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Annona Muricata as a Source of Bioactive Agents: Systematic Review of Anti-Diabetic, Anti-Cancer and Antioxidant Properties

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Abstract: Annona muricata(soursop or graviola), is a saturatedclass extensively valued in many traditional medicinal systems. Over the past several decades, research efforts have increasingly examined its diverse bioactive compounds, highlighting significant anti-diabetic, anti-cancer, and antioxidant properties. This organized review provides a comprehensive synthesis of the current sign, focusing on A. muricata's phytochemical constituents, mechanisms of action, therapeutic potential, and safety considerations.

Keywords: Annona muricata, bioactive compounds, acetogenins, anticancer, apoptosis

1. Introduction

Annona muricata(graviola), is natural to Central &South America, Southeast Asia, &Africa. It has been used for centuries to preference diseases realization from infections to metabolic &inflammatory diseases. This review critically examines recent scientific investigations into the anti-diabetic, anti-cancer, and antioxidant activities of the present subject, aiming to provide a comprehensive resource (1). Additionally, this indicates cytotoxic activity against cancer cells through apoptosis induction. Researchers have identified 212 different bioactive compounds in Annona muricata.The primary focus of the study was on the leaves and seeds, likely due to their traditional usage. The most abundant compounds include acetogenins, and also followed by alkaloids, phenols, and other constituents(2).

2.1 Major Bioactive Classes

Acetogenins: Potent, unique polyketides primarily responsible for cytotoxic activities. More than 100 distinct acetogenins have been identified in various organic extractsethanolic and methanolic extracts derived from various parts of the Annona muricata plantincluding its leaves, stems, bark, seeds, pulp, and fruit peelcontain a range of bioactive compounds(3). These molecules are characterized by a lengthy aliphatic chain consisting of 35 to 38 carbon atoms, connected to a γ-lactone ring that terminates with a β-unsaturated methyl group (ketolactone). Their structures commonly incorporate one or two tetrahydrofuran

(THF) rings within the carbon chain and often possess multiple oxygenated functional groups, such as hydroxyl, acetoxyl, ketone, and epoxide groups(4).

Flavonoids: Certain alkaloids have been linked to neurotoxic effects, with evidence suggesting neuronal death may occur via apoptosis. Flavonoids are synthesized through the **phenylpropanoid pathway**, beginning with the amino acid phenylalanine. Helps reduce oxidative stress, which is linked to these compounds have been linked to a wide range of pharmacological effects relevant to chronic illnesses, including cardiovascular diseases, diabetes, and neurodegenerative disorders. Reported biological activities include anti-acetylcholinesterase, antioxidant, antidepressant, antiepileptic, antimicrobial, antileishmanial, anti-Trypanosoma, antiplasmodial, antiproliferative, anti-ulcer, cytotoxic, immunostimulatory, larvicidal, and anxiolytic-like actions. Flavonoids such as quercetin and kaempferol, in particular, exhibit notable antioxidant potential that contributes to these therapeutic effects(5).

Phenolics: The Primary method of medicinal application is through aqueous infusion, as the phenolic compounds arecommon water-soluble. These compounds are regarded as key phytochemicals contributing to the antioxidant property of A. muricata. Phenolics have significant potential as functional food ingredients, nutraceuticals, and natural preservatives due to their antioxidant and antimicrobial activities. Furthermore,amides, carotenoids, cyclopeptides& vitamins, have also been detected in this plant. The leaves, seeds, and fruit pulp of A. muricata contain various vitamins and carotenoids. Additionally, analyses of the fruit pulp have revealed the presence of thirty-seven different volatile compounds.Moreover, eighty essential oils exhibiting parasiticidal, antidiarrheal, rheumatological, and antineuralgic properties have been found in the leaves. Contributing to both antioxidative and anti-diabetic properties(6).

2.2 Distribution in Plant Parts

S.NO	Plant Part	Major Phytochemicals
1	Leaves	Acetogenins, flavonoids, phenolics
2	Fruits	Acetogenins, phenolics
3	Seeds	Alkaloids, acetogenins
4	Bark/Roots	Alkaloids, phenolics

3. Anti-Diabetic Properties

3.1 Mechanisms of Action

Increased Insulin Secretion: Extracts stimulate insulin production and release. Particularly, flavonoids and phenolic compounds can stimulate pancreatic β-cells, encouraging these cells to increase the production and release of insulin. This effect helps in reducing elevated blood glucose levels, thus improving glycemic control. Several experimental studies using animal models of diabetes have

demonstrated that administration of A. muricata leaf and fruit extracts leads to a significant rise in insulin levels, supporting the restoration of normal carbohydrate metabolism. The improvement in insulin secretion is often accompanied by protection of pancreatic tissues from oxidative stress, suggesting that the antioxidant properties of the extracts may also play a role in preserving β-cell function and viability. Overall, these findings highlight the relevance of Annona muricata as a potential adjunct in managing hyperglycemia by targeting insulin secretion pathways(7).

