Review

Pharmacological Activities of Soursop (Annona muricata Lin.)

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Abstract: Soursop (Annona muricata Lin.) is a plant belonging to the Annonaceae family that has been widely used globally as a traditional medicine for many diseases. In this review, we discuss the traditional use, chemical content, and pharmacological activities of Annona muricata. From 49 research articles that were obtained from 1981 to 2021, A. muricata’s activities were shown to include anticancer (25%), antiulcer (17%), antidiabetic (14%), antiprotozoal (10%), antidiarrhea (8%), antibacterial (8%), antiviral (8%), antihypertensive (6%), and wound healing (4%). Several biological activities and the general mechanisms underlying the effects of A. muricata have been tested both in vitro and in vivo. A. muricata contains chemicals such as acetogenins (annomuricins and annonacin), alkaloids (coreximine and reticuline), flavonoids (quercetin), and vitamins, which are predicted to be responsible for the biological activity of A. muricata.

Keywords: soursop; Annona muricata L.; traditional medicine; pharmacological activities

1. Introduction

Presently, the use of natural ingredients as treatments for various diseases is increasing. Plants are a source of natural ingredients that are widely used as medicines. The compounds present in plants are responsible for their activities against various diseases, and studies can be performed to identify the active compounds in plants and determine their pharmacological activities against diseases [1].

Many studies on plants, their contents, and the pharmacological activities of their constituents have been conducted. Annona muricata L., commonly called soursop, is part of the Annonaceae family, which comprises more than 130 genera and 2300 species. A. muricata L. contains various compounds with pharmacological activity. This plant is widely grown in tropical and subtropical areas, such as Southeast Asia, South America, and the rainforests of Africa. The plant produces edible fruit all year round and is widely used as a traditional medicine for skin disease, respiratory disease, fever, bacterial infections, diabetes, hypertension, and cancer [1,2]. Different parts of A. muricata have different activities. The seeds combat parasitic infections; the fruit is used for the treatment of arthritis, nervous disorders, and diarrhea; and the leaves are used to treat cystitis, headaches, insomnia, and cancer [3].

The main active components of A. muricata are acetogenin, alkaloids, and flavonoids [4]. Analysis of the compounds in A. muricata leaf extract revealed secondary metabolites such as flavonoids, terpenoids, saponins, coumarins, lactones, anthraquinones, glycosides, tannins, and phytosterols [5].
In this review, we provide an overview of the botanical description, traditional uses, compounds, and pharmacological activities of *A. muricata*. We summarized the existing literature relevant to *A. muricata*, its compound contents, pharmacological activities, and the mechanisms of its pharmacological activity published during the period of 1981–2021.

2. Botanical Description

*A. muricata*, known as guanabana, soursop, graviola, or Brazilian paw paw [1,2], is a native plant of Central America [3]. This plant is distributed widely throughout Southeast Asia, South America, and the rainforests of Africa [1]. *A. muricata* is commonly known as soursop because of the sweet and sour taste of its fruit. In Portuguese, *A. muricata* is known as graviola; in Latin America, it is known as guanabana; and in Indonesia, it is known as nangka belanda or sirsak. Other traditional names include annone, araticum, araticum-manso, anona, anoda, coronsol, grande, grand corossol, gurusulu, quanabana, sauersack, taggannona, and zuurzak. *A. muricata* is a fruit-bearing plant that belongs to the kingdom Plantae, the division Angiospermae (Magnoliophyta), the class Magnolid, the order Magnoliales, the family Annonaceae family, and the genus *Annona* [6,7].

The *A. muricata* tree grows at altitudes below 1200 m above sea level, at a relative humidity of 60%–80%, a temperature range of 25–28 °C, and with more than 1500 mm of annual rainfall [6,7]. *A. muricata* is an evergreen plant that blooms and bears fruit almost throughout the year [6]. The leaves are obovate, oblate, and acuminate, with a dark green, thick, and glossy upper surface. Figure 1 shows the *A. muricata* tree, leaves, fruit, and flowers. The fruit is green and heart-shaped, with soft prickly skin containing juicy, aromatic, and acidic pulp [1,4].

