ANTICANCER, ANTIOXIDANT AND ANTIMICROBIAL ACTIVITY OF ANNONACEAE FAMILY

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ABSTRACT

The Mother Nature provided us with a huge number of flora and fauna. These flora and fauna shows so many characteristic features such as their medicinal value. Medicinal plants are the oldest known healthcare agent. Their importance is still growing although it varies depending on the ethnological, medical and historical background of each place. Medicinal plants are also important for pharmacological research and drug development, not only when plant constituents are used directly as therapeutic agents, but also when they are used as basic materials for the synthesis of drugs or as a models for pharmacologically active compounds. Some of the natural medicinal plants are so common, that we used in our daily life without knowing their medicinal importants. Annonaceae family is one of the large family showing so many characteristic features such as antitumor, anioxidant and antimicrobial activities.

Key Words: Annonaceae family, Antioxidant, Antimicrobial, Medicinal Plants, Pharmacology, Therapeutic agent.

INTRODUCTION

The Annonaceae is a very large family of plants comprising about 120 genera and more than 2000 species. On the basis of morphology and habitat, it is a very homogenous family as source of edible fruits and oils. The Annonaceae seems to be one of the least chemically as well as pharmacologically known families compared with its large size. As source of edible fruits and oils, this family has economic importance. Seed oils of certain Annonaceae plants are used in soap production and as edible oils. Flowers of some Annonaceae plants are used
in perfumery and many members of this family are used in folk medicine to treat various types of tumors and cancers.

The earlier studies on Annona species showed that this family is a potent source of a wide variety of secondary metabolites belonging to several categories\(^1\). The effect of organic and aqueous extracts obtained from the defatted seeds of *Annona squamosa* on different tumour cell lines and reported that the two extracts from *A. squamosa* seeds induced apoptotic features like formation of apoptotic bodies, DNA fragmentation and phosphotidyl serine externalization by Annexin-V staining in MCF-7 breast carcinoma and K-562 erythroleukemic cells.

**ANNONA SQUAMOSA**

*Annona squamosa* is extensively used as traditional medicine in various culture. The species of *Annona squamosa* is a small evergreen tree reaching 6-8 meters (20-26 ft) tall, is commonly found in deciduous forests, cultivated throughout India and other countries. It is commonly called as custard apple, it is native of West Indies. The plant is traditionally used for the treatment of epilepsy, dysentery, cardiac problem, worm infection, constipation, hemorrhage, antibacterial infection, dysuria, fever, and ulcer. It also has antifertility, antitumor and abortifacient properties \(^2, 3, 4\). The plant possesses potent bioactive principles in all its parts. Acetogenins, a class of natural compounds, isolated from members of Annonaceae have potent anti-neoplastic, parasiticidal, pesticidal and anti-microbial activities \(^6, 7\). Acetogenins belonging to a series of C-35/C-37, and derived from C-32/C-34 long chain fatty acids are known to be powerful inhibitors of complex I (NADH: ubiquinone oxidoreductase) in mammalian and insect mitochondrial electron transport systems \(^8, 9\). Two Acetogenins, squamocin and squamostatin, isolated from *A. squamosa* seeds have shown cytotoxic activity \(^9, 10\). Squamocin inhibited proliferation of HL-60 cells and induced apoptosis by the activation of caspase-3. Ascimicin, another acetogenin also exhibited cytotoxic activity against 9KB, A549, HT-29 and 9ASK tumour cells \(^11\). Recently, two more acetogenins, squamocin-O\(^1\) and squamocin-O\(^2\) were reported from the methanolic extracts of the seeds of *A.squamosa* \(^12\). *A. squamosa* contain ribosome-inactivating protein (RIP), an immunotoxin is found to be effective \(^13\).

**ANNONA MURICATA**

*Annona muricata* L. commonly known as graviola or soursop, belongs to the family of Annonaceae. It is a typical tropical tree with heart shaped edible fruits and widely distributed
in most of the tropical countries. The leaves are lanceolate with glossy and dark green in color had been traditionally used to treat headaches, hypertension, cough, asthma and used as antispasmodic, sedative and nervine for heart condition. Previous reports over the years have demonstrated that the leaf, bark, root, stem, and fruit seed extracts of *Annona muricata* are anti-bacterial. *Annona muricata* (soursop) is a potent anticancer plant of Annonaceae family. The therapeutic potentials of the n-butanolic extract of *Annona muricata* were studied on WRL-68, MDA-MB-435S and HaCaT cell lines. Since most of the chemotherapeutic drugs affect normal cells as well, WRL-68 cells were analysed for the relative cytotoxic response in with comparison that quantified in MDA-MB-435S and HaCaT cell lines. n-Butanolic leaf extract of *A. muricata* posses significant anticancer potentials in human cancerous cells. Plant phenolics are a major group of compounds that act as primary antioxidants or free radical scavengers.[14]

