



## EFFECTS OF *ANNONA MURICATA* ON THE TREATMENT AND PREVENTION OF CHRONIC DEGENERATIVE DISEASES

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### ABSTRACT

The concern of the world population has been increasing due to the significant augmentation of people affected by chronic degenerative diseases. These diseases are usually caused by oxidative stress, so there is a growing interest in the discovery of natural substances as an alternative medical resource that can act as antioxidants. Authors have shown that *Annona muricata* L is associated with several benefits to human health and can be associated to improve risk factors of developing some chronic degenerative diseases. Our objective in this review was to present the beneficial potentials of *Annona muricata* L. in the treatment and prevention of the central chronic-degenerative diseases found in modern society. Exclusivity of the Annonaceae family are the acetogenins that have diverse biological activities like antitumoral, immunosuppressive, pesticide, antiprotozoal, anthelmintic and antimicrobial. Regarding its antitumor activity, there are reports of the ability to selectively inhibit the growth of adriamycin-resistant cancerous and tumor cells, demonstrating its cytotoxic potential. It was also highlighted the hypoglycemic and hypolipidemic effects. It is possible to verify that *Annona muricata* L. has a wide variety of bioactive compounds that can be useful for the treatment and prevention of the relevant chronic-degenerative diseases found in modern society, such as cardiovascular diseases, rheumatism, arthritis, diabetes mellitus, hypertension, and various cancers. Therefore, we can conclude that this plant is promising and may offer an affordable alternative, low cost and without significant side effects for use in medicine.

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### INTRODUCTION

The increase in the incidence of chronic-degenerative diseases has become one of the most important global public health problems. One important reason for the significant increase in the incidence of these diseases, especially cardiovascular diseases and cancer, is associated with the global process of industrialization and increased consumption of saturated fats, sugars, preservatives, and dyes. The World Health Organization estimates that in the last ten years, 84 million

deaths were attributed to cancer, even after advances in the areas of surgeries, chemotherapy and radiotherapy, since such treatments still have limitations due to the high cost and relation to various side effects (Barbalho et al., 2018; Rady et al., 2018; Yajid et al., 2018; Silva, 2011). The western diet has been responsible for the development of several pathologies related to oxidative stress. Due to these reasons, there is a rising interest in the discovery of natural substances as an alternative medical source that can act as antioxidants, capable of containing or even reversing the damage caused by oxidative stress. Studies show that diets with high antioxidant intake contribute to a significant reduction in the incidence of chronic-degenerative diseases (Trevisan et al., 2017; Dani et al., 2010; Souza, 2010). Many plants possess compounds with beneficial effects to health, one of them is the *graviola*, which

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belongs to the family Annonaceae, subfamily Annonoideae, genus *Annona* and species *Annona muricata* L (Figure 1).



Figure 1. Leaves and fruit from da *Annona muricata* L.

This plant is cultivated in tropical countries such as Venezuela, Puerto Rico, Costa Rica, and Brazil, mainly in the northeast region. Its fruits are commonly used in the manufacture of juice, ice cream, jams, jellies, and sweets, and are extensively used as alternative therapy for several pathologies (Silva, 2011). Its peels, roots, leaves, pulps and seeds are used for the treatment of various diseases such as inflammation,

rheumatism, diabetes mellitus, hypertension, parasitic infestation, arthritis, fever and relief from spasms. Also, it has been widely studied as a potential option as a coadjuvant in the treatment of cancer. Some studies have shown positive results of *graviola* as an ally in the fight against more than twelve types of cancer without any severe side effects compared to conventional treatments (Wahab, 2018; Yajid *et al.*, 2018; Freitas, Moraes, Silva, 2017; Santos *et al.*, 2014). Based on the comments above, the objective of this study was to review the potential benefits of *Annona muricata* L. in the treatment and prevention of major chronic-degenerative diseases found in modern society. In this review, the following databases were used to consult articles: Google Scholar, Scielo and PubMed. Articles in Portuguese and English were used. Case reports, poster and letters to the editor were excluded.

