REVIEW ARTICLE

SYSTEMATIC REVIEW OF *ANNONA MURICATA* LINN. EXTRACT ON PROSTATE CANCER

Uruaka CI[1], *Nnoka V[1], Ogbu CC[1], Gboun M[2], Oboro IL[1], Ebong OO[1], Ossai-Chidi LN[3]

[1]Faculty of Basic Clinical Sciences, Rivers State University, Nigeria
[2]Centre for research on common diseases in Africa and Asia, Canada
[3]School of Public Health, University of Port Harcourt, Nigeria

***Corresponding Author:** Valentine Nnoka; Email: nnokavalentine@yahoo.com

Abstract

Introduction: Cancer is the world's most prevalent cause of death, accounting for about 10 million fatalities in 2020. Prostate cancer is the sixth leading cause of cancer death worldwide and the second most common malignancy occurring in men. Compounds *derived from Annonna muricata (A. muricata)*, a member of the Annonaceae family have been documented to have positive effects against various cancers including prostate cancer.

Methodology: The study examined scientific reports on the effects of *A. muricata* on prostate cancer, to identify the phytochemically active components that exert beneficial and/or toxic effects on prostate cancer. Scientific publications on PubMed, Google Scholar and ScienceDirect electronic databases were searched for cohort, quasi-experimental and randomized controlled trials. Keywords and MeSH terms for the search were developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results: A total of eighty-eight (88) studies were identified from the databases, among which twelve (12) were selected that met the screening criteria in line with the study objectives. This review has shown that the pharmacodynamics, safety, tolerability, and efficacy of *A. muricata* and its phytochemical constituents (including cyclic hexapeptides, flavonoids, isoquinoline alkaloids and importantly annonaceous acetogenins) on various cancers have been extensively reported. *A. muricata* extracts caused a reduction in prostatic weight, prevented, and reversed prostatic hyperplasia and attenuated inflammatory and antioxidant indices. Mechanistically, they reduced prostatic hyperplasia by hormone modulation, down-regulation and reduction of cellular proliferation and necrosis with good efficacy, safety profile and minimal toxicity were found.

Conclusion: This study has shown that the active phytochemical constituents identified in *A. muricata* extract have the potential to be employed as promising agents for management of prostate cancer. Clinical studies are therefore strongly recommended to establish their usefulness in management of prostate cancer.

Keywords: *Annona muricata*, Annonaceous acetogenins, Prostate cancer, Phytochemicals, Systematic review

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INTRODUCTION

Cancer is a leading cause of death globally accounting for about 10 million fatalities in 2020.[1] New cancer cases are expected to rise by about 70 percent over the next 20 years.[2] Prostate cancer ranks amongst the most common cancers and is the leading incident cancer in men in sub-Saharan Africa.[3] It is the second most common malignancy occurring in men and the sixth leading cause of cancer deaths worldwide.[4] It has been estimated that the cancer burden will only increase in the coming years due to engagements in lifestyles that increase risks for cancers. Although there have been developments in medical research with respect to anti-cancer agents, attention is beginning to shift towards the production of herbal products which have fewer side effects when compared to conventional anti-cancer agents.

There has been documentation dating as far back as ancient times of the importance of medicinal plant products possessing disease-modifying in which phytochemicals exert positive effects on the human body.[5,6] Studies have shown that these medicinal plants possess bioactive compounds which can inhibit cancer growth through effects on cellular proliferation, cell differentiation, apoptotic activity, angiogenesis and metastatic activity.[7] Extracts of *Annona muricata* are among a rich collection of medicinal plants that have shown great potential as a therapeutic agent against a variety of ailments including different types of cancers such as prostate cancers, pancreatic, blood, lung, breast, cervical and colon cancer. This article aims to provide an overview of *A. muricata* and its potential benefits in the treatment of prostate cancer.

METHODOLOGY

Search strategy

The search strategy was performed using resources that enhance methodological transparency and improve the reproducibility of the results and evidence synthesis. In this sense, the search strategy was elaborated and implemented before study selection, according to the PRISMA-P checklist as guidance Moher *et al*.,[8] Additionally, using the Population, Intervention, Comparison, Outcome and Study Design (PICOS) strategy Accrocding to Cochrane, (2008). The guiding question of this review in order to ensure the systematic search of available literature was: *'What is the effect of Annona Muricata Extract on Prostate Cancer?'* Studies was retrieved using eight databases: MEDLINE (via PubMed) from 2000 till date, Web of Science (1960 till date), Cochrane Central Register of Controlled Trial (CENTRAL), published by the Cochrane Library (1992 till date), Science Direct (1997 till date), and SciELO (1997 till date).

