. After termination of the treatment, all embryos were weighed and sacrificed, and the tumors were removed, dissected and weighed. Tumor inhibition was calculated according to the methodology adapted from Geran et al. (1972).

Embryogenesis Study

The eggs were incubated at 37.5 ° C, with maintained atmospheric humidity and constant air renewal. Hydroalcoholic (EHA), methanolic (EM), ω-3 and methotrexate (10 mg / mL) extracts in the experimental groups were administered 50 µg / mL. The control group received saline solution (0.9%) during the same time period (hours). The development was interrupted with 288 hours for the analysis (MAGALDI, 1974; MARQUES, 1986).

RESULTS AND DISCUSSION

The results of the energetic metabolism study indicated that there was no significant difference between the untreated, normal treated and tumor treated control groups, which received the EHA and ME extracts, as well as the group that received ω-3 supplementation. However, in relation to deformity in the shell during development, the control group showed a tumor suggestive deficiency in the structural composition of these eggs (Table 1).

Tabela 1 – Percentual e anomalias da casca de ovos (n= 30 por grupo) de *Gallus gallus domesticus* L., com idade de 288 horas mostrado dos Grupos Controle (0,9 %); Tratado EHA (50 µg/mL); Tratado ME (50 µg/mL) e Tratado ω-3 Tratados, Controle Tumorado (0,9 %); Tratado EHA Tumorado (50 µg/mL), Tratado ME Tumorado (50 µg/mL), Tradado ω-3 Tumorado, (T TEHA/50 µg/mL), Tratado Metotrexato Tumoral (T TEHA/50 µg/mL).

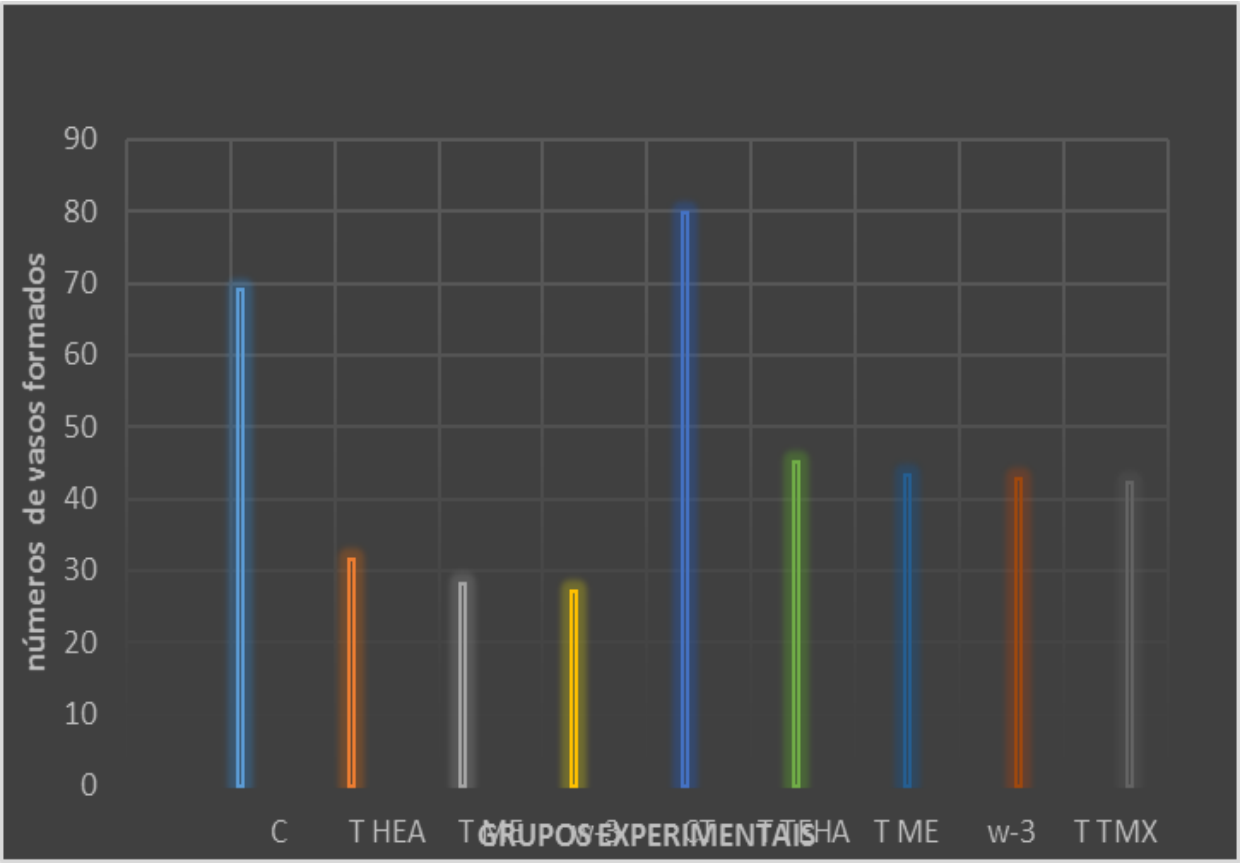
GRUPO (n=30)	Percentual da Casca (%)	Erro Padrão	Deformidades da Casca
C	9,01	0,05	---
T EHA	8, 87	0,01	---
T ME	8,90	0,01	---
T ω-3	9,00	0,00	---
C T	7,87	0,01	rugosa, áspera, mole
T EHA T	8,15	0,02	---
T ME T	8,21	0,01	---
T MEX T	8,13	0,01	---
T ω-3 T	8,07	0,00	---

Médias e Erro Padrão (p≤ 0,05).

