



International Journal of Research in Pharmacology & Pharmacotherapeutics



ISSN Print: 2278-2648
ISSN Online: 2278-2656

IJRPP |Vol.3 | Issue 4 | Oct-Dec-2014
Journal Home page: www.ijrpp.com

Review article

Open Access

Literary approach to *Annona muricata* and its role in cancer- A review

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ABSTRACT

¹*Annona muricata* L. belongs to the family of Annonaceae has a wide spread pantropical distribution and has been proudly known as corossol. ²⁰*Annonaceous acetogenins* are a new class of compounds that have been reported to have potent pesticidal, parasiticidal, anti-microbial, cell growth inhibitory activities. In this study, organic and aqueous extracts from the defatted seeds of *Annona squamosa* (custard apple) were tested on different human tumour cell lines for antitumoural activity. While organic and aqueous extracts induced apoptosis in MCF-7 and K-562 cells, they failed to do so in COLO-205 cells. Treatment of MCF-7 and K-562 cells with organic and aqueous extracts resulted in nuclear condensation, DNA fragmentation, induction of reactive oxygen species (ROS) generation and reduced intracellular glutathione levels. In addition down regulation of Bcl-2 and PS externalization by Annexin-V staining suggested induction of apoptosis in MCF-7 and K-562 cells by both the extracts through oxidative stress. On the contrary, COLO-205 cells showed only PS externalization but no change in ROS and glutathione levels. These observations suggest that the induction of apoptosis by *A. Squamosa* extracts can be selective for certain types of cancerous cells.

Keywords: *Annona muricata* L, *Annonaceous acetogenins*, anti cancer.

INTRODUCTION

¹*Annona muricata* L. belongs to the family of Annonaceae has a wide spread pantropical distribution and has been proudly known as corossol. It is a wide spread small tree and has its native in Central America. The fruits of *Annona muricata* Linn are found to be edible in Yunan province of china and their fruits are used commercially for the

production of juice, candy and sherbets. Intensive chemical investigations of the leaves and seeds of this species have resulted in the isolation of a great number of acetogenins. The isolated compounds display some of the interesting biological or the pharmacological activities, such as antitumor, cytotoxic, ant- parasitic and pesticidal properties.

Roots of these species are used in traditional medicine due to their anti-parasitical and pesticidal properties. Common Names- Graviola, soursop, guanabona, guanavana, guanaba, corrosal.

Graviola is a small upright evergreen tree 5-6 m high, with large, glossy, dark green leaves. It produces a large, heart-shaped, edible fruit that is 15-20 cm in diameter and green in color, with white flesh inside. Graviola is indigenous to most of the warmest tropical areas in South and North America including Amazon.

Annona muricata which is also called as the soursop, sir sak or guanabana has been named as popular fruit tree that is cultivated throughout the tropical regions of the world. Guanabana is found to grow more in many regions of the tropical world was extensively studied for the exploration of the new *Annonaceous acetogenins* from its bark, seeds and leaves which posses much of the diverse biological activities.

The seeds and leaves of these species were found to contain more than 50 mono-THF acetogenins. Some of the key intermediates that are involved in the biosynthesis of these acetogenins have been isolated from this species recently and were named as epomuricenins – A and B, montecrestin, cohbins – A and B, muridienins-1 and 2, muridienins 3 and 4, muricadienin and chatenaytrienins- 1, 2 1and 3 and also a new compound called as sabadelin which might be a biogenetic precursors of cis-penatellin.

The soursop from the Annonaceae family is found to be the most important tropical fruit that contributes much to the wider economic growth of some of the tropical countries such as tropical America, Australia, Africa and Malaysia. The soursop posses a maximum of 114 volatile compounds that is found to be responsible for the whole aroma profile, 44 esters, 25 terpenes, 10 alcohols, 9 aldehydes and ketones, 7 aromatic compound, 5 hydrocarbons, 3 acids, 3 lactones and 8 other miscellaneous compounds.

Esters were found to be the dominant compounds regardless of the soursop's origin with methyl-2 hexonate, methyl-2 butenoate, methyl butonoate and hexonoate being the four principal compounds.

