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Review of Biological Properties, Composition and Toxicity of Annonna Muricata

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الملخص

تعرف أيضاً بجرافيولا أو (القشطة) هي شجرة فواكه استوائية تتواجد بكثرة في الغابات المطيرة في إفريقيا وأمريكا الجنوبية و جنوب شرق أسيا، استخدمها الإنسان عبر العصور كعلاج تقليدي أوكعلاج بديل لعدة أمراض، ولديها مجموعة واسعة من الفاعليات والأنشطة الطبية و يعزى ذلك لاحتوائها على مجموعة واسعة من المركبات الكيميائية بما في ذلك أشباه القلويات أو القلويدات (الاستيوجينين) والتي تمثل المركب الأساسي في هذا النبات، حيث أوضحت الدراسات السابقة أنه قد تم عزل أكثر من ١٠٠ استيوجينين غير ضار من أجزاء مختلفة من النبات مثل الأوراق واللحاء والبذوروالجذوروثمار النبتة. بالإضافة إلى ذلك تم فصل الدهون واللاكتونات والايزوكومينولينات والتي تعتبر السبب الرئيس وراء فعالية هذه النبتة. أثارت القشطة جدلاً واسعاً في الأوساط العلمية الأمر الذي أدى إلى دراسة الخواص الطبية و الفاعلية باستفاضة لهذه النبتة و أوضحت الدراسات أن المستخلصات النباتية والإيضيات الثانوية لهذا النبات لديها خصائص دوائية واستخدامات متعددة من أهمها استخدامها كعلاج للالتهابات التي تسببها البكتيريا والطفيليات خاصة الليشمانيا وأثبتت الدراسات ايضاً فاعليتها كمضادات للأكسدة ونشاط خفض نسبة الصفراء و مضاد لمرض السكري ونشاط شفاء الجروح كما تم استعمالها للتسبب بالقيء و افراغ المعدة و المساعدة على الاسترخاء و استعملت ايضاً في الصناعات الغذائية و المشروبات. بالرغم من كون الجرافيولا أظهرت آثار مضادة للسرطان في المختبر إلا أن عدم وجود دراسات كافية ووافية على البشر منع اعتبارها علاج معتمد للسرطان بالرغم من استخدامها تقليديا لهذا الغرض.

ختاماً، يلخص هذا البحث المعلومات المتعلقة بالاستخدامات التقليدية و النشاط البيولوجي و الكيمياء النباتية بالإضافة إلى دراسة حالتين في المختبرإحداهما تم فيها استخدام القشطة على خلايا سرطان البنكرياس في فئران التجارب أما الحالة الثانية تمت دراسة تأثير النبات على الجسم الحي لمريضة بسرطان الثدي .

الكلمات المفتاحية:

نبات القشطة، مركبات الاسيتوجينين، الفعالية البيولوجية للنبات، الاستخدامات التقليدية للنبات، فعالية النبات ضد السرطان.

Abstract

Annona muricata also known as a Grviola is a fruit tree with a long history of traditional use. A. muricata, has a wide array of ethnomedicinal activities and containing wide range of chemical compounds including Alkaloids (acetogenins); which represent the major constituents of A. muricata, there were more than 100 annonaceous acetogenins have been isolated from leaves, barks, seeds, roots and fruits of A. muricata. Furthermore; lipids, isoquinoline, lactones, Annomuricatina (protein), Bullatacin and Muricoreacinetc have been isolated from this plant. The plant extracts and Secondry metabolites exhibit pharmacological properties such as anti-inflammatory, antibacterial, antioxidant, antiparasitic, hepatoprotective and bilirubin-lowering, anti-diabetic, wound healing, antiobesity, immunomodulatory, and anticancer activity. The present review summarizes the information concerning the traditional uses, phytochemistry, biological activity and two case studies one in vitro on pancreatic cancer cells and other in vivo study on breast cancer that had been carried recently to assess the effects of Graviola.

Keywords:

Grviola, Acetogenins, biological activities, anticancer activity, ethnomedicinal activities.