The egg shell provides protection against microbial invasion, controls the exchange of water and gases through the pores and is the source of calcium for the embryo during its development. This structure also attenuates the temperature fluctuations between the egg components and their external environment, which is closely related to the structural composition (ROMANOFF; ROMANOFF, 1949; RAHN et al., 1981; NYS et al., 1999).

According to Bunk; Balloun (1978) and Solomon (1991), variations in the nipple layer, deposition of calcium carbonate, were associated with changes in bark resistance. Hunton (1995) mentioned that the density of the nipple layer confers a great characteristic of resistance to the shell, and the larger the knobs, the greater the probability of fractures occurring in the intermamillary spaces. Tumor cells may have promoted a disruption in the spatial conformation of the bark of the control group, which favored the development of these deformities.

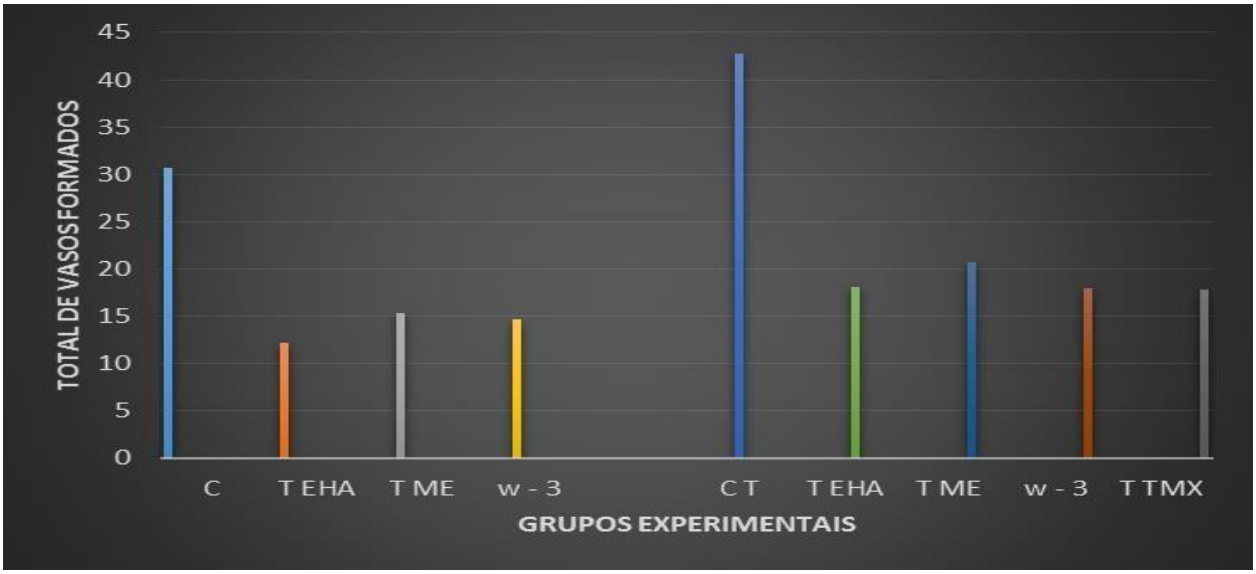
The vasculogenesis evaluation indicated a significant reduction ($p \leq 0.05$) between the control groups treated with EHA extracts (50 µg / mL) and ME (50 µg / mL) and treated with ω-3, with and without tumor (Graphic 1).



Graph 1 - Mean (x) of the vessel quantifications in the Vasculogenesis process of the Gallus gallus domesticus L. embryos at 288 hours of the Control Group (C / 0.9% if saline solution); EHA treaty (50 µg / mL); Treated ME (50 µg / mL) and Treated ω-3 Treated, Tumor Control (CT / 0.9% if saline); (TTEHA / 50 µg / mL), TMEHA / 50 µg / mL, TMEHA / 50 µg / mL), TMEHA / 50 µg / mL), Treated ω-3 Tumor (TT ω-3).

Carmo; Correia (2009) mentioned that ω-3 fatty acids are important because they are involved in suppressing the biosynthesis of eicosanoids derived from arachidonic acid, modifying the immune response to tumor cells and modulating inflammation. These responses impact cell proliferation, apoptosis, dissemination of metastases, and angiogenesis.

In the Angiogenesis study trials, with the extracts EHA (50 µg / mL) and ME (50 µg / mL), it was observed that there was significant inhibition ($p \leq 0.05$), of neovasculation mainly between the groups with and without tumor (Graph 2).



Graph 2 - Mean (x) of vessel measurements: Angiogenesis of Gallus gallus domesticus L. embryos at 288 hours of Control Group (C / 0.9% of saline solution); EHA treaty (50 µg / mL); Treated ME (50 µg / mL) and Treated ω-3 Treated, Tumor Control (CT / 0.9% saline); T-TEHA / 50 µg / mL), T-MEAT / 50 µg / mL, T-MEAT / 50 µg / mL)).

