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NATURE'S GIFT FOR VARIOUS REMEDIES-A REVIEW ON THE DIFFERENT MEDICINAL PROPERTIES OF *ANNONA MURICATA*

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ABSTRACT

Annona *muricate*, a member of custard Apple plants which belongs to the Annonaceae family is reported to be used against various ailments. Each and every part of the plant A.*muricata* is found to have high medicinal value with little side effects. The plant extracts are known to have anticancer, antioxidant, antiparasitic antihyperglycemic, antimicrobial, antinflammaory, analgesic and radical scavenging and wound healing properties. Acetogenins isolated from A. *muricata* has been widely studied and is the basis of the different medicinal properties exhibited by A. *muricata*. This review gives an account on the studies conducted ondifferent medicinal properties of different extracts of the wonder plant A.*muricata*. By proper scientific studies, research and evaluation. A.*muricata*in the near future may be an answer to various deadly diseases whichdoesn't have a reliable solution today.

KEYWORDS: Annona *Muricata*, Cancer Cell Lines, Anti-Cancer, Antimicrobial, Plant Extracts.

INTRODUCTION

Nature has provided us with rich sources of medicines from plants which can provide remedies for numerous diseases. Plants and plant-based medicaments are used as the basis of many modern Pharmaceuticals industries today for the treatment of our various ailments. Plants especially used in Ayurveda can provide biologically active molecules and lead structures for the development of derivatives with enhanced activity and reduced toxicity. Phytochemical molecules such as alkaloids, flavonoids, tannins, phenols etc from natural products which have great physiological impact on human body is being studied and characterized worldwide.[1] According to world health organization (WHO), more than 80% of the total world's population depends on the traditional medicines to satisfy their primary health care needs.[1]

Annona *muricata* L. known as Gravel, Guanabana and Soursop is a member of Custard-Apple plants in the Annonaceae family due to a custard-like texture of its fruit. It is a small deciduous tree with a height of 5–8 m and roundish canopy. This popular fruit tree has been widely cultivated in many tropical countries and traditionally used for an array of diseases and ailments. All parts of A. *muricata* are used in natural medicines in the tropics which include twigs, leaf, roots, fruits and seeds. The fruits and fruit juice of A. *muricata* have been widely consumed against worms and parasite infections and also against cool fever. Powdered seeds are known to be effective against internal and external parasites, headlice and worms. The leaves and twigs are known to have sedative and antispasmodic effect.[2]

The leaves of A.*muricata* are dark green in colour and are lanceolate with glossy appearance. It has been traditionally used in the treatment of headaches, cough, asthma, hypertension and used as nervine for heart condition. The leaves are found to possess antimalarial, antioxidant, molluscicidal properties and also have inflammatory and analgesic effect.[3]

Phytochemical screening of A.*muricata* resulted in the isolation of alkaloids, essential oils and acetogenins.A great number of acetogenins have been isolated from different parts of this species under very intensive phytochemical investigations.[4] The isolated compounds are known to have various medicinal properties such as anti tumor, antimicrobial, cytotoxic, pesticidal properties.[4] Thisshort review covers thedifferent medicinal properties of the plant- Annona *muricata*.

Anticancer activity of Annona *muricata*

All parts of A. *muricata* have been used in the anticancer studies. There are reports suggesting the use of extracts from different parts of A.*muricata* for the treatment of cancer in folk medicine. A number of compounds were isolated from different parts of the plants. They include flavonoids, flavonols, phenols etc. The leaves have been reported to have a higher concentration of polyphenols, flavonoids, flavonols when compared to bark & roots.[5]

Phytochemical screening of the leaf extracts of A.*muricta*showed the presence ofterpenoid, steriod, flavonoids, cardiacglycoside, tannin, phenol, alkaloid, in which the concentration of phenol was found significantly higher.[4] The ethanolic extract of A. *muricata* leaves was tested for antiproliferative activity. *In vivo* study showed that the ethanolic extract of A.*muricata* leaves can be used as a preventive measure against DMBA-induced breast cell proliferation in the breast tissues of female albino mice.[2] Cytotoxic activity and induction of apoptosis was reported in the ethanolic extract of the leaves of A.*muricata* in T47D breast cancer cell lines with IC_{50} of 17.149µg/mL.[4] The use of A.*muricata* extracts in were found to inhibit Human promyelocytic leukemia(HL-60 cells) a dose dependant manner with IC_{50} 6-49mg/ml.[2]