## RESULTS AND DISCUSSION

Several studies have shown the potential of *Annona muricata* L. and its beneficial effects in the treatment of several pathologies.

Table 1. Effects of *Annona muricata* L. in animal models and humans

Reference	Model	Mainresults	Conclusion
Oladipo <i>et al.</i> (2018)	Wistar rats	A significant reduction in progressive sperm motility and percentage of sperm solidity in rats treated with the methanolic extract of AM.	The study shows that daily oral ingestion of 200-800 mg/kg of extract from AM has a mild anti-spermatogenic effect on Wistar rats suggest that caution should be applied when using this extract in higher doses or for extended periods.
Morosetti <i>et al.</i> (2017)	103 Women with HPV	Control group of 53 women and a group of 50 women who received 16 mg of ellagic acid, 100 mg of AM and antioxidant factors daily for 12 months. There was a significant association between ingestion of the ellagic acid complex and the negative.	The use of antioxidants, including ellagic acid and AM, can counterbalance the harmful effects of oxidative stress, disrupting the cell cycle, promoting DNA repair and inducing apoptosis, making it difficult to progress. The results suggest that ellagic acid and AM may have chemopreventive action and that treated women were less likely to be diagnosed with positive results.
Sulistyoningrum <i>et al.</i> (2017)	Sprague Dawley rats with breast cancer	Rats were given AM leaf extract obtained positive responses as there was an improvement in the histological appearance of the breast and reduced proliferation indices of their cells that possibly interacted with DNA or DNA binding proteins.	AM extract improved the histological alterations of DMBA-induced breast cancer, with the most effective dose being 300 mg/kg and with rapid technological growth this treatment aims at a promising future.
Acevedo <i>et al.</i> (2016)	Rabbits	Rabbits were randomized into two groups. Group A received the diluted atomized extract in saline and group B received the atomized extract diluted in Freund's adjuvant by intradermal injection. The rabbits presented erythema.	Treatment with leaves of AM led to improvement in irritation, functioning as an anti-allergy. It also has an antiparasitic effect, anti-infective activity against some strains of Staphylococcus, Pseudomonas and Escherichia coli. It also exerts antioxidant action and anti-inflammatory properties.
Asare <i>et al.</i> (2015)	Rats	The animals were separated in 3 groups: 2 groups received a diet with AM leaf extract (30 and 300mg) for 60 days. Antiproliferative effects were observed with a decrease in prostate size and absence of deleterious effects on spermatogenesis.	The results showed that AM has antiproliferative effects on BPH-1 cells (benign hyperplastic prostatic epithelial cell line) and reduces prostate size, indeed by apoptosis.
Yang <i>et al.</i> (2015)	BALB/c rats	Prostate cancer cells were injected into mice. After 48 hours of treatment with AM, there was inhibition of human prostate proliferation. High doses have led to death.	The presence of acetogenins confers therapeutic benefits.
Florence <i>et al.</i> (2014)	Diabetic Wistar rats	A single administration of AM extract significantly reduced blood glucose levels by 75%.	The hypoglycemic effect possibly occurs due to hypolipidemic effects, antioxidant and protective action on pancreatic $\beta$ cells.
Souza (2010)	Wistar rats	Animals that ate AM leaf tea and $\beta$ -sitosterol showed lower dietary efficiency, both in the standard dietary groups and in the groups that ate a high-calorie diet but did not present a reduction in body weight. There was a reduction in fasting glucose in the animals that ingested AM tea and hypercaloric diet.	AM tea acted as a hypoglycemic in animals that received a hypercaloric diet, increased lipid oxidation and basal metabolic rate, and reduced the respiratory quotient). These results indicate similar effects between $\beta$ -sitosterol and leaf tea.
Sousa <i>et al.</i> (2010)	Wistar rats and mice	The animals presented paw edema induced by the injection of the edematogenic agent. The ethanolic extract of AM leaves led to a reduction in the number of reduced abdominal writhings and inhibited the time phases licking the paw, reduced the volume of exudate and leukocyte migration.	The results confirm the ethnomedicinal use of the ethanolic extract of Leaves of AM. The data analysis supported antinociceptive and anti-inflammatory activities, suggesting a potential for therapeutic purposes.
Adeyemi <i>et al.</i> (2010)	Diabetic Wistar rats	Treatment with methanolic extract of AM leaves improved physical state and decreased glycemia. The morphology of the pancreas of diabetic mice treated with AM revealed remarkable improvements in the islets of Langerhans.	The results revealed $\beta$ -cell regeneration of the pancreatic islets of rats treated with AM extract.
Adewole; Martins (2006)	Wistar rats	Diabetic rats treated with aqueous extract of AM leaves showed a significant decrease in glycemia, improvement in antioxidant activity and also in the amount of pancreatic / serum insulin.	AM treatment showed beneficial effects on pancreatic tissues submitted to induced oxidative stress.