Angiogenesis is a process consisting of new blood vessels from a pre-existing vascular branch (STOCKMANN et al., 2014). In the adult human the rate of endothelial cell proliferation is very slow compared to other cell types, but there are special occasions where the controlled expression of inducers of this event occurs, as in the process of wound healing (POLARINI, 2002; SHIBUYA, 2014). It is worth mentioning that the extracts could act as a strategy of inhibition of vessel formation.

In relation to Vasculogenesis and Angiogenesis, macroscopy revealed a significant reduction ($p \leq 0.05$) in the number of vessels between normal and treated groups treated with EHA (50 µg / mL) and ME (50 µg / mL) (Figure 1). It was evidenced that the gauge also underwent modification to the treatment.

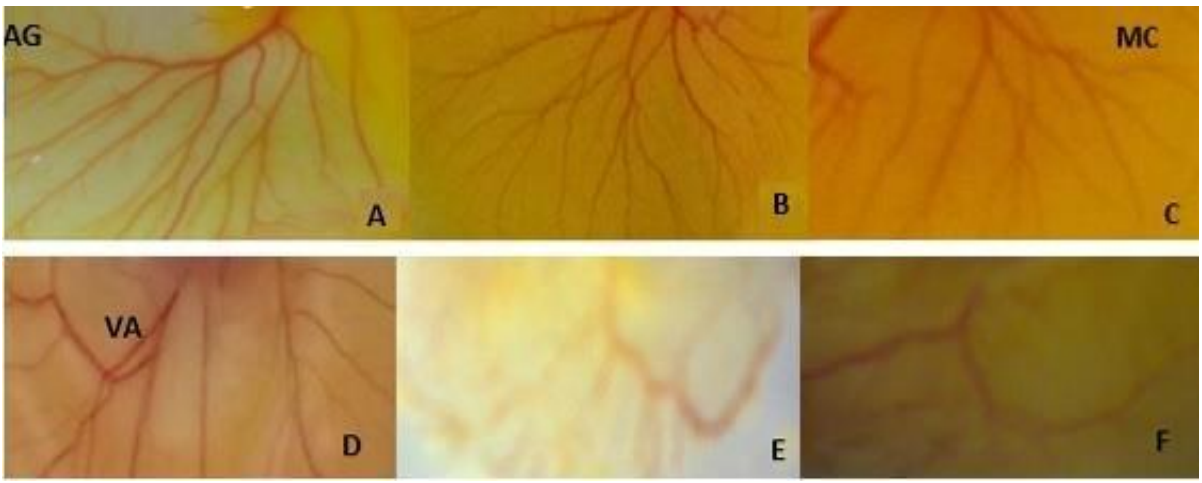


Figure 1 - Photomicrographs of embryo vessels with 288 hours of development evidencing Corioalanthic Membrane (MC); Vasculogenesis (VA) and Angiogenesis. A - Control group treated with saline solution (0.9%). B - EHA-treated group (50 µg / mL). C - Group Treated with ME extract (50 µg / mL). D - Tumorate Control Group treated with saline solution (0.9%). E - Treated Tumor Group with EHA (50 µg / mL). F - Tumor group treated with ME (50 µg / ml). 400 x.

The microscopic appearance of the chorioallantoic membrane of the control organisms treated with saline solution (0.9%) and treated with EHA (50 µg / mL) and ME (50 µg / mL), with and without tumor, maintained the structure morphology (Figure 2).

