Indonesian Journal of Health Pharmacy
Vol.1, No.1, April, 2025, Page. 20-32

Review Article

A Scoping Review : Research Trend Pharmacology Of Annona muricata

Wardah Ibnatis Tsaniyah[1], Nurbaiti[1*], Muhammad Azhari Herly[1], Alifa Marini Putri[1], Nadine Novita Stephani Situmeang[1], Laila Nursalam[1], Lily Tazkiyyah[1], Aldeva Ilhami[2]

[1]Department of Pharmacy, Faculty of Science and Health, Universitas Muhammadiyah Riau
[2]Department of Science Education, Faculty of Education and Teacher Training, Universitas Islam Negeri Sultan Syarif Kasim Riau

Article Info
Received: 10-02-2025
Revised: 25-02-2025
Accepted: 15-03-2025

***Corresponding author:**
Nurbaiti
email: nurbaiti@umri.ac.id

ABSTRACT

Annona muricata, or soursop, has gained lots of attention in the pharmaceutical field due to its broad therapeutic potential. This study aims to analyze the pharmacological activities of soursop, including its Anti-cancer, antioxidant, and antidiabetic properties. The method used was a systematic literature review involving article searches using Google Scholar as the database, yielding 2,180 articles published between 2013 and 2024. The study results indicate that 96% ethanol is the most commonly used solvent (17.07%), with human cancer cells as the primary test subjects (21.57%) and soursop leaves as the most frequently used sample part (77%). Maceration is the most commonly applied extraction method (48%), with the most prominent pharmacological effect being Anti-cancer activity (40%). The conclusion of this research highlights the significant potential of soursop for developing herbal medicines.

Keywords:
Annona Muricata; Extract; Pharmacology; Soursop

INTRODUCTION

Annona Muricata or commonly known as soursop, is a plant that originates from tropical areas in the Americas, namely the Amazon Forest, the Caribbean, and Central America, but now soursop is widely distributed in various tropical countries including Indonesia. This part of soursop, especially the leaves and fruits, is often used in various kinds of medicine. "Traditionally, soursop has been used to treat fever, indigestion, pain, and to enhance immunity. In addition, its sweet-sour fruit flavor makes it popular as a food and as a base for drinks and other processed products. Botanically, soursop belongs to the Annonaceae family and has a rich chemical content, such as acetogenin, alkaloids, flavonoids, and phenols, each of which has an important role in supporting its pharmacological effects (Cahyawati, 2020).

In today's world of pharmacology, soursop plants have become an interesting subject of research due to their diverse bioactive content. One of the most researched compounds in soursop is acetogenin, which has been shown to have Anti-cancer, antimicrobial, and antidiabetic activity. Recent studies show that soursop leaf extract can inhibit the growth of cancer cells in laboratory tests (in vitro) through the mechanism of apoptosis or programmed cell death. In addition, the flavonoid compounds in soursop leaves are also known to have strong antioxidant effects, which can protect the body from oxidative damage caused by free radicals. Thus, the role that soursop has is not limited to traditional medicine, but also makes a great contribution to the innovation of modern plant medicines (Mukarromah, 2020).

Since 2019, studies on the potential pharmacological effects of soursop plants have grown rapidly. These studies cover a wide variety of aspects, including Anti-cancer, antioxidant, and antibacterial activity. For example, a study by Foster et al, (2020) that highlighted the Anti-cancer and anti-angiogenic effects of soursop plant leaves and stems on human cancer cell cultures (Foster et al., 2020). Another study by Agung Ayu Anggreni Permatasari et al, (2013)showed antibacterial activity

against Escherichia Coli which means this shows its potential to be used as a cure for Colibasilosis disease which usually affects farm animals. Treatment of colibasilosis is usually done by giving antibiotics to farm animals. However, the use of antibiotics in animals can spur the development of antibiotic resistance in the meat of livestock (Agung Ayu Anggreni Permatasari et al., 2013).

Conducting a literature review on the pharmacological effects of soursop is very important given the increasing number of new studies published every year. By summarizing these findings, we and other researchers can understand the patterns of plant utilization in a structured and directed way. In addition, the literature study helps identify gaps in existing research, thus encouraging more in-depth research in the future. This is particularly important because, despite a lot of research done, aspects such as drug-herbal interactions and long-term toxic effects still need further exploration. Therefore, this study is expected to provide a strong scientific basis for further research.

The study of literature plays an important role in the field of pharmacy by linking traditional knowledge with modern scientific advances. The study proves the traditional use of medicinal plants, such as soursop (Annona muricata), which is known to treat diabetes, cancer, and hypertension, while identifying bioactive compounds such as alkaloids, phenols, and acetogen that are responsible for these therapeutic effects. In addition, the study promotes the sustainable use of local biodiversity, demonstrating the potential of native plants as a pharmaceutical resource. By linking the observed bioactivity with specific phytochemicals, the literature review provides a solid foundation for the development of evidence-based herbal medicines, supporting their safety and effectiveness in today's healthcare (Qomaliyah, 2022).

The main objective of this literature review is to analyze and summarize the latest findings regarding the pharmacological effects of soursop plants (Annona muricata). This study also aims to identify the mechanism of action of bioactive compounds in soursop and their pharmacological effects, as well as evaluate their benefits in treatment. Thus, it is expected to provide a more comprehensive insight into the therapeutic potential of soursop, as well as provide direction for future research.