1. REVIEW OF LITERATURE

Natural products are extensively used in population throughout history due to their pharmacological activities, they are typically complex mixtures of several chemical compounds from various classes, which are related to its toxicity and capability of moderating the biological action throughout either synergistic or antagonistic effects compared with concurrent predictable drugs[1]. Natural medicines that are produced from plants and have been extensively used as alternative and complementary medicines for health advancement. The growing intake of natural medicine has increased the concern of their safety; it has been supposed that the natural medicines are safe and side effects free. This information is appropriately not right, and often confusing[2]. According to World Health Organization (WHO), greater than 80% of the entire world's population relies on the natural medicines to satisfy their essential health care requirements. The biological activity of numerous phytochemical compounds from natural products were explained and described. These bioactive molecules for instance alkaloids, tannins, phenols and flavonoids were characterized to be most important classes regarding to activity. The phytochemical researchers depend on the ethno-pharmacological evidence systems, the effective methodology in the identify and discovery of new therapeutic agents from plants[3], Annona muricata belongs to the Annonaceae family, which is a widespread small tree having its intrinsic in Central America. Wholly parts of A. muricata tree is used as a natural

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medicine involving the seeds, roots, leafs, twigs and fruits. In general, the fruit juice and fruit are used to remove parasites and worms, enhance mother's milk after child birth, cool fever, as well as decreasing dysentery and diarrhea[4].

The main constituent of A. muricata is a annonaceous acetogenin compound, which is related to anticancer activity of the plant. Therefore, leaf extract from A. muricata are used in the studies for antitumor properties in numerous types of cancer[5].

In this review the distribution, ethnomedicinal uses of A. muricata and its biological activities and possible mechanisms of some bioactivities will be described.

Ethno-medicinal uses:

All parts of the A. muricata tree are widely used as ethnomedicines against a range of human diseases, mainly parasitic infections and cancer. The fruit is used as natural medicine for neuralgia, arthritic pain, arthritis, rheumatism, fever, diarrhea, malaria, parasites, worms and skin rushes. The leaves are active to treat diabetes, cystitis, insomnia and headaches[6].

Furthermore, oral administration of the decoction of leaves are supposed to exhibit neuralgic effects and anti-rheumatic, while topical administration of the cooked leaf is used to treat rheumatism and abscesses[7,8]. Some researchers found that the crushed seeds have anthelmintic actions against internal and external parasites and worms[9].

In tropical Africa, the whole plant is employed to treat cough as well as an astringent, pesticide, insecticide, and remove pain and skin illnesses. In India, the flowers and fruits are used as medicines against mucus, whereas the bark, root and leaves have anthelmintic and antiphlogistic activities[10]. In Malaysia, the crushed leaves mixture of A. muricata together with Hibiscus rosa-sinensis and A. squamosa is employed as a juice on the head to defend against fainting[10]. In tropical Africa, Nigeria, and South, the leaves of Graviola are arranged as an ethnomedicine against cancer and tumors[9]. In addition to traditional uses, the fruits are commonly used for the preparation of candy, beverages, ice creams, syrups and shakes[11,12].

Chemical composition:

Various phytochemical analysis studies on Graviola tree have confirmed the presence of multiple phytoconstituents as described below:

Alkaloids

A. muricata are considered to be rich in reticuline and coreximine, the highest alkaloid concentration are found the leaves[13]. The alkaloids found in A. muricata are of the isoquinoline, aporphine and protoberberine type[14]. Alkaloids isolated from Annona species possess an affinity for the 5-HT1A receptors in vitro and participate in dopamine biosynthesis , and that`s explaining the antidepressant-like effects and cytotoxic activity[14].

Acetogenins (AGEs)

They are a series of polyethers which contain either the adjacent or the non-adjacent tetrahydrofuran (THF) or tetrahydropyran (THP) ring, in addition to an α, β-unsaturated c-lactone ring[15]. However, there are five bioactive acetogenins extracted from Graviola fruit, three of them are novel compounds named annonamuricins A, B, C and annonamuricin D and one known as annonacin. Wide range of biological activities have been correlated to AGEs and the most important of which is its toxic activity against cancer cells[16].

