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The Miracle from The Yard: *Annona muricata* as Cancer Chemo-Preventive and Co-Chemotherapy

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Abstract
Cancer remains one of the biggest challenges to human health worldwide, with incidence and mortality rates continuing to rise. Popular cancer treatments to date include surgery, radiation-based therapy, chemotherapy, gene therapy, and hormone therapy. Chemotherapy is one of the primary treatment methods for cancer. However, it has unwanted side effects. It has prompted the search for new chemotherapeutic drugs with better efficacy, excellent selectivity, and fewer side effects. In recent years, there has been growing scientific interest in the potential of soursop leaf (*Annona muricata*) as an anticancer agent. This review paper discusses the phytochemical content of *A. muricata* and its potential as a co-chemotherapy against various types of cancer. Several bioactive compounds in soursop leaves have been reported, including annopentocin A, muricatetrocin A, annohexocin, isoannonacinone, annomuricin A, muricatin C, corossolin, and arianacin. Extracts from various parts of *A. muricata* have potential as co-chemotherapy in the treatment of breast cancer, colon cancer, prostate, lung, cervical, liver, and blood cancer. Studies concluded that *A. muricata* extracts have a good safety and tolerability profile. Its benefits as a co-chemotherapy agent will be even more significant when made into pharmaceutical dosage forms. *A. muricata* extracts or compounds packaged in pharmaceutical preparations are expected to improve patient's quality of life. However, more research is needed to determine the optimal dosage, route of administration, and potential side effects.

Keywords: *Annona muricata*; Co-chemotherapy; Metastasis; Network pharmacology

1. INTRODUCTION

Cancer is one of the major diseases that can cause death. According to the World Health Organization (WHO), cancer is the second leading cause of death globally, claiming an estimated 10 million lives in 2020. GLOBOCAN 2020, a global cancer statistics project, estimates that there were 19.3 million new cancer cases diagnosed worldwide in the same year, with lung cancer (11.4%) and female breast cancer (11.7%) being the most commonly diagnosed cancers (Sung et al., 2021).

Cancer development is a complex process influenced by genetic and environmental factors. In addition to genetic factors, several factors can increase the risk of cancer

development, including gender, age, nutrition, obesity, alcohol consumption, family history, radiation exposure, tobacco use, living environment, and economic conditions (Icanervilia et al., 2023; Rahmani et al., 2023). Cancer burden varies significantly across different regions. Developed countries tend to have higher incidence rates, likely due to increased life expectancy, screening programs, and improved diagnostic techniques(World Health Organization, 2024). However, low- and middle-income countries are often disproportionately affected by mortality rates due to limited access to early detection, diagnosis, and treatment options.

Popular cancer treatments to date include surgery, radiation-based therapy, chemotherapy, gene therapy, and hormone therapy (Rady et al., 2018). These methods can be used separately or in combination. Chemotherapy is one of the primary treatment methods for cancer. Although chemotherapy is effective in killing cancer cells and increasing the survival chance, it also provides unwanted side effects. For example, the use of doxorubicin causes side effects such as hepatotoxicity, cardiotoxicity, metastasis, and drug resistance (Damodar et al., 2014; Sun et al., 2022). It drives the search for new chemotherapeutic drugs with better efficacy, selectivity, and fewer side effects.

Researchers have long explored natural compounds as chemo-preventive agents. This enduring interest has led to developing numerous anticancer drugs derived from natural materials (Ko & Moon, 2015; Manna et al., 2023). Soursop (*Annona muricata*) is a tropical and sub-tropical fruit plant with potential bioactive compounds. Local people have used them in traditional medicine for centuries. Soursop is used to treat various conditions, such as fever, pain, respiratory and skin disorders, antiparasitic, bacterial infections, hypertension, inflammation, and diabetes (Cahyawati, 2020; Coria-Téllez et al., 2018; Damayanti et al., 2017). In recent years, there has been growing scientific interest in the potential of *A. muricata* as an anticancer agent. This review paper discusses the phytochemical content of soursop leaf and its potential as a chemo-preventive and co-chemotherapy against various types of cancer, with a particular focus on its promising antimetastatic properties.

2. METHODS

Experimental data were collected online by summarizing scientific literature articles. We obtained the article from several databases, such as Google Scholar, Scopus, and PubMed, using single and combination keywords related to the topic. The keywords used included " soursop," "*Annona muricata*," "cancer," "metastasis," and "cytotoxic." Data selection was used by looking at the year of writing between 2010 and 2024, whether the language used is Indonesian or English, and its relevance to the topic raised in the review article.

3. RESULTS AND DISCUSSION

3.1. Cancer chemotherapy and its limitations

Chemotherapy is a systemic therapy. The drugs can spread throughout the body and reach distant sites to kill cancer cells. Currently, chemotherapy is the primary treatment for cancer, especially for patients who do not respond to surgical resection (Prasad et al., 2016). It can significantly improve survival rates and reduce the risk of recurrence. Chemotherapy is less selective in killing cancer cells (Adelina et al., 2014). It can harm rapidly dividing healthy cells,

leading to various side effects. These side effects can be acute, occurring during or immediately after treatment, or chronic, persisting for months or even years after treatment.