METHODS

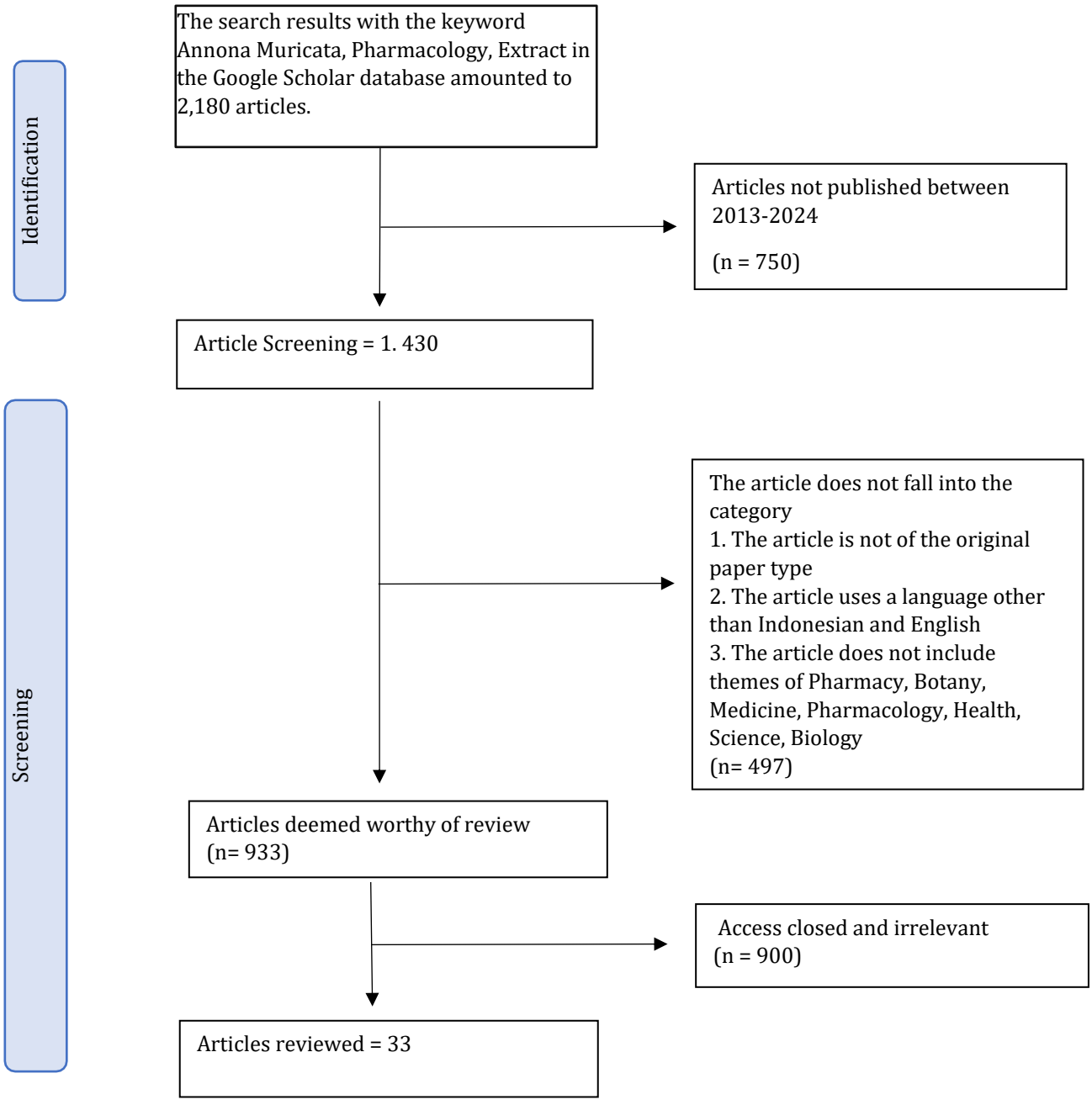
The research was conducted by searching for Journal Articles using Google Scholar as the database, which resulted in 2,180 articles published from 2013 to 2024. To ensure a broader coverage of articles, the following keywords were used: 'Annona Muricata', 'cancer', 'pharmacology', and 'Extract'. In addition, the search was also limited to articles focusing on pharmaceutical science, pharmacological effects, and research on soursop plants and their health benefits.

The PRISMA (Preferred Reporting Items for Systematic and Meta-Analyses) framework is used to guide the article selection process. The article selection process involves 3 stages, namely identification, screening, and eligibility assessment. The keywords used were identified based on the recommendations of experts and based on previous research research. An initial search yielded 2,180 article.

Table 1. Inclusion and Exclusion Criteria

Criteria	Inclusion	Exclusion
Year	Published in between 2013 - 2024	<2013
Language	Indonesian and English	Using languages other than English and Indonesian
Paper Type	Journal Articles	Review articles, Books, Conference Proceedings
Fields in Database	Pharmacy, Botany, Medicine, Pharmacology, Health, Science, Biological Sciences	Business, Psychology, Economy, Art, Architecture, Humanities

The following is the flow of literature selection used:



RESULTS AND DISCUSSION

Based on the inclusion and exclusion criteria available in Table 1.1, a total of 933 articles were obtained based on theme categories, after further review, as many as 900 articles were eliminated due to closed access, less relevant to the inclusion category, and the remaining 33 articles were further reviewed (Table 1.2)

Table 2 . Review Results

No	Author	Solvent	Sample part	Test animals/microbes	Extraction Methods	Pharmacological Effects
1	(Fatmawati et al., 2019)	Ethanol	Leaf	Human breast cancer cell (MCF-7) & normal vero cell	Soxhletation	Anti-cancer
2	(Merlín-Lucas et al., 2021)	Ethanol	Leaf	Balb/c mice breast cancer cell	Maceration	Anti-cancer
3	(Adila Putri Ramandhita & Hanum, 2022)	Ethanol 96%	Leaf	Human hepG2 liver cancer cell culture	Maceration	Anti-cancer
4	(Silihe et al., 2023)	Ethanol 96% & Distilled water	Leaf, Fruit	Female wistar rat	Maceration	Anti-cancer
5	(Foster et al., 2020)	Hexane, Ethyl Acetate, Ethanol	Leaf, Cortex	Human prostate cancer cell (DU-145, PC-3, RWPE-1)	Fractination	Proliferase Inhibition
6	(Shashanka K. et al., 2020)	Methanol, Distilled water	Fruit, seed	Human cancer cell	Soxhletation	Anti-cancer
7	(Perinbarajan et al., 2024)	Ethanol	Leaf	Human breast cancer cell	Soxhletation	Anti-cancer, Anti-proliferase, Anti-Apoptotic decrease
8	(Rosdi et al., 2024)	Ethanol	Leaf	Human lung cancer cell	Maceration & Sonication	Anti-cancer
9	(Salac et al., 2022)	Methanol, N-hexane, Ethyl Acetate	Leaf	Human lung cancer cell	Maceration	Anti-cancer
10	(Mary et al., 2024)	Distilled Water	Leaf	Human cancer cell SCC-15	Soxhletation	Anti-proliferation, apoptotic induction
11	(Almutairi et al., 2023)	N-Hexane, Chloroform, Ethyl Acetate, Methanol	Leaf	Human cancer cell	Soxhletation	Anti-cancer
12	(Salih et al., 2023)	Ethanol	Leaf	Human cancer cell	Extraction with rocking incubator	Anti-cancer
13	(Swapna B et al., 2022)	Hydro-Alcoholic, Ethyl Acetate	Fruit	Human lung cancer cell	Liquid-phase extraction	Anti-cancer

