REVIEW ARTICLE

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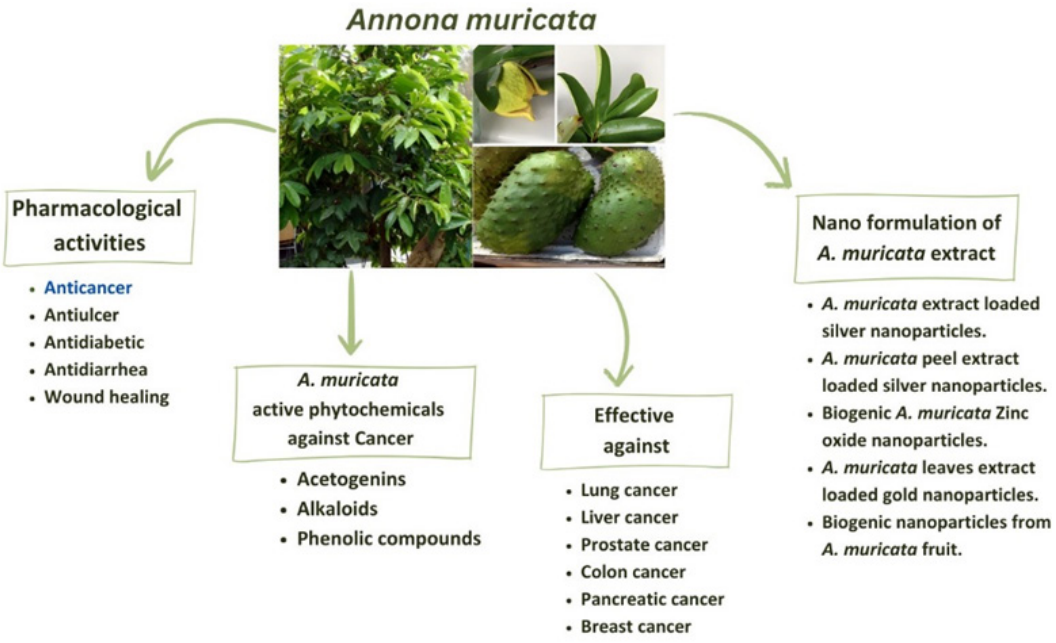
S. Samaratunga and Nuwanthi P. Katuwavila*



Highlights

- *Annona muricata* plant is rich in phytochemicals like annonaceous acetogenins, alkaloids, and flavonoids.
- *Annona muricata* has an anticancer effect against the lung, liver, prostate, colon, pancreas, and breast cancers.
- *Annona muricata* has considerable toxicity and possible adverse effects.
- The use of nanoparticles loaded with *A. muricata* is an efficient treatment for cancer.

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Evaluation of the Anticancer Properties of the Phytochemicals Present in *Annona muricata*

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Abstract: Cancer is a complex disease characterized by the unrestrained proliferation and dissemination of abnormal cells. The issue continues to be a notable public health concern on a global scale, with millions of new cases and fatalities being reported annually. Despite significant advances in cancer treatment, it remains a major challenge due to the high cost and toxicity of current therapies. Phytochemicals naturally found in plants are crucial resources for developing novel drugs and potential cancer therapies. The clinical efficacy of these anti-cancer agents has been demonstrated against diverse neoplastic cell lines. Additional investigation in this field can result in improved cancer therapies. Among many other plants effective against cancer, this literature review explores the anti-cancer properties of *Annona muricata*, a plant commonly known as soursop, which is a tropical plant species native to Central and South America, the Caribbean, and West Africa known for its edible fruit which has some medicinal merits, but also some toxicological effects. *Annona muricata* has been traditionally used for medicinal purposes, including cancer treatment. Acetogenins, alkaloids, phenolic compounds, and other active compounds are only a few of the phytochemicals that this review cites as being present in *A. muricata*. The review also looks into *A. muricata*'s biological abilities to fight lung, liver, prostate, colon, pancreas, and breast cancers. The toxicity of *A. muricata* and possible adverse effects are also covered in the review. The review also looks at the usage of nanoparticles with *A. muricata* as a cancer treatment. Overall, this literature review provides valuable insights into the potential anti-cancer properties of *A. muricata* and its potential as a therapeutic agent in cancer treatment.