Doxorubicin, an anthracycline antibiotic, is a potent chemotherapy drug widely used against various types of cancer. Its effectiveness comes from its ability to disrupt DNA replication and transcription in cancer cells (Sun et al., 2022). However, the use of doxorubicin causes side effects, such as hepatotoxicity, cardiotoxicity, metastasis, and resistance (Damodar et al., 2014; Sun et al., 2022). Doxorubicin increases migration and invasion of metastatic type 4T1 and MDA-MB-231 breast cancer cells (Bandyopadhyay et al., 2010). Doxorubicin boosts DCAF13 expression in breast cancer cells, promoting migration and invasion (Sun et al., 2022).

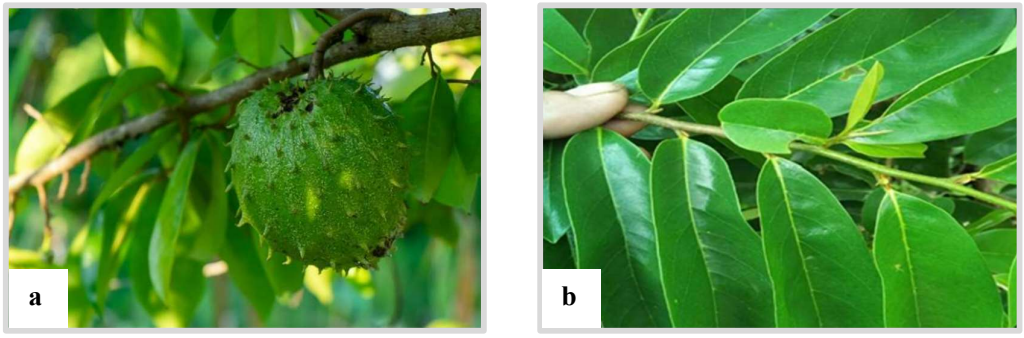

Figure 1. Anatomy of soursop. *Description*: fruit (A) and soursop leaves (B).

3.2. Cancer chemo-preventive potential of *Annona muricata*

Annona muricata is a member of the Annonaceae family with the following taxonomical description:

Kingdom: Plantae

Division: Angiosperms

Subdivision: Magnoliophyta

Class: Magnolid

Ordo: Magnoliales

Family: Annonaceae

Genus: Annona

Species: *Annona muricata* L.

A. muricata grows in the tropical and sub-tropical regions of Central and South America, West Africa, Central and East Africa, and Southeast Asia, including Indonesia. The soursop plant is about 5–10 m tall and 15–83 cm in diameter, with low branches. It tends to flower and fruit almost year-round. The fruit is an edible collective ovoid berry, dark green. The pulp is creamy white with a distinctive aroma and flavor (Lienggonegoro & Kharirie, 2020).

A. muricata extract has various pharmacological properties, including anticancer properties. In vitro testing has been widely conducted on multiple cancer cell lines. Soursop's potential as an anticancer agent is even better than other plants. The leaf extract of *A. muricata*

is reported to have excellent antitumor activity in murine models compared to curcumin, which is known as a natural chemo-preventive (Hamizah et al., 2012).

Several bioactive compounds in soursop leaves have been reported, including annopentocin A, muricatetrocin A, annohexocin, isoannonacinone, annomuricin A, muricatin C, corossolin, and arianacin (Apeh et al., 2023). There are two major classes of phytochemicals: flavonoids and acetogenins (Yang et al., 2015). The antitumor properties of *A. muricata* leaf extracts are related to the presence of several acetogenin compounds (Adelina et al., 2014; Chan et al., 2019; Moghadamtousi et al., 2015). Acetogenins have two hydroxylated tetrahydrofuran (THF) functional units and a β-unsaturated γ-lactone ring (Figure 2) (Dewayani et al., 2023). Other compounds, such as annonacin, are associated with reduced metastasis and proliferation of cancer cells at the cell membrane level. Bioactive compounds have pharmacological activities individually or in synergistic combinations (Matsushige et al., 2012; Moghadamtousi et al., 2015; Yang et al., 2015).

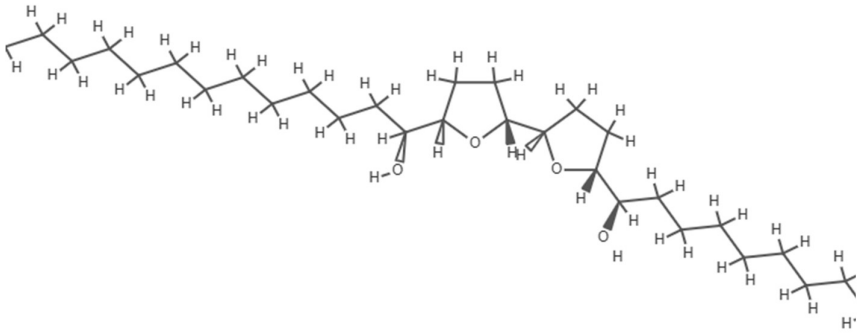

Figure 2. Structure of acetogenin compounds (Source: PubChem at https://pubchem.ncbi.nlm.nih.gov/).