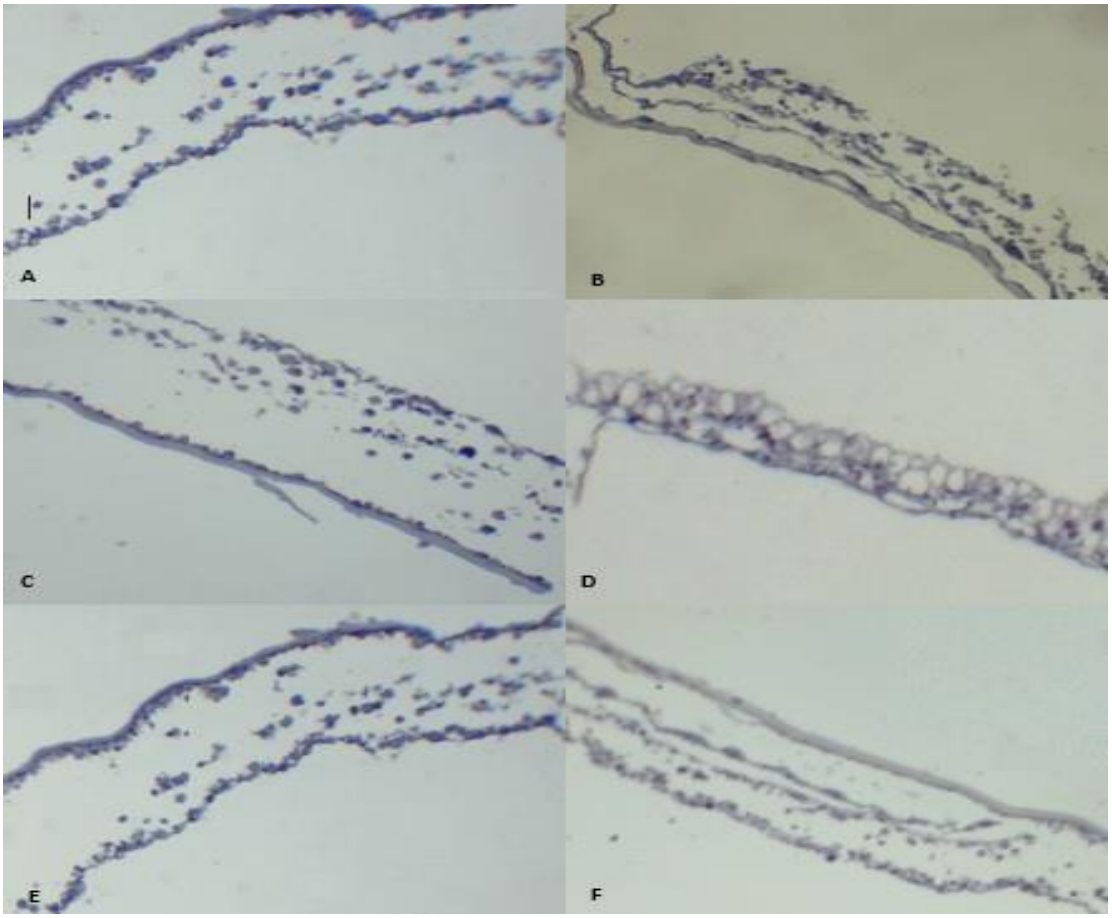


Figure 2 - Photomicrographs of transverse sections of the amniotic epithelium stained with hematoxylin-eosin (HE) from *Gallus gallus domesticus* L. embryos at 288 hours experimental groups. A - Control group treated with saline solution (0.9%). B - EHA-treated group (50 µg / mL). C - ME treated group (50 µg / mL). D - Control group treated tumor saline solution (0.9%). E - treated tumor group EHA (50 µg / mL). F - ME treated tumor group (50 µg / mL).

There is a relationship between the chorioallantoic membrane and embryonic respiration. It is through it, that the embryo has access to oxygen, which supports the fatty acid oxidation of the yolk, essential for the embryonic development (SATO et al., 2006). In addition, the O2 flux from the external environment comes into contact with the hemoglobin of the capillary vessels promoting the progressive increase of the diffusion capacity between the chorioallantoic and capillary vessels (TAZAWA, WHITTOW, 2000; WAGNER-AMOS et al., 2003).

It is possible that the extracts used in the treatment of the embryos interfered in the respiratory mechanisms of the embryos treated with the extracts, that is, possibly did not modify the demand of oxygen, which preserved the respiratory mechanics of the individual.

A significant difference ($p < 0.01$) was found in the control group, which showed a significant difference ($P < 0.05$) 05) between groups. However, about 37 % of the tumor embryos had hemorrhagic spots on the heart wall and congestion in the lumen of the vessel, as well as fragility of the tissue during handling, which was not recorded in the other groups.

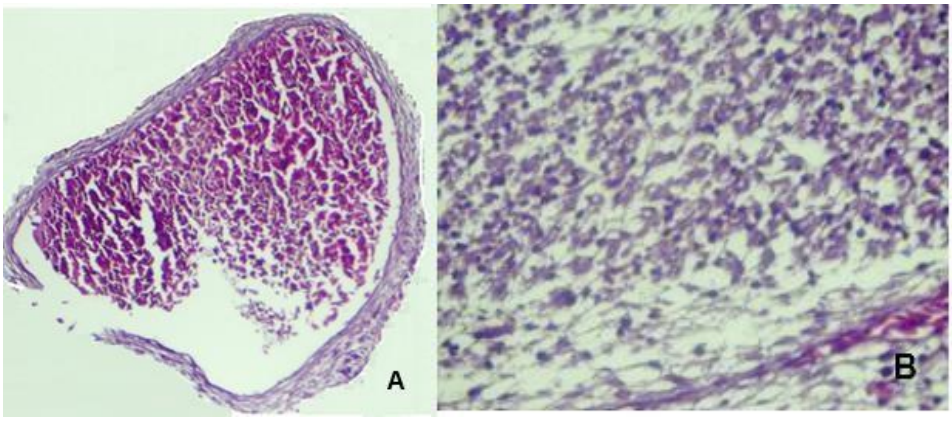


Figure 3 - Photomicrography of the frontal section of the heart stained with hematoxylin-eosin (HE) from the embryo of *Gallus gallus domesticus*, aged 288 hours in the saline solution treated group (0.9%). A - Overview. B - Heart wall detail. Hematoxylin-Eosin staining. 200 (A), 400 (B) x

The microscopic anatomy of the cardiac tissues showed that the control group showed fibular fibers that lost nuclei (*), perhaps with karyolysis (**), presence of blood infiltration and extravasation between the fibers, probably with inflammatory cells (***) (Figure 4).