The antiproliferative activity of AMEAE towards lung cancer A549 cell lines was checked by MTT assay and it was found be effective with an IC_{50} value of of 5.09 ± 0.41 µg/mL after 72 hours of treatment.[5] The mechanism behind the antiproliferative action of AMEAE was reported for the first time.[5] The NF-κB signalling pathway was found to be involved in the activation of mitochondrial mediated signaling pathway leading to cell cycle arrest and programmed cell death.[5]

Skin tumor growth in DMBA/croton oil induced Papillomagenesis was found to be inhibited by ethanolic extract of A.*muricata* even at low dosageof 30mg/Kg.[6] A.*muricata* acts as a modulator of two stage skin pailloma genesis in ICR mice since it prevents the tumor formation, delayed the tumor promotion and progression, elicited by DMBA/croton oil.[6] A *muricata* is known to have rich source of Acetogenis, which may be the underlying principle behind the chemopreventive potential of A.*muricata* leaf extract.[6]

T47D breast cancer cell lines were cultured and studied to prove the efficacy of the extracts of leaves, fruits, and seeds of A. *muricata*. A.*muricata e*xtracts and tamoxifen were found to inhibit T47Dcell proliferation.[7] A comparative study revealed that proliferation inhibitive action of soursoup leaves against T47D breast cancer cells were much higher than that of fruits and seeds.[7] Another study has shown that the aqueous extracts of A.*muricata* leaves, fruits & seeds was less toxic when compared to tamoxifen.[7] The cytotoxic effect of soursop is due to the acetogenin fraction and soursoup ethanol extract possesses anti-inflammatory activity. The IC_{50} of A.*muricata* aqueous extract was significantly different from that of tamoxifen.[7]

The action of A. *muricata* extracts on cervical cancer which is caused by Human Papilloma Virus (HPV) was studied on Hela cell lines and were compared.[8] The comparative study revealed that the ethyl acetate extract (2000 µg/ml have 131.89%; 15.625 µg/ml have 11.37%) of A. *muricata*leaves are more cytotoxic than the ethanol distillate water extract (2000 µg/ml have 35.80%; 15.625 µg/ml have 3.97%). Meanwhile the chloroform extract (2000 µg/ml have 131.89%; 15.625 µg/ml have 11.37%) shown much more cytotoxic effect than ethyl acetate extract (2000 µg/ml have 35.80%; 15.625 µg/ml have 3.97%). This study indicates the use of chloroform extract as a good candidate for chemoprevention escort chemotherapy for cancer causing viruses.[8]

HL-60 cells undergoesloss of cell viability, morphology changes, loss of membrane mitochondrial potential and G0/G1 phase cell arrest by the antiproliferative effect of A.*muricata*.[9] Thepotential of A. *muricata* as an agent of chemotherapeutic and cytostatic activity in HL-60 cells has been confirmed.[9] A. *muricata* extracts may act in synergy and might be responsible for their anti-proliferative activity through the significant decrease in the mitochondrial membrane potential through induction of apoptosis.[9]

Three cell lines EACC, MDA, and SKBR3 were selected to study the anticancer activity of A.*muricata* leaf extract. The study showed ethanolic leaf extract of A. *muricata* with high anti caner activity on these cell lines.[10] The IC_{50} values were low and very close to each other, despite the difference in the method used and source of the cells. The ethanolic leaf extract of A. *muricata* is found to be highly effective in the management and treatment of cancer. This is in line with a study which showed that any extract had anticancer and cytotoxic activity if it had an IC_{50} value less than 1000 µg/mL after 24 hr contact time, and that the smaller the IC_{50} value of a test compound the more toxic the compound was.[10]

The differentiation capability of A.*muricata* leaf extracts between normal cell and cancer cell have been under spotlight. Cytotoxicity test on normal spleen cells of the ethanolic leaves extracts of A. *muricata* indicated a very high selectivity of the extracts for cancer cells, as they showed no effect on the normal spleen cells throughout different concentrations tested. Spleen cell viability was observed100% at all tested concentrations. In cancer treatment, selectivity of the drug for cancer cells is the mostimportant aspect. *In vitro* studies have reported thatA. *muricata* extracts is selectively toxic *in vitro* to certain types of tumour cells including: lung carcinoma cell lines, human breast solid tumour lines, prostate adenocarcinoma, pancreatic carcinoma cell lines, colon adenocarcinoma cell lines, mammary adenocarcinoma cell lines, liver cancer cell lines, human lymphoma cell lines and multi-drug resistant human breast adenocarcinoma etc.[10]