14	(Jyothi et al., 2023)	Hexane	Seed	Human cancer cell	Soxhletation	Anti-proliferation
15	(Adri & Hersoelistyorini, 2013)	Methanol	Leaf	-	Drying Methods	Anti-oxidant
16	(Agung Ayu Anggreni Permatasari et al., 2013)	Aquadet	Leaf	*Escherichia Coli*	Mechanical Extraction	Anti-bacteria
17	(Adeanne C & Jonathan Schaduw, 2018)	Ethanol 96%	Leaf	-	Maceration	-
18	(Sugiharto et al., 2021)	Ethanol	Leaf	-	Maceration	Anti-hyperglycemia
19	(Novianty et al., 2022)	Distilled Water	Leaf	-	-	Anti-hyperglycemia
20	(Purnamasari, 2021)	Ethanol 70%	Leaf	-	Maceration	Anti-bacteria, anti-oxidant, anti-cancer, anti-inflamation
21	(Pertiwi et al., 2020)	Distilled Water	Leaf	Human breast cancer cell line T47D	-	Anti-cancer
22	(Saputra & Sukanty, 2024)	Ethanol 70%	Leaf	-	Maceration	Anti-oxidant, anti-microbia, anti-cancer
23	(Erlinawati & Wardani, 2022)	Ethanol 96%	Leaf	-	Maceration	Anti-oxidant, anti-cancer
24	(Latifa Putri & Simon Bambang, 2018)	Ethanol 96%	Leaf	-	Drying Methods	Anti-oxidant
25	(Arfa Yanti et al., 2020)	Distilled Water	Leaf	*Escherichia Coli & Staphylococcus Aureus*	-	Anti-bacteria
26	(Andri et al., 2022)	-	-	Hypertensive Patient	Decoction	Vasodilatation
27	(Asbanu et al., 2019)	N-Hexane. Ethyl Acetate, Methanol	Leaf	-	Maceration	Anti-oxidant
28	(Yulianto, 2019)	-	-	-	-	Hipotensve
29	(Fadel & Besan, 2021)	Ethanol 96%	Leaf	Balb/c mice	Soxhletation	Anti-hyperglycemia
30	(da Silva Santos et al., 2021)	Ethanol & distilled water	Fruit	*Saccharomyces Cerevisae*	Maceration	Anti-microbia
31	(A. Makuasa & Ningsih, 2020)	Ethanol 96%	Leaf	-	Maceration	Anti-oxidant
32	(Naik et al., 2021)	Methanol & Dimethyl Sulfoxide	Leaf	Mice	Soxhletation	Anti-cancer
33	(El-Wakil et al., 2021)	Dimethyl Sulfoxide	Leaf	Mice	-	Anti-helmintic

Solvents Used

Based on the data from the article attached in Figure 2.1, water and 96% ethanol are the most commonly used solvents, each reaching 17.07%. This highlights the flexibility and effectiveness of water as a polar solvent in extracting water-soluble active compounds. Meanwhile, 96% ethanol is often used due to its ability to dissolve polar and semi-polar compounds, which are often the main bioactive constituents in extracting compounds from plants, such as phenolic compounds and flavonoids. Ethanol itself is an organic solvent frequently used for extraction processes, and there are already numerous reports or research articles on the use of ethanol. Some reasons for the widespread use of ethanol include its relatively low toxicity compared to acetone and methanol, low cost, applicability in various extraction methods, and safety for extracts intended for pharmaceuticals and food (Hakim & Saputri, 2020).

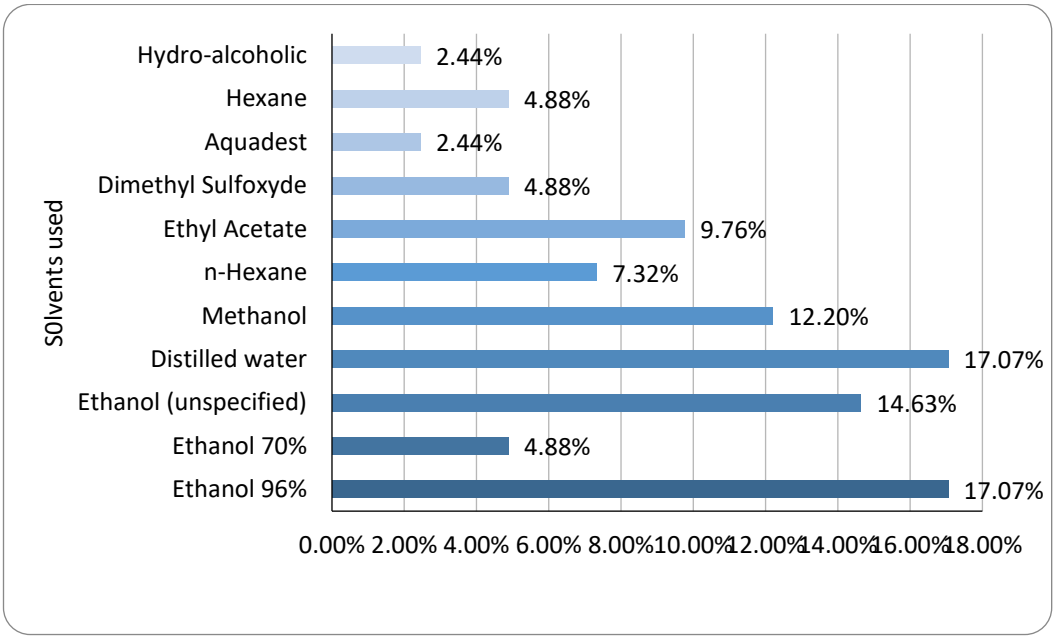


Figure 2. Percentage diagram of the solvent used

12.2% of the articles used Methanol as a solvent, and methanol itself is a polar solvent that is commonly used due to its efficiency in extracting highly polar bioactive compounds. Ethyl acetate, used in 9.76%, is preferred for semi-polar compounds such as alkaloids. Other solvents, like n-hexane (7.32%), are primarily used for non-polar compounds, including lipids and essential oils. This difference reflects that the selection of solvents in each article is made based on the chemical properties of the targeted compounds.

