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REVIEW OF PHARMACOLOGICAL AND MEDICINAL PROPERTY OF ANNONA MURICATA L.

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ABSTRACT

Annona muricata L. belongs to the Annonaceae family and is a fruit tree that has been traditionally used for many years. Also known as soursop, graviola, and guanabana, Annona muricata L. is an evergreen plant primarily found in tropical and sub-tropical regions around the world. In tropical regions, extracts from Annona muricata L. have been traditionally employed to treat various conditions such as fever, diabetes, and cancer. Over 100 chemical compounds have been identified and isolated from this plant, with the most significant ones being acetogenins, phenols, and alkaloids. Different parts of the Annona muricata plant exhibit a wide range of ethnomedicinal activities, and indigenous communities in Africa and South America extensively utilize this plant in their folk medicine practices. Research studies have unveiled several activities, including anticancer, antiparasitic, antimalarial, antiarthritic, anticonvulsant, and antidiabetic effects. Therefore, further investigation is required to determine the extent of these effects, mechanisms of action, therapeutic dosage, long-term safety, and potential side effects. More than 120 Annonaceae acetogenins have been isolated from the leaves, seeds, barks, roots, and fruits of the graviola plant. Considering the extensive research conducted on Annona muricata leaves, this review aims to provide a comprehensive overview of its pharmacological and medicinal activities."

KEYWORDS: Annonaceae, Acetogenins, Pharmacological activities, Toxicological activity, biological activities.

INTRODUCTION

The use of natural ingredients for treating various diseases is currently on the rise. Plants serve as a rich source of natural ingredients that are extensively utilized in medicinal applications. The compounds present in plants play a crucial role in their effectiveness against different disease conditions, and studies can be conducted to identify these active compounds and determine their pharmacological activities against diseases [1] (Moghadamtousi, S.Z., 2015).

Numerous studies have been carried out on plants, their constituents, and the pharmacological activities associated with them. Annona muricata leaves, commonly known as soursop, belong to the Annonaceae family, which comprises over 13 genera and 2300 species. Annona muricata leaves contain various compounds with pharmacological activities. This plant is widely cultivated in tropical and subtropical regions, including Southeast Asia, South America, and the rainforests of Africa. It produces edible fruits throughout the year and is commonly used in traditional medicine for treating skin diseases, respiratory diseases, fever, bacterial infections, diabetes, hypertension, and cancer [1, 2] (Moghadamtousi, S.Z., 2015; De Souza, E.B.R., 2009).

Different parts of Annona muricata exhibit different activities. The seeds are known to combat parasitic infections, the fruit is used for treating arthritis, nervous disorders, and diarrhea, while the leaves are employed in the treatment of cystitis, headaches, insomnia, and cancer [3] (Wele, A., 2004).

The primary active components of A. muricata include acetogenins, alkaloids, and flavonoids [4] (Coria-Tellez, A.V., 2018). Analysis of A. muricata leaf extract has revealed the presence of secondary metabolites such as flavonoids, saponin, coumarins lactones, anthraquinones, glycosides, tannins, and phytosterols [5] (Gavamukulya, Y., 2014)

BOTANICAL DISCREPTION

A. Muricata is commonly known as soursop in English, graviol in Portuguese, and guanabana in Latin American Spanish. It belongs to the genus Annona within the Annonaceae family, under the order Magnoliales and the division Magnoliophyta. Among the over 70 species within the genus Annona, A. muricata is the most widely cultivated. It is also known as A. bonplandiana Kunth in some contexts.

The soursop tree typically reaches a height of 5-10 meters and has a diameter of 15-83 centimeters, with low branches. While it tends to bloom and bear fruit throughout

the year, there are more distinct seasons depending on the altitude. It is distributed in tropical regions of Central and South America, Western Africa, and Southeast Asia, at altitudes below 1200 meters above sea level. The optimal temperature range for its growth is between 25 and 28 degrees Celsius, with relative humidity ranging from 60% to 80%, and annual rainfall above 1500mm. The flesh of the fruit is white and creamy, characterized by a distinct aroma and flavor [6] (Pinto et al., 2005).