3.3. *Annona muricata* as chemo preventive agent

Annona muricata bioactive compounds have demonstrated a selective cytotoxic effect, targeting cancer cells while sparing normal cells. However, in vitro studies are still limited. For example, the selectivity is exemplified by their lack of cytotoxic effects on normal spleen cells (Gavamukulya et al., 2014). This property makes these compounds promising candidates for cancer chemoprevention and as co-chemotherapy agents. By selectively targeting cancer cells, these compounds may offer a therapeutic advantage with reduced side effects compared to traditional chemotherapy.

Breast cancer is a disease in which abnormal breast cells grow out of control and form tumors (Bhanuwati & Pakpahan, 2022). More than 2.3 million women were diagnosed with breast cancer, with 685,000 deaths globally in 2020 (World Health Organization, 2024). WHO predicts the global incidence of breast cancer will increase to 3.2 million cases per year by 2050 (Momenimovahed & Salehiniya, 2019). For women, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death (World Health Organization, 2024).

The soursop extract is toxic against breast cancer cell models, including MCF-7, 4T1, T47D, MDA-MB, MDA-MD, SK-BR, and HCC-1954 (Table 1).

Table 1. Potential use of *A. muricata* against breast cancer

Source	Cancer type	Cell line	IC_{50} (µg/ml)	Reference
Fruit	Breast	MDA-MB-468	4.8	(Dai et al., 2011)
Fruit	Breast	MDA-MD-231	>200	(Dai et al., 2011)
Fruit	Breast	MCF-7; MCF-10A	>200	(Dai et al., 2011)
Leaves	Breast	MCF-7	14.68	(Andrini et al., 2014)
Leaves	Breast	SK-BR-3	202.33	(Gavamukulya et al., 2014)
Leaves	Breast	MDA-231	248.77	(Gavamukulya et al., 2014)
Leaves	Breast	MDA-MB-231	9.37 - 100	(Moghadamtousi et al., 2014)
Leaves	Breast	MCF-7	6.39 – 85.58	(Moghadamtousi et al., 2014)
Seeds	Breast	T47D	20.36	(Arifianti et al., 2014)
Leaves	Breast	MCF-7	220	(Najmuddin et al., 2016)
Leaves	Breast	4T1	250	(Najmuddin et al., 2016)
Leaves	Breast	MDA-MD-231	350	(Najmuddin et al., 2016)
Leaves	Breast	MCF-10A	1,000	(Najmuddin et al., 2016)
Leaves	Breast	T47D	5	(Roham et al., 2016)
Leaves	Breast	MCF-7	44.94	(Fatmawati et al., 2018)
Leaves	Breast	MCF-7	9.12	(Suhendar, 2019)
Leaves	Breast	MCF-7	220	(Manshour et al., 2018)
Leaves	Breast	MCF-7	56.6	(Haryanti & Widiyastuti, 2017)
Leaves	Breast	T47D	109.91	(Fertilita et al., 2020)
Leaves	Breast	MCF-7	85.55	(Naik & Sellappan, 2020)
Leaves	Breast	MCF-7	2.86 - 48.31	(Hadisaputri et al., 2021)
Leaves	Breast	4T1	63	(Salsabila et al., 2021)
Leaves	Breast	4T1	79.2	(Merlín-Lucas et al., 2021)
Leaves	Breast	HCC-1954	125	(Lopez et al., 2023)
Leaves	Breast	MCF-7	200	(Lopez et al., 2023)

Ethyl acetate leaf extract of *A. muricata* has significant cytotoxicity activity against MCF-7 with an IC_{50} of 6.4 µg/ml and MDA-MB-31 cells with an IC_{50} of 11.4 µg/ml (Moghadamtousi et al., 2014). The soursop fruit extract is selective in reducing the viability of MDA-MB-468 breast cancer cells with an IC_{50} of 4.8 µg/ml (Dai et al., 2011). A study confirmed the ability of soursop leaf extract through apoptotic parameters (Naik & Sellappan, 2020). The study showed that soursop leaf extract treatment increased the G1phase by 30%. It induced cell cycle arrest in the G1 phase, paralleling the S phase decrease. Inaddition, there was also an increase in caspase-3 regulation. The caspase-3 in the MCF-7 cellwas upregulated compared to the control, cultured at 50 µg/ml and 100 µg/ml of soursop leaf extract. Soursop extract showed moderateto solid cytotoxicity in metastatic breast cancer, such as 4T1 and T47D (Merlín-Lucas et al., 2021; Salsabila et al., 2021). A single compound, acetogenin, showed more potent anticancer effects, with an IC_{50} of 14.69 µM on drug-resistant breast tumors (Yuan et al., 2016).

Prostate cancer is the second most commonly diagnosed cancer among men, with an estimated 1.4 million cases diagnosed worldwide in 2020. It is also the fifth leading cause of cancer death in men. Research shows that soursop is a potential anticancer agent against prostate cancer (Table 2). The soursop fruit extract was cytotoxic to prostate cancer cell lines

with varying IC_{50} values, ranging from 73 to 200 µg/ml, after 48 hours of treatment (Torres et al., 2012). Meanwhile, soursop leaf extract provided greater IC_{50} values ranging from 1.36 to 63 µg/ml (Asare et al., 2015; Foster et al., 2020; Yang et al., 2015).