To reflect contemporary practice, a search of the literature from the year of first publication of the databases till January 2023 was performed. In addition, the reference section in the studies returned by the above search was scrutinized for additional relevant articles.

Study selection criteria

A summary of the participants, interventions, comparators and outcomes considered, as well as the type of studies included according to the PICOS strategy, is provided in Table 1.

Table 1 Inclusion and exclusion criteria for study selection

	Inclusion Criteria
Population	Individuals with prostate cancer
Intervention	*Annona Muricata* Extract
Comparison	The control group not receiving *Annona Muricata* Extract as part of the treatment
Outcome	This can include parameters such as tumour size, cancer cell proliferation, patient survival rates, or other relevant measures of prostate cancer progression or regression.
Study Design	Randomized control trials, Quasi-experimental studies (Case-Control studies), Cohort studies, Cross-sectional studies

Screening and data extraction

Initial screening of studies was based on the information contained in their titles and abstracts and was conducted by two independent investigators (UCI and VN). When the reviewers disagreed, the article was re-evaluated and, if the disagreement persisted, a third reviewer (CO) would make a final decision. The full-paper screening was conducted by the same independent investigators. For data extraction, two independent Microsoft Excel spreadsheets were used to summarize the data from the included studies. Then, the spreadsheets were combined into one. Disagreements were resolved by a third investigator.

Quality assessment

The methodological quality of the Case-Control was assessed using the JBI Critical Appraisal Checklist for Case-Control Studies, a widely used tool for the classification of the quality of the evidence from Case-Control JBI[9]. Two independent reviewers (IO and OE) assessed the methodological quality of eligible trials and scored the selected studies and disagreements were resolved by a third reviewer (LOC).

