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Annona muricata in modern medicine and its broad spectrum therapeutic potential

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Abstract

Background: Bioactive compounds from plants have gained significant attention in modern medicine, demonstrating therapeutic potential in cardiovascular, dermatological and oncological conditions. *Annona muricata* is a candidate with documented multidirection therapeutic potential, especially when it comes to acetogenins.

Aim of the study: This review evaluates the status of *Annona muricata* (Graviola) in modern medicine, analyzes characteristics of the plant and its phytochemicals with their multidirectional activities, such as anticancer, antidiabetic and antinflammatory.

Materials and methods: A systematic review of PubMed (last 20 years) was conducted using the keywords: „Annona muricata", „bioactive compounds".

Conclusions: *A. muricata*'s extract demonstrates anticancer, antidiabetic, antioxidant and gastroprotective effects through mechanisms like oxidative stress modulation, apoptosis, cellular signalling pathways, inflammation. Anticancer activity has been the most studied. *A. muricata* represents a promising pharmaceutical, but further clinical studies are needed to establish its efficacy, safety and pharmacokinetic profile.

Keywords: Annona muricata, graviola, phytochemicals, bioactive compounds, ethnomedicine, natural medicine, antioxidant, antidiabetic, anticancer

Introduction

Bioactive compounds obtained from plants seem to be an important direction in the development of modern medicine. In recent years, phytochemicals have proven their place in the treatment of various ailments - cardiovascular diseases, skin diseases and cancer. Despite its technological advancement, cancer and neoplastic proliferation are still in the area of research of many scientists, and even now researchers are looking for sources of new substances among known plant species. *Berberis vulgaris*, Holy basil, fireweed or nettle are just a few examples of pharmaceutical discoveries. They have been known for their long history of use in ethno medicine and were involved in maintaining the health of mankind, and have now become a hot topic of scientific articles. Another plant that could be highlighted as a natural remedy is *Annona muricata* Linn. (*Annonaceae*) [1]. *A. muricata* stands out with its anticancer, antioxidative, antifungal, antibacterial, antidiabetic and anti-inflammatory activities. *Annona muricata* extract is where traditional medicine and modern research meet, bringing hope as a new therapeutic agent. Among numerous compounds, acetogenins are pointed out as the most relevant [2].

In this article, we would like to provide a comprehensive review of the available literature on the wide range of applications of *Annona muricata* in medicine.

1. *Annona muricata* - characteristics

Annona muricata L. is a lowland tropical tree from the genus *Annona*, of the *Annonaceae* family, native to Central and South America. It is commonly known as soursoup, graviola or guanabana, but also as guanaba, huanaba, jaca do Pará, sinini, corossol, durian belanda and thu-rian-khack - depending on the part of tropical or subtropical region of the world [2]. The name soursoup refers to its sweet and sour taste [1]. Among over 70 species *Annona muricata* is the most widely spread. It has many local names with various preparations or applications differing between regions [3].

Geographical Distribution:

This plant is capable of thriving in tropic and subtropic zones, remarkably adapted to humid lowlands. Graviola's natural habitat spans Mexico, Caribbean islands, Central and South America from Venezuela to Peru and Bolivia. It commonly grows on coasts and slopes. Graviola can be found in domestic gardens, but also in rural settings such as volcanic and limestone islands. Although originally it has been cultivated for fruits, it has spread through diverse habitats, like thickets, pastures and along roadsides. In general, it doesn't grow on atolls. Graviola prefers areas that are situated 1200m above sea level, with medial temperatures between 25 and 28 degrees Celsius. Areas are characteristic with high humidity (60 to 80%) and large amounts of annual rainfall (more than 1500 mm) [3,4].

Stem:

This species is characterised by an evergreen erect stem that can grow to heights ranging from 5 to 8-10 meters, 15-83 cm in diameter. It blooms and harvests fruits through most of the year [3]. Graviola is an ever green tree with an open, rounded canopy of low branches, framed by large, dark green leaves. The stem architecture serves a dual functional role, providing structural mechanical support while simultaneously facilitating the translocation of nutrients, thereby promoting the robust vegetative growth of the plant [1,3].