In the research conducted by Puspa Yani et al, (2023), the difference in the type of solvent used for extracting, particularly flavonoids from soursop leaves, has a significant impact. This study shows that the total flavonoid content varies according to the polarity level of the solvent used. In this study, three solvents, namely 96% ethanol, ethyl acetate, and n-hexane, were used for the extraction process using the maceration method. The results showed that the highest flavonoid content was found in the semi-polar solvent ethyl acetate at 97.2381 mgQE/g, followed by n-hexane (73.6667 mgQE/g), and the lowest in 96% ethanol (68.9048 mgQE/g). This difference is due to the polarity characteristics of flavonoids and solvents, where certain flavonoid compounds are more soluble in semi-polar solvents compared to polar or non-polar solvents (Puspa Yani et al., 2023).

Test Animals/Microbes

The diagram in Figure 2.2 shows the distribution of test subjects, including animals, microbes, and human samples used in each reviewed study. The largest percentage (58.82%) is comprised of hypertensive patients, and this large percentage is found in a quasi-experimental study conducted by Andri et al. in 2022. This study aims to determine the comparison of the use of soursop leaf decoction on blood pressure reduction in hypertensive patients in the Working Area of the Lingkar Barat Health Center in Bengkulu City (Andri et al., 2022).

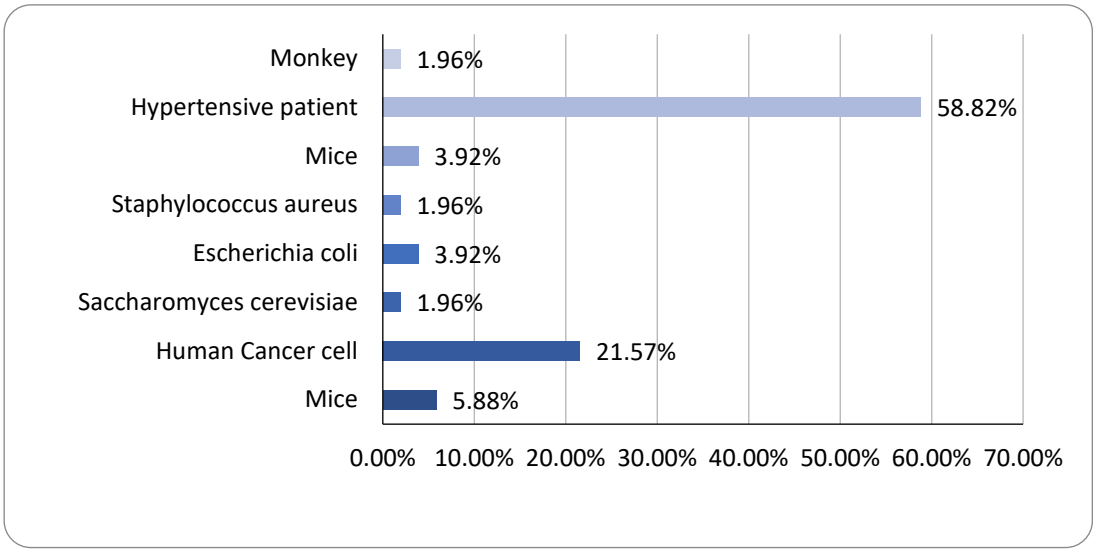


Figure 3. Percentage diagram of the test animals/microbes used

The second most common research test model is human cancer cells, with a percentage of 21.57%. This focus indicates the growing interest of researchers in the Anti-cancer properties of soursop, as this plant is known to contain bioactive compounds such as acetogenins and alkaloids, which exhibit cytotoxic effects on various cancer cell lines. The use of cancer cell models allows researchers to explore more about the mechanisms of action of bioactive compounds, such as the induction of apoptosis or cell cycle arrest, and can provide insights into the potential of soursop as a natural Anti-cancer agent.

Animals and bacteria are also used in some research, although not as much as cancer cells and humans. The use of animals such as mice is important in preclinical studies to assess pharmacokinetics, toxicity, and in vivo effects. Mice are widely used as laboratory animals because they have advantages such as a relatively short life cycle, a large number of offspring per birth, ease of handling, reproductive characteristics similar to other mammals, and anatomical, physiological, and genetic structures that are similar to humans(Herrmann et al., 2019; Mutiarahmi et al., 2021). The use of microbes such as Saccharomyces cerevisiae, Escherichia coli, and Staphylococcus aureus accounts for a smaller percentage (ranging from 1.96% to 3.92%), mainly for antimicrobial and antibacterial studies.

Sample

Some of the previous studies have shown that soursop leaves contain high concentrations of flavonoids and acetogenins, which have cytotoxic activity against cancer cells, making them the most researched part in the context of treatment (Diputra et al., 2023). Meanwhile, soursop seeds also contain bioactive compounds, but in different proportions; the seeds contain more toxic compounds that can function as natural insecticides (Siswarni MZ et al., 2016). The fruit, although not as popular as the leaves in health research, also has nutritional and health benefits, such as important vitamin and mineral content (da Silva Santos et al., 2021). The stem has the highest carbohydrate content and also contains annonaceous acetogenins that have cytotoxic effects against cancer cells (van de Grift, 2020).

Leaf

Out of 32 studies reviewed, the leaves are the most commonly used sample part compared to other parts of the soursop plant. A total of 27 out of 33 articles reviewed used soursop leaves as a sample. This may be due to the fact that soursop leaves contain several secondary metabolite compounds such as polyphenols, triterpenoids, saponins, and flavonoids. One of the compounds found in soursop leaves, flavonoids, belongs to the group of phenolic compounds that are widely available as plant pigments in red, purple, blue, and yellow colors found in various plants. Soursop leaves have effective properties for curing cancer (Erlinawati & Wardani, 2022).