RESULTS

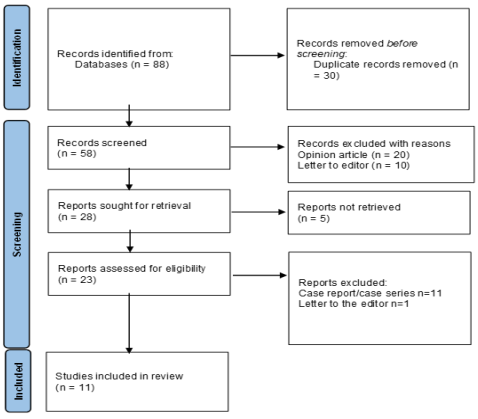

Figure 1: PRISMA Flowchart of selected studies

Table I: Characteristics of included studies

S/No	Lead Author	Type of Study	Year of Publication	Geographical Location	Study Population/ Specimen	Part of Plant Studied	Findings
1	Adaramoye, O. A. et al. (2019)	Quasi-Experimental	2019	Nigeria	Rats	Seed	The hexane fraction of *A. muricata* seed mitigated benign prostatic hyperplasia induced by testosterone in rats. This suggests a potential protective effect against prostatic hyperplasia.
2	Bogis, A. et al. (2016)	Quasi-Experimental	2016	South America	Prostate cancer cells	Extract	*A. muricata* extract exhibited antiproliferative and apoptotic effects on prostate cancer cells, indicating its potential in inhibiting the growth of prostate cancer cells.
3	Chinwe, A. E. et al. (2022)	Quasi-Experimental	2022	Nigeria	Adult Male Wistar Rats	Pulp Extracts	Aqueous soursop pulp extracts demonstrated anti-inflammatory properties and ameliorated induced benign prostatic hyperplasia in adult male Wistar rats. This suggests a potential therapeutic role in managing prostatic hyperplasia.
4	Hashem, S. A. et al. (2023)	Quasi-Experimental	2023	Jordan	Rats' Plasma, Breast and Prostate Cancer Cell Lines	Leaves Extract	Graviola leaves extract influenced the pharmacokinetics of metformin in rats' plasma and exhibited pharmacological activity against breast and prostate cancer cell lines. This indicates a potential interaction between graviola extract and metformin, as well as its potential in cancer treatment.
5	Hong, G. U. et al. (2021)	Quasi-Experimental	2021	Korea	Rats	Stem Bark Extracts	Graviola stem bark extracts showed anti-inflammatory effects on a testosterone-induced benign prostatic hyperplasia rat model suggesting a potential role in managing prostatic hyperplasia.
6	Lienggonegoro, L. A. et al. (2020)	Quasi-Experimental	2020	Indonesia	NA	Leaf	Soursop leaf demonstrated potential as an anti-cancer agent, indicating its possible use in cancer treatment.
7	Mohitha, P. & Shanmugam, H. (2023)	Quasi-Experimental	2023	India	NA	Leaves	Chemometric analysis revealed major anti-cancer activity compounds from soursop leaves, providing insights into the compounds responsible for the anti-cancer properties.
8	Mutakin, M. et al. (2022)	Review	2022	Indonesia	NA	NA	Soursop exhibited pharmacological activities, suggesting potential therapeutic applications. Specific details of the activities were not provided.
9	Qazi, A. K. et al. (2018)	Review	2018	USA	NA	NA	Therapeutic potential of chemical constituents of different parts of Graviola plant, highlighting their potential as anti-cancer agents.
10	Sun, S. et al. (2016)	Quasi-Experimental	2016	China	Human prostate cancer cell PC-3	Fruit	Annonaceous acetogenins from graviola fruit exhibited anti-proliferation effects on human prostate cancer cell PC-3, indicating their potential as anti-cancer agents for prostate cancer treatment.
11	Zambrano, A. et al. (2018)	Quasi-Experimental	2018	Venuzuela	NA	Pulp	Functional beverages based on soursop pulps exhibited cytotoxic and antioxidant properties in vitro, suggesting potential health benefits of soursop-derived products.
12	Zuhrotun, A. et al. (2013)	Quasi-Experimental	2013	Indonesia	Prostate Cancer Cell Line	Leaves	Soursop leaves demonstrated antitumor activity against a prostate cancer cell line, suggesting a potential role in prostate cancer treatment.

DISCUSSION

Botanical description of *Annona muricata* and distribution

The specie, *Annona muricata* is a fruit-bearing plant belonging to the genus Annona which is of the Annonaceae family.[8] Although the fruit is native to Central America, it has a wide distribution, not limited to Southeast Asia, South America, and the rainforests of Africa.[9] *A. muricata* is very common in the United States of America and commercially, it is marketed as capsules and tea using different trade names.[10] Due to its sweet and sour taste, especially when ripe, *A. muricata* is commonly called soursop. The fruit is known as Graviola in Portuguese while in Latin America, it is called guanabana.[11]

A. muricata is an evergreen tree which grows vertically to a height of about 30 feet,[8] has hairy branches with oval to round leaves. The fruits which are dark green and thorny can contain as little as five to as many as 200 dark seeds interspersed in a creamy white flesh with a characteristic pleasant smell.[2,12,7] The flesh and pulp of Graviola have a great content of water, vitamins, carbohydrates and salts and therefore is optimal for drinks and juices and may also be eaten readily.[13] Although all parts of *A. muricata* have been used historically as a remedy for various illnesses and ailments, the roots, stem and leaves are the most widely used portions for obtaining herbal products and medicines which have found use globally.[14,15,16,17,2] The Seed, leaves, barks, stems, roots and flowers of Graviola have been used as an insecticide.[18,19] The leaf has been used for the amelioration of fever, respiratory illnesses, gastrointestinal disorders and as sedatives.[20,21,22,23] The fruit has been used for liver, heart and renal disorders.[24,9,25] The Leaf, fruit, stem, bark, and branch have all shown benefits as anticancer agents for various types of cancers.

Phytochemical properties of *A. muricata*

A. muricata consists of numerous phytochemically active compounds and secondary metabolites, amongst which are acetogenins, carotenoids, alkaloids, vitamins, flavonoids, amides, cyclopeptides, minerals and essential oils.[11,20,26,27]

