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A Review on a Miracle Plant *Annona muricata* L.

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Abstract-

Annona muricata L.is a member of the Annonaceae family and is a fruit tree with a long history of traditional use. *A. muricata* L, also known as soursop, graviola and guanabana, is an evergreen plant that is mostly distributed in tropical and subtropical regions of the world. *Soursop* extracts have been identified in tropical regions to traditionally treat diverse conditions ranging from fever to diabetes and cancer. More than 200 chemical compounds have been identified and isolated from this plant, the most important being alkaloids, phenols and acetogenins.. A wide array of ethnomedicinal activities is contributed to different parts of *A. muricata*, and indigenous communities in Africa and South America extensively use this plant in their folk medicine. Studies have revealed activities, including anticancer, anticonvulsant, anti-arthritic, antiparasitic, antimalarial, hepatoprotective and antidiabetic activities and therefore, these crude extracts and isolated compounds need to be further investigated to define the magnitude of the effects, optimal dosage, and mechanisms of action, long-term safety, and potential side effects. More than 120 annonaceous acetogenins have been isolated from leaves, barks, seeds, roots and fruits of Graviola plant. Phytochemical studies reveal that annonaceous acetogenins are the major constituents of Soursop. In view of the immense studies on *A. muricata* L, this review strives to unite available information regarding its phytochemistry, traditional uses and biological activities.

Keywords: *Annonaceae*, Phytochemicals, Acetogenin, Phytochemistry, Ethanomedical.

Introduction-

Medicinal plants have been used for the treatment of illness since before recorded history. The sacred Vedas dating back between 3500 B.C and 800 B.C gives many references of the utilization of the medicinal plants. "Virikshayurveda" is one of the remotest works in the traditional herbal medicine which was compiled even before the beginning of Christian era. "Rig Veda" is one of the oldest literatures which was written around 2000 B.C. and mentions the use of Cinnamon (Cinnamomum verum), Ginger (Zingiber officinale), Sandalwood (Santalum album) etc was used not only in the religious ceremonies but also in the medical preparations(Prasad Palthur M, Sajala Palthur, Ss, Suresh Kumar)

According to world health organization (WHO), greater than 80% of the total world's population depends on the traditional medicines in order to satisfy their primary health care needs. The chemical substances of the medicinal plants which have the capacity of exerting a physiologic action on the human body were the primary features. It also suggested in improving the technologies for cultivation of medicinal plants. The bioactive compounds of plants such as alkaloids, flavonoids, tannins and phenolic compounds were considered to be most important. The phytochemical research that has been done based on the ethno-pharmacological information forms the effective approach in the discovery of new anti-infective agents from higher plants (Duraipandiyan V. et. al., 2003)

Annona muricata L. is a species of the Annonaceae family that has been widely studied in the last decades due to its therapeutic potential. Plant used in treating diseases is as old as civilization and traditional medicines are still a major part of habitual treatments of different maladies. The medicinal uses of the Annonaceae family were reported long time ago and since then, this species has attracted the attention due to its bioactivity and traditional uses. Chronic degenerative diseases have reached epidemic proportions and are considered as a serious health problem; therefore, the treatments of these diseases are of clinical importance. In recent times, folk medicine has taken an important place especially in developing countries where limited health services are available. Medicinal plants are considered as the basis for health preservation and care worldwide. The absence of scientific evaluation of medicinal plants to validate their use may cause serious adverse effects (World Health Organization).

A. muricata commonly known as Graviola or soursop belongs to the family of Annonaceae and is the most tropical semi deciduous tree with the largest fruits of the Annona genus (Ukwubile CA., 2003). It is widely distributed and native to subSaharan Africa countries. Often the different components in an herb have synergistic activities or buffer toxic effects. This study therefore aimed to determine the phytochemical composition, anti-oxidant activity as well as determine the in vitro anti-

cancer potential of ethanolic and water leaves extracts of *A. muricata* from Eastern Uganda, as an alternative medicine in the prevention and treatment of cancer and other oxidative stress related diseases.