Annonaceous acetogenins are a series of polyethers which contains either the adjacent or the non-adjacent tetrahydrofuran or the non- adjacent tetrahydrofuran (THF) or Tetrahydropyran (THP) ring and also an a,b-unsaturated c- lactone ring. They possess the most beneficial anti-tumors cytotoxic, antimalarial

and anti-feedant properties. Acetogenins gets interacted with the NADH- ubiquinone oxidoreductase (complex1) in mammalian and in the insect's mitochondrial electron transport system and or with ubiquinone-linked NAD (P) H oxidase in the cancer cells cytoplasmic membranes.

The first cyclopeptide germicidin S has been discovered in almost 20th century of around 1940's. Naturally occurring cyclopeptides has been usually isolated from various sources which include marine invertebrates and higher plants and their characteristic structures and stability to enzyme offered them with the extensive and remarkable biological activities such as anti-tumor, antifungal, antivirus, enzyme inhibition etc that is closely associated to their molecular conformation.

Tribal and Herbal Medicine uses

All parts of the graviola tree are used in natural medicine in the tropics, including the bark leaves, roots, fruits and fruit seeds. Different properties and uses are attributed to the different parts of the tree. Generally, the fruit and fruit juices are taken for worms and parasites, to cool fevers, to increase mother's milk after child birth and as an astringent for diarrhea and dysentery. The crushed seeds are used against internal and external parasites, head lice and worms. The bark leaves and roots are considered anti-spasmodic, hypotensive, and sedative and a tea is made for various disorders towards those effects.

Graviola has a long, rich history of use in herbal medicines as well as lengthy recorded indigenous use. In the Peruvian Andes, a leaf tea is used for catarrh and the crushed seed is used to kill parasites. In the Peruvian amazon the bark, roots and leaves are used for diabetes and as a sedative and antispasmodic. Indigenous tribes in Guyana use a leaf and or bark tea as a sedative and heart tonic. In the Brazillian Amazon a leaf tea is used for liver problems, and the oil of the leaves and unripe fruits is mixed with olive oil and used externally for neuralgia, rheumatism and arthritis pain. In Jamaica, Haiti and West Indies the fruit or fruit juice is used for fevers, parasites and diarrhea; the bark or leaf is used as an anti-spasmodic, sedative and nervine for heart conditions, coughs, flu, difficult child-birth, asthma, hypertension and parasites.

Role of *Annona muricata* in cancer

³Seven new annonaceousacetogenins, muricins A-G (1-7), as well as five known compounds, a mixture of muricatetrocin A (8) and muricatetrocin B (9), longifolicin (10), corossolin (11), and corossolone (12), were isolated from the seeds of *Annona muricata*. The structures of all isolates were elucidated and characterized by spectral and chemical methods. These acetogenins showed significantly selective in vitro cytotoxicities toward the human hepatoma cell lines Hep G (2) and 2,2,15.

⁴Bioactivity-directed fractionation of the leaves of *Annona muricata* resulted in the isolation of annopentocins A (1), B (2), and C(3), and cis- and trans-annomuricin-D-ones (4, 5). Compounds 1-3 are the first acetogenins reported bearing a mono-tetrahydrofuran (THF) ring with one flanking hydroxyl, on the hydrocarbon side, and another hydroxyl, on the lactone side that is one carbon away from the THF ring. Compounds 4 and 5 were obtained in a mixture and are new mono-THF ring acetogenins bearing two flanking hydroxyls and an erythro-diol located between the THF and the ketolactone rings. Compound 1 was selectively cytotoxic to pancreatic carcinoma cells (PACA-2), and 2 and 3 were selectively cytotoxic to lung carcinoma cells (A-549); the mixture of 4 and 5 was selectively cytotoxic for the lung (A-549), colon (HT-29), and pancreatic (PACA-2) cell lines with potencies equal to or exceeding those of Adriamycin.

⁵Bioactivity-directed fractionation of the seeds of *Annona muricata* L. (Annonaceae) resulted in the isolation of five new compounds: cis-annonacin (1), cis-annonacin-10-one (2), cis-goniothalamycin (3), arianacin (4), and javoricin (5). Three of these (1-3) are among the first cis mono-tetrahydrofuran ring acetogenins to be reported. NMR analyses of published model synthetic compounds, prepared cyclized formal acetals, and prepared Mosher ester derivatives permitted the determinations of absolute stereochemistries. Bioassays of the pure compounds, in the brine shrimp test, for the inhibition of crown gall tumors, and in a panel of human solid tumor cell lines for cytotoxicity, evaluated relative potencies. Compound 1 was selectively cytotoxic to colon adenocarcinoma cells (HT-29) in which it was 10,000 times the potency of Adriamycin.