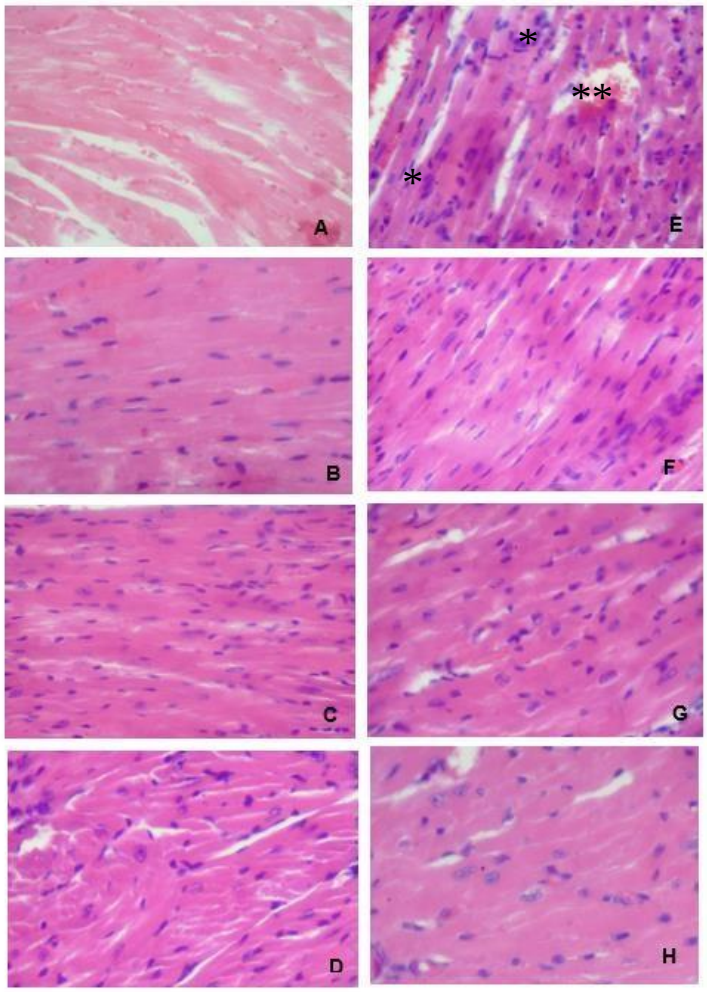
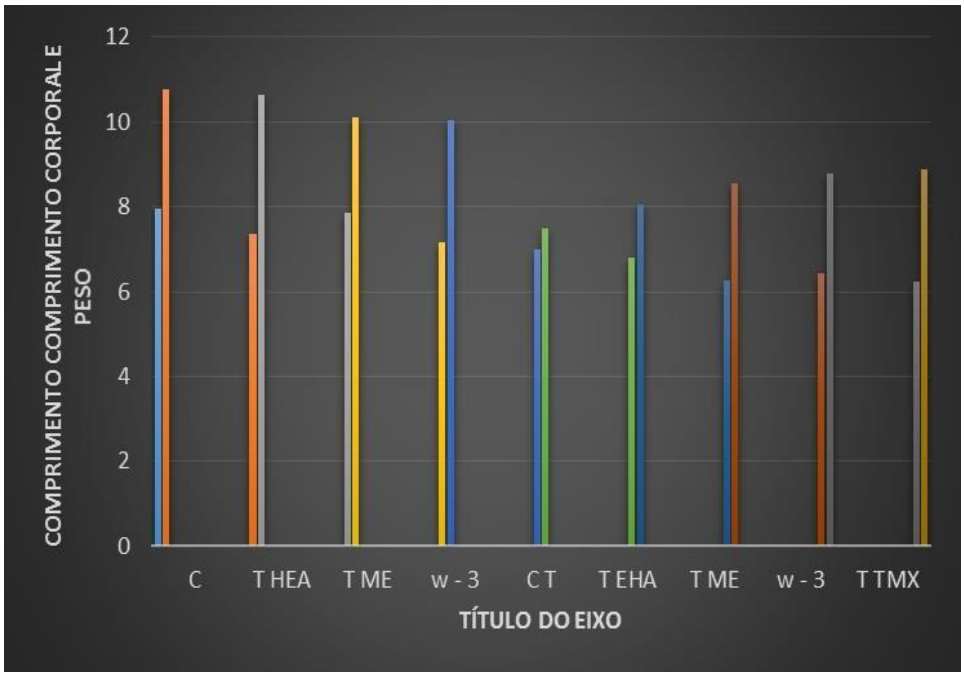


Figure 4 - Photomicrography of cross sections of the cardiac tissue stained with hematoxylinaeosin (HE) of Gallus gallus domesticus L., aged 288 hours. A - Control Group (0.9% if saline). B - Treated EHA (50 µg / mL). C - ME (50 µg / mL). D - Treaty ω-3 Treaties. E - Tumorate Control (0.9% if saline solution) F - EHA Tumorate (50 µg / mL). G - ME Tumorate (50 µg / mL). H - Treated ω-3.

Regarding the pattern of body development, measurements performed from the cephalic-cervical-caudal region showed no significant difference between the control and treated groups without tumor. However, when analyzing the tumor group, the interference between them was evidenced. However, the growth response between the normal and tumor groups. It is noteworthy that the tumor control group had a significant nutritional depletion ($p < 0.05$) (Graph 3).