Botanical Description and Distribution

A. muricata L., commonly known as soursop, graviola, guanabana, paw-paw and sirsak, is a member of the Annonaceae family comprising approximately 130 genera and 2300 species (Mishra, S. et. al., 2013) *A. muricata* is native to the warmest tropical areas in South and North America and is now widely distributed throughout tropical and subtropical parts of the world, including India, Malaysia and Nigeria (Adewole, S.O. and Caxton-Martins, E.A., 2006)

A. muricata is an evergreen, terrestrial, erect tree reaching 5–8 m in height and features an open, roundish canopy with large, glossy, dark green leaves. The tree has larger individual yellow flowers on woody stalks (pedicels). Three outer petals are broadly ovate with heart-shaped base, inner 3 also large, elliptical and rounded. The edible fruits of the tree are large, heart-shaped and green in color, and the diameter varies between 15 and 20 cm. *A. muricata* is an evergreen, terrestrial, erect tree reaching 5–8 m in height and features an open, roundish canopy with large, glossy, dark green leaves. Flowers are large and solitary, yellowish or greenish-yellow in color. The edible fruits of the tree are large, oval or heart-shaped and green in color, and frequently irregular lopsided composite soursop fruit is derived from the fusion of many fruit lets and can weigh more than 4 kg. And the diameter varies between 15 and 20 cm the fruit pulp consists of white fibrous juicy segments surrounding an elongated receptacle. (De Souza, R. et. al., 2009)

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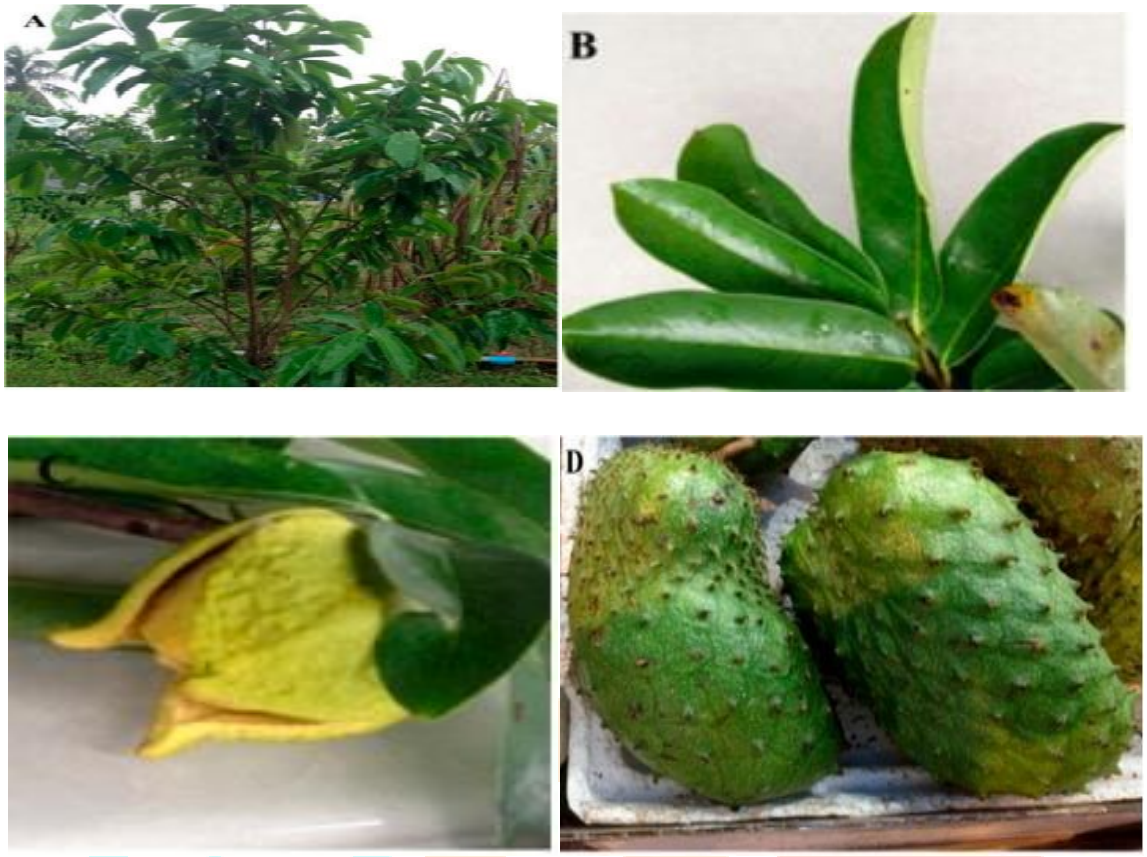