Annonaceous Acetogenins

Acetogenins are in the majority, with regard to other compounds found in *A. muricata*. They are derivatives of long-chain fatty acids whose long aliphatic chain consists of about 35 – 38 carbon atoms attached to a g-lactone a-ring substituted at the terminal by b-unsaturated methyl, with tetrahydrofurans (THF) positioned along the hydrocarbon chain.[11,28] Over 500 acetogenins have been identified from different plant parts all of which are specific for targeting cancerous cells; examples of acetogenins include Annomuricin A, B, and C, cis-Annonacin, Muricatacin, Muricatocin C, Arianacin, Annonacin-10-one, cis-Goniothalamicin, and Javoricin.[7] 15-acetyl guanacone elucidated from *A. muricata* had free radical scavenging capabilities against the ABTS and DPPH radicals while annonacin showed cytotoxic activity against the Human B lymphoblastoid cell line.[7,29,30] Annonacin also showed significant genotoxic activity against cancer cells of the human breast. AA005 is an Annonaceous acetogenin mimic that inhibited tumour growth by promoting nuclear translocation of apoptosis-inducing factor (AIF) and inducing AIF-dependent cell death in vivo human colon cancer cell lines. In vivo SW620 (human colorectal cancer) and in vitro RKO (poorly differentiated colon carcinoma) cell lines revealed that treatment with AA005 showed down-regulation in Bcl 2 and Mcl-1. An acetogenin mimic, AA005 was shown to halt the growth of tumour cells through the promotion of nuclear translocation of apoptosis-inducing factor (AIF) and induction of AIF–dependent cell death in invivo cancer cell lines of the human colon.[31] Acetogenins have been classified into several categories based on their aliphatic chain substituents, hydroxyl group, terminal Y-lactone ring and tetrahydrofuran. They include linear structure, epoxy acetogenin, mono THF, mono tetrahydrofuran, mono tetrahydropyran acetogenin, bis THF-non-adjacent acetogenin and bis THF-adjacent acetogenin.[11] Acetogenins has shown activity against the formation of mitochondrial ATP which in turn suppresses growth of cancer cells through its effects on cancer cells that produce more ATP when compared to normal cells.[32] In the electron transport system of the mitochondria of cancerous cells, acetogenin Induces apoptotic processes through blockage of ATP production by suppressing the NADH:ubiquinone oxidoreductase. The cancer cells therefore lose their supply of energy, become fragile and eventually die.

Alkaloids

Alkaloids which possess cytotoxic activities are also important constituents of *A. muricata*. They include xylopine, reticuline, nornuciferin, anonaine, argentinine, isolaureline, atherospermine and assimilobin.[33,34] Xylopine has been shown to marked effect in inhibiting the growth of cancer cells in human myelogenous leukemia and human lung adenocarcinoma.[7]

Phenolic compounds

Phenolic compounds extracted from *A. muricata* include kaempferol, catechin, pro-cyanidins, and quercetin. Kaempferol possesses antioxidant activity[35] while Polyphenols like quercetin and catechin possess cytotoxic activity against certain cancer cell lines like HeLa and 3T3 fibroblast cells.[36,7]

A. muricata contains other phytochemicals like vitamins, cyclopeptides, carotenoids and amides. The leaves contain vitamins, carotenoids and numerous essential oils.[22,37] The seeds and pulp also contain vitamins and carotenoids. Cyclopeptides derived from the seed have been reported to possess both anti-cancer and anti-inflammatory activities.[7]

Role of *Annona muricata* against Prostate Cancer

Many prostate cancers grow slowly, while in other cases, they experience life-threatening prostate cancer where the cancer grows and spreads rapidly. Although there have been some advancements concerning early detection, coupled with newer treatment modalities aimed at improving the quality of care of patients, some patients still present late and/or develop virulent tumours with poor outcome.[13] Treatment options include surgery, radiotherapy and hormonal treatments which are often invasive, expensive, and debilitating on patients, and even then, may not offer cure. Moreover, various significant adverse effects of

treatment such as impotence, incontinence and bowel symptoms also discourage men from seeking early treatment. Hence there is an urgent need for less debilitating treatment options such as the use of medicinal plants. According to the World Health Organization, approximately 80% of the global population relies on traditional medicines, plant extracts, or plant-based substances for primary healthcare.[3] (WHO, 2022) Of the 1881 medicinal entities approved over nearly four decades, from 1981 to 2019, over 23% were derived from natural sources, i.e., unaltered natural products (N; 3.8%), botanical drugs (NB; 0.8%), or natural product derivatives (ND; 18.8%).[38] An estimated 25% of the 247 newly approved anti-cancer drugs were also derived from natural products.[38]

A. muricata has been widely used informally in many countries in the treatment of cancer and diseases, to interrupt the process of carcinogenesis and to prevent or delay tumour growth.[39,40] Several research efforts have linked *A. muricata*-derived compounds with anticancer effects, such as inhibition of proliferation, cytotoxicity, necrosis, and induction of apoptosis in several cancer cell lines. *A. muricata* and its derivatives have been documented to have positive effects not only against prostate cancer but also against other types of cancer like pancreatic cancer, lung carcinoma, breast cancer, colon carcinoma, head and neck squamous cell carcinoma, haematological malignancies, liver cancer, and cervical cancer.