Table 2. Potential use of *A. muricata* against prostate cancer

Source	Cancer type	Cell line	IC_{50} (µg/ml)	Reference
Leaves	Prostate	COLO-357	200	(Torres et al., 2012)
Leaves	Prostate	CD18/HPAF	73	(Torres et al., 2012)
Leaves	Prostate	PC-3	63	(Yang et al., 2015)
Leaves	Prostate	BPH-1	1.36	(Asare et al., 2015)
Leaves	Prostate	PC-3	80	(Manshour et al., 2018)
Leaves	Prostate	DU-145	55.501	(Foster et al., 2020)

The soursop leaf-derived compound, murihexocin C, was reported to have selective cytotoxicity against prostate adenocarcinoma cell lines (PC-3) (Wahab et al., 2018). The bioactive compound suppresses the reduction of the Δ4,5 double bond of testosterone to synthesize DHT. Inhibition of the physiological role of DHT activates transcriptional activity and androgen receptor signaling (Yu et al., 2020). This condition decreases prostate cell growth and proliferation.

Soursop bioactive compounds can inhibit the activity of P-glycoprotein (P-gp), an efflux protein. Efflux proteins play a role in drug transportation from inside the cell back to outside the target cell (König et al., 2013). Inhibition of P-gp activity increases the bioavailability of anticancer compounds. Like enzymes in drug metabolism, P-gp substrates act as inhibitors or inducers. The annopentocin A, muricatetrocin A, and annohexocin compounds from *A. muricata* have good inhibition against P-gp in prostate cancer cell lines (Apeh et al., 2023).

The bioactive compounds of *A. muricata* can also prevent and suppress metastasis in prostate cancer cell lines. The activity of soursop fruit extract is associated with decreased glucose uptake and cell ATP content (Torres et al., 2012). The study also showed the downregulation of proteins involved in cancer cell invasion and metastasis, including matrix metalloproteinase 9 (MMP-9), phosphorylated focal adhesion kinase (pFAK), and mucin 4 (MUC4) in cells.

Soursop leaf extract inhibits motility in the highly metastatic PC-3 cell line, thus preventing wound healing. In addition to significantly inhibiting extracellular vascular endothelial growth factor (VEGF) production, the extract also inhibited the formation of new blood vessels during angiogenesis (Foster et al., 2020). Angiogenesis is one of the leading mechanical steps for tumor growth, invasion, and metastasis in all cell types. In addition, *A. muricata* extract is reported to inhibit TNF-α, a transcription factor that plays a role in the expression of VEGF (Laksmitawati et al., 2016).

Colorectal cancer (CRC), also known as colon cancer, is a significant health concern worldwide. CRC is the third most common cancer and the second leading cause of cancer-related deaths globally. In 2020, estimates suggest over 1.9 million new cases and 930,000 deaths due to CRC (World Health Organization, 2024). Table 3 summarizes research on the

potential of soursop asa colon anticancer. The ethanol leaf extract of *A. muricata* is reported to inhibit the migration of colon cancer cell lines WiDr and produced an IC_{50} value of 905.77 µg/ml. The fruit extract of *A. muricata* also has good selectivity (Astuti et al., 2021).

Table 3. Potential use of *A. muricata* against colorectal cancer

Source	Cancer type	Cell line	IC_{50} (µg/ml)	Reference
Leaves	Colorectal	HT-29	11.43	(Moghadamtousi et al., 2014)
Leaves	Colorectal	HCT-116	8.98	(Moghadamtousi et al., 2014)
Leaves	Colorectal	HT-29	1.62	(Moghadamtousi et al., 2015)
Leaves	Colorectal	COLO-205	189.6	(Abdullah et al., 2017)
Leaves	Colorectal	WiDr	905.77	(Astuti et al., 2021)

Ethanol leaf extract of *A. muricata* inhibits angiogenesis and migration of colon cancer cell lines WiDr by reducing VEGF production and increasing E-cadherin. A study showed that the extract increases the amount of E-cadherin in WiDr cancer cells (Astuti et al., 2023). Decreased production of E-cadherin is one of the hallmarks of cancer cells and contributes to cancer metastasis. The loss of cell-cell adhesion and E-cadherin allows cells to separate from the primary tumor, penetrate surrounding tissues, and migrate to other sites (Astuti et al., 2023; Shamir et al., 2014).

Bioactive compounds of *A. muricata* leaves reduce the levels of molecules involvedin the cell invasion process, i.e., intercellular cell-adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in the blood (Indrawati et al., 2023). Cell migration is inhibited when acetogenin compounds attach to cell wall receptors and damage ATP in the mitochondrial wall (Gavamukulya et al., 2017); therefore, energy production in cancer cells stops. Furthermore, cancer cells are arrested in the G0/G1 phase, resulting in apoptosis (Gavamukulya et al., 2017; Moghadamtousi et al., 2014; Najmuddin et al., 2016).

Table 4. Potential use of *A. muricata* against lung cancer.