Figure1. (**A**) *Annona muricata* L.; the appearance of the (**B**) leaves; (**C**) flowers and (**D**)fruits

Ethnomedicinal Uses

All portions of the *A. muricata* tree, similar to other *Annona* species, including *A. squamosa* and *A. reticulata* are extensively used as traditional medicines against an array of human ailments and diseases, especially cancer and parasitic infections. In tropical Africa, the plant is used as an astringent, insecticide and piscicide agent and to treat coughs, pain and skin diseases (Adewole, S. and Ojewole, J.2009). The fruit is used as natural medicine for arthritic pain, neuralgia, arthritis, diarrhea, dysentery, fever, malaria, parasites, rheumatism, skin rushes and worms, and it is also eaten to elevate a mother's milk after childbirth (Adewole, S.O. et. al., 2006). The crushed seeds are believed to have anthelmintic activities against external and internal worms and parasites. In India, the fruit and flower are employed as remedies against catarrh, while the root-bark and leaves are believed to have antiphlogistic and anthelmintic activities (Watt, J.M. and Breyer-Bnodwijk, M. 1962.). The leaves are employed to treat cystitis, diabetes, headaches and insomnia. Moreover, internal administration of the leaf's decoction is believed to exhibit anti-rheumatic and neuralgic effects, whereas the cooked leaves are topically used to treat abscesses and rheumatism (De Sousa et.al. 2010.). In South America and tropical Africa, including Nigeria, leaves of *A. muricata* are deployed as an ethnomedicine against tumors and cancer. In Malaysia, the crushed leaf mixture of *A. muricata* together with

A. squamosa and *Hibiscus rosa-sinensis* is used as a juice on the head to protect against fainting (Ong, H. and Norzalina, J. 1999). In addition, the anti-inflammatory, hypoglycemic, sedative, smooth muscle relaxant, hypotensive and antispasmodic effects are also attributed to the leaves, barks and roots of *A. muricata* (Mishra, S, et. al., 2013).

Phytochemistry

Phytochemicals

Two hundred and twelve bioactive compounds had been reported to be found in *A. muricata*. These 212 bioactive compounds, their structures and corresponding biological activities have been enlisted in the review (Coria-Tellez A. et. al., 2016). Leaves and seeds were the main plant studied organs, probably because they are the most traditionally used. The predominant compounds are acetogenins followed by alkaloids, phenols and other compounds.

Acetogenins

More than 120 acetogenins have been identified in ethanolic, methanolic or other organic extracts of different organs and tissues of *A. muricata* such as leaves, stems, bark, seeds (Chang FR et.al., 2003), pulp (Ragasa CY et.al., 2012), and fruit peel(Champy P, et.al.,2005). Acetogenins are characterized by a long aliphatic chain of 35–38 carbons bonded to a g-lactone a ring, terminally substituted by b-unsaturated methyl (ketolactone), with one or two tetrahydrofurans (THF) located along the hydrocarbon chain and a determined number of oxygen groups (hydroxyl, acetoxyls, ketones, epoxy). Most of the acetogenins found in *A. muricata* contain a THF ring, Extensive phytochemical evaluations on different parts of the *A. muricata* plant have shown the presence of various phytoconstituents and compounds, including alkaloids (ALKs) (Yang, C. et al., 2015). Identification of phenolic compounds in soursop (*Annona muricata*) pulp by high-performance liquid chromatography with diode array and electrospray ionization mass spectrometric detection.cyclopeptides (CPs) and essential oils . However, *Annona* species, including *A. muricata*, have been shown to be a generally rich source of annonaceous acetogenin compounds (AGEs) (Rupprecht et.al., 1990). The presence of different major minerals such as K, Ca, Na, Cu, Fe and Mg suggest that regular consumption of the *A. muricata* fruit can help provide essential nutrients and elements to the human body (Gyamfi, K. et. al., 2011)