AM: *Annona muricata*; HPV: Human papilloma virus;

Table 2. In vivo effects of *Annona muricata* L

Reference	Model	Main results	Conclusion
Kim <i>et al.</i> (2018)	Breast Cancer Cells	AM leaf extract produced a significant decrease in the viability of breast cancer cells after incubation for 48 hours at increasing concentrations. It showed cytotoxicity in breast cancer cells in a dose-dependent manner and suppressed cell proliferation.	The crude extract of AM leaves induced mitochondrial apoptosis, suppressed cell proliferation of breast cancer and decreased cell motility in experimental cells.
Olugbuyiro <i>et al.</i> (2017)	<i>Escherichia coli</i> , <i>Pseudomonasaeruginosa</i> , <i>Staphylococcus aureus</i> and <i>Candidaalbicans</i> .	Extracts from AM leaves exhibited antimicrobial activities. The ethyl acetate extract was highly active against Gram-positive bacteria, <i>S. aureus</i> and <i>P. aeruginosa</i> Gram-negative resistant to ampicillin. Also, the ethyl acetate extract exhibited moderate activities against <i>E. coli</i> and <i>C. albicans</i> . AM extract showed the highest zone of inhibition and activity index against <i>E. coli</i> .	AM leaf is rich in phenolic compounds, flavonoids, tannins, alkaloids, saponins, and glycosides. Extracts of ethyl acetate and hexane showed higher antimicrobial properties. The methanolic extract increases the potency of its fractions.
Liu <i>et al.</i> (2016)	Liver Cancer Cells	The ethanolic extract of AM was able to reduce viability and trigger apoptosis of cancer cells. Proteomic analysis identified 14 proteins associated with apoptosis induced by the extract.	Results indicate that the ethanolic extract of AM leaves causes apoptosis of liver cancer cells.
Dani <i>et al.</i> (2010)	Lymphocyte culture	The AM samples (infusion and lyophilized capsule) showed significantly increased values of total polyphenols about the pulp, which correlated positively with the antioxidant activity against the DPPH (2,2-diphenyl-1-picrylhydrazyl).	Leaf infusion and lyophilized presented relevant antioxidant activity, preventing the damage caused by the oxidizing agent hydrogen peroxide.

AM: *Annona muricata*.

A survey was conducted to provide information on the pathologies, doses administered and the role of *Annona muricata* L. in these treatments. Studies of the last 12 years were selected. Eleven articles involving animal and human tests were selected and are shown in Table 1. Four studies involved *in vitro* tests and are presented in Table 2. In total, fifteen selected studies met the criteria for inclusion. The main biomolecules that orchestrate the bioactive properties of *Annona muricata* L. are acetogenins, which have selective toxicity to tumor cells, reinforcing their strong antitumor and antiviral properties. In addition to acetogenins, *graviola* also has other antioxidant compounds, such as polyphenols, carotenoids and vitamin C, which may exert additional benefits in the treatment of cancer and other diseases (Chun *et al.*, 2018; Dani *et al.*, 2010).