***Keywords*:** *Annona muricata*; Anti-cancer; Phytochemicals; Nanoparticles

INTRODUCTION

Annona muricata, commonly called graviola or soursop, is a species of the Annonaceae family (Nirmala et al., 2011; Padmanabhan & Paliyath, 2016). *Annona muricata* is an important plant, and many studies have identified its therapeutic effects (Gavamukulya et al., 2017; Prasad et al., 2019). It is a tropical fruit indigenous to Mexico, Brazil, Cuba, Peru, and Venezuela (Bhat & Paliyath, 2016). However, it is presently widespread in tropical and subtropical regions of the world, including Sri Lanka, India, Malaysia, and Nigeria. Furthermore, the fruits of the *A. muricata* tree are ingested raw or processed into various foods. This fruit is an excellent source of dietary fiber and vitamins C, B1, and B2 (Pinto et al., 2011). *Annona muricata* is a 5–8 m tall, evergreen, terrestrial, erect tree with an open, roundish canopy and large, lustrous, dark green leaves. The diameter of edible fruits ranges between 15 to 20 cm, and they are large, heart-shaped, and green in color (Moghadamtousi et al., 2015). Various parts of the *A. muricata* plant, like the leaves, bark, fruit, and seeds, have been used in traditional medicine for generations (Badrie & Schauss, 2010; Coria-Téllez et al., 2018). Medicinal plants are considered to be the foundation of health maintenance and treatment across the world. Since chronic degenerative illnesses have become widespread and are regarded as severe health issues, it is crucial to find effective therapies (Sofowora et al., 2013). Cancer is a pathological disorder that has cell cycle dysfunction as its fundamental cause. The capacity to impede the advancement of the cell cycle in malignant cells can significantly enhance the anti-neoplastic efficacy of naturally occurring substances (Mantena et al., 2006). The main objective of this review is to understand the anti-cancer properties of *A. muricata* plant derivatives, particularly those extracted from its leaves and fruit, and to find the safest suitable substitute for synthetic drugs that have been used for a long time to treat cancer. These synthetic drugs may have harmful side effects, which can be avoided mostly with naturally derived drugs (Tewari et al., 2019). Accordingly, this article discusses which *A. muricata* derivatives are more effective on specific cancer conditions. Also, focuses on specific phytochemicals present in *A. muricata* with anti-cancer properties, extraction methods and processes of identification of phytochemicals and importance of using *A. muricata* phytochemical loaded nanoparticles for cancer treatment. According to previous research studies carried out during the period of the year 2016 to 2023, *A. muricata*-derived compounds show various anti-cancer properties, including cytotoxicity, induction of apoptosis, necrosis, and inhibition of various cancer cell lines such as breast cancer, liver cancer, prostate cancer, pancreatic cancer, Lung cancer, and colon cancer (Torres et al., 2012; Asare et al., 2014; Endrini et al., 2014; Liu et al., 2016; Abdullah et al., 2017; Kim et al., 2018; Rady et al., 2018; Yajid et al., 2018; Salac et al., 2022). According to the previous literature, more than two hundred chemical compounds have been identified and isolated from the *A. muricata* plant (Coria-Téllez et al., 2018). Acetogenins, alkaloids, and phenols are the most common classes of compounds found in plant extractions (Gavamukulya et al.,

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2017). Previous research studies relied heavily on leaves and seeds as primary plant organs in their investigations (Gavamukulya et al., 2017). Several *in-vitro* studies of *A. muricata* extracts have identified their anti-microbial, anti-inflammatory, anti-protozoan, antioxidant, insecticidal, larvicidal, and cytotoxic activities. Further, *in-vivo* studies on *A. muricata* crude extracts confirmed that its isolated compounds possess anxiolytic, anti-stress, anti-inflammatory, contraceptive, anti-tumor, antiulcer, wound healing, hepato-protective, anti-icteric, and hypoglycemic activities (Coria-Téllez et al., 2018).

Figure 1: *Annona muricata* tree

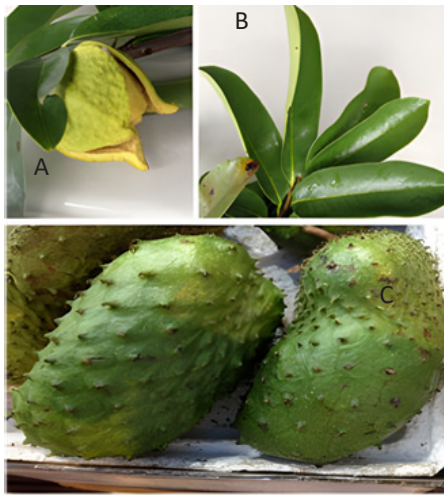

Figure 2: Annona muricata plant parts
(A: Flower, B: Leaves, C: Fruit)

Annona muricata: Active phytochemicals, anti-cancer properties, and toxicity studies

Active phytochemicals in *Annona muricata*

Phytochemicals are constitutive metabolites produced by various plant components through their primary or secondary metabolism. They support vital functions for plant growth and protection against animals, insects, microorganisms, and abiotic stress (Coria-Téllez et al., 2018). Previous studies have proved the presence of various compounds and secondary metabolites in the *A. muricata* plant. The principle chemical constituents of *A. muricata* are acetogenins, alkaloids, flavonoids, essential oils, vitamins, carotenoids, amides, and cyclopeptides (Coria-Téllez et al., 2018). The plant also contains minerals, including K, Ca, Na, Cu, Fe, and Mg. Furthermore, it has been proven that regular consumption of *A. muricata* fruit can provide essential nutrients and elements to the human body (Moghadamtousi et al., 2015; Mutakin et al., 2022).