Alkaloids

Alkaloids are naturally occurring compounds containing basic nitrogen atoms.). The alkaloids reported in *A. muricata* are mainly of the isoquinoline, aporphine and protoberberine type. The most abundant in *A. muricata* are reticuline and coreximine (Leboeuf M et.al., 1981), and leaves contain the higher alkaloid concentration (Matsushige A et.al., 2012) , although they have also been found in roots, stems and fruit(Hasrat J et.al., 1997). Previous studies have shown that alkaloids isolated from *Annona* species possess

an affinity for the 5-HT1A receptors *in vitro* and participate in dopamine biosynthesis (Hasrat Jet.al., 1997). Thus, it has been proposed that alkaloids derived from the *Annona* could induce antidepressant-like effects. Neurotoxic effects have also been reported for some alkaloids, and suggested that neuronal death occurred by apoptosis (Lannuzel A et.al., 2002.)

Phenolic compounds

Thirty seven phenolic compounds have been reported to be present in *A. muricata*. The important phenolic compounds found in *A. muricata* leaves include quercetin (Nawwar M et.al.,2012) and gallic acid (Correa-Gordillo J et.al., 2012). The presence of flavonoids and lipophilic antioxidant compounds such as tocopherols and tocotrienols has been reported to be present in the pulp. Phenolic compounds are considered as the major phytochemicals responsible for the antioxidant activity (George VC et.al., 2015)

Other compounds

Other compounds such as vitamins, carotenoids, amides, and cyclopeptides have also been identified in *A. muricata*. Vitamins and carotenoids have been found in leaves, seeds and fruit pulp(Vijayameena C et.al., 2013). The presence of the amide N-p-coumaroyl tyramine(Wu F, et.al.,1995) and cyclopeptides (Wélé A et.al., 2005) have been reported in the seeds and showed to have anti-inflammatory and anti-tumor effects. On the other hand, 37 volatile compounds have been identified in the fruit pulp of *A. muricata*, and most of these compounds are aromatic and aliphatic esters (Cheong K et. al., 2011). In addition, 80 essential oils, mainly sesquiterpenes derivates (Thang TD et. al., 2013), have been identified in the leaf (Owolabi MS et. al., 2013).

Biological Activities

Anticancer Activity

The isolates have been investigated on their biological and pharmacological activities especially anti-inflammatory and anticancer activities. The annonaceous acetogenins are a class of natural products that distinctively belong to Annonaceae family. These bioactive compounds exhibited an array of bioactivities such as immunomodulatory, anti-inflammatory, anticancer, antiparasitic, insecticidal, antimicrobial, neurotoxic, antileishmaniasis, and antioxidant. Annonacin is the ubiquitous acetogenin present in *A. muricata* leaves (Yuan et al., 2003). The leaves, as well as the stems of *A. muricata*, exhibited active cytotoxicity against cancer cells, owing to these acetogenins, which did not show toxicity toward normal cells, but highly toxic to cancerous cells (Villo, 2008). The annonacin displayed its toxic effects on the cell by the suppression of mitochondrial complex I which resulted in the ATP depletion (Yuan et al., 2003) and the repression of ubiquinone-linked NADH oxidase that is vital expression in cancer cells membrane which will kill the cancer cell and arrest the proliferation of cells (Woo et al., 1999).

Antioxidant Activity

Immoderate generation of intracellular reactive oxygen species (ROS) is a precursor of oxidative stress which subsequently catalyzes metabolic deficiency and cellular death through biochemical and physiological lesions (Chance B et.al., 1979). DRSA, FRAP and HRSA tests on aqueous and methanolic leaf extracts of *A. muricata* revealed the marked antioxidative activities of both extracts accompanied with DNA protective effects against H2O2-induced toxicity (George VC et.al., 2015). The identification of antioxidants from natural products has become a matter of great interest in recent studies for their noteworthy role in nullifying the destructive effects of ROS (Liao JC et. al., 2012). The seeds and leaves of the plant are reported to possess enzymatic antioxidants, including catalase and superoxide dismutase, and non-enzymatic antioxidants, including vitamin C and E (Vijayameena C et. al., 2013). The antioxidant activity of the *A. muricata* leaves was found to be stronger than *A. squamosa* and *A. reticulata* species as shown through different *in vitro* models, such as ABTS, nitric oxide and hydroxyl radicals (Baskar R et. al., 2007). These findings strongly suggest the potential use of *A. muricata* as a natural source of antioxidants.