![Figure 1](image-url)

**Figure 1.** (a) Leaves of *A. muricata* with an obovate, oblate, and acuminate shape. The leaf surface is dark green, with a thick and glossy upper surface. (b) The fruits are dark green and prickly. (c) The flower petals are thick and yellowish. The outer petals meet at the edges without overlapping and are broadly ovate, tapering to a point with a heart-shaped base. The inner petals are oval-shaped and overlap.

*A. muricata* has been widely used to treat many disorders, such as parasitic infections, inflammation, diabetes, and cancer [8]. All parts of *A. muricata* are used in traditional medicine by people who live in tropical areas, with the leaves, stem bark, roots, and seeds primarily used as medicinal ingredients [9]. *A. muricata* leaves are used to treat headaches,
insomnia, cystitis, and cancer, the seeds are used to treat parasitic infections [1], and the fruit is used to treat diarrhea and neuralgia, eliminate worms and parasites, increase milk production in lactating women, and reduce fever [10].

3. Traditional Uses

Ethnobotanical studies have reported that A. muricata is used to treat bacterial and fungal infections, as it possesses anthelmintic, antihypertensive, anti-inflammatory, and anticancer activities. It has also been used as an analgesic and to treat fever, respiratory and skin illnesses, diabetes, and internal and external parasites. In several tropical sub-Saharan countries such as Uganda, all parts of the plant are used to treat malaria, stomach ache, parasitic infections, diabetes, and cancer [7,11].

Additionally, the seeds are used as anthelmintic and antiparasitic treatments, and the leaves, bark, and roots of A. muricata have been used for their anti-inflammatory, antihypertensive, smooth muscle relaxant, and antispasmodic effects [1,12,13]. The leaves are used to treat cystitis, diabetes, headaches, hypertension, insomnia, and liver problems and as an antioxidant, anti-inflammatory, and antispasmodic agent. The cooked leaves are applied topically to treat abscesses [14]. In tropical African countries, including Nigeria, the leaves are traditionally used to treat skin diseases [12].

In South America, A. muricata fruit juice is used to treat many diseases, such as heart and liver disease, and has antidiarrheic and antiparasitic effects [15]. The fruit flesh is used to increase breast milk production after childbirth and treat rheumatism, arthritic pain, fever, neuralgia, dysentery, heart and liver diseases, and skin rashes, and it has antidiarrheic, antimalarial, antiparasitic, and anthelmintic properties [1,16]. Table 1 summarizes the results of previous studies on the pharmacological activities of A. muricata and the underlying molecular mechanisms.

### Table 1. Pharmacological activities of A. muricata.

| Pharmacological Activity | Plant Parts | Mechanisms | Refs. |
|--------------------------|-------------|------------|-------|
| Anticancer               | Fruit, stem, seed, and twigs | Inhibits MMP-2 and MMP-9, which play an important role in cancer progression, in HT1080 fibrosarcoma cells. | [17] |
|                          | Leaf, twigs, and root | Disrupts MMP function, reactive oxygen species (ROS) generation, and G0/G1 cell cycle arrest in HL-60 leukemia cells. | [10] |
|                          | Leaf          | Increases Bax expression and decreases Bcl-2 expression, cell cycle arrest at G0/G1 phase in A-549 lung cancer cells. | [18] |
|                          |              | Induces apoptosis by enhancing caspase-3 expression in COLO-205 colorectal cancer cells. | [19] |
|                          |              | Induces apoptosis by enhancing the expression of caspase-3 in MDA-MB-231 breast cancer cells. | [20] |
|                          |              | Inhibits the proliferation of PC-3 human prostate cancer cells. | [21] |
| Antidiarrhea             | Fruit        | Inhibits intestinal motility and secretion. | [28] |
|                          | Leaf         | Antiprotozoal activity against Toxoplasma gondii. | [29] |
| Antiprotozoal            | Seed         | Antiprotozoal activity against Leishmania spp. and Trypanosoma cruzii. | [30] |
|                          | Bark and roots | Antiprotozoal activity against Plasmodium falciparum. | [31] |
| Antidiabetic             | Fruit        | Inhibits α-amylase and α-glucosidase enzymes. | [33] |
|                          | Leaf         | Decreases lipid peroxidation and indirectly affects insulin production and endogenous antioxidants in streptozotocin-induced mice. | [12] |
| Antibacterial            | Leaf         | Attacks the bacterial membrane. | [34] |
| Antihypertensive         | Fruit and leaves | Inhibits angiotensin-I-converting enzyme and blocks calcium ion channels. | [33,35] |

4. Phytochemical Properties

Various compounds and secondary metabolites are present in the A. muricata plant (Table 2). The major compounds are acetogenins, alkaloids, flavonoids, essential oils,
vitamins, carotenoids, amides, and cyclopeptides [4,36]. Additionally, the plant contains minerals such as K, Ca, Na, Cu, Fe, and Mg [37].