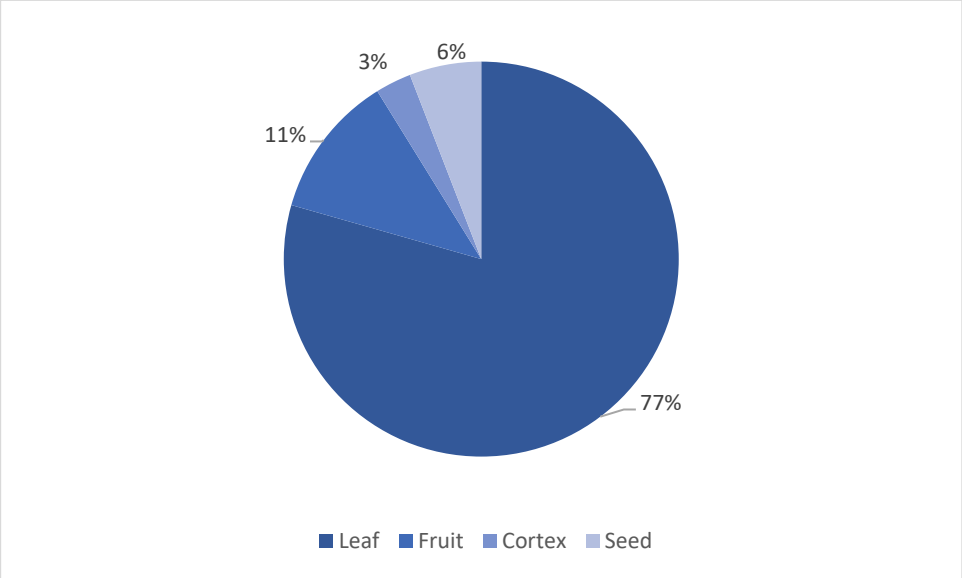


Figure 4. Diagram of Sample Part used in the research

Fruit

In addition to its leaves, soursop fruit also contains many beneficial components for the body. Although it is not used for research as much as the leaves, soursop fruit also plays a significant role in studying pharmacological effects. Soursop fruit is known for its high nutritional value, containing vitamins, minerals, and fiber, as well as bioactive compounds such as phenolics and ascorbic acid. Research focusing on the fruit often explores its antioxidant potential and possible applications in managing metabolic disorders such as diabetes or obesity. One study that utilized the fruit, conducted by Swapna B et al, (2022), concluded that the hydroalcoholic and ethyl acetate extracts from Annona Muricata have Anti-cancer potential against human lung and oral carcinoma (Swapna B et al., 2022). However, its lower usage percentage compared to the leaves suggests that the primary value of the fruit is considered to be more nutritional than pharmacological.

Cortex

Other parts, such as the bark and seeds, are less frequently studied. Only 1 out of 32 articles used samples of soursop plant stems, a study by Foster et al, (2020) explained the selective and strong cytotoxic effects of the bark extract of A. muricata on prostate cancer cell lines (PC3 and DU-145) compared to normal cells. Through an in-vitro biochemical panel, the standard ethyl acetate extract from the bark showed a necrotic cell death pathway without triggering reactive oxygen species, inhibiting angiogenesis markers, and enhancing the impact of docetaxel chemotherapy on DU-145 cells. These findings suggest the potential of annonacin and the bark extract of A. muricata as selective cytotoxic agents with antimetastatic and antiangiogenic potential, and further in-vivo research is needed to determine physiological sizes and a complete understanding of the observed cytotoxicity mechanisms(Foster et al., 2020).

Seed

Soursop seeds contain bioactive components such as annonacin, and 2 reviewed articles show the potential of soursop seed extracts as anti-cancer agents, particularly for breast cancer in women. The low percentage of the use of these parts in research may be attributed to challenges in accessibility or the limited amount of bioactive compounds compared to the leaves. Overall, the difference in the number of these sample usages highlights the flexibility of soursop as a medicinal plant, while emphasizing the central role of its leaves in pharmacological research.

Extraction Methods

Maceration is the most commonly used method, accounting for 48% of studies. This technique involves soaking plant materials in a solvent at room temperature, allowing for the efficient extraction of thermolabile bioactive compounds such as flavonoids, tannins, and alkaloids. Maceration is popular due to its simplicity, cost-effectiveness, and ability to extract polar and semi-polar compounds commonly found in soursop.

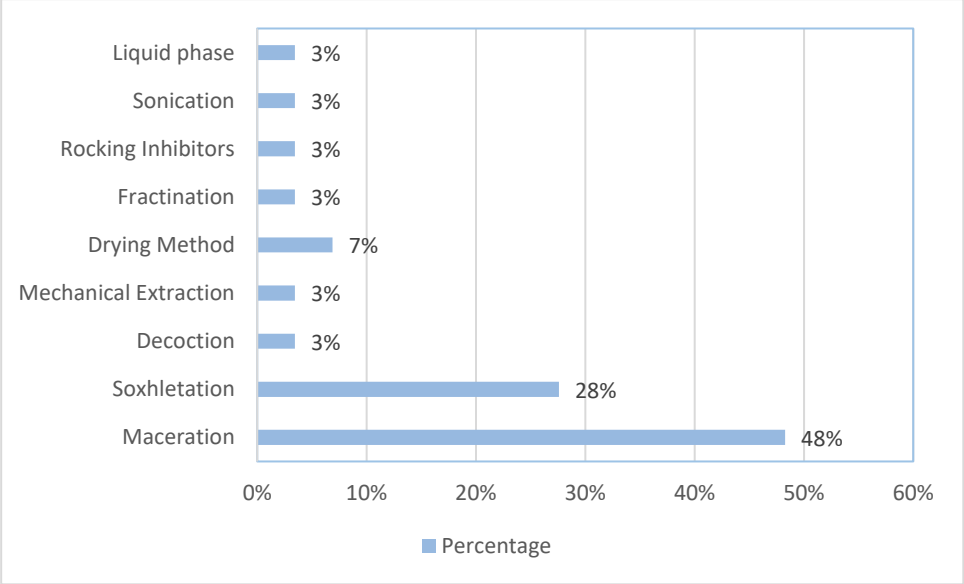


Figure 5. Diagram of Extraction methods used in reviewed researches

The second commonly used method is Soxhlet extraction, with 28% of the reviewed articles using this method. This method utilizes continuous solvent circulation to extract compounds at high temperatures, making it more effective for non-polar or less polar compounds. Although Soxhlet extraction is more time-efficient and yields higher concentrations of bioactive substances compared to maceration, its dependence on heat can damage thermolabile compounds, which may explain its lower usage compared to maceration.

Other methods, such as the drying method (7%), mechanical extraction, sonication, and shaking incubators, each contribute 3%. These methods are less commonly used and are more often applied in specific contexts where targeting certain bioactive compounds is necessary or when standard techniques such as maceration and Soxhlet extraction are inadequate. The limited use of these extraction methods indicates that simpler and established methods like maceration and Soxhlet extraction remain the primary choice for extracting bioactive compounds from soursop in most pharmacological studies.