⁶Bioactivity-directed fractionation of the leaves of *Annona muricata* L. (Annonaceae) resulted in the isolation of two new *Annonaceous acetogenins*, muricoreacin (1) and murihexocin C (2). Compounds 1 and 2 showed significant cytotoxicities among six human tumor cell lines with selectivities to the prostate adenocarcinoma (PC-3) and pancreatic carcinoma (PACA-2) cell lines.

⁷A methylene chloride extract of the pulp of *Annona muricata* L. was fractionated in search for scarcely functionalized *Annonaceous acetogenins* (type E). Previously known C-35 and C-37 mono-epoxy unsaturated compounds, epomuricenins-A and -B (1+2) and epomusenins-A and -B (3+4), were obtained. Two new mono-epoxy saturated C-35 representatives, epomurinins-A and -B (5+6) were also isolated.

⁸Muricatenol (1) is a new C37 non-THF ring acetogenin with four hydroxyls and one isolated double bond in the long aliphatic chain. 2,4-cis-Gigantetrocinone (2) and 2,4-trans-gigantetrocinone (3) have been isolated as their acetates by preparative TLC. 2,4-trans-Isoannonacin-10-one (4) and 2,4-trans-isoannonacin (5) have been isolated as only 2,4-trans-form for the first time (no cis-form). Also four known acetogenins, gigantetrocin-A (6), gigantetrocin-B (7), annomontacin (8), gigantetronenin (9) and a mixture of N-fatty acyl tryptamines have been isolated (10). Their structures have been established on the basis of spectral analyses. The CHCl₃ fraction of the seeds showed strong antitumor activities.

⁹Phytochemical investigation of roots of *Annona muricata* led to the identification of seven mono-tetrahydrofuran (mono-THF) acetogenins. Six new acetogenins having the unusual cis-configuration of the THF ring, cis-solamin (1), cis-panatellin (2), cis-uvariamicin IV (3), cis-uvariamicin I (4), cis-reticulatacin (5), and cis-reticulatacin-10-one (6) were identified, in addition to a known compound, solamin.

¹⁰Bioactivity-directed fractionation of the leaf extract of *Annona muricata* L. (Annonaceae) has resulted in the isolation of two new *Annonaceous acetogenins*, annomuricine (1) and muricapentocin (2). Compounds 1 and 2 are monotetrahydrofuran ring acetogenins bearing two flanking hydroxyl groups; however, each has three additional hydroxyl groups. Compound 1 has an erythro 1,2-diol, and 2 has a

1,5,9-triol moiety. Both 1 and 2 showed significant cytotoxicities against six types of human tumors, with selectivities to the pancreatic carcinoma (PACA-2) and colon adenocarcinoma (HT-29) cell lines.

¹¹Annonaceous acetogenin (or polyketide) is a kind of potential antineoplastic agents from Annonaceae plants. Two new acetogenins, Muricatalicin (I) and muricatalin (VI), a mesitoate of a new acetogenin, annonacin-B mesitoate (Vb), and three known acetogenins, annonacin (II), annonacin-A (III) and annonacin-10-one (IV) have been isolated from *Annona muricata* L. The structures and relative stereochemistry of I, VI and Vb were elucidated on the basis of spectral analysis and examination of their acetates and/or mesitoate.

¹²During the course of continuing search for acetogenins from Annonaceae, a new metabolite, montecristin, possibly involved in the biogenesis of acetogenins, was isolated from the roots of *Annona muricata*. Its structure was elucidated on the basis of UV, IR, (1)H and (13)C NMR, and mass spectrometry. The identification of the main structural features of montecristin (1) was obtained from the NMR spectra whereas their locations on the alkyl chain were evidenced by using mass spectrometry. The attribution of each carbon and location of substituents on the alkyl chain of this fatty acid gamma-lactone was evidenced by using tandem mass spectrometry (MS/MS) and high-energy collisional activation of [M + Li](+) lithium complexes. Finally, the structure determination of montecristin was strengthened by epoxidation and transformation leading to a known adjacent bis-tetrahydrofuran acetogenin.