**ANNONA RETICULATA**

Phytochemicals are secondary metabolic compounds found in plants. Many of these are known to provide protection against insect attacks and plant diseases, stimulation of the immune system, modulation of hormone metabolism and antibacterial and antiviral effect.[15, 16] The most important of these bioactive constituents of *Annona reticulata* are Alkaloids, Tannins, Flavonoids, Cardiac glycosides, Steroids and Saponins.[16] The Ethyl acetate extract of leafs showed 19mm of zone of clearance in both *Pseudomonas putida* and *Lactobacillus acidophilus*. The Butanol extract of leaf showed highest zone of inhibition in *Streptococcus mutans* with 18mm. The Methanol extract showed high zone (19.5mm), which is approximately equal to the commercially available synthetic antibiotic (22mm). Thus the *Annona reticulata* leaf extract showed antibacterial activity against both gram positive and gram negative bacterial strains.[17]

The leaves are used as insecticides, anthelmintic, and are also used externally as suppurant. The bark as a powerful astringent is used as anti dysentetic and vermifuge. Root bark, leaves and stem possess isoquinolone alkaloids.[18] It shows *in vitro* antiproliferative activity of ethanol extract of roots against A-549, K-562, HeLa and MDA-MB human cancer cell lines.[19]

**ANNONA MONTANA**

*Annona montana* contains monotetrahydrofuranic acetogenins which have toxicity to liver cancer in Hep G2 cells.[20] A novel Annonaceous acetogenin, montanacin F, with a new type
of terminal lactone unit, was isolated from the leaves of *Annona montana*. In addition, the cytotoxicity of montanacin F was evaluated in vitro against Lewis lung carcinoma (LLC) tumor cell lines. Furthermore, the previously isolated cytotoxic acetogenin annonacin against LLC was examined for *in vivo* antitumor activity with LLC tumor cells [21].

**ANNONA CRASSIFLORA**

The traditional use of this plant includes the treatment of wounds, venereal diseases, snake bites, louses and as antimicrobial, antidiarrheal and antirheumatic [22, 23, 24]. The seeds of *Annona crassiflora* have high antioxidant activity [25]. Annonaceous acetogenins, aporphine alkaloids, and steroids were isolated from ethanolic extract of wood. The extract and some fractions presented antimalarial and antimicrobial activities [26]. The ethanolic extract of *Annona crassiflora* seeds exhibited *in vitro* significant cytotoxicity to human lung carcinoma (A-549) and melanoma (RPMI 7951) cells. From this extract, an acetogenin (ACG – acetogenin) named araticulin was isolated [27]. The biological effects of many annonaceous have been related to the ability of ACGs to inhibit the NADH: ubiquinone oxiredutase (complex 1) of the mitochondrial electron transport chain [28]. This class of molecules has been suggested to be a group of potential anti-neoplastic agents [29, 30]. However, cytotoxicity could be associated with genotoxicity, as observed in many anti tumoral substances of natural or synthetic origin. The presence of genotoxic action in anti tumoral compounds does not benefit the organism in the long term [31].

**ANNONA CHERIMOLA**

The plant contain alkaloids, flavonoids, glycosides, saponins, tannins, carbohydrates, proteins, phenolic compounds, phytosterols, and amino acids. The anti stress activity of cherimoya is mainly attributed to these constituents with established antioxidant activity [32]. The chemical composition of the essential oils of leaves, flowers and fruits of *Annona cherimola* were studied for its anti microbial activity. Five Gram Positive (*Staphylococcus aureus, Enterococcus faecalis, E.coli, Shigella sonei and Proteus mirabilis*) and one fungus (*Candida albicans*) were selected for screening. The screening results showed that highest zone of inhibition were observed in leaf extract against *E.coli* [33]. Volatile compound (cherimolacyclopeptide E) of this plant was also studied for its anti microbial activity [34]. The methanolic extracts of the leaves and a pure compound isolated from *Annona cherimola* plant exhibit anti viral activity against *Herpes simplex* type2 (HSV-2) viruses [35]. The plant *Annona cherimola* is a well known source of cytotoxic compounds and previously
acetogenins have been reported. Annomolin and annocherimolin were isolated from the seeds of *Annona cherimola*, collected in Peru[^36]. Annomolin was selectively cytotoxic against the human prostate tumour cell line (PC-3), with a potency of over 10,000 times that of Adriamycin[^37]. *Annona cherimola* possessed cytotoxic potencies about 10,000 times those of adriamycin in the breast (MCF-7) and colon (HT-29) cancer cell lines[^38].