In Mexico [7] (Ojeda et al., 2007) and Nicaragua [8] (Benavides, 2003), the average weight of the fruit ranges between 0.4 and 1.0 kg. Each fruit may contain 55-170 black seeds. A. muricata is also referred to as Nangka Beland or sirsak in Indonesia, and it has various traditional names such as Annona, araticum, sauresack, taggannona, and zuurzak. It is classified as a fruit-bearing plant within the Plantae kingdom, Angiospermae division (Magnoliophyte), Magnolid class, Magnoliales order, Annonaceae family, and Annona genus [6, 12] (Pinto et al., 2005; Gavamukulya, Y., 2017)

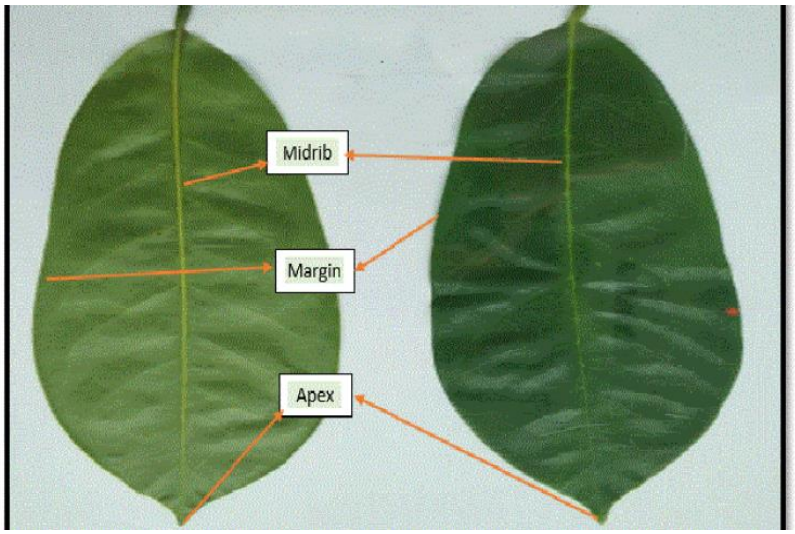

Figure 1: Leaves of A. muricata with an obovate, oblate, and acuminate shape. The leaf surface dark green

Figure 2: The fruit are dark green and prickly

Figure 3: The flower petals are thick and yellowish. The Outer petals meet at the edge without over lapping and broadly ovate, tapering to a point with a heart shaped base. The inner petals are oval-shaped and overlap

Annona muricata, commonly known as soursop, has been extensively utilized in the treatment of various disorders, including parasitic infections, inflammation, diabetes, and cancer [13] (Nugraha, A.S., 2019). In traditional medicine, all parts of the A. muricata plant are used, with the leaves, stem bark, roots, and seeds being the primary medicinal ingredients [14] (Badrie, N., 2010). The leaves of A. muricata are employed in the treatment of headaches, insomnia, cystitis, and cancer, while the seeds are used to address parasitic infections [6] (Pinto et al., 2005). Additionally, the fruit of A. muricata is utilized for treating diarrhea and neuralgia, eliminating worms and parasites, increasing milk production in lactating women, and reducing fever [15] (Pieme, A.A., 2014)."

PHYTOCHEMISTRY

Phytochemicals

A total of 212 bioactive compounds have been reported to be found in Annona muricata. These compounds, along with their structures and corresponding biological activities, have been compiled and listed in a review [16] (Coria-Tellez A. et al., 2016). Among the various organs of the plant studied, the leaves and seeds have received the most attention, likely due to their extensive traditional use. Acetogenins are the predominant compounds, followed by alkaloids, phenols, and other compounds.