Source	Cancer type	Cell line	IC_{50} (µg/ml)	Reference
Leaves	Lung	A549	5.1	(Moghadamtousi et al., 2014)
Leaves	Lung	H1299	146	(Manshour et al., 2018)
Leaves	Lung	A549	194	(Manshour et al., 2018)
Leaves	Lung	A549	6	(Meenakshisundaram et al., 2020)
Leaves	Lung	A549	70 - 100	(Shaniba et al., 2022)

Lung cancer is the most common cancer and the leading cause of cancer death. The main risk factor for lung cancer is smoking (World Health Organization, 2024). Lung cancer rates are declining in some countries due to reduced smoking rates. However, lung cancer rates are still rising in some developing countries. Researchers explore soursop extract as a lung anticancer with various cell lines (Table 4). In vitro studies showed that soursop leaf extract has significant cytotoxicity against the A549 lung cancer cell line, with an IC_{50} value of 5.1 µg/ml (Moghadamtousi et al., 2014). High flavonoid content correlates with anticancer potential against lung cancer cells (Hasmila et al., 2019; Widyastuti & Rahayu, 2017). Meanwhile,

another study reported a higher IC_{50} value of soursop leaf extract, which was 70–100 µg/ml (Shaniba et al., 2022). Soursop leaf extract may inhibit nuclear factor-κB (NF-κB) signaling, increase ROS production, enhance the Bax/Bcl-2 ratio, and activate caspase-3in the A549 cell line (Moghadamtousi et al., 2014).

Table 5. Potential use of *A. muricata* against cervical cancer

Source	Cancer type	Cell line	IC_{50} (µg/ml)	Reference
Leaves	Cervix	HeLa	111.75	(Rachmawati et al., 2012)
Leaves	Cervix	HeLa	120	(Yuniarti et al., 2014)
Leaves	Cervix	HeLa	77.096	(Prayitno et al., 2016)
Leaves	Cervix	HeLa	25	(Jepkorir et al., 2018)
Leaves	Cervix	HeLa	200	(Manshour et al., 2018)
Leaves	Cervix	HeLa	5.91 – 35.53	(Qorina et al., 2020)

Globally, cervical cancer is the fourth most frequent cancer in women, with an estimated 660,000 new cases diagnosed in 2022. Cervical cancer is a preventable cancer that arises from the abnormal growth of cells in the cervix, the lower part of the uterus that connects to the vagina. Most cervical cancer cases correlate to infection with certain strains of human papillomavirus (HPV), a sexually transmitted virus. While most HPV infections are clear on their own, persistent infections with high-risk types can lead to cervical cancer (World Health Organization, 2024).

Current cervical cancer treatments have limitations due to significant side effects, such as altering cell metabolism, nephrotoxicity, vomiting, nausea, and anemia (Qorina et al., 2020). Some studies showed the cytotoxic activity of *A. muricata* leaf extract against cervical cancer cells (Table 5). Soursop leaf extract has good cytotoxicity against cervical cancer cells HeLa, with IC_{50} values ranging from 5.91 to 35.51 µg/ml (Qorina et al., 2020). Similarly, the cytotoxicity of soursop fruit has an IC_{50} of 25 µg/ml against HeLa cell lines (Jepkorir et al., 2018). In comparison, several other studies that used soursop leaves showed higher IC_{50} values,which ranged from 77.096 to 120 µg/ml against cervical cancer cells HeLa (Manshour et al., 2018; Prayitno et al., 2016; Rachmawati et al., 2012; Yuniarti et al., 2014). The synergistic effects of phytochemical content in plant extracts, including acetogenins, act as antiproliferation agents and significantly reduce MMP production. Acetogenin compounds inhibit the activity of enzymes or proteins, which are only found in tumor cell membranes (Manshour et al., 2018).

Table 6. Potential use of *A. muricata* against liver cancer

Source	Cancer type	Cell line	IC_{50} (µg/ml)	Reference
Leaves	Hepatocarcinoma	HepG2	9.3	(Moghadamtousi et al., 2014)
Leaves	Hepatocarcinoma	HepG2	150	(N. Liu et al., 2016)
Leaves	Hepatocarcinoma	HCT-116	150	(N. Liu et al., 2016)
Leaves	Hepatocarcinoma	Huh71T-1	<0.3	(Apriyanto et al., 2018)
Fruits	Hepatocarcinoma	Hepg2	53.7	(Thomas et al., 2019)

The most common type of liver cancer is hepatocellular carcinoma (HCC). The significant risk factors for liver cancer include chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), excessive alcohol consumption, obesity, and type 2 diabetes (World Health Organization, 2024). The current treatment regimen comprises the MAP-kinase inhibitor sorafenib, which is typically well tolerated. Sorafenib commonly causes unacceptable adverse events, such as diarrhea, skin toxicity, and hypertension (Thomas et al., 2019).

Table 6 summarizes the potential of *A. muricata* extracts against liver cancer. Ethyl acetate leaf extract of *A. muricata* showed significant cytotoxicity against the HCC cell line HepG2, with an IC_{50} value of 9.3 µg/ml (Moghadamtousi]et al., 2014). While soursop fruit extract demonstrated less potent cytotoxicity than its leaf counterpart, it exhibited significant inhibition of cell migration (Thomas et al., 2019). Another study reported a lower IC_{50} value in the Huh71T-1 cell line. The extract significantly inhibits cancer cell migration at 55 µg/ml. It also validated the induction of apoptosis and cell arrest at the G0/G1 phase of the HepG2 cell cycle (Apriyanto et al., 2018).

