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REVIEW ARTICLE **OPEN ACCESS**

Annona muricata L.: A Review on its Medicinal Values, Phytochemical and Pharmacological Activity

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ABSTRACT
Annona muricata L.(Annonaceae) is mostly distributed in the tropical and subtropical region of the world.This review focuses on the bioactivity of phytochemicals and pharmacological activity of extract and isolated compounds.The active components of these plant possess the potential to cure a number of diseases.The phytochemical studies reveal lots of phytochemicals, such as biologically active secondary metabolites like alkaloids, terpenoids, saponins, steroids, glycosides and tannins found in different parts of the plant.The biologically active compounds used for curing various ailments and possess potential anticancer,antidiabetic,anti-inflammatory,antioxidant,antimicrobial and immune enhancing effects,leads to the isolation and purification of new and novel biologically active compounds.
***Key words**:Annona muricata L.,natural products,bioactive compounds and bioactivity.*

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INTRODUCTION

Medicinal plants are the richest bio-resource of drugs of traditional system of medicine, modern medicines, nutraceuticals, food supplements, folk medicines, pharmaceutical intermediaries and chemical entities for synthetic drugs [1]. Phytochemicals are non-nutritive plant secondary metabolites that have protective or disease preventive properties[2].The knowledge of these phytoconstituents is very helpful in drug discovery and new drug molecule formulation [3,4,5].The WHO also has recognized the importance of traditional medicines and has been active in creating strategies, guidelines and standards for botanical medicines [6]. Phytochemical boost the host's anti-inflammatory defense and sensitize malignant cells to cytotoxic agents [7]. Efficacy testing of the traditional and new herbal products in experimental screening method is important to establish the active component and appropriate extract of the plant [8].Traditionally used medicinal plants produce a variety of bioactive compounds of known therapeutic properties [9,10]. The active substances inhibit the growth of pathogens or kill them and have no or least toxicity to host cells developing new antimicrobial drugs [11].

*Annona muricata L.*is a tropical fruit bearing tree in thr Annonaceae family.Annona muricata also known as Soursop or Graviola.The name soursop is due to sour and sweet flavour of its large fruit.This fruit is naturally occuring in warmest tropical area in south and north America,including Amazon and few parts of India.The plant became the basis of traditional medicine system all over the world for thousands of years and provide mankind with new and novel remedies.A review on a medicinal plant *Annona muricata* has a potent anticancer agents as acetogenine play a key role towards many types of cancer.The fruit is medicinally and economically valuable.The plant possess major pharmacological activities includes anticarcinogenic,antimalerial,antibacterial,antiparatic,wound healing activity.[12]

MEDICINAL VALUES

Annona muricata L. is substantially used as traditional medicines against many human diseases, especially cancer and parasitic infections. The fruit is a good source of natural medicine for arthritic pain, neuralgia, arthritis, diarrhea, dysentery, fever, malaria, parasites, rheumatism, skin rushes, and worms. Leaves are used to cure diabetes, headaches, and insomnia. Leaf's decoction is used to treat antirheumatic and neuralgic effects and cooked leaves are used to treat abscesses and rheumatism [13]. Seeds should be crushed can used to treat anthelmintic activities against worms and parasites both internally and externally. *A. muricata* is used for astringent, insecticide and pesticide and also used to cure coughs, pain

and skin diseases. Fruits and flower are used to cure catarrh and the root-bark and leaves are used to treat antichloristic and anthelmintic activities in India [14]. *A. muricata* leaves are used as an ethno medicine for tumors and cancer. Leaves, barks, and roots are used to treat the antimicrobial, anti-inflammatory, hypoglycemic, sedative, smooth muscle relaxant, hypotensive, and antispasmodic effects.

Phytochemicals:

Phytochemicals are important metabolites that areproduced using different parts of plants via theirprimary or secondary metabolism, have essentialfunctions in the plant for general growth and defenseagainst animals, insects and microorganisms [15,16].Primary metabolites such ascarbohydrates, lipids, and proteins have a directrelationship to the growth and metabolism of the plant.Secondary metabolites are derived from primary metabolites, which are notnecessary for survival, but are involved in significantfunctions in the plant, such as protection, competition,and species interactions [17,18]. These can be classified into three major groups based on theirbiosynthetic origins, phenolic compounds, terpenoids,and nitrogen/sulfur-containing compounds [19]. Thesecompounds investigated for use incarcinomatous-related diseases and revealed variousanti-cancer properties including, anti-proliferation andapoptotic cell death activity. In this review, wecategorize the plant metabolites according to theirstructure and discuss their anti-cancer activity. Phytochemical evaluations ondifferent parts of the A. muricata plant shown thepresence of various biological active compounds including alkaloids [20,23], megastigmanes[15], flavonol triglycosides [21], phenolics [22], cyclopeptides.A. muricata is rich source of annonaceous acetogenin compounds .