Acetogenins

Acetogenin (AGE) is the most abundant of the main compounds in *A. muricata*. The acetate pathway produces the long-chain fatty acid derivative acetogenin, which is abundant in the Annonaceae family (Mutakin et al., 2022). Acetogenins contain a long aliphatic chain of 35–38 carbons bonded to a g-lactone a-ring, terminally substituted by β-unsaturated methyl and tetrahydrofurans (THF) positioned along the hydrocarbon chain (Sun et al., 2016). Over 120 acetogenins have been identified in ethanolic, methanolic, or other organic extracts of the leaves, stems, bark, seeds, pulp, and fruit peel of *A. muricata*. Notable examples include annonacin, annohexocin, muricoreacin, and murihexocin (from leaves), reticuline, coclaurine, coreximine, atherosperminine, stepharine, anomurine, and anomuricine (from stems and bark), and sabadelin, annohexocin (from fruit pulp) (Ragasa et al., 2012; Coria-Téllez et al., 2018). These acetogenins exhibit diverse biological activities, including cytotoxic effects against various cancer cell lines. However, annonacin (Figure 3) is the most prevalent acetogenin isolated from *A. muricata* leaves (Champy et al., 2004). Acetogenins are significantly more cytotoxic than alkaloids and rotenone (Errayes et al., 2020). Biological and phytochemical investigations of the fruit of *A. muricata* also revealed a diverse array of AGE compounds (Errayes et al., 2020). The acetogenins present in the *A. muricata* plant can play a substantial role in treating various types of cancers, because acetogenins are potent inhibitors of nicotinamide adenine dinucleotide oxidase in the mitochondrial membrane of cancer cells, and it generates reactive oxygen species (ROS) (Bedard & Krause, 2007). Cancer cells often rely on ROS for signaling pathways that promote their growth and survival (Singh & Manna, 2022). Nicotinamide adenine dinucleotide oxidase inhibition disrupts this ROS pathway by hindering the production of detrimental molecules and potentially compromising the metabolic advantage of cancer cells (Jacob et al., 2022). The anti-cancer properties of AGEs are initiated by inhibiting the cell's mitochondrial complex 1 enzyme, mitochondrial NADH: ubiquinone oxidoreductase, leading to a decrease in ATP production, which is crucial for cancer cell survival and proliferation. This inhibition disrupts the energy production in cancer cells, induces oxidative stress, and triggers apoptotic pathways (Daddiouaissa & Amid, 2018; Urra et al., 2017). According to various research, the acetogenins in *A. muricata* exhibit neurotoxic effects in rodents (Coria-Téllez et al., 2018). The effects mentioned involve a decrease in energy production in cells that produce dopamine and the degeneration of nerve cells in the basal ganglia. Annonacin, a compound, is more harmful than the pesticide rotenone (Lannuzel et al., 2006; Escobar-Khondiker et al., 2007; Höllerhage et al., 2009). Surprisingly, certain investigations have not detected alterations in behavior or movement in these

animals, despite the occurrence of neurodegeneration. Additional investigation is required to comprehend this neurodegeneration's extended ramifications and possible behavioral outcomes. Additional research is required to determine the precise mechanisms of action, long-term safety, optimal dosage, and potential adverse effects of acetogenins (Daddiouaissa & Amid, 2018).

Alkaloids are a heterogeneous class of naturally occurring secondary metabolites derived from amino acids or the transamination process. According to previous studies, approximately 22 alkaloids have been identified in *A. muricata* leaves (Dey et al., 2017; Wahab et al., 2018). Reticuline (figure 4) and coreximine (figure 5) (Leboeuf et al., 1981) are the most abundant alkaloids in *A. muricata*, and leaves contain the highest alkaloid concentration (Fofana et al., 2012; Matsushige et al., 2012), although they have also been detected in roots, stems, and fruit (Hasrat et al., 1997; Coria-Téllez et al., 2018). Notably, isoquinoline, aporphine, and protoberberine alkaloid types were the most frequently isolated from *A. muricata* (Mohanty et al., 2008).

Phenolic compounds

Annona muricata has reportedly been found to contain thirty-seven phenolic compounds. Important phenolic compounds present in the leaves of *A. muricata* include quercetin (figure 6) (Nawwar et al., 2012) and gallic acid (Correa Gordillo et al., 2012; Wahab et al., 2018). Because most phenolic compounds are water-soluble, they are considered essential phytochemicals, as the aqueous infusion is the most commonly used extract in traditional medicine (Coria-Téllez et al., 2018).

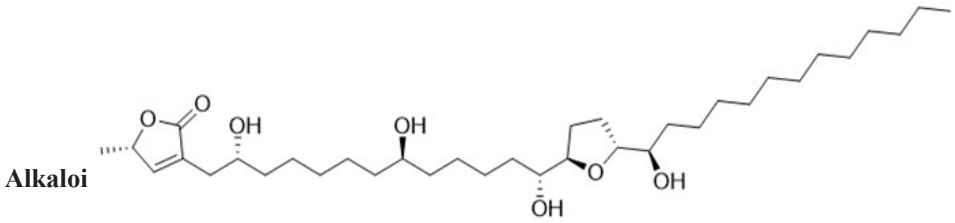

Figure 3: Annonacin (Most common acetogenins in *A. muricata*)

Table 1: Common Alkaloids and their Medical Applications.

Alkaloid	Medicinal Applications	Plant Part	Reference
Reticuline	Anti-cancer, Anti-angiogenic, Anti-bacterial, Anti-viral, Anti-inflammatory, Analgesic, Anti-proliferative	Seeds, Leaves, Peel, Fruit pulp	Cárdenas et al., 2021; Ilango et al., 2022; Patil et al., 2023
Coreximine	anti-inflammatory, Antibacterial, Antioxidant, Antiparasitic, Anti-cancer	Leaves, Seeds, Fruit pulp	Addai et al., 2020; Algeryani et al., 2020; Mutakin et al., 2022
Isoquinoline	Anti-proliferative, Anti-parasitic, Anti-fungal, Anti-cancer, Anti-inflammatory	Leaves, Seeds, Fruit pulp	Errayes et al., 2020; Miranda et al., 2021; Kazman & Hanrahan, 2022; Campos et al., 2023
Aporphine	Antidepressant, Antidiabetic, Anti-proliferative, Anti-fungal, Anti-cancer	Stem bark, Leaves, Seeds	Addai et al., 2020; Ilango et al., 2022; Bikomo et al., 2023; Campos et al., 2023; Zubaidi et al., 2023
Protoberberine	anti-cancer, anti-microbial, antioxidant, anti-ulcer, anti-diabetic, anti-hypertensive, Antidepressant	Leaves, Seeds, Stem bark, Fruit peel	Addai et al., 2020; Abdallah et al., 2023; Bikomo et al., 2023; Zubaidi et al., 2023