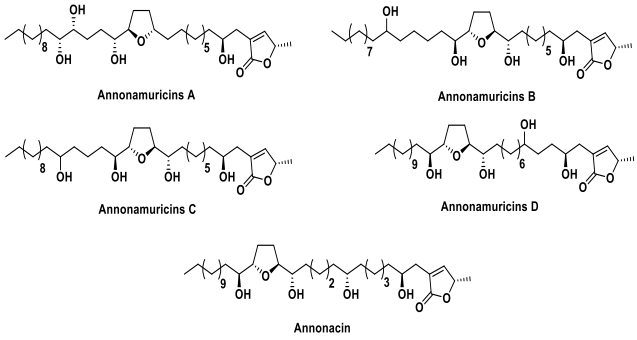


Figure 1: Structures of annonaceous acetogenins isolate from Graviola fruit

Phenolic compounds:

More than thirty phenolic compounds have been isolated from to A. muricata and considered to be responsible for the antioxidant activity of Graviola, the most important of which is quercetin that is found mainly in leaves[17].

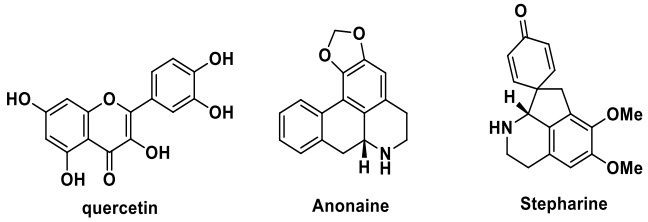


Figure 2: Structure of phenolic compounds isolated from Graviola fruit.

Other compounds:

Other compounds such as vitamins, amides, carotenoids, megastigmanes and cyclopeptides have also been detected in A. muricata. leaves, seeds and fruit pulp[18], in addition to 80 essential oils, mainly sesquiterpenes derivatives in the leaves and have revealed cytotoxic activity against MCF-7 (human breast carcinoma) cell line[19].

Biological activities:

Anti- arthritic and Anti-inflammatory

The anti-arthritic activity of ethanolic extract from A. muricata leaves has been studied in vivo in complete Freund's adjuvant (CFA)-induced arthritis in rats. As well as ear edema in mice induced by xylene, based on the ethnomedicines application of Graviola, after the administration of the plant extract orally for couple of weeks the edema has been decreased in a dose dependent way. Moreover, by increasing the dose the pro-inflammatory cytokines has been inhibited which lead to suppression of TNF-α and IL-1β expression in local tissue. These results explained the anti-arthritic activity of Graviola, demonstrating that the leaves could be used against both acute and chronic inflammation[20].

Antibacterial:

The antibacterial activity of Graviola was investigated use the leaves, bark and plant stem against different strains of bacteria. The antibacterial effect of the aqueous extract of Graviola leaves was tested against gram-positive bacteria: Staphylococcus aureus,Streptococcus pyogenes and Bacillus subtilis. As well as gram-negative bacteria: Escherichia coli, Klebsiella pneumonia, Enterobacter Aerogenes, Proteus vulgaris and Salmonella typhimurium. The strongest antibacterial activity of the leaves extract was against S. aureus, B. subtalis, P. vulgaris and K. pneumonia[21].

More bacterial growth inhibition was resulted from the use of the petroleum ether extract of the stem bark and leaves of Annona muricata, compared to the methanol and aqueous extract; this contributed to the phytochemical analysis results which showed that the latter two lack anthraquinones, flavonoids, alkaloids and phenols. While they are located in the petroleum ether extract[22].

Moreover, the fruit hydroalcoholic extract of Annona muricata was also studied for antimicrobial activity, and was found to own powerful antimicrobial activity against gram positive and gram negative bacteria strains[3].

Antioxidant Activity:

Reactive Oxygen Species (ROS) are natural byproduct of the normal metabolism of oxygen and have important roles in cell signaling. However, during times of environmental stress, ROS levels can increase dramatically. This may result in significant damage to cell structures, this process is known as oxidative stress which catalyzes cellular death through biochemical and physiological lesion[23]. Therefore, the development of antioxidants from natural products has become the center of attention in recent studies as results of their remarkable role in reversing the destructive effects of ROS, numerous investigations on methanolic and aqueous leaf extracts of Graviola showed antioxidative activities of the two extracts. Furthermore, the plant showed DNA shielding activity against H2O2-induce toxicity[24].