The anticancer activity of the ethanolic leaf extract fractions showed the highest single activity to be caused by the EEAM10 (Ethanol Extract of A.*muricata*) fraction at a cytotoxic level of more than 80% of cell death. Anticancer activity of ethanolic leaf extracts of A.*muricata* and isolation of the most active fractions represent an important step towards the effective

purification, characterization of the active principles in this extract and to understand the mechanism of cytotoxicity of these extracts. This study showed A. *muricata* is a promising new antioxidant and anticancer agent.[10]

The Potential of Ethyl Acetate Extract of A.*muricata* (EEAML) leaves to suppress the Azoxymethane (AOM) induced development of Colonic Aberrant Crypt Foci (ACF) in rats have been studied. The use of A. *muricata* leaves against cancer have been substantiated. After the EEAML oral administration in rats ACF was suppressed and it was followed by PCNA and BCl-2 protein down regulation. Meanwhile Bax Protein was up-regulated indicating a molecular level mechanism. AnnomuricinE, an Acetogenin was isolated from the extract which may be the partial reason for the pharmaceutical properties of A.*muricata* leaf extract. The proliferation of HT-29 cells was suppressed by this acetogenin selectively & resulted in apoptosis which was proven to be associated with G1 cell cycle arrest & mitochondrial mediated pathways.[11]

A comparative study was performed among the phytochemical constituents of graviola leaf extract (GLE), flavonoid –Enriched fractions (FEF)and Acetogenin enriched fractions. A seven fold enrichment of Rutin and three fold enrichment of Quercetin-3-glucoside (Q3G) in FEF was found compared to GLE. Rutin in FEF was found to be enhanced in *in vivo* pharmacokinetics & *in vitro* absorption kinetics of flavonoids compared to GLE. *In vitro* prostrate cancer proliferation, viability and toxigenic capacity was inhibited more effectively by GLE than FEF. GLE efficacy in tumor growth inhibition was observed 1.2 fold when orally administered 100 mg/kgthan FEF in human prostrate tumor xenografts. In FEF the concentration of Rutin and Q-3-G was more. There is a contradiction to the result which states the death of mice due to toxicity despite the superior *in vitro* and *in vivo* efficacy of AEF. GLE being absorbed in very low amount and its bioavailability achieved maximum efficacy, which also comprises other phytochemical groups including acetogenins that make up its natural complex environment.[12]

A study on the effect of A. *muricata* on human BPH-1 cells and prostrate organ was conducted by Asare G A et al.[13] The anti-proliferative effect of A. *muricata* was observed with IC_{50} of 1.36 mg/ml after 48 hours and at 72 hrs near cell extinction was observed. Bax gene found to be up-regulated while Bcl-2 was down regulated. All tests showed normal histological architecture. Test groups demonstrated marked atrophy and significantly reduced seminal vesicle ($P<.05$) with increased cellularity and the acnii, empty of secretion. Apoptosis of the glandular epithelium lining showing pyknotic nucleus, condensation and marginalization of the nuclear material were observed with reduced prostrate of test groups. Also to add prostrate secretion was scanty and with flattened acinar epithelial lining. A. *muricata* showed promising anti-proliferative effects on BPH-1 cells and possibly through apoptosis reduced prostrate size.[13]

MTT and LDH assays were conducted to observe the significance of EEAM leaves on HCT-116 and HT-29 cells, which showed significant cytotoxic effects. EEAM exhibited IC_{50} value of 11.43 ± 1.87 µg/ml and 8.98 ± 1.24 µg/ml against HT-29 and HCT-116 cells after 24 hour treatment. Cell cycle arrest was observed at G_1 phase by Flowcytometric analysis. The induction of apoptosis was confirmed by externalization of Phosphatidyl serine. Excessive accumulation of ROS followed by disruption of MMP by EEAM treatment. Both colon cancer cells showed cytochrome C leakage and activation of the initiator and executioner caspases. EEAM treatment was found to up regulate Bax and down regulate Bcl-2 proteins by Immunofluorescence analysis. HT -29 and HCT-116 cells migration and invasion was conspicuously blocked by EEAM. These findings provide a scientific basis for the use of A.*muricata* leaves in the treatment of cancer.[14]

Anti hyperglycemic activities of Annona *muricata*

A study on diabetic rats showed the leaf extracts of A. *muricata* have a significant reduction in the blood glucose concentration. Daily intraperitoneal administration of A. *muricata* extracts at 100mg/Kg to diabetic rats 15 consecutive days showed a statistically significant body weight increase despite the decrease in food and fluid intake. The study is with a promising result of improved glycemic control produced by extracts of A.*muricata*.[15]