Flowers and Seeds:

Graviola enters the flowering phase at the age 3 to 4. The fruiting happens through most of the years, but it may differ in various environments and become seasonal. *A. muricata* fruit is an edible, ovoid to heart-shaped berry. Its diameter is between 15 and 20 cm. In some countries fruit reaches 4kg of weight. The fruit are sensitive to poor pollination and when so fail to emerge. The skin is soft with delicate curved thorns. Fruits are green on the outside, but hide edible white and creamy flesh with indigestible black seeds. The pulp is used for many gastronomical purposes, the production of ice cream, creams, sweet beverages as nectars or smoothies [1,5].

Leaves:

The soursoup's leaves are simple, alternate and petiolate with an elliptical lamina. The leaf blade is leathery in texture and smooth on both sides. The upper surface presents a darker glossy green coloration, but the undersurface is paler. The leaf apex is acute, while the base is cuneate to rounded. The venation pattern is feather-like, with a prominent midrib. The petiole is short and stout. Upon crushing, the leaves emit a characteristic strong odor [5,6].

Root System:

The root architecture of *Annona muricata* is defined by a relatively undeveloped central taproot, accompanied by an extensive network of thin, fibrous lateral roots. The rooting profile is rather shallow due to the wide in range, but thin network of lateral roots. During prolonged dry seasons, the plant is not resistant to water deficiency, exposed to dehydration. There is the need to maintain adequate soil moisture, in particular by mulching around the base of the tree. Due to its shallow and highly fibrous root structure, Graviola is significantly susceptible to uprooting due to physical forces under stress conditions of for example strong wind. The network of lateral roots extend primarily within the topmost layers of soil, to maximise absorption of water and nutrients and provide rapid and robust growth [7, 8].

2. *Annona muricata* in traditional medicine

In the home regions like Africa, South America, Southeast Asia - graviola is a well-founded natural pharmaceutical agent. Even though nowadays scientists' eyes focus on *A.muricata*, it has been incorporated in the folk medicine practices of indigenous communities for ages. Every

part of the plant has been utilised for specific and individual treatment purposes - from fruits and seeds to roots, stem and leaves. Across tropical regions *A. muricata* has been used in treatment of fever, pain, respiratory and skin illness, in bacterial and parasitic infections, but also in diabetes or hypertension. In Malaysia leaf extracts were applied to protect from fainting. Without modern research it has been noticed that *A. muricata* has demonstrated anti-inflammatory and anti-neoplastic activity. The seeds and the fruit were administered in parasitic infections, also to reduce the fever [1, 2, 9, 10]. Moreover the fruit were specifically used to stimulate lactogenesis among breastfeeding women [10]. The leaves were particularly utilized as a therapeutic agent in treatment of headaches, insomnia [1,2,3]. Leaves, fruits and pulp have been specifically used in diabetes treatment. It has been believed that ethanolic extract from leaves can control seizures, lowers seizure mortality rate and lowers the fever. *A. muricata* demonstrated antibacterial action in the treatments of urinary tract infection, pneumonia or skin disease, acting against certain bacteria like *Staphylococcus aureus, Pseudomonas, Bacillus, Klebsiella, and E. coli*.

These ethnomedicinal applications have been gradually validated by modern pharmacological research and it has been well documented in the review of studies conducted from 1980s that *A. muricata* exhibits certain pharmacological activities - anticancer, antiulcer, antidiabetic, antiprotozoal, antidiarrhea, antibacterial, antihypertensive and wound healing properties [10]. To support some of these findings, important in-vitro studies have been conducted and have characterised extracts from *A. muricata* as anti-cancer - acetogenins found in A. muricata are found to induce cell apoptosis and inhibit cancer cell proliferation [11, 12]. Moreover, clinical studies have definitely supported the thesis of hypoglycemic activity of ethanolic leaf extracts. It gained its antidiabetic potential due to the ability to inhibit α-glucosidase and α-amylase and increase insulin release, resulting in lower glucose absorption, better glucose tolerance and peripheral glucose intake [2].