Graph 3 - Mean (x) and standard error (sd) of total cephalic-cervical-caudal body length (cm) (and weight (g) of the Gallus gallus domesticus embryos at 288 hours of the Control Group C), Treaty EHA, Treaty ME and Treaty ω-3 Treaties, Control Tumorado (CT); Treated EHA Treaty (TTEHA), Treated ME Treaty (TTME), Traded ω-3 Tumorado (TT ω-3) and Treated with Methotrexate (10 mg / mL).

Courneya; Friedenreich (1997) reported that cancer patients may develop a complex metabolic syndrome. It is characterized by progressive weight loss, anorexia, asthenia, anemia, chronic nausea, immunosuppression, depression, decreased aerobic capacity, fatigue, decreased muscle strength and flexibility, muscular atrophy and marked loss of muscle mass. For Camps et al. (2006) weight loss is essentially related to a decrease in muscle mass, promoting subsequent changes in cardiac and respiratory functions (TISDALE, 2000).

The catabolic and energetic demand is the increase of the fat breakage in detriment of the liberation of glycerol and fatty acids, as a consequence of the inhibition of protein lipase and increase of the activity of the sensitive hormone lipase (HLS). Inhibition of glucose transport to tissues and the "de novo" fatty acid synthesis capacity, due to the lower activity of key process enzymes (acetyl-CoA carboxylase and AG synthase) (ARGILÉS; BUSQUETS; LOPES- SORIANO, 2005). Treated with EHA and ME extracts seems to attenuate the metabolic changes of the tumor, as evidenced in the group treated with ω-3, which functioned as a supplement.

The microscopic anatomy of the spinal cord of the treated and control embryos during embryonic development demonstrated that there was a significant difference ($p < 0.05$) between the normal and tumored groups (Figure 5).