Acetogenins

More than 120 acetogenins have been identified in various tissues of A. muricata, including leaves, stem, bark, seeds [17] (Chang FR et al., 2003), pulp [18] (Ragasa CY et al., 2012), and fruit peel [14] (Champy P et al., 2005). Acetogenins are characterized by a long aliphatic chain of 35-38 carbon atoms bonded to a gamma-lactone ring, with beta-unsaturated methyl (ketolactone) substitutions at the terminal position. They may also contain one or two tetrahydrofuran (THF) rings along the hydrocarbon chain, along with various oxygen groups such as hydroxy, acetoxyls, ketones, and epoxy. The majority of acetogenins found in A. muricata contain a THF ring. Extensive phytochemical evaluations on different parts of the A. muricata plant have revealed the presence of various phytoconstituents and compounds. Furthermore, the fruit of A. muricata contains significant amounts of essential minerals such as potassium (K), calcium (Ca), sodium (Na), copper (Cu), iron (Fe), and magnesium (Mg), suggesting that regular consumption of A. muricata fruit can provide essential nutrients and elements to the human body [19] (Gyamfi, K. et al., 2011)

Alkaloids

Alkaloids are naturally occurring compounds that contain basic nitrogen atoms. In A. muricata, the reported alkaloids primarily belong to the isoquinoline, aporphine, and protoberberine types. The most abundant alkaloids in A. muricata are reticuline and coreximine [20] (Leboeuf M et al., 1981). Among the various plant parts, the leaves have been found to contain the highest concentration of alkaloids [21] (Matsushige A et al., 2012). However, alkaloids have also been identified in the roots, stems, and fruits of the plant [22] (Hasrat J et al., 1997).

Phenolic compound

A total of thirty-seven phenolic compounds have been reported to be present in A. muricata. Among these, important phenolic compounds found in A. muricata leaves include quercetin [23] (Nawwar A et al., 2012) and gallic acid [24] (Correa Gordillo J et al., 2012). In the pulp of A. muricata, the presence of flavonoids and lipophilic antioxidant compounds such as tocopherols and tocotrienols has been reported. Phenolic compounds are considered the major phytochemicals responsible for the antioxidant activity [25] (George VC et al., 2015)

Other compounds

In addition to the previously mentioned compounds, other compounds such as vitamins, carotenoids, amides, and cyclopeptides have also been identified in A. muricata. Vitamins and carotenoids have been found in the leaves, seeds, and fruit pulp [26] (Vijayameena C et al., 2013). The presence of the amide N-P-Coumaroyl tyramine [27] (Wu F et al., 1995) and cyclopeptides [28] (Wele A et al., 2005) has been reported in the seeds, and these compounds have demonstrated anti-inflammatory and anti-tumor effects. Moreover, thirty-seven volatile compounds, primarily aromatic and aliphatic esters, have been identified in the fruit pulp of A. muricata [29] (Cheong K et al., 2011). Furthermore, eighty essential oils, predominantly sesquiterpene derivatives, have been identified in the leaves [30] (Thang TD et al., 2013) [31] (Owolabi MS et al., 2013).

BIOLOGICAL ACTIVITIES

Anticancer Activity

The isolates from A. muricata have been extensively studied for their biological and pharmacological activities, particularly their anti-inflammatory and anticancer properties. The annonaceous acetogenins, a class of natural compounds unique to the Annonaceae family, have been shown to possess diverse bioactivities, including immunomodulatory, anti-inflammatory, anticancer, antiparasitic, insecticidal, antimicrobial, neurotoxic, antileishmaniasis, and antioxidant effects. Annonacin is the predominant acetogenin found in A. muricata leaves [32] (Yuan et al., 2003). Both the leaves and stems of A. muricata have demonstrated cytotoxicity against cancer cells, attributed to these acetogenins. Importantly, these compounds exhibited minimal toxicity towards normal cells while displaying high toxicity towards cancerous cells [33] (Villo, 2008). The mechanism of action of annonacin involves the suppression of mitochondrial complex I, leading to ATP depletion [34] (Yuan et al., 2003). Additionally, it represses ubiquinone-linked NADH oxidase, a crucial component expressed on the membrane of cancer cells, which contributes to the elimination of cancer cells and inhibition of cell proliferation [35] (Woo et al., 1999)