Altogether, the conducted botanical research combined with ethnomedicinal knowledge establishes *A. muricata* as one of the most promising and pharmacologically diverse medicinal plants in tropical medicine. It demands continuing further rigorous investigation and clinical correlation to adjust clinical applications and safety profile.

3. Bioactive compounds

As mentioned before, numerous parts of *A. muricata*, such as the leaves and bark, have been a source of interesting biochemical compounds. More than 200 chemical substances have been discovered and subjected to tests and used as a therapeutic agent in natural medicine. Even though Graviola has yet to be fully validated and examined, its potential therapeutic role alongside conventional medicine demands acknowledgement [3].

Graviola stands out as a remarkably rich source of bioactive compounds like acetogenins, alkaloids, phenolics and essential oils that can be found in various parts of the plant. The conducted pharmacological research evaluated through *in vitro* and *in vivo* studies *A. muricata'*s therapeutic potential - anticancer, antioxidant, and antimicrobial [1]. Nevertheless, there is a significant gap between laboratory findings and clinical prevalence which remains a major limitation - only 2% of published studies have been conducted as clinical trials. *Annona* species are particularly known as a rich source of annonaceous acetogenins. The fruit is also mentioned as an important source of minerals like potassium, calcium, sodium, copper, iron and magnesium and could be a future supplement source [1]. The GC and GC-MS analyses of Graviola leaf oil from Cameroon revealed a predominance of sesquiterpenes, with β-caryophyllene as the major constituent, while Vietnamese specimens were characterised by β-pinene (20.6%), germacrene D (18.1%), ρ-mentha-2,4(8)-diene (9.8%), α-pinene (9.4%), and β-elemene (9.1%), alongside δ-cadinene, epi-α-cadinol, and α-cadinol. In the fruit pulp essential oils were mostly found aliphatic acid esters, particularly 2-hexenoic acid methyl and ethyl esters, with notable amounts of β-caryophyllene, 1,8-cineole and linalool [1].

Acetogenins (AGEs) are considered the hallmark bioactive compounds of the *Annonaceae* family and represent the most pharmacologically significant class of constituents in *A. muricata*. Structurally, they are classified as C-35/C-37 secondary metabolites derived from long-chain fatty acids via the polyketide pathway, typically featuring a 2-propanol unit at C-2 forming a methyl-substituted α,β-unsaturated γ-lactone. Their structure is further characterized by a long aliphatic chain of 35–38 carbons linked to a γ-lactone ring, with one or two tetrahydrofuran rings distributed along the hydrocarbon chain and varying oxygen-containing functional groups. While forms containing two adjacent or non-adjacent THF rings have been reported, the majority of acetogenins identified in *A. muricata* contain a single THF ring, and their biological activity is believed to be closely dependent on structural configuration [2, 5]. Since the isolation of uvaricin from *Uvaria accuminata* in 1982 - marking the first discovery

of an acetogenin - over 500 compounds of this class have been identified across the *Annonaceae* family, with more than 100 documented in *A. muricat*a alone. Among these, annonacin has consistently been identified as the most abundant acetogenin across multiple plant parts, including leaves, fruit, seeds, peel and roots, with acetogenin concentrations in leaf extracts measured between 3.38 and 15.05 mg/g. In terms of cytotoxicity, acetogenins have demonstrated greater potency than both alkaloids and rotenone, with reported activities encompassing not only anticancer effects but also antimalarial, antiparasitic, and pesticidal properties, primarily attributed to their ability to inhibit mitochondrial complex I [2,3,5].

The alkaloid fraction of *A. muricata* is mainly composed of isoquinoline, aporphine, and protoberberine-type compounds, with reticuline and coreximine identified as the most abundant. However alkaloids are present in all parts of the plant - including the roots, stems and fruit; the highest concentrations are consistently found in the leaves. Pharmacologically, alkaloids obtained from the *Annona* genre have shown affinity for 5-HT1A receptors and involvement in dopamine biosynthesis, suggesting potential antidepressant-like properties alongside cytotoxic activity. More importantly, certain alkaloids have also been associated with neurotoxic effects, with evidence pointing to neuronal death occurring through apoptosis. However, the neurotoxic adverse effect of alkaloids remain a subject of ongoing scientific debate, asking a question - where is a compromise between a therapeutic promise and a safety profile [3]?