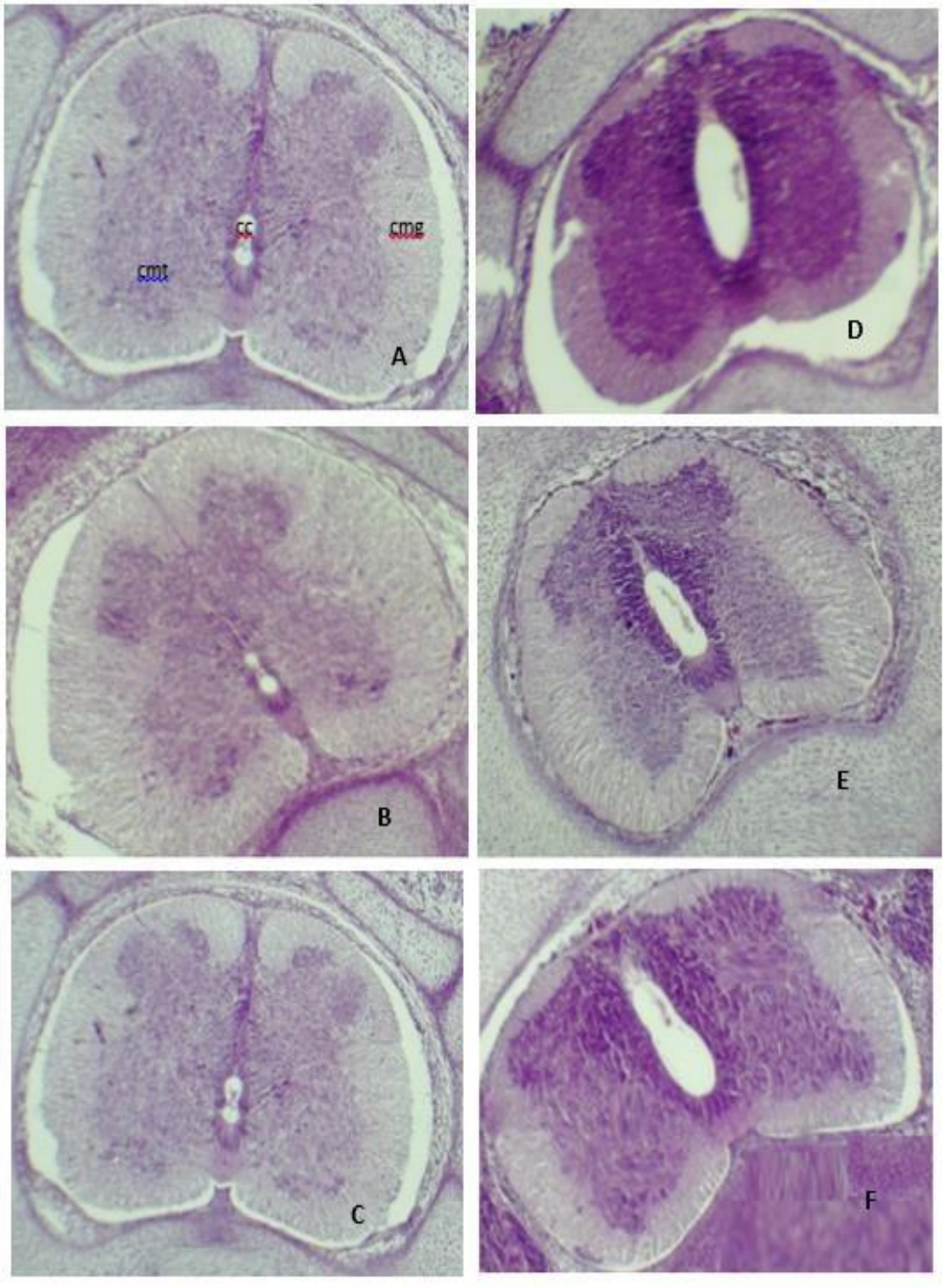


Figure 5 - Cross-sectional photomicography of the spinal cord (me) stained with hematoxylin-eosin (HE) from the *Gallus gallus domesticus* embryo at 288 hours, showing the marginal layer (cmg); mantle layer (cmt) and center channel (cc). A - Control treated with saline solution (0.9%). B - EHA Treaty. C - Treaty ME. D - Tumor Control (CT). E - Treated EHA Treaty (TEHA T). F - Treated ME (TME). Hematoxylin-Eosin staining. 200 x.

The histological study of the marrow of the investigated groups showed that the tissue was preserved, as well as the vessels and neurons. However, the tumor group had discrete hemorrhagic points (*) on the evaluated tissue (Figure 6).

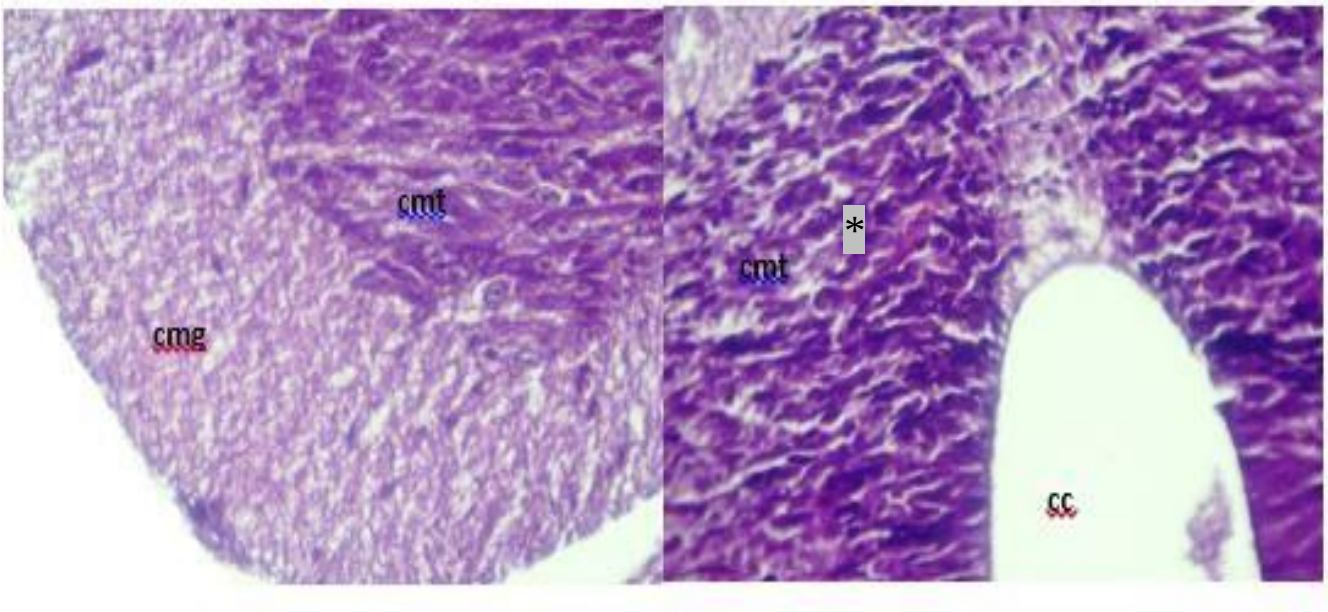


Figure 6 - Cross-sectional photomicrograph of the hematoxylin-eosin (HE) sputum of the *Gallus gallus domesticus* embryo, aged 288 hours, from the control group with saline solution (0.9%). (cm) and mantle (cmt) and central channel (cc) and mantle layer (cmt). Hematoxylin-Eosin staining. 400 x.

The morphometric patterns of the medulla and encephalon of the embryos presented linear behavior between the control and treated groups with EHA, ME, ω-3 and methotrexate (Table 2, 3 and 4). However, the tumor control group responded differently.

Tabela 2 – Parâmetros morfométricos do diâmetro, altura e camadas do manto e marginal da medula espinhal de embriões (n= 30 por grupo), de *Gallus gallus domesticus* L., com idade de 288 horas dos Grupos Controle (C); Tratado EHA; Tratado ME e Tratado ω-3 Tratados, Controle Tumorado (CT); Tratado EHA Tumorado (T TEHA), Tratado ME Tumorado (T TME), Tradado ω-3 Tumorado (T T ω-3), Tratado com Metotrexato (10 mg/mL).