**ANNONA GLABRA**

*Annona glabra* (pond apple), a tropical tree growing wild in the America and Asia, is used in traditional medicine against several human ailments, including cancer. To validate the ethno pharmacological claims against cancer, the anti cancer effects of alcoholic extracts prepared from pond apple leaves, pulp and seed, were investigated in human leukemia cell lines. The alcoholic extracts were not cytotoxic to normal human lymphocytes. However, these extracts were highly cytotoxic to drug sensitive (CEM) and multidrug-resistant leukemia (CEM/VELB) cell lines[^39].

*Annona glabra* has been reported to have a group of compounds called Acetogenins. Acetogenins are reported to possess potent cytotoxic activity and are potent inhibitors of mitochondrial complex I respiratory chain[^40].

The leaves and bark of *Annona glabra* are used in Chinese medicine against cancer and other ailments. If the extracts of leaf, pulp and seed are compared, the seed extracts are more potent than other extracts. Li et al isolated four cytotoxic cytopeptides i.e Glabrin A, B, C and D from seeds[^41].

Cochrane et al has been reported the anti-cancer activity of *Annona glabra* extracts in human leukemia cell line[^39]. The results reported by Cochrane et al showed that the total ethanolic extract of *Annona glabra* seeds induced apoptosis when analyzed by annexin-V. A concentration-dependent increase in the percentage of apoptotic cells was observed with increasing concentrations of extract. The cytotoxicity measurements of *Annona glabra* leaf, pulp and seed extracts are significantly better than other anti cancer compounds[^39]. On a preliminary screening, substantial antimicrobial, and cytotoxic activities were observed for the hexane extract of the stem bark of *Annona glabra*[^42].

**ANNONA SYLVATICA**

The essential oil from the leaves of *Annona sylvatica* (EOAS) was extracted by hydro
distillation, and the analysis was performed by gas chromatography-mass spectrometry. The main compounds identified in the EOAS were sesquiterpenes, such as hinesol, z-caryophyllene, β-maaliene, γ-gurjunene, silphiperfol-5-en-3-ol, ledol, cubecol-1-epi, and muurola-3, 5-diene. Oral administration of the EOAS (20 and 200 mg/kg) and subcutaneous injection of dexamethasone (0.5 mg/kg, reference drug) significantly inhibited carrageenan- and complete Freund's adjuvant-induced mouse paw edema. EOAS showed growth inhibitory activity on all cell lines when administered in a high concentration. The EOAS inhibited the growth of human cancer cell lines with GI (50) values in the range of 36.04-45.37 µg/mL on all of the cell lines tested \[43\]. This work describes for the first time the anti-inflammatory and anti-cancer effects of the essential oil of A. sylvatica and its composition. Considering that drugs currently available for the treatment of inflammatory and cancer conditions show undesirable side-effects, the present results may have clinical relevance and open new possibilities for the development of novel anti-inflammatory and anticancer drugs \[43\].

CONCLUSIONS

Plants have been a prime source of highly effective conventional drugs for the treatment of many forms of cancer. Plants provide active constituents which acts directly against various ailments or indirectly by providing leads for the development of potential novel agents. Large number of herbal species have been used traditionally or as folk medicines against cancer. Many of them have been studied scientifically and proved to be beneficial anti-cancer agents. In medicine, particularly in the field of cancer, the use of herbs is increasingly enhanced especially with the excessive use of synthetic drugs and awareness of their toxicity, which contributed in oncology, leading to a favorable reconsideration of the medicinal practices made from natural herbal. Despite the divergent bioactivities of the plant medicines against various diseases, active components of most plant extracts have not been elucidated thoroughly, due their complex mixtures. The ability of agents to attach to carrier molecules directed to specific tumors, shows highly cytotoxic natural products to the tumors. A better understanding of the characteristics of tumor cells has recently led to the development of more targeted treatments, and therefore generally less toxic. In conclusion, the use of naturally occurring molecules in the treatment of cancer and other disease has greatly contributed to the improvement of the therapeutic efficacy of drugs used today. In this review some anti-cancer, anti-microbial and anti-oxidant plants with their phytochemical and pharmacological profile are presented. These plants exhibit good characteristic against
leading lifestyle diseases. This article provides the knowledge of Annonaceae medicinal plants.

REFERENCE