There are a total of 37 phenolic compounds identified from *Annona muricata* and they are another important class of phytochemicals. In the leaves you can find quercetin and gallic acid, while the fruit pulp has also been reported to contain flavonoids alongside lipophilic antioxidants such as tocopherols and tocotrienols. Phenolic compounds are responsible for the antioxidative effect of the plant. An important methodological consideration in this context is that the quantity of extractable phenols varies considerably depending on the solvent used. The most common preparation of the extract of the plant is an aqueous extract and that the phenolic compounds are water - soluble [3, 5].

In *A. muricata* there are also other biologically important compounds to be found, like vitamins and carotenoids identified in the leaves, seeds and fruit pulp. Cyclopeptides and the amide N-p-coumaroyl tyramine, present in the seeds, have demonstrated anti-inflammatory and antitumor effects. Megastigmanes extracted from the leaves have not shown cytotoxic or antioxidant activity. In the fruit pulp, 37 volatile compounds have been identified, the majority

of which are aromatic and aliphatic esters. Moreover, 80 essential oils have been isolated from the leaves and have shown notable cytotoxic activity against the MCF-7 human breast carcinoma cell line, achieving 99.2% cell kill at a concentration of 100 µg/ml. This topic will be covered over next paragraphs in this article [3].

Annona muricata definitely demonstrates a considerably promising source of bioactive compounds. They present broad pharmacological activities, however the duality of their nature, especially acetogenins and alkaloids, brings both opportunities and challenges. Cytotoxicity and antioxidant properties highlight a really strong therapeutic potential, yet they are associated with neurotoxic adverse effects (neuronal apoptosis). There is a need for further investigation to fully explore the neurotoxicity concerns - particularly a well-designed in vivo and human studies, validation of extraction methods and dosages - without them it will be difficult to adjust its potential to actual clinical applications.

4. Anticancer properties

Annona muricata L. has gained substantial scientific attention because of its rich composition of biologically active phytochemicals, including annonaceous acetogenins, alkaloids, flavonoids, and phenolic compounds, many of which have demonstrated potential anticancer properties. According to ethnomedicinal observations, preparations obtained from the leaves, fruits, bark, stems, and roots of the plant are commonly utilized in traditional medicine systems, including supportive cancer care. Surveys conducted among oncology patients in Jamaica, Trinidad, Peru, Mexico, and the Philippines revealed frequent use of *A. muricata*-based preparations among individuals diagnosed with breast, prostate, colorectal, liver, and gastric malignancies [13]. Most currently available evidence regarding the anticancer potential of *A. muricata* originates from preclinical research. One pharmacological review reported that nearly 60% of studies were performed in vitro, approximately 36% involved murine in vivo models, while clinical investigations accounted for only 2% of the available literature. The majority of experimental studies focused on organic solvent extracts derived from leaves, which are characterized by relatively high concentrations of acetogenins and alkaloids [14]. Among the phytochemicals identified in *A. muricata*, annonaceous acetogenins are generally considered among the principal contributors to its anticancer activity. Nevertheless, increasing evidence indicates that other classes of phytochemicals, including alkaloids, flavonoids, and phenolic compounds, may also participate in the observed anticancer effects, either through their intrinsic biological activity or through synergistic interactions with acetogenins. Among these