GRUPOS	DIÂMETRO (mm)	ERRO PADRÃO	ALTURA (mm)	ERRO PADRÃO	MARGINAL (mm)	ERRO PADRÃO	MANTO (mm)	ERRO PADRÃO
C	9, 32	0,01	9, 00	0,02	3, 10	0,00	1, 50	0,00
T EHA	9, 13	0,02	8, 70	0,05	3, 06	0,00	1, 78	0,01
T ME	9, 20	0,04	8, 75	0,01	3, 09	0,01	1, 84	0,01
T ω-3	9, 00	0,01	8,70	0,03	3,10	0,01	1,96	0,01
C T	7, 40	0,02	6, 30	0,01	1, 89	0,03	2, 00	0,00
T EHA T	7, 80	0,00	7, 00	0,00	2, 03	0,02	2, 13	0,00
T ME T	7, 65	0,02	6, 80	0,00	1, 98	0,02	2, 15	0,00
T Ω-3 T	7,55	0,01	7,06	0,01	2,00	0,00	2,11	0,00
T MEX T	7,70	0,00	6,89	0,02	2,01	0,02	2,09	0,01

Médias e Erro Padrão (p≤ 0,05)

Tabela 3 – Parâmetros morfométricos do diâmetro e altura do canal central espinhal, espaço direito e esquerdo da medula espinhal de embriões (n= 30 por grupo), de *Gallus gallus domesticus* L., com idade de 288 horas mostrado dos Grupos dos Grupos Controle (C); Tratado EHA; Tratado ME e Tratado ω-3 Tratados, Controle Tumorado (CT); Tratado EHA Tumorado (T TEHA), Tratado ME Tumorado (T TME), Tradado ω-3 Tumorado e Tratado com Metotrexato (10 mg/mL) (T T ω-3).

GRUPOS	DIAMETRO (mm)	ERRO PADRAO	ALTURA (mm)	ERRO PADRAO
C	1,94	0,01	3,07	0,01
T EHA	1, 93	0,00	2,95	0,01
T ME	1, 95	0,00	2, 76	0,00
T ω-3	1, 90	0,01	2,80	0,00
C T	0, 53	0,01	0, 90	0,00
T EHA T	0, 68	0,01	0, 87	0,02
T ME T	0, 65	0,02	0, 80	0,02
T ω-3	0,67	0,02	0,81	0,00
T MEX	0,66	0,01	0,82	0,01

Médias e Erro Padrão (p≤ 0,05)

Tabela 4 – Parâmetros morfométricos do diâmetro da cabeça e diâmetro e altura do encéfalo de embriões (n= 30 por grupo), de *Gallus gallus domesticus* L., com idade de 288 horas mostrado dos Grupos dos Grupos Controle (C); Tratado EHA; Tratado ME e Tratado ω-3 Tratados, Controle Tumorado (CT); Tratado EHA Tumorado (T TEHA), Tratado ME Tumorado (T TME), Tradado ω-3 Tumorado (T T ω3) e Tratado com Metotrexato (10 mg/mL).

GRUPO	CABEÇA (mm)	ERRO PADRAO	DIAMETRO (mm)	ERRO PADRAO	ALTURA (mm)	ERRO PADRÃO
C	2, 17	0,01	0, 89	0,01	1, 35	0,00
T EHA	2, 05	0,00	0, 90	0,01	1, 30	0,01
T ME	2, 14	0,02	0, 89	0,00	1, 32	0,01
T ω-3	2,08	0,00	0,91	0,00	1, 34	0,00
C T	2, 13	0,01	0, 70	0,00	1, 13	0,00
T EHA T	2, 20	0,01	0, 80	0,02	1, 20	0,00
T ME T	2, 20	0,01	0, 90	0,02	1, 27	0,00
T ω-3 T	2,13	0,02	0,89	0,01	1, 22	0,00
TMEX	2, 10	0,03	0,87	0,02	1,15	0,01

Médias e Desvio Padrão (p≤ 0,05).

ACOBSON (1991) comments that neural tube organization occurs differently in the spinal cord in the brain. In the brain, the processes of migration, proliferation, differentiation and cell death produce changes in the formation of distinct layers, due to the physiology of its various regions. Borgart; Ort (2008) mention that during embryonic development, the central lumen of the neural tube narrows, allowing the extensive development of the mantle and the marginal zones, evolving to the central channel. Regarding the structural formation of the tumor control group, it was possibly interfered by tumor cells.

The spinal cord carries sensitive signals to the Central Nervous System (KANDEL et al., 2006). Thus, several induction molecules participate in promoting the differentiation of the primitive neural, such as notochord, sensory neurons and oligodendrocytes in the spinal cord (HIB, 2007).

Klaassen (2003) comments that the metabolites of some chemicals are responsible for their toxic effects. According to him, the systemic toxic effects depend on the absorption and distribution of the compound, which affects one or some organs, and the central nervous system (CNS) is affected.

It is concluded that the solution compounds present in the extracts of Caulerpa taxifolia (Vahl) Agardh (1817) can be considered a potential antitumor agent of marine origin, which may act on the intrinsic mechanisms related to the extracellular matrix, stabilizing and remodeling vascular structure and the induction capacity of neovasculogenesis.

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