Among the major compounds, acetogenin is the most abundant in *A. muricata*. Acetogenin is a long-chain fatty acid derivative that is widely present in the Annonaceae family and is produced via the polyketide pathway. Acetogenins have a long aliphatic chain of 35–38 carbons bonded to a γ-lactone a-ring, terminally substituted by β-unsaturated methyl, with tetrahydrofurans (THF) located along the hydrocarbon chain (Figure 2) [38,39]. The most abundant alkaloid compounds in *A. muricata* are reticuline and coreximine (Figure 3).

![Acetogenin compounds in A. muricata](image)

*Figure 2.* Acetogenin compounds in *A. muricata*. (a) Linear structure, (b) epoxy acetogenin, (c) mono THF, (d) mono tetrahydrofuran, mono tetrahydropyran acetogenin, (e) bis THF-nonadjacent acetogenin, (f) and bis THF-adjacent acetogenin [4].

![The most abundant alkaloids in A. muricata](image)

*Figure 3.* The most abundant alkaloids in *A. muricata*: (a) coreximine and (b) reticuline.

The most common alkaloids present in this plant are the isoquinoline, aporphine, and protoberberine types [4,40]. The most common flavonoid is quercetin (Figure 4) [41–43], although the most abundant flavonoid in the leaf extract is rutin, followed by quercetin and kaempferol [21].
Figure 4. The most abundant flavonoid in *A. muricata*: (a) kaempferol (b) quercetin, and (c) rutin.

Table 2. Phytochemical properties of *A. muricata*.

| No. | Compound            | Part of Plant          | Type     | Refs. |
|-----|---------------------|------------------------|----------|-------|
| 1   | Anomuricine         | Leaf, root, stem, bark| Alkaloid | [44]  |
| 2   | Anomurine           | Leaf, root, stem, bark| Alkaloid | [44]  |
| 3   | Annonaine           | Fruit, leaf            | Alkaloid | [45,46]|   |
| 4   | Annonamine          | Leaf                   | Alkaloid | [47]  |
| 5   | Asimilobine         | Fruit                  | Alkaloid | [45,46,48]| |
| 6   | Atherospermine      | Stem                   | Alkaloid | [44]  |
| 7   | Atherosperminine    | Root, bark             | Alkaloid | [44]  |
| 8   | Casuarine           | Leaf                   | Alkaloid | [40]  |
| 9   | Cochlaurine         | Root, bark             | Alkaloid | [44,45]|   |
| 10  | Coreximine          | Leaf, root, stem, bark| Alkaloid | [44]  |
| 11  | DMDP (2,5-Dihydroxymethyl-3,4-dihydroxypyrrolidine) | Leaf | Alkaloid | [40]  |
| 12  | deoxymannojirimycin | Leaf                   | Alkaloid | [40]  |
| 13  | deoxynojirimycin    | Leaf                   | Alkaloid | [40]  |
| 14  | (R)-O,O-dimethylcoclaurine | Leaf | Alkaloid | [47]  |
| 15  | Isoboldine          | Leaf                   | Alkaloid | [45]  |
| 16  | Isolaureline        | Leaf                   | Alkaloid | [48]  |
| 17  | Liriodenine         | Leaf                   | Alkaloid | [45]  |
| 18  | (R)-4’O-methylcocaurine | Leaf | Alkaloid | [47]  |
| 19  | N-methylcocaurine   | Leaf                   | Alkaloid | [45]  |
| 20  | (S)-narcorydine     | Leaf                   | Alkaloid | [47]  |
| 21  | Normuciferine       | Fruit                  | Alkaloid | [46]  |
| 22  | Remerine            | Leaf                   | Alkaloid | [45]  |
Table 2. Cont.