compounds, annonaceous acetogenins have been most strongly associated with inhibition of mitochondrial complex I activity and reduction of intracellular ATP synthesis, thereby disrupting energy metabolism in malignant cells [13]. Since many cancer cells exhibit increased energetic demands and altered metabolic requirements, mitochondrial inhibition may contribute to the preferential cytotoxicity observed in tumor tissues [14]. Experimental studies have also demonstrated that *A. muricata* extracts can induce apoptosis through several interconnected molecular pathways, including suppression of antiapoptotic proteins such as Bcl-2, upregulation of Bax expression, cytochrome c release, and activation of caspase-3/7 and caspase-9 signaling cascades [9, 13]. Additional reported mechanisms include inhibition of PI3K/Akt and ERK signaling, reduced glucose uptake and glycolytic activity, as well as induction of oxidative stress and mitochondrial dysfunction in cancer cells. Pharmacological reviews have further indicated that *A. muricata* extracts may promote cell-cycle arrest in the G0/G1 phase and suppress pathways associated with tumor invasion and metastasis, although most of these findings remain limited to preclinical studies [9, 16]**.** Preclinical evidence further indicates that *A. muricata* extracts may modulate molecular pathways associated with cellular stress responses and photoprotection. In a rat model of ultraviolet-induced skin damage, administration of *A. muricata* leaf extracts increased the expression of the tumor suppressor genes *p53* and retinoblastoma (*Rb*), indicating possible involvement in cellular responses to UV-induced damage and tumor-suppressor signaling pathways [16].

4.1 Breast cancer

Breast cancer is among the most extensively investigated malignancies in studies evaluating the anticancer potential of *A. muricata*. In murine 4T1 breast cancer cells, aqueous leaf extract promoted autophagy-dependent cell death through decreased mTOR expression and increased Beclin-1 and LC3 gene expression. The treatment was also associated with concentration-dependent cell-cycle arrest in the sub-G1 and S phases. When combined with cisplatin, *A. muricata* appeared to shift the predominant mechanism of cell death toward autophagy-related pathways, accompanied by reduced caspase-3 activity and decreased expression of inflammatory mediators, including TNF-α and IL-6. Several observed molecular alterations reached statistical significance ($p < 0.05$) [17]. Studies performed in MDA-MB-231 triple-negative breast cancer cells demonstrated that *A. muricata* infusion enhanced the cytotoxic activity of selected conventional antineoplastic agents. In parallel experiments using healthy cells, the infusion increased cytotoxicity in human leukocytes but exhibited low toxicity and potential protective effects in a non-tumorigenic murine lung cell line. Molecular docking

analyses further indicated that quercetin and hyperoside may interact with the A2B receptor, potentially contributing to the modulation of antineoplastic drug responses observed in combination-treatment models [18]. While the studies discussed above focused primarily on triple-negative breast cancer models, computational analyses have also explored the possible relevance of *A. muricata*-derived compounds in hormone-responsive breast cancer. In silico and molecular dynamics studies identified reticuline and calamenene isolated from *A. muricata* as candidate inhibitors of 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1), an enzyme implicated in estrogen-dependent breast cancer progression. Reticuline exhibited favorable binding affinity, high stability during molecular dynamics simulations, and a promising predicted pharmacokinetic profile compared with epirubicin, without indications of hepatotoxicity or carcinogenicity in computational analyses. Collectively, these findings support further evaluation of selected *A. muricata*-derived phytochemicals as candidate lead compounds in hormone-responsive breast cancer models [19].

4.2 Prostate Cancer

The anticancer potential of *A. muricata* has also been explored in prostate cancer models. Several phytochemicals isolated from *A. muricata* have been reported to inhibit 5-α-reductase type 2, suggesting a potential influence on androgen-dependent signaling pathways involved in prostate carcinogenesis. Although not a cancer model, in vivo studies performed in testosterone-induced benign prostatic hyperplasia (BPH) rats demonstrated antioxidant and anti-hyperplastic effects, accompanied by reductions in PSA levels and prostate enlargement. Treatment was associated with improvement of histopathological architecture and reduction of oxidative stress markers, with several parameters showing statistically significant differences compared with untreated controls ($p < 0.05$), indicating a potential protective effect on prostate tissue under conditions of androgen-induced hyperplasia [20]. Green-synthesized silver nanoparticles obtained from *A. muricata* fruit and leaf extracts have also been investigated for their activity against prostate cancer cells. These nanoparticles exhibited cytotoxic and antiproliferative effects in PC3 cells and were associated with reduced migratory and clonogenic potential. Further mechanistic analyses indicated the involvement of apoptosis-related signaling, including increased CASP9 expression, together with modulation of the CXCL1/CXCR2 axis. Given the recognized role of these pathways in cell survival, inflammation, and tumor progression, the findings suggest that *A. muricata*-derived AgNPs may interfere with multiple processes involved in prostate cancer development and maintenance [21].