A. muricata leaves and seeds analysis revealed the presence of enzymatic antioxidants such as superoxide dismutase and non-enzymatic antioxidants such as vitamin C and E . Padma and colleagues reported the adaptogenic and antioxidant activity of the stem bark of A. muricata[25].

Anti-parasitic Activity:

Parasitic disease has infected a large percent of world population; the difficulty in their treatment lies in the drug resistance exhibited by large number of infecting parasite in addition to their relatively high toxicity in long treatment protocol. Therefore, a natural antiparasitic remedy became of a huge interest recently[26]. A. muricata antiparasitic activity has been investigated use different assay protocols .Where the leaf and seed extracts has been tested against man parasitic species: Trypanosoma cruzi, L. braziliensis, Leishmania and L. panamensis the extract reported to possess antileishmanial effect against numerous Leishmania species. And a considerable antiparasitic activity against the infective larvae Molinema dessetae. Furthermore, the leaf extract anthelmintic activity has been investigated in vitro and resulted in immobilization of adult worms of Haemonchus contortus[27].

Hepatoprotective and Bilirubin-Lowering Activity:

Graviola have been used as remedy in the treatment of jaundice in Ghana, this lead to further investigation to study the role of the leaves extract of Annona muricata in vitro against phenylhydrazine-induced jaundice in adult rats, the investigation had shown considerable decrease almost to normal, of the elevated bilirubinemia. Moreover, the hepatoprotective activity was also investigated against acetaminophen and carbon tetrachloride induced liver damage, where they pretreated the animal with Graviola extract, the normal liver function was regained. These results demonstrated the possible hepatoprotective activity[28,29].

Antidiabetic and Hypolipidemic Activity:

The need of a natural remedy to treat diabetes mellitus has become of a great interest. Due to the ethn-omedicinal use of A. muricata against DM, numerous studies have examine the antidiabetic activity of the Graviola extract in-vivo using streptozotocin-induced diabetes in rats and came out with the same pleasing antidiabetic results. This may be contributed to the rejuvenation of β-cells effect Graviola extract on the pancreas islets, the extract also significantly decreased the serum total cholesterol, low-density lipoprotein, triglyceride and very low-density lipoprotein cholesterol[30].

Wound Healing Activity:

A. muricata extract has been used as a wound healing agent, studies prove that extract significantly demonstrated wound healing activity and decrease in the area of the wound[31].

Antiobesity activity:

Obesity is a worldwide problem, which has been the attention of scientific researcher lately due to its implications on human health and wellbeing. As the prevalence of obesity is dramatically increasing, recently many plants has been utilized by obese people for weight loss purposes. Two studies conducted in Brazil and Mexico and Central America indicated that, Annona muricata plus other plants may have helpful activity against obesity. However, there is no medical evidence that guarantee the biological effects these plants[32].

Immunomodulatory activity:

According to a recent study in Malaysia, the methanolic extract of A. muricata showed significant immunostimulation activity in dose dependent manner[33]. This effect is thought to be contributed to stimulating effect of Graviola on the complement pathway as well as generating C3b and C3bi which will attach to the pathogen, the later will be recognized by phagocyte receptor such as CR1 (CD35) and CR3 (CD11b) to start the phagocytosis process[34].

Anticancer Activity:

Cancer mortality percent has increased worldwide, and due to the toxicity of the current chemotherapeutic drugs, and with the upsurge of several studies which revealed that compounds achieved from natural sources are fairly effective in cancer treatment with less toxicity to normal tissues[35].

The leaves from Graviola The main bioactive compounds that have been extracted from different parts of Graviola are identified as Annonaceous acetogenins have been used for treatment cancer. Annonaceous acetogenins are long chain fatty acids (C35 or C37) which derived from the polyketide pathway that have selectively and cytotoxicity effect on different cancer cell lines, involving multidrug-resistant cancer cell lines[36].

Acetogenins produce cytotoxicity via inhibiting the mitochondrial complex I, which is included in ATP synthesis. Cancer cells have a greater demand for ATP than the normal cells, thus mitochondrial complex I inhibitors have a possible effect in cancer therapeutics. Some of in vitro studies have observed that the anticancer effect of Graviola on numerous cell lines for instance: pancreatic cancer cell lines (FG/COLO357 and CD18/HPAF), SKBR3 (Breast adenocarcinoma cell line), Ehrlich ascites carcinoma cells (EACC), and breast cancer cell lines MD Anderson [MDA][37].