Antihypertensive Activity

To evaluate the antihypertensive properties of *A. muricata* leaves, aqueous leaf extract (9.17-48.5 mg/kg) was administered to normotensive Sprague–Dawley rats. The results demonstrated that treatments of rats with the leaf extract significantly decreased blood pressure in a dosedependent manner without affecting heart rates. This effect was suggested to be induced through peripheral mechanisms involving the antagonism of Ca2+ (Nwokocha CR et. al., 2012)

Antiparasitic Activity

Protozoal infections because debilitating diseases, such as leishmaniasis and trypanosomiasis, which have both afflicted a noteworthy proportion of the world population. The same promising antileishmanial effect was reported against *L. braziliensis* and *L. panamensis* species with a toxicity effect higher than Glucantime, which was used as a positive control (Jaramillo M et.al., 2000). A bioassay-guided investigation on the seeds of *A. muricata* against two forms of *L. chagasi*, promastigote and amastigote, also led to the isolation of the same bioactive AGE compounds, annonacinone and corossolone (Vila-Nova NS et. al., 2011). The development of resistance to empirically discovered drugs represents a major hindrance to treatment of protozoal diseases. In addition, the methanolic extract of *A. muricata* seeds showed significant antiparasitic activity against the infective larvae of *Molinema dessetae*, and this activity was contributed to its isolated AGEs [Osorio E et.al., 2007)

Other Biological Activities

Besides the anti-parasitic and anticancer properties, the leaves of *A. muricata* have also been thoroughly investigated for other pharmacological and biological properties. Bento et al. revealed that the *A. muricata* leaves showed significant antiulcer activity against lesions (Bento et al., 2016). In another investigation, the *A. muricata* leaves were showed to possess enzymatic antioxidants; superoxide dismutase and catalase, together with the non-enzymatic antioxidants for instance vitamin C and vitamin E (Vijayameena et al., 2013). Besides that, a remarkable wound healing properties by the ethyl acetate leaf extract of *A. muricata* has been discovered by Moghadamtousi et al. (2015b). The DPPH test revealed the significant antioxidant activity of the aqueous and ethanol extracts of *A. muricata* leaves (Gavamukulya et al., 2014). In addition, *A. muricata* leaves were also found to exhibit anti-plasmodial, anti-arthritic, anti-protozoal, antibacterial, antimicrobial, anticonvulsant, antidiabetic and hypolipidemic, antihypertensive, antiparasitic, insecticidal, gastroprotective, molluscicidal, hepatoprotective, and bilirubin-lowering activities (Moghadamtousi et al., 2015a)

Conclusion

A. muricata, once studied to perfection, is surely conclusively; *A. muricata* leaf and its secondary metabolites produce anti-inflammatory, anti-cancer and other immune system related effects. In vitro and in vivo studies support the majority of the traditional uses. More than 200 phytochemicals have been identified in this plant, mainly acetogenins, alkaloids and phenols. These phytochemicals have shown pharmacological activities such as antimicrobial, antioxidant, insecticide, larvicidal, selective cytotoxicity to tumoral cells, anxiolytic, antistress, anti ulceric, wound healing, anti-jaundice, hepato protective, hypoglycemic, immunomodulatory, and antimalarial among others. Hence, future research on *A. muricata* should focus on extensive phytochemical investigations in isolating and identifying the active metabolites. Many new phytochemicals are also yet to be identified in *A. muricata*. Because the majority of the previous studies were focused on the biological activities of the plant extract, further investigations on the biochemical and physiological functions of active compounds and the detailed mechanisms underlying these activities are completely pivotal for the development of pharmaceutical and agricultural products.

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