¹³In a continuation of research on bioactive components from the leaves of *Annona muricata*, three novel monotetrahydrofuran *Annonaceous acetogenins*, namely, annomutacin [1], (2,4-trans)-10R-annonacin-A-one [2], and (2,4-cis)-10R-annonacin-A-one [3], have been identified. Their structures were deduced by ms, NMR, ir, and uv spectral and chemical methods, and the absolute configurations were determined by Mosher ester methodology. A known bioactive amide, N-p-coumaroyl tyramine, was also found. Compound 1 and the mixture of compounds 2 and 3 showed selective cytotoxicities against the human A-549 lung tumor cell line.

¹⁴The leaves of *Annonamuricata* have yielded two additional monotetrahydrofuran *Annonaceous acetogenins*, annomuricin C [1] and muricatocin C [2]. Compounds 1 and 2 each possess five hydroxyl groups; two hydroxyl groups are at the C-10/C-11 and C-10/C-12 positions in 1 and 2, respectively. The absolute configurations of 1 and 2, except for positions C-10 and C-11 or C-12, were determined by Mosher ester methodology. The C-10/C-11 and C-10/C-12 acetonides (1c, 2c) suggested relative stereochemistry and significantly enhanced the cytotoxicities against the A-549 human lung and the MCF-7 human breast solid tumor cell lines. One known monotetrahydrofuran acetogenin, gigantetrocin, not described previously from this plant, was also found.

¹⁵The leaves of *Annonamuricata* have yielded the novel monotetrahydrofuran *Annonaceous acetogenins*, muricatocins A [1] and B [2]. Each compound possesses five hydroxyl groups, with two hydroxyl groups at the C-10 and C-12 positions. The absolute configurations of 1 and 2 (except for positions C-10 and C-12) were determined by Mosher ester methodology. The C-10, C-12 acetonides (1c, 2c) suggested relative stereochemistry and significantly enhanced cytotoxicity against the A-549 human lung tumor cell line. Three known monotetrahydrofuran acetogenins, annonacin A, (2,4-trans)-isoannonacin, and (2,4-cis)-isoannonacin, were also found.

¹⁶The leaves of *Annonamuricata* have yielded eight monotetrahydrofuran *Annonaceous acetogenins*. Two of them, annomuricins A [1] and B [2], whose chemical structures were deduced by ms, nmr, ir, and uv spectral and chemical methods, are novel and unusual. Compounds 1 and 2 each possess five hydroxyl groups; two hydroxyl groups are vicinal, with the vicinal group of 1 threo and that of 2 erythro. The absolute configurations of 1 and 2 were determined by Mosher ester methodology. Six monotetrahydrofuran acetogenins, previously described in the seeds, were found in the leaves; these are gigantetrocin A, annonacin-10-one, muricatetrocins A and B, annonacin, and goniothalamicin.

¹⁷*Annona muricata* L (Annonaceae), commonly known as soursop has a long, rich history in herbal medicine with a lengthy recorded indigenous use. It had also been found to be a promising new anti-

tumor agent in numerous in vitro studies. The present investigation concerns chemopreventive effects in a two-stage model of skin papillomagenesis. Chemopreventive effects of an ethanolic extract of *A. muricata* leaves (AMLE) was evaluated in 6-7 week old ICR mice given a single topical application of 7,12-dimethylbenza(α)anthracene(DMBA 100ug/100 ul acetone) and promotion by repeated application of croton oil (1% in acetone/ twice a week) for 10 weeks. Morphological tumor incidence, burden and volume were measured, with histological evaluation of skin tissue. Topical application of AMLE at 30, 100 and 300mg/kg significantly reduced DMBA/croton oil induced mice skin papillomagenesis in (i) peri-initiation protocol (AMLE from 7 days prior to 7 days after DMBA), (ii) promotion protocol (AMLE 30 minutes after croton oil), or (iii) both peri-initiation and promotion protocol (AMLE 7 days prior to 7 day after DMBA and AMLE 30 minutes after croton oil throughout the experimental period), in a dose dependent manner ($p < 0.05$) as compared to carcinogen-treated control. Furthermore, the average latent period was significantly increased in the AMLE-treated group. Interestingly, At 100 and 300 mg/ kg, AMLE completely inhibited the tumor development in all stages. Histopathological study revealed that tumor growth from the AMLE-treated groups showed only slight hyperplasia and absence of keratin pearls and rete ridges. The results, thus suggest that the *Annona muricata* leaves extract was able to suppress tumor initiation as well as tumor promotion even at lower dosage.