Antioxidant Activity

The excessive generation of intracellular reactive oxygen species (ROS) is a precursor to oxidative stress, which can lead to metabolic deficiencies and cellular death through biochemical and physiological damage [36] (Chance B et al., 1979). Tests using DRSA, FRAP, and HRSA on aqueous and methanolic leaf extracts of A. muricata have revealed significant antioxidative activities in both extracts, along with DNA protective effects against H2O2-induced toxicity [37] (George VC et al., 2015). The identification of antioxidants from natural products has gained significant interest in recent studies due to their remarkable ability to counteract the destructive effects of ROS [38] (Liao JC et al., 2012). The seeds and leaves of the A. muricata plant have been reported to possess enzymatic antioxidants, including catalase and superoxide dismutase, as well as non-enzymatic antioxidants such as vitamin C and E [39] (Vijayameena C et al., 2013). The antioxidant activity of A. muricata leaves has been found to be stronger compared to A. squamosa and A. reticulata species, as demonstrated through various in vitro models, including ABTS, nitric oxide, and hydroxyl radicals [40] (Baskar R et al., 2007). These findings strongly indicate the potential use of A. muricata as a natural source of antioxidants

Antihypertensive Activity

In order to assess the antihypertensive properties of A. muricata leaves, a study administered an aqueous leaf extract (at doses ranging from 9.17 to 48.5 mg/kg) to normotensive Sprague–Dawley rats. The results revealed that the treatment with the leaf extract significantly reduced blood pressure in a dose-dependent manner, while heart rates remained unaffected. This effect was proposed to be mediated through peripheral mechanisms, potentially involving the antagonism of Ca2+. (Nwokocha CR et. al., 2012)

Antiparasitic Activity

Protozoal infections cause debilitating diseases such as leishmaniasis and trypanosomiasis, which have affected a significant proportion of the global population. A promising antileishmanial effect was reported against L. braziliensis and L. panamensis species, with a higher toxicity effect compared to Glucantime, which was used as a positive control [42] (Jaramillo M et al., 2000). A bioassay-guided investigation on the seeds of A. muricata against two forms of L. chagasi, namely promastigote and amastigote, resulted in the isolation of the bioactive

compounds annonacinone and corossolone, which exhibited the same bioactivity [43] (Vila-Nova NS et al., 2011). The development of resistance to empirically discovered drugs represents a significant challenge in the treatment of protozoal diseases. Furthermore, the methanolic extract of A. muricata seeds demonstrated significant antiparasitic activity against the infective larvae of Molinema dessetae, and this activity was attributed to its isolated acetogenins [44] (Osorio E et al., 2007)

Other Biological Activities

In addition to its anti-parasitic and anticancer properties, the leaves of A. muricata have been extensively investigated for various pharmacological and biological properties. Bento et al. demonstrated significant antiulcer activity of A. muricata leaves against lesions [45] (Bento et al., 2016). Another study revealed that the leaves of A. muricata possess enzymatic antioxidants such as superoxide dismutase and catalase, along with non-enzymatic antioxidants like vitamin C and vitamin E [39] (Vijayameena et al., 2013). Additionally, the ethyl acetate leaf extract of A. muricata demonstrated remarkable wound healing properties [46] (Moghadamtousi et al., 2015). The aqueous and ethanol extracts of A. muricata leaves exhibited significant antioxidant activity as determined by the DPPH test [47] (Gavamukulya et al., 2014).

Furthermore, A. muricata leaves have been found to exhibit a wide range of activities, including anti-plasmodial, anti-arthritic, anti-protozoal, antibacterial, antimicrobial, anticonvulsant, antidiabetic, hypolipidemic, antihypertensive, antiparasitic, insecticidal, gastroprotective, molluscicidal, hepatoprotective, and bilirubin-lowering effects [43] (Moghadamtousi et al., 2015).

5.TOXICOLOGICAL STUDIES

Both formal and informal information is available regarding the association of A. muricata consumption with the occurrence of atypical Parkinson's disease [48, 49] (Caparros-Lefebvre D., 2002, Lannuzel A., 2006). The reported toxicity of the extracts varies depending on the specific plant part used and the solvent employed. Several studies have been conducted to assess the acute toxicity and neurotoxicity associated with these extracts. However, in 2010, it was concluded that the occurrence of atypical Parkinson's disease is not directly linked to the consumption of extracts from the Annonaceae family, which includes A. muricata.