Table 1.Phytochemical compounds isolated from Annona muricata.

S.N.	Plant part	Bioactive compound	Secondary metabolite/Class	Biological Activity	Refernces
1.	Leaves, Pericarp	Annomuricin A,B,C	Annonaceousacetogenin	Toxicity against brine shrimp, lung A 549, breast MCF-7 and colon HT-29 cancer cells	[24,33,34]
2.	Leaves	Annomutacin	Annonaceousacetogenin	Toxicity against lung A549 cancer cells	[35]
3.	Leaves	Muricatocin A ,B and C	Annonaceousacetogenin	Toxicity against lung A549 cancer cells	[34,36]
4.	Leaves	Annopentocin A,B and C	Annonaceousacetogenin	Toxicity against pancreatic MIA PaCa-2 cancer cells and toxicity against lung A549 cancer cells	[39]
5.	Leaves	Murihexocin A,B and C	Annonaceousacetogenin	Toxicity against different cancer cells	[40,41]
6.	Leaves	Muricoreacin	Annonaceousacetogenin	Toxicity against different cancer cells	[41]
7.	Leaves	Cis-corossolone, Annocatalin, Annocatacin B	Annonaceousacetogenin	Toxicity against human hepatoma cells	[42,43]
8.	Leaves	AnonaineIsolaurelineXylopine Annonamine	Alkaloids	Neurotoxic	[44,45]
9.	Leaves	GallicacidEpicatechineCatechineChlorogenic acid QuercetinKaempferol	Flavonoltriglycoside	Neurotoxic	[26]
10.	Leaves	Rutin, Annoinol A,B and C ,Annoionoside, Vomifoliol, Roseoside, Turpinionoside A, Citroside A, Blumenol C, Loliolide	Megastigmane	Neurotoxic	[25]

11.	Fruits	Annonaine, Nornuciferine, Asimilobine	Alkaloids	Anti-depressive	[28,29]
12.	Fruits	Epomusenin-A and B, Epomurinin-A and B,	Annonaceousacetogenin	Anti-depressive	[30]
13.	Fruits	Muricin J,K and L	Annonaceousacetogenin	Toxicity against prostate PC-3 cancer cells	[32]
14.	Fruits	Cinnamic acid derivative, Coumaric acid hexose, p- Coumaric acid, Caffeic acid derivative, Dicaffeoylquinic acid, Feruloylglycoside	Phenolic	Toxicity against prostate PC-3 cancer cells	[27]
15.	Fruits	p- Coumaric acid methyl ester, Dihydrokaempferol-hexoside, 4-feruloyl-5-caffeoylquinic acid	Phenolic	Toxicity against prostate PC-3 cancer cells	[27]
16.	Roots	Montecristin, Cohibin A and B,	Annonaceousacetogenin	Neurotoxic	[46,47]
17.	Roots	*cis*-solamin,*cis*-panatellin,*cis*-uvariamicinI,IV,*cis*-reticulatacin, *cis*-reticulatacin-10-one	Annonaceousacetogenin	Neurotoxic	[48]
18.	Roots	Chatenaytrienin 1,2 and 3	Annonaceousacetogenin	Neurotoxic	[49]
19.	Roots	Muridienin 3 and 4	Annonaceousacetogenin	Neurotoxic	[49]
20.	Roots	Muricadienin, Coronin	Annonaceousacetogenin	Neurotoxic	[49,50]
21.	Seeds	Muricin A,B,C,D,E,F,G,H,I	Annonaceousacetogenin	Toxicity against human hepatoma cells	[42,52]
22.	Seeds	*cis*-annomontacin, Annonacinone, Xylomaticin	Annonaceousacetogenin	Toxicity against human hepatoma cells	[42]
23.	Seeds	Annoreticuin-9-one	Annonaceousacetogenin	Toxicity against human hepatoma cells	[31]
24.	Seeds	N-fatty acyl tryptamines	Alkaloids	Toxicity against human hepatoma cells	[37]
25.	Seeds	Donhexocin, cohibin C and D, Muricatenol, Annomontacin	Annonaceousacetogenin	Crown gall tumor inhibition, toxicity against brine shrimp,A549,breast MCF-7 and colon HT-29 cancer cells	[37,38,51]