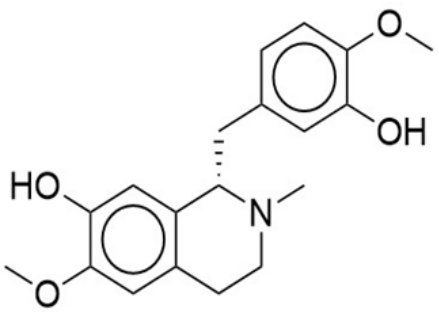

Figure 4: Reticulin

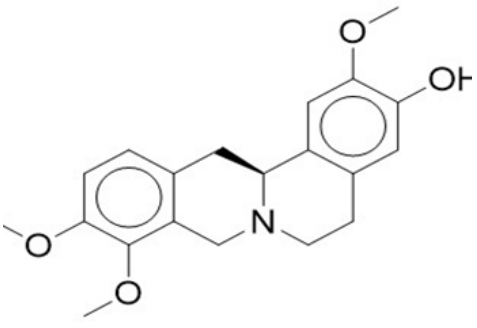

Figure 5: Coreximine

Table 2: Common Phenolic compounds and their Medicinal Applications.

Phenolic compound	Medicinal Applications	Plant Part	Reference
Quercetin	Antioxidant, Anti-inflammatory, Anti-angiogenic	Leaves, Bark, Seeds, Fruit peel	(Addai et al., 2020; Cárdenas et al., 2021; Abdallah et al., 2023; A. U. Ezirim et al., 2024)
Gallic acid	Antioxidant, Anti-inflammatory, Anticancer, Antidiabetic, antiproliferative	Leaves, Bark, Fruit	(A. U. Ezirim et al., 2024; Olude & Omoregie, 2023; Onyeike et al., 2023; Rameshwari & Keerthiga, 2023)
Epicatechin	Anticancer, Antiproliferative, Anti-tumorigenic, Antioxidant	Leaves, Seeds, Fruit peel, Fruit pulp	(Addai et al., 2020; Dalal & Medithi, 2022; Abdallah et al., 2023; A. U. Ezirim et al., 2024)
Rutin	Antidiabetic, Antioxidant, Anti-inflammatory, Anticancer	Roots, Leaves, Bark	(Bidzhieva & Chiriapkin, 2023; Rameshwari & Keerthiga, 2023; Zubaidi et al., 2023)

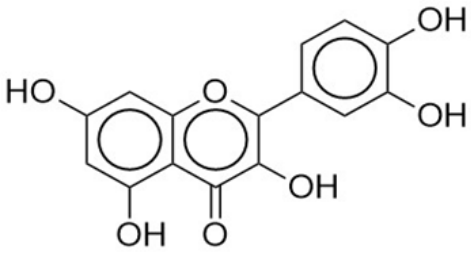

Figure 6: Quercetin

Other compounds

In addition to the significant compounds found in *A. muricata* plants, vitamins, carotenoids, amides, cyclopeptides, and megastigmanes have also been identified. According to the literature, vitamins and carotenoids have been found mainly in leaves, seeds, and fruit pulps (Correa Gordillo et al., 2012; Vijayameena et al., 2013). The seeds also contain amide, N-p-coumaroyl tyramine and cyclopeptides (Wélé et al., 2004), demonstrating anti-inflammatory and anti-tumor properties (Coria-Téllez et al., 2018). According to a previous study megastigmanes are present in the leaves of *A. muricata,* which are neither cytotoxic nor antioxidant active (Matsushige et al., 2012). According to previously published data, the fruit content of *A. muricata* contains 37 volatile compounds, most of which are aromatic and aliphatic esters (Leite Neta et al., 2019). Additionally, 80 essential oils, primarily sesquiterpenes derivatives (Thang et al., 2013), have been identified in the leaf and have demonstrated cytotoxic activity against the MCF-7, a human breast carcinoma cell line (99.2% kill at 100 g/ml). The bioactivity of *A. muricata* volatile compounds makes their investigation promising (Owolabi et al., 2013; Coria-Téllez et al., 2018).