The differences in extraction methods have a significant impact on the yield and quality of compounds extracted from soursop leaves. The maceration method, although simple and commonly used, requires a longer time and can produce lower yields compared to more modern methods such as Microwave Assisted Extraction (MAE) or sonication. Research shows that MAE, which uses microwave energy, can enhance extraction efficiency by reducing the time and amount of solvent needed, as well as yielding higher antioxidant activity (Latifa Putri & Simon Bambang, 2018). Furthermore, the use of different solvents also affects the levels of bioactive compounds; for example, methanol has been shown to provide higher yields of flavonoids compared to 70% ethanol. Therefore, the selection of appropriate extraction methods and solvents is crucial to optimize the extraction results of compounds from soursop leaves (Sumantri et al., 1988).

Pharmacological Effects

Based on several previous studies, it is known that the extract from soursop leaves can inhibit the growth of cancer cells and has cytotoxic activity against several types of cancer, such as breast and lung cancer (Cahyawati, 2020). In addition, in vivo studies indicate that soursop leaves can improve glucose tolerance and reduce glucose absorption, thus potentially lowering blood sugar levels in diabetes patients (Djunarko et al., 2022; Pribadi, 2020). This extract also has antioxidant properties that can reduce oxidative stress, which plays a role in preventing diabetes complications(Cahyawati, 2020; Djunarko et al., 2022).

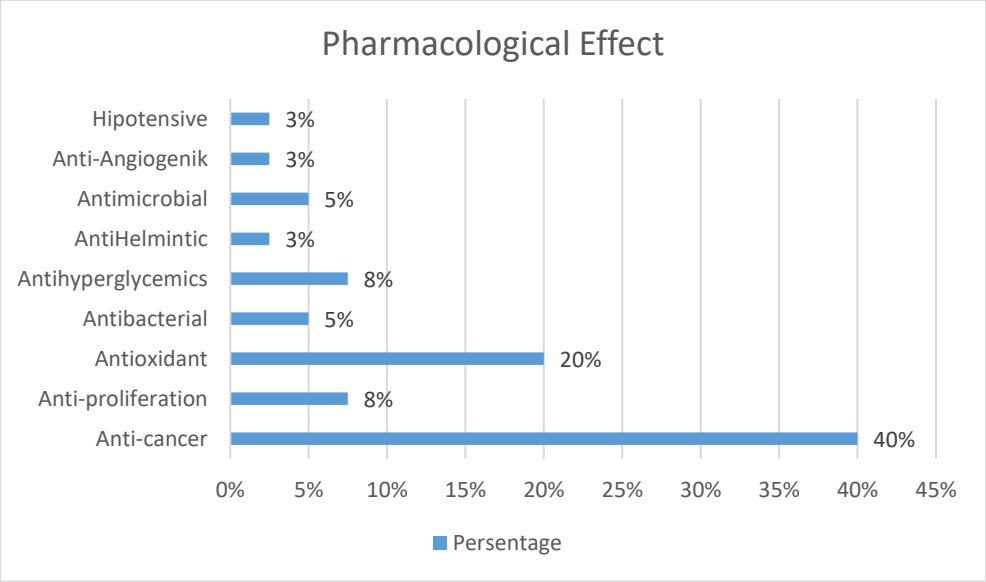


Figure 6. Diagram of Pharmacological Effects

In general, based on several reviewed studies, soursop shows strong Anti-cancer properties, reaching 40% of the effects of other reported pharmacological agents. This is supported by many studies demonstrating its ability to induce apoptosis (programmed cell death) in cancer cells and inhibit tumor growth. The antiproliferative effect, which contributes 8% to the diagram, further supports its potential as an Anti-cancer agent by blocking the uncontrolled proliferation of cancer cells.

Aside from its properties as an Anti-cancer agent, soursop has various other beneficial effects. Soursop demonstrates significant antioxidant activity (20%), which can neutralize harmful free radicals and protect cells from oxidative damage. This antioxidant capability may play a role in preventing chronic diseases such as cardiovascular diseases and neurodegenerative disorders. Additionally, soursop shows antihyperglycemic properties (8%), indicating its potential as a complementary therapy for diabetes management. Soursop also exhibits antimicrobial (5%) and antiparasitic (3%) activities, which could be explored for the treatment of infectious diseases.

Although soursop shows potential in various pharmacological fields, it should be noted that further research is needed to fully understand its mechanisms of action and possible side effects. This is because, in addition to having many benefits, the consumption of extracts from soursop leaves also needs to be considered as it can cause side effects such as liver and kidney disorders if consumed excessively(Cahyawati, 2020). Clinical trials are necessary to ensure its efficacy and safety on human subjects before it can be widely recommended as a therapeutic agent(Mutakin et al., 2022).

CONCLUSIONS

Research findings indicate that soursop has potential as an Anti-cancer and antioxidant agent, particularly due to bioactive compounds such as acetogenins and flavonoids. A review of 33 articles highlights the primary focus on the Anti-cancer properties of soursop, with maceration being the most commonly used extraction method. The results of this study emphasize the importance of developing innovative and sustainable pharmaceutical products based on soursop, as well as recommending further studies to explore herbal-drug interactions and toxic effects in long-term use to provide broader recommendations for its use in modern medicine.

REFERENCES

A. Makuasa, D. A., & Ningsih, P. (2020). The Analysis of Total Flavonoid Levels In Young Leaves and Old Soursop Leaves (Annona muricata L.) Using UV-Vis Sepctrofotometry Methods. *Journal of Applied Science, Engineering, Technology, and Education*, *2*(1), 11–17. https://doi.org/10.35877/454ri.asci2133

Adeanne C, W., & Jonathan Schaduw, A. N. K. W. (2018). Identifikasi kandungan pada daun sirsak (Annona muricata L.). *JIF-Jurnal Ilmiah*, *3*(2), 54–56. https://ejurnal.poltekkes-manado.ac.id/index.php/jif/article/download/278/247/

Adila Putri Ramandhita, & Hanum, L. (2022). Efek Antikanker Nanopartikel Alginat Ekstrak Etanol Daun Sirsak (Annona muricata Linn) pada Kultur Sel Kanker Hepar (HepG2). *Jurnal Riset Kedokteran*, *1*(2), 130–133. https://doi.org/10.29313/jrk.v1i2.566

Adri, D., & Hersoelistyorini, W. (2013). Aktivitas Antioksidan dan Sifat Organoleptik Teh Daun Sirsak (Annona muricata Linn .) Berdasarkan Variasi Lama Pengeringan Antioxidant Activity and Organoleptic Charecteristic of Soursop (Annona muricata Linn .) Leaf Tea Based on Variants Time Drying. *Jurnal Pangan Dan Gizi*, *04*(07).