Enzyme Inhibition: Suppression of α-glucosidase and α-amylase reduces carbohydrate breakdown, lowering blood glucose. The ability to suppress the activity of essential digestive enzymes that regulate carbohydrate breakdown, specifically α-glucosidase and α-amylase. By suppressing these enzymes' activities, the breakdown of complex carbohydrates into glucose is delayed, resulting in a slower and reduced absorption of glucose into the bloodstream. This enzymatic inhibition contributes significantly to controlling postprandial (after-meal) blood glucose spikes, thereby aiding in the management of hyperglycemia in diabetic conditions(8).

Oxidative Stress Modulation: The strong antioxidant properties of Annona muricata play an important role in shielding pancreatic β-cells from oxidative stress. Since these cells possess relatively weak natural antioxidant defenses, they are highly vulnerable to oxidative damage. The rich presence of phenolic and flavonoid compounds in A. muricata extracts aids in neutralizing reactive oxygen species (ROS) and free radicals, thereby decreasing oxidative pressure within the cells. This protective mechanism supports the preservation of β-cell structure and function, leading to improved insulin secretion and glucose regulation. Studies conducted on diabetic animal models have shown that treatment with A. muricata extracts enhances the activity of vital antioxidant enzymessuch as superoxide dismutase (SOD), catalase, and glutathione peroxidasehelping to reduce oxidative harm in pancreatic tissue(9)

3. Anti-Cancer Activities

3.1 Mechanisms of Action

Induction of Apoptosis

Acetogenins—especially annonacin—extracted from Annona muricata are reported to initiate the apoptotic pathway leading to cell death in various cancer cells.These compounds activate intrinsic mitochondrial pathways, leading to DNA fragmentation, caspase activation, and eventual cell death. The selective cytotoxicity of acetogenins makes them particularly effective in targeting tumor cells while sparing non-malignant tissue(10).

Inhibition of Proliferation

Extracts from A. muricata have been shown to restrict the multiplication of malignance cells by impairing function of MC- I, a key enzyme complex involved

in cellular energy production.By disrupting energy production, A. muricata compounds effectively stifle cancer cell metabolism, thereby curbing their ability to proliferate and spread(11).

Anti-Angiogenic Effects

Extracts from Annona muricata have demonstrated anti-angiogenic properties, allowing them to suppress the formation of new blood vessels that are crucial for tumor development and the spread of cancer cells.By impeding angiogenesis, these extracts limit nutrient and oxygen supply to tumor masses, which in turn restricts their expansion and potential to invade other tissues(12).

4. Antioxidant Activity

Demonstrates significant antioxidant properties, largely outstanding to its high levels of phenolic compounds, flavonoids, &many other bioactive plant-derived chemicals. These antioxidants function by scavenging harmful free radicals and reactive oxygen species (ROS), thereby ROS which is implicated in several chronic diseases as well as diabetes and cancer. Leaf, fruit, and seed extracts display strong free radical scavenging capacity (DPPH, ABTS, FRAP assays)(13).

5. Synergy in Disease Modulation

The synergistic antioxidant effects of Annona muricata play a significant role in disease modulation by providing protection against oxidative damage to vital tissues. This activity is likely central to both its anti-diabetic and anti-cancer properties. The antioxidants in A. muricata help maintain cellular structure and function by neutralizingROS and mitigating oxidative stress, especially in cells vulnerable to damage in chronic diseases.In the context of diabetes, this protective effect supports pancreatic β-cell function, enhancing insulin secretion and glycemic control. Similarly, in cancer, limiting oxidative injury to healthy tissues may slow disease progression and reduce collateral damage during cellular responses. Thus, the combined antioxidant actions not only help prevent tissue degeneration but also complement other therapeutic mechanisms, making A. muricata a promising adjunct in managing oxidative stress–related conditions(14).

6. Safety, Toxicity, and Risks

Neurotoxicity: Chronic consumption, particularly of seeds or high-concentration extracts, is linked to the development of atypical Parkinsonism, attributed to certain acetogenins. Chronic consumption of Annona muricata, especially the seeds or extracts with high acetogenin concentrations, has been associated with neurotoxic effects. Notably, such exposure has been linked to the development of atypical Parkinsonism, a neurological disorder that mimics symptoms of Parkinson's disease. This risk is primarily attributed to certain acetogenins present in the plant, which, when consumed in excessive amounts or over

prolonged periods, may adversely affect neurological health. As a result, caution is advised when using A. muricata products—particularly non-traditional preparations or concentrated extracts—to minimize potential neurotoxic risks, especially among populations with increased susceptibility(15).

7. Conclusion and Future Directions

Annona muricata holds significant promise as a source of anti-diabetic, anti-cancer, and antioxidant compounds, owing to its diverse and complex phytochemical composition. Extensive laboratory research has validated its bioactive potential; however, clinical translation remains limited due to ongoing concerns about toxicity and the scarcity of robust human studies. Future research should prioritize well-designed clinical trials coupled with detailed toxicological evaluations to better elucidate safety and efficacy profiles. Additionally, exploring optimized extraction methods and bioavailability enhancement strategies may further advance its therapeutic development. Addressing these areas will be pivotal in unlocking the full medicinal potential of Annona muricata.

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