4.3 Colorectal Cancer

Although a limited number of clinical studies have been conducted, current evidence regarding the role of *A. muricata* in colorectal cancer is derived predominantly from computational and preclinical investigations. In silico analyses identified several *A. muricata*-derived phytochemicals with favorable predicted binding affinity toward the MLH1 protein, a molecular target implicated in colorectal carcinogenesis, with α-tocopherol exhibiting the most favorable binding profile among the compounds evaluated. Molecular dynamics simulations further supported the stability of the ligand–protein complexes; however, these findings still require experimental validation [22]. One of the few available clinical investigations was a randomized placebo-controlled study evaluating *A. muricata* leaf extract supplementation in colorectal cancer patients. The study demonstrated that serum obtained from supplemented patients exhibited increased ex vivo inhibitory activity against colorectal cancer cell lines, particularly DLD-1 and COLO 205 cells, while maintaining stable nutritional parameters, including BMI and hemoglobin levels. However, the study was limited by a relatively small sample size, short supplementation period, and lack of long-term oncological endpoints such as progression-free survival or overall survival [23].

4.4 Hematological Malignancies

Emerging evidence suggests potential applications of *A. muricata* in hematological malignancies, particularly leukemia. A recent comprehensive review summarized available preclinical studies and highlighted that extracts and bioactive compounds derived from *A. muricata* exert cytotoxic and antiproliferative effects against various leukemic cell lines. The review further emphasized the growing interest in natural products as potential adjuncts to conventional leukemia therapies because of their diverse mechanisms of action and potential therapeutic benefits. Collectively, these findings support further investigation of *A. muricata*-derived compounds as candidate agents for leukemia treatment [24]. Among the bioactive constituents, alkaloids isolated from *Annona* species, including xylopine and isocoreximine, have demonstrated cytotoxic activity against leukemia cell lines such as HL-60 and K-562. Specifically, xylopine exhibited cytotoxic effects against HL-60 cells, with reported IC_{50} values ranging from approximately 20 to 80 μM. These findings indicate that specific alkaloids may contribute to the anti-leukemic properties of *Annona* species and warrant further investigation to elucidate their molecular mechanisms of action and potential therapeutic applications [13].

4.5 Summary of Anticancer Properties

Despite substantial preclinical evidence, clinical data regarding the anticancer efficacy of *A. muricata* remain limited. Existing human evidence is largely restricted to anecdotal reports, complementary medicine use, and small non-standardized studies rather than controlled anticancer interventions. Although graviola preparations are commonly used by cancer patients as complementary products, robust randomized clinical trials evaluating tumor response, survival outcomes, and long-term safety are still lacking [13]. Concerns have also been raised regarding the safety profile of certain *A. muricata* constituents. Experimental studies indicate that some isolated acetogenins and alkaloids may exert neurotoxic effects in cellular and animal models. In particular, annonacin has been shown to impair cellular energy metabolism, reduce ATP production, and induce neurodegenerative changes in experimental systems. Nevertheless, the clinical relevance of these observations remains uncertain because of limited human data and the reportedly low bioavailability of these compounds [14]. Some alkaloids may also interfere with CYP450-mediated drug metabolism, particularly CYP2D6-dependent pathways, raising the possibility of herb–drug interactions in patients receiving conventional chemotherapy [25]. The clinical significance of these findings remains difficult to establish because of the limited availability of pharmacokinetic data concerning the bioavailability, metabolism, tissue distribution, and achievable therapeutic concentrations of annonaceous acetogenins in humans [14]. Taken together, the available studies suggest that *A. muricata* possesses multifaceted anticancer potential mediated through mechanisms such as apoptosis induction, autophagy modulation, mitochondrial dysfunction, inhibition of proliferative signaling pathways, and regulation of inflammatory responses. However, the translational applicability of these findings remains uncertain because of the predominance of in vitro, in vivo, and in silico studies, the heterogeneity of plant extracts, and the scarcity of rigorously designed clinical trials [14, 26]. Consequently, current evidence remains insufficient to support *A. muricata* as an evidence-based anticancer therapy in clinical oncology. Future studies should prioritize standardized extract characterization and well-designed randomized clinical trials incorporating validated oncological endpoints [13, 14].