Agung Ayu Anggreni Permatasari, G., Nengah Kerta Besung, I., & Mahatmi, H. (2013). *Daya Hambat Perasan Daun Sirsak Terhadap Pertumbuhan Bakteri Escherichia coli*. *2*(2), 162–169.

Almutairi, B. O., Mater, A. S., Abutaha, N., & Almutairi, M. H. (2023). In vitro antiproliferative efficacy of Annona muricata seed and fruit extracts on several cancer cell lines. *Open Chemistry*, *21*(1). https://doi.org/10.1515/chem-2022-0350

Andri, J., Padila, P., Sugiharno, R. T., & Anjelina, K. (2022). Penggunaan Rebusan Daun Sirsak terhadap Penurunan Tekanan Darah Penderita Hipertensi. *Jurnal Keperawatan Silampari*, *6*(1), 79–88. https://doi.org/10.31539/jks.v6i1.4169

Arfa Yanti, N., Ambardini, S., Ode Leni Marlina, W., Dwi Cahyanti Jurusan Biologi FMIPA Universitas Halu Oleo Kampus Hijau Bumi Tridharma, K., Kendari Sulawesi Tenggara, A., & Korespondensi, P. (2020). Aktivitas Antibakteri Kombucha Daun Sirsak (Annona muricata L.) Dengan Konsentrasi Gula Berbeda (Antibacterial Activity of Soursoup Leaves Kombucha (Annona muricata L.) With Different Sugar Concentration). *Jurnal Biologi FMIPA Universitas Halu Oleo*, *8*(2), 35–40.

Asbanu, W. A. Y., Wijayati, N., & Kusumo, E. (2019). Identifikasi Senyawa Kimia Ekstrak Daun Sirsak (Annona muricata L.) dan Uji Aktivitas Antioksidannya dengan Metode DPPH (2,2-Difenil-1-Pikrilhidrasil). *Indonesian Journal of Chemical Science*, *8*(3), 153–160. http://journal.unnes.ac.id/sju/index.php/ijcs

Cahyawati, P. N. (2020). EFEK FARMAKOLOGI DAN TOKSIK SIRSAK (Annona muricata): A MINI-REVIEW. *Biomedika*, *12*(2), 107–116. https://doi.org/10.23917/biomedika.v12i2.10691

da Silva Santos, M. A., Ribeiro, P. V. L., Andrade, C. P., Machado, A. R. G., de Souza, P. G., & de Souza Kirsch, L. (2021). Physicochemical and Sensory Analysis of Craft Beer Made With Soursop (Annona Muricata L.). *Acta Scientiarum Polonorum, Technologia Alimentaria*, *20*(1), 103–112. https://doi.org/10.17306/J.AFS.2021.0845

El-Wakil, E. S., Abdelmaksoud, H. F., Aboushousha, T. S., & Ghallab, M. M. I. (2021). Evaluation of Annona muricata (Graviola) leaves activity against experimental trichinellosis: In vitro and in vivo studies. *Journal of Helminthology*, *95*. https://doi.org/10.1017/S0022149X21000481

Erlinawati, N. A., & Wardani, D. (2022). PENETAPAN KADAR FLAVONOID PADA EKSTRAK DAUN SIRSAK (Annona Muricata L.) YANG TUMBUH DI KP. CIHUNI DENGAN METODE SPEKTROFOTOMETRI UV-Vis. *Jurnal Ilmu Kesehatan Prima Insan Cendikia (JPIC)*, *1*(1), 1–10. https://jpic.lp4mstikeskhg.org

Fadel, M. N., & Besan, E. J. (2021). UJI AKTIVITAS ANTIDIABETES EKSTRAK DAUN SIRSAK (Annona muricata L.) PADA MENCIT YANG DIINDUKSI ALOKSAN. *Indonesia Jurnal Farmasi*, *5*(2), 1. https://doi.org/10.26751/ijf.v5i2.1170

Fatmawati, D., Islam, U., Agung, S., Suparmi, S., Islam, U., Agung, S., & Yusuf, I. (2019). *Selektivitas Antikanker Daun Sirsak (Annona muricata) pada Lini Sel Kanker Payudara muricata) PADA LINI SEL KANKER PAYUDARA ANTI-CANCER SELECTIVITY OF SIRSAK (Annona muricata) LEAF*. *January*. https://doi.org/10.22437/bs.v4i2.5440

Foster, K., Oyenihi, O., Rademan, S., Erhabor, J., Matsabisa, M., Barker, J., Langat, M. K., Kendal-Smith, A.,

Asemota, H., & Delgoda, R. (2020). Selective cytotoxic and anti-metastatic activity in DU-145 prostate cancer cells induced by Annona muricata L. bark extract and phytochemical, annonacin. *BMC Complementary Medicine and Therapies*, *20*(1), 1–15. https://doi.org/10.1186/s12906-020-03130-z

Hakim, A. R., & Saputri, R. (2020). Narrative Review: Optimasi Etanol sebagai Pelarut Senyawa Flavonoid dan Fenolik. *Jurnal Surya Medika*, *6*(1), 177–180. https://doi.org/10.33084/jsm.v6i1.1641

Jyothi, S. R., Malathi, H., & Patil, S. J. (2023). Efficacy of Graviola Seed Extract (Annona muricata: Annonaceae) on E-Cadherin Gene Regulation and Cytotoxicity in MDA-MB-231 Cell Lines. *Asian Journal of Pharmaceutics*, *17 (1)*(Jan-Mar), 38–43.

Latifa Putri, A., & Simon Bambang, W. (2018). *Optimasi Proses Ekstraksi Daun Sirsak (Annona muricata L) Metode MAE (Microwave Assisted Extraction) dengan Respon Aktivitas Antioksidan dan Total Fenol*. *4*(April), 79–87.

Mary, S. J., Veeravarmal, V., Thankappan, P., Arumugam, P., Augustine, P. I., & Franklin, R. (2024). Anti-cancer effects of green synthesized gold nanoparticles using leaf extract of Annona muricata. L against squamous cell carcinoma cell line 15 through apoptotic pathway. *Dental Research Journal*, *21*(1), 14. https://doi.org/10.4103/drj.drj_521_23

Merlín-Lucas, V., Ordoñez-Razo, R. M., Calzada, F., Solís, A., García-Hernández, N., Barbosa, E., & Valdés, M. (2021). Antitumor potential of annona muricata linn. An edible and medicinal plant in mexico: In vitro, in vivo, and toxicological studies. *Molecules*, *26*(24). https://doi.org/10.3390/molecules26247675

Mukarromah, T. A. (2020). *NARRATIVE REVIEW: POTENSI DAUN SIRSAK (Annona muricata L) SEBAGAI SUMBER ANTIOKSIDAN, ANTIINFLAMASI, DAN ANTIDIABETES*.