Antimicrobial properties of Annona *muricata*

The cytopathic effects of Herpes simplex virus -1(HSV-1) was observed to be inhibited by stem bark ethanolic extracts of A. *muricata*. In another study the lytic activity of HSV-2 was found to be inhibited by methanolic extract of Annona sp. Antibacterial effect of A. *muricata* aqueous skin extract was observed against *Staphylococcus aureus* and *Vibrio cholera* at 50,100,150 and200µL/dish.[8]

Extracts from Soursop (A. *muricata*) pods made from water and ethanol were tested for effects against Staphylococcus aureus, Vibrio cholerae, at a concentration of 1:5, 1:10 in 50, 100, 150, 200µl volumes. Soursop aqueous extracts showed antibacterial effect against S.aureus and V.cholerae where as ethanolic extracts showed no activity. The greatest halos (16 and 23 mm) were observed at 200 µL/dish.[16]

Annona *muricata* against parasites.

A lot of studies on the antiparasitic activity of the extracts of A.*muricata* were conducted. A.*muricata* pericarp extracts from hexane, ethyl acetate and methanol were tested *in vitro* against Leishmania *braziliensis* and L.*panamensispromastigotes*. The ethyl extract was found to be more active than the other

extracts. Three acetogenins were isolated by fractionation namely Annonacin, Annonacin A and Annomuricin A.[17]

Anti-parasitic activity against E. *histolytica*, N. *brasiliensis*, M. *dessetae*and A. *salina* were tested by methanolic extracts of A.*muricata* and A.*cherimolia* (Annonaceae) seeds. The very effective activity on infective larvae of Molinemadestae was due to the isolated acetogenins from these extracts.[18]

Green synthesized silver nano particles using Annona *muricata* leaf extract was used to test the larvicidal activity against third instar larvae of three medically important mosquitoes, i.e., Aedes *aegypti*, Anopheles stephensi, and Culex *quinquefasciatus*. The aqueous crude leaf extract at different concentrations (30,60,90,120,150µg mL(-1)) and green synthesized Ag nanoparticles at different concentrations (AgNPs; 6, 12, 18, 24, 30 µg mL (-1)) against the larvae was tested for 24h. After the treatment of A. *muricata* significant larval mortality was observed in all mosquitos with lowest LC50 and LC90 values viz., A. *aegypti* (LC50 and LC90 values of 12.58 and 26.46 µg mL (-1)), A. *stephensi* (LC50 and LC90 values of 15.28 and 31.91 µg mL (-1)) and C. quinquefasciatus (LC50 and LC90 values of 18.77 and 35.72 µg mL (-1)), respectively. The green synthesized Ag NPs from A. *muricata* approach is a novel method to control mosquitos at a very low cost and in an eco friendly manner and seems to be very promising.[19]

Avery good to moderate level of anti-plasmodial activity was observed in the ethyl acetate and MeOH extract of A.*muricata* against CQ sensitive Plasmodium *falciparum* strain F32 (IC50 ranging from 7.2 to 9.2 µg/ml) but this activity seems to be ineffective against CQ resistant strain W2 (IC50 ranging from 10.4 to 38.6 µg/ml). A promising result with not only the antiplasmodial activity of A.*muricata* (DCM, MeOH and H2O extracts) (EC50< 10 µg/ml) but also the non toxicity of the extract to MDBK cells (SI = 66-756) was observed.[20]

Other important studies on A. *muricata*

Analgesic and Anti-inflammatory effect

There are a lot of other medicinal applications for the extracts from A.*muricata*. Some of them are listed below. In African traditional medicine unripe fruit of Annona *muricata* Linn. (Annonaceae) (soursop) is widely used for the treatment of neuralgia, rheumatism and arthritic pain. The analgesic and anti-inflammatory effects of lyophilized fruit extract A.*muricata* was studied in rodents. The mouse writhing, formalin and hot-plates tests were used to evaluate the analgesic activity where as the carrageenan-induced rat paw edema and xylene-induced ear edema tests were used to investigate the anti-inflammatory action. A. *muricata* pretreatment (50,100,200 mg/kg, p.o) caused the inhibition of writhes and formalin –induced pain in the late phase in a dose dependent manner (P<.001). In hot plate test time bounded increase in pain threshold was produced by A *muricata*. A *muricata* (50 or 100mg/kg) treatment caused the xylene induced ear edema. The anti-inflammatory effect exhibited by A *muricata* was prevented by pretreatment of mice with N(G)-nitro-l-arginine (20mg/kg, i.p., nitric-oxide synthase inhibitor) 15min before AM (200mg/kg, p.o.). The efffect of A.*muricata* was through the interaction with opiodergic pathway and through inhibition of chemical mediators of inflammation caused the anti inflammatory property.[21]