Table 7. Potential use of *A. muricata* against leukemia

Source	Cancer type	Cell line	IC_{50} (µg/ml)	Reference
Twigs	Leukemia	HL-60	49	(Pieme et al., 2014)
Roots	Leukemia	HL-60	9	(Pieme et al., 2014)
Leaves	Leukemia	HL-60	14	(Pieme et al., 2014)
Seeds	Leukemia	CCRF-CEM/ADR5000	0.36	(Kuete et al., 2016)
Leaves	Leukemia	CCRF-CEM/ADR5000	0.57	(Kuete et al., 2016)
Fruits	Leukemia	CCRF-CEM/ADR5000	4.58	(Kuete et al., 2016)

Leukemia is a cancer of the blood and bone marrow. Leukemia can affect people of all ages but is most common in children and adults over 55 (World Health Organization, 2024). Soursop is one of the plants that can potentially be an anticancer for leukemia (Table 7). A study analyzed the cytotoxic effects of twig, root, and leaf extracts of *A. muricata* on HL-60 leukemia cell lines (Pieme et al., 2014). Soursop extracts from different parts of the plant inhibited HL-60 cell proliferation in specific doses. The root extract had the highest cytotoxic activity, with an IC_{50} value of 9 µg/ml. Similarly, methanol extracts from soursop seeds, leaves, and fruits induce cytotoxicity in the multidrug-resistant leukemia cell line, CCRF-CEM/ADR5000 (Kuete et al., 2016). *A. muricata* has antiproliferative effects on the HL-60 leukemia cell line by inducing inhibition of cell proliferation, the formation of reactive oxygen species (ROS), and decreased MMP protein production, followed by G0/G1 phase cell cycle arrest (Pieme et al., 2014).

3.4. In vivo evaluation

In vitro studies evaluate the soursop extract using various cancer cell lines. However, cytotoxicity testing and in vivo anticancer activity are still few. In vivo studies confirmed the anticancer activity of soursop extracts and their single compounds. A study induced the carcinogenic compound 7,12 dimethylbenz-a-antracene (DMBA) in animal models (Adelina et al., 2014). DMBA metabolites are toxic and cause oxidative stress, leading to cell structure

damage and causing cell necrosis. The results showed that soursop leaf extract can significantly inhibit the development of hepatic tumors through decreased cell proliferation.

A comparative study evaluated the effect of *A. muricata* fruit and leaf extracts on DMBA-induced breast cancer in rats (Silihe et al., 2023). The study reported that *A. muricata* leaf and fruit extracts and a chemotherapeutic drug (tamoxifen) significantly reduced tumor incidence, volume, and weight. The extracts had antioxidant activity through increased glutathione levels, superoxide dismutase, and catalase activity. In addition, INF-γ, TNFα, and IL-6 levels were reduced (Silihe et al., 2023). Similarly, administering soursop leaf extract affected the histopathology of hepatocellular carcinoma in Wistar rats that received sorafenib standard therapy (Sinaga & Susilaningsih, 2019).

One study has examined the anticancer activity of soursop leaf extract in humans. A study performed an anticancer survey of human colorectal cancer cell lines (Indrawati et al., 2017). The effects of soursop extract consumption were evaluated consecutively for eight weeks in 30 patients with colorectal cancer. The extract displayed selectivity by suppressing the development of colorectal cancer cells. The results showed the correlation of extract supplementation with the patient's nutritional status, quality of life, and inflammation. In this study, several chemotherapy patients felt better after supplementing *A. muricata* leaf extract. In addition, longer extract supplementation periods may enhance patients' nutritional condition. A clinical study involved metastatic breast cancer patients (Hansra et al., 2014). The results showed that consuming boiled *A. muricata* leaves could halt the progression of chemotherapy-resistant metastatic tumors.

3.5. Unlock the new potential: antimetastatic agent

The cytotoxicity exhibited by *A. muricata* extracts and their bioactive compounds has been widely reported as an initial parameter of anticancer potential. However, few reports specifically explore its antimetastatic potential against cancer. Metastasis is the spread of cancer cells from the primary tumor to distant sites. It is also an essential factor in poor cancer prognosis. Despite advances in conventional therapies such as surgery, chemotherapy, and radiation, metastasis remains a significant challenge. Therefore, exploring new therapeutic agents that target metastasis is urgently needed.

Several factors contribute to metastasis, including the angiogenesis, invasion, and migration of cancer cells (Figure 3). The production of vascular endothelial growth factor (VEGF) and activation of matrix metalloproteinase (MMP)-2 and MMP-9 play essential roles in cancer metastasis. VEGF is a signaling protein that plays a vital role in angiogenesis and the formation of new blood vessels. VEGF is produced by tumor and surrounding stromal cells. VEGF attracts endothelial cells, cells lining blood vessels, to migrate and form new blood vessels (Bhattacharya et al., 2016, 2017). These new blood vessels supply the tumor with the oxygen and nutrients it needs to grow and thrive. The soursop fruit extract reduces the viability of MDA-MB-468 breast cancer cells that overexpress the epidermal growth factor receptor (EGFR) (Dai et al., 2011).