Naik, A. V., Dessai, S. N., & Sellappan, K. (2021). Antitumour activity of Annona muricata L. leaf methanol extracts against Ehrlich Ascites Carcinoma and Dalton's Lymphoma Ascites mediated tumours in Swiss albino mice. *Libyan Journal of Medicine*, *16*(1). https://doi.org/10.1080/19932820.2020.1846862

Novianty, S. D., Lestari, R. D., & Damayanti, D. S. (2022). Potensi Kombucha Daun Sirsak (Annona muricata Linn.) dalam Menghambat DPP4 dan SDF-1 sebagai Antidiabetes dengan Studi In Silico. *Jurnal Kedokteran Komunitas*, *10*(1).

Perinbarajan, G. K., Sinclair, B. J., Mossa, A. T., Ohja, N., & Jeelani, P. G. (2024). Silica/Annona muricata nano-hybrid: Synthesis and Anti-cancer activity against breast cancer. *Heliyon*, *10*(3), e25048. https://doi.org/10.1016/j.heliyon.2024.e25048

Pertiwi, W., Arisanty, D., & Linosefa, L. (2020). Pengaruh Ekstrak Daun Sirsak (Annona muricata lin) Terhadap Viabilitas Cell Line Kanker Payudara T47D Secara In Vitro. *Jurnal Kesehatan Andalas*, *9*(1S), 165–170. https://doi.org/10.25077/jka.v9i1s.1173

Purnamasari, F. (2021). Identifikasi Senyawa Aktif dari Ekstrak Daun Sirsak (Annona muricata L.) dengan Perbandingan Beberapa Pelarut pada Metode Maserasi. *Window of Health : Jurnal Kesehatan*, *04*(03), 231–237. https://doi.org/10.33096/woh.v4i03.234

Puspa Yani, N. K. L., Nastiti, K., & Noval, N. (2023). Pengaruh Perbedaan Jenis Pelarut Terhadap Kadar Flavonoid Total Ekstrak Daun Sirsak (Annona muricata L.). *Jurnal Surya Medika*, *9*(1), 34–44. https://doi.org/10.33084/jsm.v9i1.5131

Qomaliyah, E. N. (2022). Etnofarmakologi dan Potensi Bioaktivitas Daun dan Buah Sirsak (Annona Muricata): Artikel Review. *Biocity Journal of Pharmacy Bioscience and Clinical Community*, *1*(1), 36–55. https://doi.org/10.30812/biocity.v1i1.2488

Rosdi, M. N. M., Husin, F., & Yaakob, H. (2024). Evaluation of Annona muricata Linn Leaves Extracts from Maceration and Ultrasonic-Assisted Methods for Anti-cancer Activity on HLFa Cells. *Malaysian Journal of Fundamental and Applied Sciences*, *20*(5), 985–997.

https://doi.org/10.11113/mjfas.v20n5.3400

Salac, E. L. O., Alvarez, M. R., Gaurana, R. S., Grijaldo, S. J. B., Serrano, L. M., Juan, F. de, Abogado, R., Padolina, I., Deniega, F. M., Delica, K., Fernandez, K., Lebrilla, C. B., Manalo, M. N., Heralde, F. M., Completo, G. C. J., & Nacario, R. C. (2022). Biological Assay-Guided Fractionation and Mass Spectrometry-Based Metabolite Profiling of Annona muricata L. Cytotoxic Compounds against Lung Cancer A549 Cell Line. *Plants*, *11*(18). https://doi.org/10.3390/plants11182380

Salih, S. M., Ahmed, A., & Issa, Y. W. (2023). Cytotoxic Effect of Annona muricata leaf extracts on tumor cell lines in vitro. *Journal of Al-Nahrain University Science*, *16*(1), 137–142. https://doi.org/10.22401/jnus.16.1.20

Saputra, I. P. B. A., & Sukanty, N. M. W. (2024). Analisis GC-MS dari Senyawa Bioaktif Ekstrak Etanol Daun Tanaman Sirsak (Annona muricata L.) sebagai Obat Tradisional. *Bioscientist : Jurnal Ilmiah Biologi*, *12*(1), 565. https://doi.org/10.33394/bioscientist.v12i1.10330

Shashanka K., P., Veeresh, P. M., Ramesh, P. S., Natraj, S. M., Madhunapantula, S. V., & Devegowda, D. (2020). Phytochemical fractions from Annona muricata seeds and fruit pulp inhibited the growth of breast cancer cells through cell cycle arrest at G0 /G1 phase. *Journal of Cancer Research and Therapeutics*, *14*(7), 1525–1534. https://doi.org/10.4103/jcrt.JCRT

Silihe, K. K., Mbou, W. D., Ngo Pambe, J. C., Kenmogne, L. V., Maptouom, L. F., Kemegne Sipping, M. T., Zingue, S., & Njamen, D. (2023). Comparative Anti-cancer effects of Annona muricata Linn (Annonaceae) leaves and fruits on DMBA-induced breast cancer in female rats. *BMC Complementary Medicine and Therapies*, *23*(1), 1–16. https://doi.org/10.1186/s12906-023-04073-x

Sugiharto, M. I., Bintari, Y. R., & Damayanti, D. S. (2021). Mekanisme Senyawa Aktif Daun Sirsak (Annona muricata Linn.) Sebagai Anti Diabetes : Studi In Silico. *Jurnal Kedokteran Komunitas*, *9*(2), 1–13.

Swapna B, M., Rao, R., Kotha, S., S, S., & Setty, R. S. (2022). In vitro Cytotoxic Activity using Fruits of Annona muricata and Aerial Parts of Euphorbia tirucalli against Lung and Oral Cancer Cell Lines. *Pharmacognosy Magazine*, *13 (Suppl*(62), 179–188. https://doi.org/10.4103/pm.pm

Yulianto, S. (2019). Pengetahuan Masyarakat Tentang Daun Sirsak Untuk Hipertensi. *Jurnal Kebidanan Dan Kesehatan Tradisional*, *4*(2), 2. https://doi.org/10.37341/jkkt.v4i2.119