Table 1 encompasses studies demonstrating that *Annona muricata* L. promotes apoptosis of cells to various types of cancer cells in animal and human models, making disease progression difficult. This is due to its chemopreventive activity, its ant proliferative effects and the presence of acetogenins that confer therapeutic benefits (Morosetti *et al.*, 2017; Asare *et al.*, 2015; Yang *et al.*, 2015). We can also highlight the hypoglycemic effect that possibly occurs due to hypolipidemic effects, antioxidant and protective action on pancreatic  $\beta$  cells, which regenerate the pancreatic islets, decreasing the rate of glucose in the blood (Florence *et al.*, 2014; Souza, 2010; Adeyemi *et al.*, 2010; Adewole; Martins, 2006). In Table 2 we find results that highlight that the leaf of *Annona muricata* L. is rich in phenolic compounds, flavonoids, tannins, alkaloids, saponins, and glycosides. Its extract exerts relevant activity against bacteria resistant to ampicillin, indicating its antimicrobial activity (Olugbuyiro *et al.*, 2017). Still, in Table 2, studies show the anticancer activity of *graviola* *in vitro*. According to Kim *et al.* (2018) its crude extract induced mitochondrial apoptosis suppressed cell proliferation of breast cancer and decreased cell motility in experimental cells. A study by Liu *et al.* (2016) reveals that the ethanolic extract of leaves of this plant causes apoptosis of liver cancer cells, which supports the ethnomedicinal use of this herb as an alternative or complementary therapy for cancer. The antitumor activity of *Annona muricata* L. is related to the presence of acetogenins that exert selective cytotoxicity on tumor cells, but not interfering with normal cells. In addition to acetogenins, it also has other compounds of various classes, such as polyphenols, carotenoids, vitamin

C, acetogenins, alkaloids, terpenoids, carbohydrates, lipids, and amino acids, and some of these substances are associated with the sequestering of free radicals formed degenerative processes. Therefore, they are useful in the fight against oxidative stress, which is related to numerous chronic-degenerative diseases (Dani *et al.*, 2010; Santos *et al.*, 2014). Acetogenins are found exclusively in plants of the Annonaceae family, possess several biological activities as antitumor, immunosuppressive, pesticide, antiprotozoal, anthelmintic and antimicrobial. Regarding its antitumor activity, there are reports of the ability to selectively inhibit the growth of adriamycin-resistant cancer and tumor cells. They also exhibit cytotoxic activities against pancreatic tumor cells, lung carcinoma, and prostate carcinoma, due to inhibition of tumor proliferation (Santos *et al.*, 2014; Liu *et al.*, 2016; Asare *et al.*, 2015). The antioxidant capacity of the polyphenols of *Annona muricata* L. was evaluated by Dani *et al.* (2010) based on the ability of the antioxidant to donate hydrogen to the free radical, causing the scanning of this radical. The samples from leaves (infusion and lyophilized capsule) showed significantly increased values of total polyphenols in relation to the pulp. Phenolic compounds, especially flavonoids, are responsible for neutralizing free radicals and, consequently, decrease the incidence of cardiovascular and circulatory diseases, cancer, diabetes, and Alzheimer's disease. The presence of vitamin C, carotenoids and other phenolic compounds also help prevent chronic-degenerative diseases (Santos *et al.*, 2014). The bioactive compounds of *graviola* may also have anti-hyperglycemic action, acting through several mechanisms, stimulating the secretion of insulin and activating its effects, regenerating the  $\beta$  cells or even increasing the proliferation of the same. Also, it has no adverse side effects and has been used as an herbal product as an antidiabetic source (Adeyemi *et al.*, 2010).

## Conclusion

*Annona muricata* L. has a wide variety of bioactive compounds of great interest for the treatment and prevention of chronic-degenerative diseases found in modern society, such as cardiovascular diseases, rheumatism, arthritis, diabetes mellitus, hypertension, and cancers. It may also play a role as antiparasitic, anti-infectious, antioxidant and anti-inflammatory. Therefore, we can conclude that this plant is promising and may offer an affordable alternative, low cost and without significant side effects for use in medicine.

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