Toxicology of *Annona muricata* on normal cell lines

The toxicological profile of *Annona muricata* varies depending on the specific plant part utilized and the solvent employed, and the reported toxicity of the extracts is subject to variation based on these factors (Coria-Téllez et al., 2018). This section focuses on the effects of *Annona muricata* extracts on normal cell lines. Additionally, the toxicity may manifest as acute or neurotoxic (Coria-Téllez et al., 2018). The results of the studies indicate that the aqueous extracts of the leaves, flowers, and pulp exhibited an LD_{50} value greater than 5 g/kg and the methanolic and ethanolic extracts demonstrated an LD_{50} value greater than 2 g/kg, classifying these extracts as non-toxic (de Sousa et al., 2010; Coria-Téllez et al., 2018). The lethal dose median of the aqueous extract of leaves surpasses the anticipated human consumption rate of approximately 211 mg/kg per day, based on the average individual's intake of one cup of soursop tea thrice daily (Arthur et al., 2011). Thus, for an individual to attain a fatal dosage of soursop leaf infusion, it would necessitate the consumption of over 71 cups of tea per day. According to the report, it has been observed that administration of the aqueous extract at doses exceeding 5 g/kg may result in renal impairment (Arthur et al., 2011). In contrast, a dose of 1 g/kg has been found to exhibit hypoglycemic and hyperlipidemic properties. The study conducted by M. Syahida indicates that the consumption of *A. muricata* pulp for 28 days did not exhibit any discernible impact on blood hematology and serum biochemistry (Syahida et al., 2012). Another study examined the toxicity of crude leaf extract and its flavonoid and acetogenin-enriched extracts. The findings indicate that the acetogenin-enriched extract exhibited more toxicity than the other extracts (C. Yang et al., 2015). A research study suggested that the entire extract may possess comparable bioactive

properties to its fractions or isolated constituents, albeit without their associated toxicity (Coria-Téllez et al., 2018). There are research endeavors to evaluate the neurotoxic impact of the primary bioactive constituents of *A. muricata*, namely alkaloids and acetogenins (Caparros-Lefebvre et al., 2002; Shaw & Höglinger, 2008). The findings of these research studies suggest that certain isolated compounds can potentially induce neurotoxicity and neurodegenerative diseases in murine models (Coria-Téllez et al., 2018). According to a previous study (Lannuzel et al., 2006; Escobar-Khondiker et al., 2007; Höllerhage et al., 2009) the reticuline and coreximine alkaloids, as well as solamin, annonacinone, isoannonacinone, and annonacin acetogenins, exhibited toxicity towards dopaminergic cells by hindering energy production. In one of the studies the toxicity of *A. muricata*-derived annonacin was found to exceed that of the pesticide rotenone, which was employed as a positive control (Lannuzel et al., 2006). According to other research investigations, it has been reported that annonacin penetrates the brain parenchyma in murine models, leading to a reduction in ATP levels and the onset of neurodegeneration in the basal ganglia (Champy et al., 2005; Lannuzel et al., 2006). As per these findings, neurodegeneration did not elicit any alterations in the behavior or locomotor activity of the rodents. According to published data regarding neurotoxicity a total of seven acetogenins were assessed through the utilization of mesencephalic dopaminergic neurons, rat striatal neuron cells, and laboratory rats. According to another study the neurotoxicity of annonacin and reticuline, the primary acetogenin and alkaloid in *A. muricata*, was observed (Guadaño et al., 2000; Champy et al., 2005; Lannuzel et al., 2006; Escobar-Khondiker et al., 2007). The toxicity of annonacin towards neuronal cell cultures exhibits significantly a greater magnitude than that of reticuline, estimated to be approximately 1000. In addition, it exhibits a potency level estimated to be approximately 100 times greater than 1-methyl-4-phenyl pyridinium (MPP), a widely recognized neurotoxin accountable for inducing Parkinsonism in human and animal subjects. The current study involved the intravenous administration of isolated annonacin to laboratory rats. The administered dosage to the rats was determined through a calculation that considered the estimated intake of annonacin by an individual who habitually consumes fruit or canned nectar for a year. The results obtained from the neurotoxicity investigations carried out on annonacin suggest that the manifestation of its impacts in murine models requires extended exposure to this molecule. Furthermore, pharmacokinetic investigations have approximated the diminished bioavailability of annonacin and reticuline (Chan et al., 2019). The research findings indicate that *A. muricata* and its components possess properties that safeguard the liver, induce neurotoxicity, alleviate pain, prevent ulcers, and prevent the onset of cancer. Furthermore, the translation of toxicity effects from animal studies to humans may not be directly applicable due to differences in the dose and duration of exposure, and based on the research (Chan et al., 2019), it can be concluded that *A. muricata* exhibits a favorable safety and tolerability profile. The concentrations of *A. muricata* extracts, particularly their effectiveness against cancerous cells, indicate that there are variations in the metabolic rates and energy levels between cancerous cells and normal cells. Cancer cells rely heavily on oxidative phosphorylation for energy and have a faster metabolic rate compared to normal cells. As a result, they are more susceptible to the effects of complex I mitochondrial enzymes caused by acetogenins. The inhibition of certain processes disrupts the normal functioning of mitochondria and the synthesis of ATP, leading to the programmed cell death of cancer cells. Regular cells, with their lower metabolic activity and alternative energy production pathways, are not as greatly affected by these disruptions. In addition, cancer cells generate elevated levels of ROS, which enhances the effectiveness of cholesterol acetogenin in killing cancer cells by inducing oxidative stress and apoptosis. Normal cells exhibit a higher tolerance to oxidative stress, resulting in a specific susceptibility to the effects of *A. muricata* extracts (Wahab et al., 2018; Hadisaputri et al., 2021; López et al., 2023).