While anticancer activity remains the most extensively investigated pharmacological property of *A. muricata*, the plant has also demonstrated a range of other biological effects with potential therapeutic relevance. Among the best-documented are its antidiabetic, antioxidant, and gastroprotective activities. More recently, scientific interest has expanded toward its potential

influence on hematopoietic function and urinary tract disorders, highlighting several emerging areas of research that extend beyond oncology [2, 27, 28, 29, 30].

5. Antidiabetic Properties and Effects on Glucose Metabolism

Although the anticancer potential of *A. muricata* has attracted the greatest scientific attention, increasing evidence suggests that this plant may also exert significant effects on glucose metabolism and glycemic control. In recent years, *A. muricata* has attracted considerable interest as a potential source of compounds with antidiabetic activity. Preclinical studies indicate that extracts derived from the leaves, fruits, and other parts of the plant may contribute to glucose homeostasis through multiple mechanisms, including inhibition of carbohydrate-digesting enzymes, enhancement of tissue insulin sensitivity, stimulation of glucose uptake by peripheral tissues, and protection of pancreatic β-cells against oxidative damage [2]. One of the most extensively documented antidiabetic mechanisms of *A. muricata* is the inhibition of α-amylase and α-glucosidase activity. In vitro studies have demonstrated that leaf extracts reduce the activity of these enzymes, which may contribute to the attenuation of postprandial hyperglycemia. Additional support for this effect comes from in vivo studies reporting reductions in blood glucose levels, improved glucose tolerance, and decreased insulin resistance [2, 31].These effects may be partially attributable to the presence of flavonoids and other phenolic compounds, which possess antioxidant and glucose-lowering properties. Studies in diabetic rats demonstrated that *A. muricata* extracts improved glycemic control, increased serum insulin levels and β-cell function, and reduced insulin resistance. These effects were accompanied by attenuation of oxidative stress and inflammation, modulation of carbohydrate-metabolizing enzymes, upregulation of the PI3K/AKT pathway, and increased expression of the anti-apoptotic gene *Bcl2* in hepatic and pancreatic tissues, suggesting protection against β-cell apoptosis and preservation of pancreatic function [32]. Moreover, *A. muricata* extracts have been suggested to exert beneficial effects on hepatic glucose metabolism and the regulation of glycolysis and gluconeogenesis. Despite these promising findings, the available evidence is derived predominantly from experimental studies. Consequently, further clinical investigations are required to confirm the efficacy and safety of *A. muricata* in patients with diabetes mellitus [33].

6. Antioxidant Properties

Antioxidant activity represents one of the most extensively investigated biological properties of *A. muricata*. Various parts of the plant, including the leaves and fruits, have been shown to

be rich sources of phenolic compounds and flavonoids capable of scavenging reactive oxygen species and mitigating oxidative stress. In vitro studies have confirmed the strong antioxidant potential of *A. muricata* extracts, which is thought to be associated with their high content of phenolic compounds and flavonoids, including rutin, quercetin, catechin, naringenin, gallic acid, vanillin, and eugenol. Antioxidant activity has been demonstrated using DPPH, ABTS, and ferric-reducing antioxidant power (FRAP) assays, while additional studies have shown protective effects against oxidative damage in biological systems, including antihemolytic activity in erythrocytes [27, 34]. Experimental studies conducted in vivo have also demonstrated that *A. muricata* extracts may enhance endogenous antioxidant defenses by increasing the activity of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, while reducing lipid peroxidation markers, thereby improving the oxidative–antioxidative balance under conditions of oxidative stress. The antioxidant properties of *A. muricata* may partially account for several of its other reported biological effects, including protective actions toward various tissues and organs. Current evidence suggests that this plant represents a valuable source of natural antioxidants; however, further clinical studies are necessary to fully assess its therapeutic potential [20].