Acute toxicity

The aqueous extracts of A. muricata showed an LD50 (median lethal dose) greater than 5 g/kg, while the methanolic and ethanolic extracts of leaves, flowers, and pulp exhibited an LD50 greater than 2 g/kg [50] (Sousa OV., 2010), which is considered non-toxic according to the OECD guidelines [51] (OECD Guidelines., 2016). The median lethal dose of the aqueous extract of leaves exceeds the expected human consumption, which is approximately 211 mg/kg per day based on an average person consuming one cup of tea three times a day [52] (Arthur F., 2011). Therefore, for a human to reach a lethal dose of A. muricata leaf infusion, it would require consuming more than 71 cups of tea per day. Regarding organ toxicity, doses greater than 5 g/kg of the aqueous extract have been reported to potentially cause kidney damage, whereas a 1 g/kg dose showed hypoglycemic and hyperlipidemic properties [52] (Arthur F., 2011). The most toxic extracts reported are methanol extracts of the pericarp, fruit pulp, or seed [53] (Boyom FF., 2011). A study evaluating the consumption of A. muricata pulp for 28 days showed no effects on blood hematology and serum biochemistry [54] (Syahida M., 2012). Another study that assessed the toxicity of crude leaf extract and its flavonoid and acetogenins-enriched extracts found that the acetogenins-enriched extract was more toxic than the others [55] (Yang C, 2015). However, this study suggested that the whole extract could possess similar bioactive properties as its fractions or isolated constituents, but without their associated toxicity.

Neurotoxicity

The association between the consumption of A. muricata fruit and homemade preparations and the occurrence of atypical parkinsonism in the Caribbean island of Guadeloupe was based on a case study published in 1999 [48] (Caparros-Lefebvre D., 2002). This association has also been reported among patients from New Caledonia and Caribbean individuals living in London [57] (Shaw CA., 2008). Subsequent studies aimed to assess the neurotoxic effects of the main bioactive compounds in A. muricata, specifically alkaloids and acetogenins. It became evident that certain isolated compounds induce neurotoxicity and neurodegenerative diseases in murine models. Reticuline and coreximine alkaloids, as well as solamin, annonacinone, isoannonacinone, and annonacin acetogenins, were found to be toxic to dopaminergic cells by impairing energy production [58, 59, 60, 49, 61] (Hollerhage M., 2009., Champy P., 2003., Lannuzel A., 2002., Lannuzel A., 2006., Escobar-khonbiker M., 2007). Annonacin demonstrated greater toxicity compared to the pesticide rotenone, which was used as a positive control. Studies reported that in murine models, annonacin enters the brain parenchyma, decreases ATP levels, and

induces neurodegeneration in the basal ganglia [62, 49] (Champy P., 2003., Lannuzel A., 2006.). However, according to these authors, this neurodegeneration did not result in changes in behavior or locomotor activity in rodents. In terms of neurotoxicity, seven acetogenins were evaluated using mesencephalic dopaminergic neurons, rat striatal neurons, and laboratory rats. Annonacin and reticuline, which are the most abundant acetogenin and alkaloid in A. muricata, respectively, were found to be neurotoxic [62] (Champy P., 2003). Annonacin exhibited approximately 1,000 times greater toxicity to neuronal cell cultures compared to reticuline, and it was 100 times more potent than 1-methyl-4-phenylpyridinium (MPP), a known neurotoxin that induces parkinsonism in humans and animal models. This study involved intravenous administration of isolated annonacin to laboratory rats, and the dosage administered to the rats was determined based on estimating the amount of annonacin a human would consume by ingesting fruit or canned nectar daily for one year. Neurotoxicity studies of annonacin suggest that prolonged exposure to this compound is necessary to observe its effects in murine models, while pharmacokinetic studies estimated low bioavailability of this compound. In 2010, AVIS (l'Agence Française de Sécurité des Aliments) issued a statement concluding that based on available experimental data, it is not possible to establish a direct link between cases of atypical parkinsonian syndromes observed in Guadeloupe and the consumption of species belonging to the Annonaceae family.

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