VEGF signaling induces endothelial cell migration in normal physiological processes and tumors. Autocrine VEGF signaling, through its receptors, mediates the migration of various tumor cells. Multiple receptor tyrosine kinases and downstream AKT signaling regulate VEGF in colorectal cancer. Loss of VEGF expression significantly decreases cell proliferation, increases apoptosis, and improves the chemotherapy sensitivity of CRC cells (Bhattacharya et al., 2016).

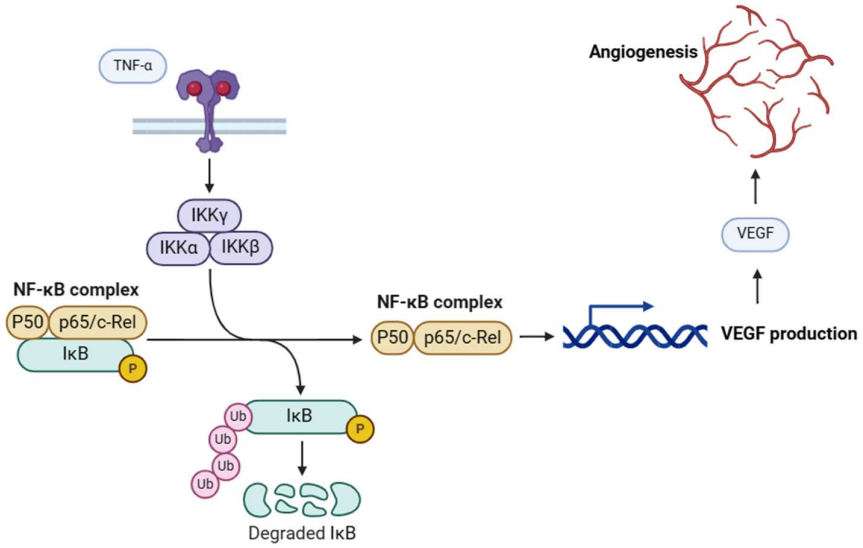

Figure 3. The schematic of TNF-α/NF-κB/VEGF pathway initial to angiogenesis. Angiogenesis contributes to the invasion and migration of cancer cells (Bhattacharya et al., 2016, 2017).

Tumor cells will produce extracellular matrix-degrading enzymes, e.g., the matrix metalloproteinase (MMP). The activity of this protein paves the way for tumor cells to expand in the metastatic process. *A. muricata* extracts, such as fruits, stems, seeds, and twigs, showed significant inhibition of MMP-2 and MMP-9 proteins in the HT1080 cell line,a highly metastatic fibrosarcoma cell (Mutakin et al., 2022). In addition, this extract also increased the expression of several endogenous inhibitors of MMP-2 and MMP-9, such as cysteine-rich protein-induced reversion with kazal motif (RECK) and tissue inhibitor of metalloproteinase-2 (TIMP-2) (Drishya et al., 2020). In addition, primary cells developed from tumor tissue obtained from patients who did not undergo chemotherapy also showed similar results. The observed inhibition of MMP-2 and MMP-9 was tumor-specific (Drishya et al., 2020). *A. muricata* extract inhibited potent migration in highly metastasized Caco and HepG2 cells (Mohammed et al., 2024). Bioactive compounds of *A. muricata* can also prevent and suppress metastasis in prostate cancer cell lines through decreasing MMP-9, phosphorylated focal adhesion kinase (Torres et al., 2012), vascular endothelial growth factor (Foster et al., 2020), and TNF-α (Laksmitawati et al., 2016). TNF-α plays a role in the expression of VEGF (Laksmitawati et al., 2016). Ethanol extract of *A. muricata* leaf inhibits angiogenesis and migration of WiDr colon cancer cell lines by increasing the amount of E-cadherin and reducing VEGF production (Astuti et al., 2023).

3.6. Future direction

Traditional herbal medicines have been used for centuries and continue to be today. Cancer drug resistance poses a significant barrier to the efficacy of conventional chemotherapy. By exploring new agents, such as *A. muricata*, that may work through different mechanisms than standard chemotherapy drugs, we can potentially overcome drug resistance and improve treatment outcomes for cancer patients. In vitro and in vivo studies show the potential of using *A. muricata* extract as a co-chemotherapeutic of existing drugs. In addition, a comprehensive literature review concluded that *A. muricata* has a good safety and tolerability profile (Chan et al., 2019).

In the community, herbal medicines are consumed separately or in combination with chemotherapy drugs. Combined use may reduce the side effects of cancer treatment. However, the use of co-chemotherapy can lead to herbal-drug interactions (HDIs). HDIs can increase toxicity, but on the other hand, they can decrease the pharmacological effect of drug components. For example, combining Lingzhi with cytotoxic drugs can improve survival and reduce the side effects of conventional chemotherapy (Lam et al., 2020). Combining soursop leaf extract with doxorubicin, the most common cancer drug, had higher cytotoxic activity against cancer than single-use (Salsabila et al., 2021). This combination also caused cell cycle arrest in the G1 phase as a single treatment and G2/M arrest in combination with doxorubicin (Salsabila et al., 2021). Although existing studies do not report harmful activity using *A. muricata* extract, developing *A. muricata* as a cancer co-chemotherapeutic requires comprehensive research.