Anticancer activity of *Annona muricata*

The medicinal potential of *A. muricata* extracts has been observed among various botanical products (Nwokocha et al., 2012; Lee et al., 2016). Several studies have established a correlation between compounds derived from *A. muricata* and various anti-cancer effects, such as cytotoxicity (Wu et al., 1995; Zeng et al., 1995), apoptosis induction (Ezirim et al., 2013; Pieme et al., 2014), necrosis (Torres et al., 2012), and proliferation inhibition on different cancer cell lines (Moghadamtousi et al., 2014; Sun et al., 2014; Moghadamtousi, Rouhollahi, et al., 2015). These cancer types include breast (Zeng et al., 1995), prostate (Sun et al., 2014), colorectal (Moghadamtousi, Rouhollahi, et al., 2015), lung (Kim et al., 1998), leukemia (Valencia et al., 2011), renal (Zeng et al., 1995), pancreatic (Zeng et al., 1995), hepatic (Kuete et al., 2016), oral (Hla Myint et al., 1991), melanoma (Ménan et al., 2006), cervical (Astirin et al., 2013), and ovarian cancers (Ge et al., 2011). Moreover, all aerial parts of this plant, including the bark, fruit, leaves, seeds, and root system, are used as natural medicines in the tropics. Further research is required to establish the safety and efficacy of care regimes (Rady et al., 2018).

***Annona muricata* against breast cancer**

The global incidence of breast cancer has increased, making it the second most prevalent cancer among women. Complementary and alternative medicine is a common practice to manage treatment-related symptoms, mitigate side effects, improve survival rates, and enhance the quality of life among individuals diagnosed with breast cancer (Liao et al., 2013). One such conventional medicinal plant that has gained popularity as an anti-cancer treatment for breast cancer is *A. muricata*. However, further comprehensive investigation is necessary to fully understand its potential as a cancer treatment (Hadisaputri et al., 2021). In this study, four solvent extracts were prepared from *A. muricata* leaves. The four solvents were ethanol, ethyl acetate, n-hexane, and water. This study evaluated and compared the anti-proliferation and cytotoxic activity of these extracts in MCF7 (Michigan Cancer Foundation-7) breast cancer cells compared with that on CV1 normal kidney cells. The

cell morphology of both MCF7 breast cancer cell lines and CV1 normal kidney cells was observed by staining with a mixture of propidium iodide and 4′,6-diamidino-2-phenylindole, indicating the treatment triggered a continuous process of apoptotic cell death in MCF7 cells. According to the study, the IC_{50} values of the ethanol, ethyl acetate, n-hexane, and water extracts of *A. muricata* leaves were determined to be 5.3, 2.86, 3.08, and 48.31 µg/mL, respectively, in MCF7 cells. These results suggest that the ethyl acetate extract has the highest cytotoxic activity against MCF7 cells, followed by the n-hexane and ethanol extracts, while the water extract shows the least. The lower IC_{50} values of the organic solvent extracts indicate that they are more effective in extracting anticancer compounds from *A. muricata* leaves, highlighting their potential for inducing apoptosis in breast cancer cells. However, the researchers have not observed any activity in CV1 cells. However, a 6-hour exposure to *A. muricata* leaf extract and ethyl acetate fraction caused significant changes in cancer cells' shape, indicating strong cytotoxic effects. Specifically, the apoptotic cancer cells exhibited notable disruptions in both their membrane and nucleus, including membrane and nuclear ruptures and losses. According to Hadisaputri and coworkers (Hadisaputri et al., 2021), the cytotoxic activity observed in MCF7 cells was found to be facilitated by a reduction in Bcl-2 mRNA expression and an elevation in caspase-9 and caspase-3 mRNA expression. So according to this study the compounds present in the *A. muricata* leaves have been found to exhibit potent anti-cancer properties against breast cancer by inducing apoptotic cell death upon extraction (Hadisaputri et al., 2021). Another research investigated the cytotoxic activity in MCF-7 cells through an MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide) assay at 25 to 250 µg/mL concentrations. That study involved the exposure of MCF-7 cells to leaf methanol extracts of *A. muricata* (LMAM) at concentrations of 50 and 100 µg/mL for 24 hours. To identify apoptosis induced by LMAM, the researchers utilized flow cytometric analysis to assess Hoechst 33342 staining, cell cycle analysis, Annexin-PI probe, and oxidative stress damage caused by reactive oxygen species (ROS) (Naik & Sellappan, 2020). In this research the qRT-PCR method was utilized to examine the expression levels of caspase-3. According to the respective research results LMAM exhibited significant inhibition of MCF-7 cells with an IC_{50} value of 85.55 µg/mL. Hoechst staining showed that LMAM-treated cells had apoptotic morphology (Naik & Sellappan, 2020). The cell cycle study showed that 100 µg/mL LMAM increased the G1 phase by 30%, arresting the cell cycle in the G1 phase and increasing the sub-G0–G1 population while decreasing the S phase. When treated with 100 µg/mL LMAM, Annexin V-FITC-PI staining showed a 3.38% and 19.47% increase in early and late apoptotic cells. 100 µg/mL LMAM increased intracellular ROS by 3334.08. MCF-7 cells grown at 50 and 100 µg/mL LMAM showed upregulation of 2.18- and 32.47- fold caspase-3, suggesting caspase-dependent apoptosis (Naik & Sellappan, 2020). Another research study tested the anti-cancer properties of copper oxide nanoparticles (CuONPs) made from *A. muricata* plant extract. The synthesized nanoparticles were tested against AMJ-13 and MCF-7 breast cancer cell lines and the human breast epithelial normal cell line (HBL-100) (Mahmood et al., 2022). According to this study, CuONPs inhibited AMJ-13 and MCF-7 cell proliferation. However, several concentrations and test periods did not inhibit HBL-100 cells. The results indicate that copper oxide nanoparticles inhibited breast cancer cell lines (Mahmood et al., 2022).