PHARMACOLOGICAL ACTIVITY

Anticancer activity

A lot of studies report the significance antitumor effects of different extract of the plant and isolated Annonaceous acetogenin towards various cancer cell lines[33,62-65],few of these studies have illustrated the underlying mechanism of action (Table 2).Recent in vitro studies to determine the mechanism of action ethyl acetate extract of *Annona muricata L.* leaves against colon cancer cells(HT-29 and HCT-116)and lung cancer cells (A-549).The leaf extract was able to induce apoptosis in colon and lung cancer through the mitochondrial mediated pathways. This cyto- protective effect was associated with cell cycle arrest in the G1 phase[52,54].In addition the migration and invasion of colon cancer cells were significantly inhibited by the leaf extract. The activation of caspase 3 by the ethanolic extract of the leaves also demonstrated an apoptosis inducing effect in myelogenous leukemia K562 cells, which was confirmed with a TUNEL assay [55].

Table 2.Anticancer studies on *Annona muricata L.*

S.N.	Plant part	Subject of study	Effect	Reference
1.	Leaves extract of ethyl acetate	Lung A549 cancer cells	Mitochondrial-mediated apoptosis, cell cycle arrest at G1 phase	[52]
2.	Leaves extract of ethyl acetate	Colon HT-29 and HCT-116 cancer cells	Mitochondrial-mediated apoptosis, cell cycle arrest at G1 phase, suppression of migration and invasion	[54]
3.	Leaves extract of ethyl acetate	Azoxymethane induced colon cancer	Reduction of ACF formation	[61]
4.	Leaves extract of ethyl acetate	Colon HT-29 cancer cells	Bioassay-guided isolation of annomuricin E and its apoptosis inducing effect	[61]
5.	Leaves extract of water	Rat's prostate	Reduction of prostate size	[56]
6.	Leaves extract of ethanol	Breast tissues of mice	Prevention of DMBA-induced DNA damage	[57]
7.	Leaves extract of ethanol	DMBA/croton oil induced mice skin papillomagenesis	Suppression of tumor initiation and promotion	[58]
8.	Leaves extract of ethanol	DMH induced colon cancer	Reduction of ACF formation	[59]
9.	Leaves extract of ethanol	K562 chronic myeloid leukemia cells	Induction of apoptosis	[55]
10.	Leaves boiled in water	Metastatic breast cancer	Stabilization of disease	[60]

Antiparasitic activity

Protozol infections because crippling disease, such as leishmaniasis and trypanosomiasis, which have both, afflicted a noteworthy proportion of the world population. The development of resistance to empirically discovered drugs represents a major hindrance to treatment of protozoal disease. A natural agent, *Annona muricata* has been subjected to various pathogenic parasites to determine its cytotoxic effects [66,67,68](Table 3)

Table.3.Antiparasitic studies on *Annona muricata* L.

S.No.	Plant part	Subject of study	Result	Reference
1.	Leaves extract of ethyl acetate	*Leishmania* species (PH8, M2903, PP75), *T. cruzi*	IC50 values lower than 25 µg/mL	[68]
2.	Pericarp extract of ethyl acetate	*L. braziliensis*, *L. panamensis*	Toxicity effect higher than Glucantime as a positive control	[33]
3.	Seed extract of methanol	*L. donovani*, *L. mexicana*, *L.major*	Bioassay-guided isolation of annonacinone (EC50: 6.72–8.00 µg/mL) and corossolone (EC50: 16.14–18.73 µg/mL)	[66]
4.	Seed extract of methanol water	*L. chagasi*	Bioassay-guided isolation of annonacinone and corossolone	[67]
5.	Leaves extract of water	*H. contortus*	Toxicity against larvae (89.08%) and egg (84.91%)	[69]
6.	Leaves extract of pentane	*P. falciparum*	Toxicity against chloroquine sensitive and (IC50: 16 µg/mL) and resistant strains (IC50: 8 µg/mL)	[70]