There is still a lack of clinical trials to evaluate the safety and efficacy of *A. muricata* in cancer patients, particularly those investigating its antimetastatic effects. Future research should focus on well-designed clinical trials to assess the safety and effectiveness of *A. muricata* as an adjunctive therapy for cancer patients, particularly those with metastatic disease. In addition, its benefits as a co-chemotherapeutic agent are even more significant when made into pharmaceutical dosage forms. *A. muricata* extracts or compounds packaged in pharmaceutical preparations are expected to improve patient's quality of life. Therefore, more research is needed to determine the optimal dosage, route of administration, and potential side effects of *Annona muricata*.

Further elucidation of the molecular mechanism underlying the antimetastatic effect of *A. muricata* is needed to optimize its therapeutic potential. Researchers can use the network pharmacology approach to determine a drug's molecular mechanism of action on the target (Figure 4). Network pharmacology opens the door to drug discovery by considering the complex linkages of molecules and their interactions, resulting in more effective, personalized, and multi-targeted therapeutics for various disorders (Muhammad et al., 2018).

The in-silico study reported that acetogenin compounds could potentially bind to several cancer biomarker proteins, including EGFR, AKT1, KDR, MMP-2, MMP-9, ERBB2, IGF1R, MTOR, and HRAS (Grijaldo et al., 2023). Similarly, the bioactive compounds of soursop leaves are reportedly involved in the biological process of cell survival (Romli et al., 2022). The mechanism involves many target proteins, including CDK1, CCNB1, CCNB2, CDK6, APC,

PLK1, PPARG, PPARA, INSR, TP53, TERT, RB1, EGFR, AHR, ESR1, APEX, F2, and SYK. This study also mentions the biological processes involved and interrelated: cell cycle regulation, miRNA transcription, ATP metabolic processes, and reactive oxygen species (ROS). Target proteins regulate cancer cells' proliferation, apoptosis, invasion, and metastasis (Ilango et al., 2022; N. Liu et al., 2016).

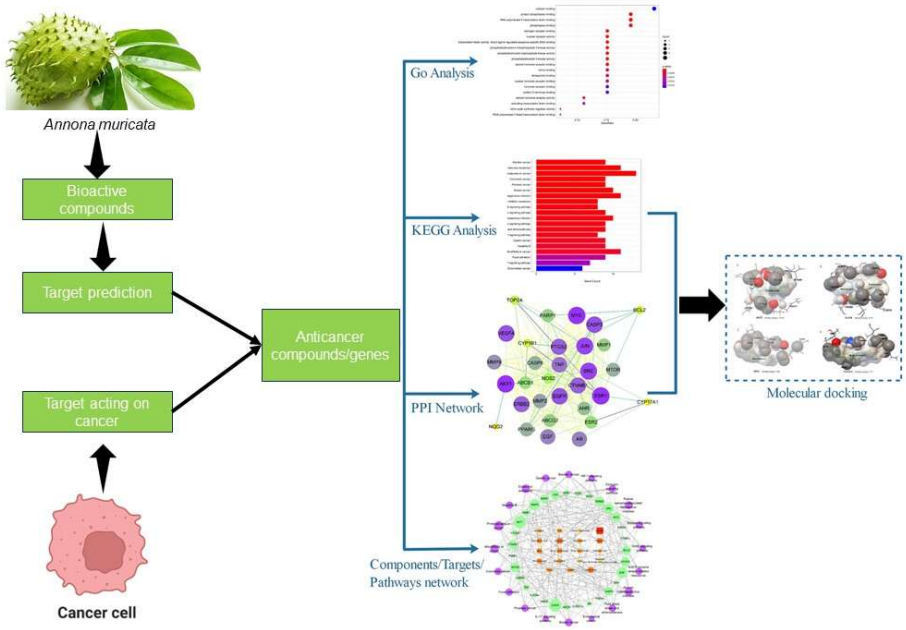

Figure 4. Schematic of network pharmacology approach in oncology (Hermawan et al., 2021; Rovik et al., 2024).

Another study revealed that *A. muricata* extract targeted six genes in colon cancer cells, namely ABCC1, ERBB2, STAT3, AR, SRC, and ABCG2 (Pandiyan et al., 2022). ABCG2 gene expression is essential in tumor progression and cell metastasis (Liu et al., 2010). In addition, overexpression of ERBB2 and STAT3 genes promotes colon cancer cell resistance to chemotherapy (Pectasides & Bass, 2015; Spitzner et al., 2014).

4. CONCLUSION

As an early parameter of anticancer potential, the cytotoxicity of *A. muricata* extracts has been widely studied on various cell lines in vitro. *A. muricata* extract has potential as a co-chemotherapy in the treatment of breast cancer, colon cancer, prostate, lung, cervical, liver, and blood cancer. Despite many studies on antiproliferation, *A. muricata* extract also has the potential to be an antimetastatic agent, overcoming drug resistance and improving treatment outcomes for cancer patients. More research is needed to determine the optimal dosage, route of administration, and potential side effects of *A. muricata*.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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