7. Anti-Ulcer Properties

Gastroprotective activity has emerged as another well-documented biological property of *A. muricata*. Preclinical studies have demonstrated that leaf extracts may reduce the severity of ulcerative lesions and exert protective effects on the gastric mucosa. Experimental studies in rodents have shown significant protection against ulcers induced by ethanol, acidified ethanol, and nonsteroidal anti-inflammatory drugs, with reductions in gastric lesion area comparable to those achieved by conventional anti-ulcer agents. Furthermore, mechanistic investigations indicated that these effects are mediated, at least in part, by endogenous prostaglandins and nitric oxide, both of which play key roles in maintaining gastric mucosal integrity [35]. Additional studies demonstrated that *A. muricata* extracts enhance endogenous gastric defense systems by preserving gastric wall mucus, increasing prostaglandin E_2 and nitric oxide levels, and attenuating gastric acidity. As outlined in the previous section, *A. muricata* contains numerous antioxidant phytochemicals, and its extracts have been shown to increase the activity of antioxidant enzymes, including superoxide dismutase, catalase, and glutathione, while reducing malondialdehyde levels as a marker of lipid peroxidation. Experimental evidence further suggests the involvement of cytoprotective and anti-apoptotic pathways, including upregulation of Hsp70 and downregulation of Bax expression in gastric tissues. Although the

available findings are encouraging, most evidence derives from experimental animal studies, highlighting the need for further clinical research to establish the efficacy and safety of *A. muricata* in the prevention and treatment of peptic ulcer disease [28].

8. Other Biological Activities

Besides the better-characterized effects described above, *A. muricata* has also been reported to exhibit antiparasitic, antimalarial, hypotensive, sedative, and insecticidal properties. Collectively, these observations emphasize the remarkable diversity of biological activities attributed to this species and suggest that its therapeutic potential may extend beyond the currently best-characterized indications. Although several other biological and pharmacological effects of *A. muricata* have been reported, their comprehensive discussion falls outside the scope of this review. Nevertheless, most of these reported activities remain insufficiently explored and await confirmation in clinical settings [13]. More recently, scientific interest has expanded toward previously unexplored therapeutic applications of *A. muricata*. Emerging evidence suggests that bioactive compounds present in this plant may indirectly support hematopoietic function through antioxidant, anti-inflammatory, and immunomodulatory mechanisms that contribute to the preservation of bone marrow homeostasis and hematopoietic regulation under conditions of physiological or inflammatory stress [29]. Furthermore, recent studies have indicated a potential role of *A. muricata* in nephrolithiasis management. Experimental findings suggest that plant extracts may attenuate pathological processes associated with urinary stone formation, improve renal antioxidant defenses, and contribute to protection against oxidative stress- and inflammation-related renal injury [30]. In summary, *A. muricata* is characterized by broad-spectrum biological activity. Taken together, the available evidence indicates that *A. muricata* possesses a wide range of pharmacological properties extending beyond its anticancer effects, including antidiabetic, antioxidant, gastroprotective, and organ-protective activities. More recent studies have also highlighted its potential relevance to hematopoietic support and nephrolithiasis management. Nevertheless, the majority of currently available evidence is derived from preclinical studies, underscoring the need for further clinical investigations to establish its therapeutic significance more comprehensively [13].

Conclusion

A. muricata is a medicinal plant characterized by a rich phytochemical composition and a broad spectrum of biological activities. Current evidence indicates that its extracts and bioactive

constituents exhibit anticancer, antidiabetic, antioxidant, and gastroprotective properties through multiple molecular mechanisms, including modulation of oxidative stress, apoptosis, inflammation, cellular metabolism, and signal transduction pathways. Among the reported pharmacological effects, anticancer activity remains the most extensively investigated. However, despite promising results obtained in experimental and computational studies, the available clinical evidence remains limited. Similar limitations apply to other therapeutic applications of *A. muricata*, including its potential roles in glucose metabolism, gastric protection, hematopoietic support, and nephrolithiasis management. Overall, *A. muricata* represents a promising source of biologically active compounds with potential therapeutic relevance. Nevertheless, further studies are required to establish the efficacy, safety, pharmacokinetic profile, and clinical applicability of *A. muricata*-derived preparations in human health and disease.

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Author's contribution

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