¹⁸Natural products have been the target for cancer therapy for several years but there is still a dearth of information on potent compounds that may protect normal cells and selectively destroy cancerous cells. The present study was aimed to evaluate the cytotoxic potential of n-butanolic leaf extract of *Annona muricata* L. on WRL-68 (normal human hepatic cells), MDA-MB-435S (human breast carcinoma cells) and HaCaT (human immortalized keratinocyte cells) lines by XTT assay. Prior to cytotoxicity testing, the extract was subjected to phytochemical screening for detecting the presence of compounds with therapeutic potential. Their relative antioxidant properties were evaluated using the reducing power and DPPH*radical scavenging assay. Since most of the observed chemo-preventive

potential invariably correlated with the amount of total phenolics present in the extract, their levels were quantified and identified by HPLC analysis. Correlation studies indicated a strong and significant ($P < 0.05$) positive correlation of phenolic compounds with free radical scavenging potential. The results revealed that the extract was moderately cytotoxic to normal cells with a mean IC₅₀ value of 52.4 μ g when compared with those obtained for cancerous cells (IC₅₀ values of 29.2 μ g for MDA-MB-435S and 30.1 μ g for HaCaT respectively). The study confirms the presence of therapeutically active antineoplastic compounds in the n-butanolic leaf extract of *Annona muricata*. Isolation of the active metabolites from the extract is in prospect.

¹⁹The antibacterial and phytochemical activities of methanolic and aqueous leaf extract of *Annona muricata* was evaluated on Staphylococcus aureus, Escherichia coli Streptococcus pyogenes, Bacillus subtilis, Salmonella typhimurium and Klebsiella pneumonia. The antibacterial activity was done using agar cup method. The most inhibited gram positive bacteria were Bacillus subtilis and Staphylococcus aureus at minimum inhibitory concentration of 400mg/ml with zone diameter of 19.5+ 0.5m and 20.5+ 0.5m, while the most inhibited gram-negative bacteria was Escherichia coli at minimum concentration of 200mg/ml, 16.5+ 0.5m. Klebsiella pneumonia was inhibited at almost every concentration of the methanolic extract. Both extracts showed antibacterial properties but the methanolic extract was more effective as it inhibited a wide range of organism at varying concentrations. There was a significant difference ($P < 0.05$) between the methanolic and aqueous extract. The phytochemical screening of methane and aqueous extracts of the leaf revealed the presence of Steroids, Alkaloids, Saponnins, Tannins, Flavonoid, and Cardiac glycosides. Antibacterial activity of extracts was compared with the standard antibiotic, streptomycin (100mg/ml). The results obtained in the present study suggest that *Annona muricata* can be used as an antibacterial substance.

²⁰*Annonaceous acetogenins* are a new class of compounds that have been reported to have potent pesticidal, parasiticidal, anti-microbial, cell growth inhibitory activities. In this study, organic and aqueous extracts from the defatted seeds of *Annona squamosa* (custard apple) were tested on different

human tumour cell lines for antitumoural activity. While organic and aqueous extracts induced apoptosis in MCF-7 and K-562 cells, they failed to do so in COLO-205 cells. Treatment of MCF-7 and K-562 cells with organic and aqueous extracts resulted in nuclear condensation, DNA fragmentation, induction of reactive oxygen species (ROS) generation and reduced intracellular glutathione levels. In addition downregulation of Bcl-2 and PS externalization by Annexin-V staining suggested induction of apoptosis in MCF-7 and K-562 cells by both the extracts through oxidative stress. On the contrary, COLO-205 cells showed only PS externalization but no change in ROS and glutathione levels. These observations suggest that the induction of apoptosis by A. Squamosa extracts can be selective for certain types of cancerous cells.

Conclusion

Medicinal plants are being used from decades for culminating diseases of the human society. Traditionally many herbs are being used for many diseases and show good and significant results. Many tribes in the North Eastern States of India are treating people with the help of herbal medicines and thus showing a ray of hope for the creation of disease free society. *Annona muricata* has attracted many researchers and scientist around the world and with their tiresome efforts many significant results could have been ruled out showing good results in controlling cancer related diseases. Hence it can be concluded that a new outcome can be evaluated in the near future where a cancer free society can be seen.

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