The pulp extract of *A. muricata* has significant antiproliferative activity in certain cell lines of prostate cancer like the LNCaP and PC-3.[41] It was also found out that by reducing HIF-expression and impeding the activity of NOX, *A. muricata* fruit extract possessed antiproliferative effects.[42] The hexane fraction of Annona muricata seed mitigated benign prostatic hyperplasia induced by testosterone in rats via its anti-oxidative, anti-inflammatory and apoptotic activities in prostate of rats with benign prostatic hyperplasia.[43] Aqueous soursop pulp extracts demonstrated anti-inflammatory properties and ameliorated induced benign prostatic hyperplasia in adult male Wistar rats.[44] Graviola leaves extract influenced the pharmacokinetics of metformin in rats' plasma and exhibited pharmacological activity against breast and prostate cancer cell lines. This indicates a potential interaction between Graviola extract and metformin, as well as its potential in cancer treatment.[45] Graviola stem bark extracts showed anti-inflammatory effects on a testosterone-induced benign prostatic hyperplasia model in rats, suggesting a potential role in managing prostatic hyperplasia.[46] Graviola and its constituents showed emerging therapeutic potential in cancer treatment, highlighting their potential as anti-cancer agents.[13] Functional beverages based on soursop pulps exhibited cytotoxic and antioxidant properties in vitro, suggesting the potential health benefits of soursop-derived products.[47] Soursop leaves demonstrated anti-tumour activity against a prostate cancer cell line, suggesting a potential role in prostate cancer treatment. Annonaceous acetogenins from Graviola fruit exhibited anti-proliferation effects on human prostate cancer cell PC-3, indicating their potential as anti-cancer agents for prostate cancer treatment.[10] Chemometric analysis revealed major anti-cancer activity compounds from soursop leaves, providing insights into the compounds responsible for the anti-cancer properties.[48] Annona muricata extract exhibited antiproliferative and apoptotic effects on prostate cancer cells, indicating its potential to inhibit the growth of prostate cancer cells.[49]

Toxicology

Some studies reported untoward effects of *A. muricata*, and the degree of toxicity appeared to vary with the part of the plant and/or solvent used for the study.[11] One study showed that aqueous extract of *A. muricata* leaves possesses an LD_{50} of more than 5g/kg while the ethanolic extract had an LD_{50} of more than 2g/kg.[50] According to Arthur et al,[51] aqueous extract of *A. muricata* leaves with doses above 1g/kg can produce a lowering of blood glucose and doses above 5g/kg can lead to renal toxicity. According to a study by Escobar-Khondiker et al,[52] a link has been found between consumption of acetogenin (from leaves or fruits of *A. muricata*) and emergence of neurodegenerative disease. The major acetogenin, annonacin resulted in death of striatal neurons in vitro and gave rise to the presence of tau protein on cell bodies. Annonacin as well as certain alkaloids like reticulin also produce neuro toxic effects.[13] In rat models, annonacin extracted from the fruits and leaves of *A. muricata* was shown to cause a reduction in levels of ATP in brain cells, and cause damage in the basal ganglia following entrance to the brain.[53] It is important to note that this neurotoxic effect of *A. muricata* only came into play following continuous/daily consumption of large doses for prolonged periods and therefore moderate consumption is advised.[11]

Conclusion

This review highlights the anticancer potential of *A. muricata* on prostate cancer, with special attention to the phytochemical compounds responsible for these effects. *Annona muricata* is an indigenous medicinal plant extensively reported to possess a wide range of beneficial activities. Its active metabolites including Annonaceous acetogenins and other products of secondary metabolites such as alkaloids have been shown to halt the growth of cancer cells The studies that have elucidated these benefits of Graviola have largely been invitro and preclinical invivo studies, therefore, clinical studies are required to further ascertain the effects and safety profile of Graviola for use in human. More extensive study of this plant possibly, its development for standardized clinical use, could provide a more efficient, less expensive, and more acceptable mode of management of prostate cancer and other diseases.

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