Annona muricata against liver cancer

Several *in vitro* studies have suggested that the *A. muricata* plant extracts possess cytotoxic properties and may have potential therapeutic applications against liver cancer. These studies used cultured liver cancer cells (Yajid et al., 2018). The research findings indicate that the ethanol extract of *A. muricata* has the potential to inhibit the growth and viability of HepG2 liver cancer cells. The observed cytotoxicity in the HepG2 cell line is postulated to be a consequence of the activation of the apoptosis pathway via the generation of reactive oxygen species (ROS) (Yang et al., 2016). This supports the traditional medicinal application of this plant as a potential alternative or supplementary treatment for liver cancer. Another research carried out by the same researcher also indicated that *A. muricata* extracts induce apoptosis in diverse cancer cells *in vitro* and impede tumor growth *in vivo* in animal models (Liu et al., 2016). That study was mainly conducted to examine the molecular mechanisms involved in the induction of apoptosis in liver cancer cells by the ethanol extract of *A. muricata* leaves. The results suggest that the ethanol extract from the leaves of *A. muricata* induces apoptosis in liver cancer cells via the ER (endoplasmic reticulum) stress pathway (Liu et al., 2016).

Annona muricata against prostatic cancer

The acetogenin and flavonoid-enriched *A. muricata* extracts have also been administered *in vivo* and *in vitro* against prostatic cancer. Moreover, the extracts are shown to be effective against prostatic cancer (Yajid et al., 2018). A study indicates that the coexistence of flavonoids and annonaceous acetogenins in *A. muricata* leaf extract provides additional advantages for achieving optimal therapeutic outcomes and demonstrated superior efficacy in down-regulating prostate cancer (Yang et al., 2015; Yajid et al., 2018). So, this study also demonstrated the effectiveness of *A. muricata* extracts in inhibiting prostate cancer and emphasized the significance of utilizing whole-leaf extracts to attain optimal inhibitor efficacy in cancer treatment (Yang et al., 2015; Yajid et al., 2018).

Annona muricata against lung cancer

Few research articles have proved that *A. muricata* plant extracts have anti-cancer properties against lung cancer cell lines. Research by (Moghadamtousi et al., 2014) assessed the molecular mechanisms of ethyl acetate extract of *A. muricata* leaves (AMEAE) and its impact on A549 lung cancer cells (Moghadamtousi et al., 2014). According to that research study, the *A. muricata* ethyl acetate leaf extract hindered A549 cell growth by inducing cell cycle arrest and programmed cell death, which were achieved by activating the mitochondrial-mediated signaling

pathway, followed by the nuclear factor kappa light chain enhancer of activated B cells (NF-kB) signaling pathway (Moghadamtousi et al., 2014). Another study with *A. muricata* leaf extract found that it provides a faster, safer, and environmentally friendly method for synthesizing silver nanoparticles. The leaf extract containing phytochemicals exhibited anti-proliferative activity against A549 lung cancer cells, but its efficacy was increased in nano-form. The study revealed the suppression of cell cycle regulator genes such as cyclin D, E, and B. Based on the research findings, the researchers propose that leaf extract-mediated silver nanoparticles may have the potential as anti-cancer agents for lung cancer (Meenakshisundaram et al., 2020).

Annona muricata against colon cancer

Extracts derived from *A. muricata* have demonstrated the ability to induce G1 cell cycle arrest (Moghadamtousi et al., 2014). The investigation revealed that administering treatments to HCT116 and HT-29 colorectal cell lines led to the activation of the apoptotic pathway, as indicated by an elevation in ROS generation, a rise in visual cytochrome c, and an increase in initiator and executioner caspases in both the examined cell types (Moghadamtousi et al., 2014; Yajid et al., 2018).

Annona muricata against pancreatic cancer

Annona muricata is known to possess significant bioactive compounds, specifically Annonaceous acetogenins. A study was conducted to assess the viability of Capan-1, a human pancreatic ductal adenocarcinoma cell line, following treatment with extracts of *A. muricata*. The study utilized the 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay. The findings of this study indicate that *A. muricata* hexane and commercially available extracts elicited a slight degree of cytotoxicity in Capan-1 pancreatic cancer cells (Rosdi et al., 2015). Another research used silica gel chromatography of the dichloromethane extract of *Annona muricata* seeds (Ragasa et al., 2012). The results revealed the presence of annoreticuin-9-one, whereas the flesh of the fruit contained cis-annoreticuin and sabadelin (Roblot et al., 1993; Chen et al., 1996). The compound known as acetogenin annoreticuin-9-one has been found to possess cytotoxic properties against the PACA-2 human pancreatic tumor cell line (Ragasa et al., 2012).