The identification of A. muricata leaves acetogenins has positively determined through different techniques. Recently, some of in vitro studies identified the mechanism of action of ethyl acetate which is extracted from Graviola leaves against different cell lines such as lung cancer cells (A549) and colon cancer cells (HCT-116 and HT-29). The ethyl acetate extract was capable to enhance apoptosis in lung and colon cancer cells by the mitochondrial-mediated pathways. This cytotoxic effect was related with detention in the G1 phase cell cycle[38].

Apoptosis is the most mode of action of anticancer agents, involving the drugs from natural source. Moreover, there are some specific biochemical and morphological changes occur during apoptosis for instance DNA fragmentation, membrane blabbing, chromatin condensation, membrane cell shrinkage, etc. Stimulation of apoptosis is the significant point to success of natural products as chemotherapeutic agents[39].

A. muricata has antiproliferative effects of Human promyelocytic Leukemia HL-60 cells via stimulating loss of cell viability, G0/G1 phase cell arrest, loss of membrane mitochondrial, and morphology changes. Therefore, A. muricata is considered as a chemotherapeutic agent and have cytotoxic activity in HL-60 cells, this information proposed that the extracts of the plant have a potential effect for treatment of cancer. In another study, the spread and invasion of colon cancer cells were highly inhibited via A. muricata leaves extract. Moreover, the stimulation of caspase 3 by the ethyl acetate extract of the leaf as well as apoptosis-enhancing effect in myelogenous leukemic K562 cells, which was established with a TUNEL assay[40].

Recently, in vivo and in vitro studies were conducted to evaluate the activity of A. muricata leaves against the benign prostatic hyperplasia (BPH-1) cell lines and prostates of rats, a suppression effect on BPH-1 cells was observed. The size of the rats prostates were also suppressed after following the treatment for additional two months, which was related to apoptosis induction[41].

Furthermore, an in vivo study on 7,12-dimethylbenzene anthracene (DMBA)-induced cell proliferation in the breast tissues of mice, which revealed that the A. muricata leaves may possess protective against the development of breast carcinogenesis[42].

The leaves extract inhibition effect on the initiation and promotion stage of skin papilloma genesis in the leaves ethanolic extract activity against colonic aberrant crypt foci (ACF) in rats was studied and resulted in suppression of (ACF) in rats. Investigation on A. muricata anticancer activity was not exclusive on in vitro and in vivo studies. A case study of a 66-year old woman with a metastatic breast cancer revealed that utilization of the leaves boiled in water and Xeloda produsedstable state of the disease[43].

Toxicology:

Recent research revealed that the excessive consumption of Graviola can cause atypical Parkinsonism, which was attributed to the AGEs, as they are thought to be neurotoxins and responsible for neurodegenerative disorders, including Guadeloupean atypical Parkinsonism. Correspondingly, in a study carried on rats, it was concluded that the consumption of one Graviola fruit or its juice daily for one year is enough to stimulate brain lesions in rats through intravenous infusion[44].

2. CONCLUSION

Medicinal plants has been a potent source of human health remedies. Annona muricata, a time-honored tropical tree has become an important subject of interest in pharmacological and chemical studies in the last few decades and as a result much useful knowledge has been gathered. Regarding the constituents and the bioactive compounds which produce the medicinal properties. In the field of ethnomedicine all parts of Graviola plant has been utilized; the bark, leaves, fruit and seeds, where they were commonly used to relive fever ,eliminate worms and parasite , and also to treat wounds.

The chemical composion of Graviola is complex and many compounds of different classes have been isolated, including antioxidant, vitamins, alkaloids and the most important was the isolation of Acetogenins. They have not all been linked to biological activity. Researchers effort on this plant expose its beneficial characteristic in the field of pharmacy, A. muricata is confirmed to possess a wide spectrum of biological activities. The most promising activities are found to be its anticancer, antiparasitic and antidiabetic activity, further work studies should be performed on the biochemical and physiological functions of active compounds and to target detailed mechanisms underlying these activities. However, it was still unclear whether the adverse effects exhibited by A. muricata appear to occur in human. Therefore, further study should be conducted in term of toxicology study.

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