Antioxidant activity

A.*muricata* leaf extract have been reported to have antioxidant and anti inflammatory activities. The ethyl acetate extract of A.*muricata* leaves (EEAM) were used to study the gastro protective effects against ethanol induced gastric injury in rat models. The safety of the plant A *muricata* was demonstrated by the acute toxicity test of EEAM carried out in rats in a lower doses of 1 g/kg and in a higher dose of 2 g/kg. The EEAM antiulcer activity was performed in rats (five groups, n=6) with two doses of the extract (200 mg/kg and 400 mg/kg) and with omeprazole (20mg/kg) as a standard anti ulcer drug. The anti-ulcerogenic characterization of EEAM was observed in histological reports. The ulcer lesion index of rats was found to be significantly suppressed by the pretreatment of EEAM. The result was comparable to the omeprazole effect in the omeprazole control group.[22]

A significant increase in the level of nitric oxide and antioxidant activities which includes catalase, glutathione, and superoxide dismutase associated with attenuation in gastric acidity was caused to rats which were orally administered with EEAM. The loss of gastric wall mucus was also a compensatory effect. The marker for oxidative stress malondialdehyde was significantly reduced in rats pretreated with EEAM and also in addition to it prostaglandin E2 activity was also increased. Bax proteins were observed to be down regulated in immunohistochemical staining by EEAM where as Hsp7o was found to be upregulated after the pretreatment. Therefore it can be stated that the EEAM has the potential to be treated against ulcer by the suppressive effect against oxidative damage and the gastric wall mucus preservative effect.[22]

Radical scavenging action

The phytochemicals present in the methanolic and aqueous leaf extracts of A. *muricata* was characterized and its radical scavenging action was validated as well as the DNA protection activities were studied.[4] The active metabolites in the extracts were determined by the isolation of total phenolic contents which were subjected to HPLC analysis. A number of complementary assays were done to premeditate the radical scavenging activities. The study conducted to evaluate the A. *muricata* leaf extract revealed a rich source of numerous phytochemicals including luteolin, homoorientin, tangeretin, quercetin, daidzein, epicatechingallate, emodin and coumaric acid. The radical scavenging

activities ($p<0.05$) were significantlyshown by both the extracts. H_2O_2 induced DNA damage protection was found to be more in methanolic extract compared to aqueous extract. The total phenolic contents and radical scavenging potential of the extracts was found to be positively correlated.[4]

Wound healing potential

One of the numerous activities of A.*muricata* is its wound healing potential. The EEAM wound healing potential was evaluated by excisional wound models in rats. Antioxidants in the wound tissue homogenate namely catalase, glutathione peroxidase and superoxide dismutase and malondialdehyde (MDA) were measured. A significant wound healing activity was observed in the macroscopic and microscopic analysis of wounds by EEAM administration at two doses. The EEAM containing ointment when compared with the vehicle control was observed to cause a significant surge in antioxidants activities and MDA level decrease in the wound tissues. A conspicuous up–regulation of Hsp70 proteins in EEAM treated wounds was observed in the immunohistochemical evaluation, which suggest the anti-inflammatory effect of EEAM.[23]

Acetogenins from Annona *muricata*

Annonaceous acetogenins are a series of polyethers which contains either the adjacent or non adjacent tetrahydrofuran (THF) or Tetrahydropyran ring (THP) and also a.b unsaturated c-lactone ring. They possess the most beneficial antitumor, cytotoxic, antimalarial and antifeedant properties[24] (Ragasa Consolacion Y). Silica gel chromatography of the dichloromethane extract of the freeze-dried fruit of Annona *muricata* afforded annoreticuin-9-one, *cis*-annoreticuin and sabadelin. The structures of 1 and 2 were elucidated by extensive 1D and 2D NMR spectroscopy and confirmed by mass spectrometry.[20]

CONCLUSION

The use of traditional medicinal plants in modern medicine is widely increasing. The various active compounds present in the traditional medicinal plants possess cure for almost all remedies. Annona *muricata*, a traditional medicinal plant has undergone years of investigation and which is still under study is known to possess various phytochemicals which can be used for various ailments. It can be called as a "Complete plant" as none of its part is useless. Cancer which is one of the greatest maladies affecting the modern world can be tamed in the near future as this plant has the potential to become a wonder drug which can kill cancer cells sparing the normal cells with least side effects. A proper scientific investigation and dedicated research will open up the path to conquer dreadful diseases like cancer in the near future by *Annona muricata*.

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