Antioxidant activity

Several reports described the antioxidant properties of various *A.muricata* derived extracts. Gavamukulya *et al*. tested the antioxidant potential of ethanolic and aqueous extracts of graviola found in Eastern Uganda using 2,2-diphenyl-2-picrylhydrazyl (DPPH•) and reducing power assays [72].Results indicated that the ethanolic extract was superior to the aqueous extract with respect to both reducing power and in vitro antioxidant activity and the ethanolic extract, but not the aqueous extract, was selectively cytotoxic to three tumor cell lines as opposed to no effect on normal spleen cells [72]. George et al. compared methanolic and aqueous extracts of graviola with respect to their free radical scavenging and DNA protective properties using several assays including a ferric reducing antioxidant property assay, a DPPH•radical scavenging assay, a hydroxyl scavenging activity assay (HRSA), and a DNA damage

protective activity [73]. These authors also carried out HPLC analysis of phenolic compounds in methanolic and aqueous extracts. Both graviola extracts were found to possess significant radical scavenging assays, and a strong positive correlation was seen between the total phenolic content and the radical scavenging activity of each extract. The methanolic extract was found to confer superior protection against hydrogen peroxide-induced DNA damage [73]. Moghadamtousi *et al.* applied an ethyl acetate extract of graviola leaves to skin wounds in rats [71]. Son et al. studied the antioxidant properties of steam and 50% ethanol extracts of *A.muricata* leaves in HepG2 cells [74]. Their results, standardized in some cases to vitamin C equivalents, indicated that the 50% ethanol extracts superior than steam extracts in scavenging peroxy and nitrogen radicals, although both were effective.

Antidiabetic activity

The chronic disease of diabetes mellitus afflicts a large proportion of people all over the world. The traditional application of *A. muricata* against diabetes, various studies have investigated this potential *in vivo*. Adeyemi and colleagues reported that daily intraperitoneal injection of streptozotocin-induced diabetic Wistar rats with methanol extract of *A. muricata* leaves (100 mg/kg) for two weeks significantly decrease their blood glucose concentration from 21.64 to 4.22 mmol/L . and the extract at the same dose significantly reduce the serum total cholesterol, low-density lipoprotein, triglyceride and very low-density lipoprotein cholesterol.[75]

Anti-inflammatory and anti-nociceptive activity

Anti-inflammatory activity similar to the activity presented by indomethacin, which is a non-steroidal anti-inflammatory, reported in [76,78].The anti-nociceptive effect of ethanolic and alcoholic extracts of *Annona muricata* has been reported using various chemical and thermal nociceptive models. *Annona muricata* produced anti-nociception action of activity in both neurogenic and inflammatory phases [77]. Metabolites of arachidonic acid are involved in inflammation process [76]these metabolites are produced by cyclooxygenase and lipoxygenase; cell is activated by mechanical trauma, cytokines, growth factors orother stimuli. It has been proposed that the mechanism of antinociception may be by inhibition of cyclooxygenase and lipoxygenases.[76].

Anti-microbial activity

The antibacterial effect of the methanolic, ethanolic and aqueous extract of theleaves,roots,fruits of *Annona muricata* was tested against various bacterial strains such as *Staphylococcus aureus, Escherichia coli, Proteus vulgaris, Streptococcus pyogenes, Bacillus subtilis, Salmonella typhimurium, Klebsiella pneumonia, Vibrio cholerae* and *Enterobacter aerogenes*. Different plant part extract of *Annnona muricata* is used in the treatment of various bacterial infectious diseases such as pneumonia, diarrohea, urinary tract infection and some skin disease. *Annona muricata L.* methanolic, ethanolic extracts contains activity against a group of bacteria that are responsible for the most common bacterial diseases. Thus, the plant possesses an abundant of the antimicrobial compounds.[79,80]

CONCLUSION

Medicinal plants were the potent source of human health due its bioactive compounds that is responsible for its various pharmacological activities. In contempt enhanced synthetic small molecule-based targeted anticancer therapies with improved patient prognosis, cancer remains a leading cause of death worldwide, as a result of challenges including increased toxicity and development of resistance to treatment agents. Secondary metabolite found in medicinal plant has great promise for the treatment of cancer. This review demonstrates *Annona muricata L.* anticancer potential and other health-related benefits by providing insights into its biologically active chemical constituents as well as the in vitro and in vivo studies that have been carried out in order to interpret the molecular mechanisms of action of these constituents.

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