Annona muricata loaded nanoparticles as a cancer treatment and future prospects

Expanding upon the noteworthy anti-cancer properties of phytochemicals found in *Annona muricata*, recent studies have delved into innovative delivery methods to maximize their therapeutic effectiveness. One approach that has gained attention is the utilization of nanoparticles, which provide enhanced stability, precise delivery, and decreased toxicity. Nanoparticles have emerged as a significant breakthrough in nanotechnology, revolutionizing the field of cancer detection and therapy (Yao et al., 2020). Considering the encouraging potential of *A. muricata* in fighting cancer, it is reasonable to explore its bioactive compounds in nanoparticle formulations to address the limitations of using direct extracts. The emergence of nanotechnology has transformed the cancer detection and therapy field. Utilizing nanoparticles ranging from 1-100 nm in size is a promising approach for cancer treatment. Nanoparticles have distinct advantages, including biocompatibility, reduced toxicity, improved stability, heightened permeability, retention effect and accurate targeting (Gavas et al., 2021). Due to these various advantages, researchers have been finding ways to utilize *A. muricata*-loaded nanoparticles as an effective therapy for cancer. Research carried out (Sabapati et al., 2019) using solid lipid nanoparticles loaded with an extract from the fruit of *A. muricata* indicates that these nanoparticles are much more effective against cancer than the free extract (Sabapati et al., 2019). The primary aim of the study was to synthesize solid lipid nanoparticles (SLNs) containing the extract from the *A. muricata* fruit and investigate its potential cytotoxic effects on breast cancer cells in an *in vitro* model (Sabapati et al., 2019). This research showed that *A. muricata* fruit extract-loaded SLNs have a significant apoptotic impact and superior effectiveness in inducing cell death in MCF7 cancer cells compared to the free extract. These SLNs have the potential to serve as an alternative dosage form that may regulate therapeutic efficacy while minimizing adverse effects (Sabapati et al., 2019). Another successful study was the *A. muricata* peel extract loaded silver nanoparticles against human leukemia (Jabir et al., 2021). This study showed that the anti-proliferative activity of *A. muricata* fruit peel extract-loaded silver nanoparticles (AgNPs) are more potent against THP-1, a human leukemia monocytic cell line which was achieved through the induction of apoptosis via mitochondrial damage and activation of the p53 protein pathway (Jabir et al., 2021). Another study which aimed to synthesize gold nanoparticles (AuNPs) stabilized by *A. muricata* leaves ethanolic extract, assessed their potential anti-cancer activity against melanoma and breast cancer (Imran et al., 2021). This study reported the successful synthesis of gold nanoparticles utilizing the extract of *A. muricata* leaves (Imran et al., 2021). The involvement of multi-functional groups in the extract facilitated the stabilization of the synthesized nanoparticles. According to the results, the anti-cancer activity of the extract significantly improved against all cancer cells upon being loaded onto the surfaces of the synthesized nanoparticles (Imran et al., 2021). A biochemical assessment of the anti-cancer properties of silver nanoparticles (AgNPs) synthesized through the ethanolic extracts of the fruits (AgNPs-F) and leaves (AgNPs-L) of *A. muricata* (Gavamukulya et al., 2021). The study findings indicated that biosynthesized silver nanoparticles, particularly those designated as AgNPs-F, possessed the potential for application in advancing improved and innovative anti-cancer pharmaceuticals. The AgNPs operated by activating the intrinsic apoptosis pathway via the upregulation of CASP9 and coordinated downregulation of the CXCL1/CXCR2 gene axis (Gavamukulya et al., 2021). Another study compared the apoptotic potency of silver nanoparticles made from *A. muricata* leaves versus the activity of the plant's crude aqueous leaf extract on A549 lung carcinoma epithelial cells (Meenakshisundaram et al., 2020). This study showed that making silver nanoparticles using the *A. muricata* leaf extract is a speedier, safer,

and more environmentally friendly process, and the leaf extract, which contained phytochemicals, exhibited an anti-proliferative effect on A549 cells. However, the research study observed increased activity when the extract was in nano-form (Meenakshisundaram et al., 2020). Other data has been published on synthesizing biogenic zinc oxide nanoparticles (ZnO NPs) utilizing an aqueous leaf extract derived from *A. muricata* (Chabattula et al., 2021). The physicochemical properties of the *A. muricata*-ZnO nanoparticles have been characterized and were used on 2D and 3D tumor models (Chabattula et al., 2021). Moreover, the outcomes of this research investigation indicate that the *A. muricata*-ZnO nanoparticles synthesized in this study exhibited potent anti-cancer properties against 2D and 3D tumor models (Chabattula et al., 2021). According to this research, cancer cells treated with *A. muricata*-ZnO NPs underwent programmed cell death accompanied by depolarization in their mitochondrial membrane potential (Chabattula et al., 2021). So, the findings indicated that biogenic zinc oxide nanoparticles exhibit exceptional characteristics that render them suitable for various biomedical applications (Chabattula et al., 2021).

Based on extant literature, using nanoparticles containing *A. muricata* exhibits considerable potential as a therapeutic modality for cancer, representing a promising avenue in the ongoing battle against this disease. The selective targeting of cancer cells by nanoparticles while sparing healthy cells represents a noteworthy progression in cancer treatment. Furthermore, the inherent bioactive constituents in *A. muricata* have demonstrated a significant anti-neoplastic potential, rendering it as a promising contender for employment in oncological interventions.

Further investigation is required to comprehensively comprehend the effectiveness and safety of nanoparticles containing *A. muricata*. However, the preliminary findings are exceedingly promising. Upon further advancement and enhancement, this technological innovation harbors the capacity to transform the field of cancer therapy and ameliorate the quality of life for a vast populace across the globe.

CONFLICT OF INTEREST

The authors declare that they do not have any conflict of interest regarding the publication of this paper.

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