| No. | Compound          | Part of Plant       | Type       | Refs.   |
|-----|-------------------|---------------------|------------|---------|
| 23  | Reticuline        | Leaf, root, stem,   | Alkaloid   | [44]    |
|     |                   | bark                |            |         |
| 24  | Stepharine        | Leaf                | Alkaloid   | [44]    |
| 25  | Swainsonine       | Leaf                | Alkaloid   | [40]    |
| 26  | Xylopine          | Leaf                | Alkaloid   | [48]    |
| 27  | 15-acetylguanacine| Fruit               | Acetogenin | [49]    |
| 28  | Annocatalin       | Leaf                | Acetogenin | [50]    |
| 29  | Annocatacin A     | Seed                | Acetogenin | [51]    |
| 30  | Annocatacin B     | Leaf                | Acetogenin | [51]    |
| 31  | Annomontacin      | Seed                | Acetogenin | [50]    |
| 32  | Annomuracin       | Leaf                | Acetogenin | [52]    |
| 33  | Annomuracin A     | Leaf                | Acetogenin | [53]    |
| 34  | Annomuracin B     | Leaf                | Acetogenin | [53]    |
| 35  | Annomutacin       | Leaf                | Acetogenin | [54]    |
| 36  | Annonacin         | Leaf, seed          | Acetogenin | [50, 54]|
| 37  | Annonacin A       | Leaf                | Acetogenin | [54]    |
| 38  | Annonacinone      | Leaf                | Acetogenin | [50]    |
| 39  | Annoreticuin-9-one| Seed                | Acetogenin | [55]    |
| 40  | Annoreticuin, cis | Pulp                | Acetogenin | [55]    |
| 41  | Bullatacin        | Seed                | Acetogenin | [38]    |
| 42  | Cohibin A         | Root                | Acetogenin | [56]    |
| 43  | Cohibin B         | Seed                | Acetogenin | [56]    |
| 44  | Cohibin C         | Seed                | Acetogenin | [57]    |
| 45  | Cohibin D         | Seed                | Acetogenin | [57]    |
| 46  | Corepoxylone      | Seed                | Acetogenin | [58]    |
| 47  | Corossolin        | Seed, leaf          | Acetogenin | [59, 60]|
| 48  | Corossolone       | Leaf                | Acetogenin | [50]    |
| 49  | Epomurinins A, B  | Pulp                | Acetogenin | [61]    |
| 50  | Epomurisenins A, B| Pulp                | Acetogenin | [61]    |
| 51  | Gigantecin        | Seed, leaf          | Acetogenin | [60]    |
| 52  | 2,4 Cis or trans  | Gigantetrocinone    | Seed       | [62]    |
| 53  | Gigantetroneninen | Leaf, seed          | Acetogenin | [63]    |
| 54  | Goniothalamicin   | Seed, leaf          | Acetogenin | [64]    |
| 55  | Javoricin         | Seed                | Acetogenin | [64]    |
| 56  | Longifolicin      | Seed                | Acetogenin | [59]    |
| 57  | Montanacin        | Leaf                | Acetogenin | [60]    |
| 58  | Montanacin D      | Leaf, pulp          | Acetogenin | [60]    |
| 59  | Montanacin E      | Leaf, pulp          | Acetogenin | [60]    |
| 60  | Montanacin H      | Leaf                | Acetogenin | [60]    |
| 61  | Montecristin      | Pulp                | Acetogenin | [60]    |
| 62  | Muricateno1       | Seed                | Acetogenin | [65]    |
| 62  | Muricatetrocin A  | Seed                | Acetogenin | [59]    |
| 63  | Muricatetrocin B  | Seed                | Acetogenin | [59]    |
| 64  | Muricatocin A     | Leaf                | Acetogenin | [66]    |
| 65  | Muricatocin B     | Leaf                | Acetogenin | [66]    |
| 66  | Muricatocin C     | Leaf                | Acetogenin | [63]    |
Table 2. Cont.

| No. | Compound          | Part of Plant | Type           | Refs. |
|-----|-------------------|---------------|----------------|-------|
| 67  | Muricin           | Seed          | Acetogenin     | [50]  |
| 68  | Muricenin         | Pulp          | Acetogenin     | [67]  |
| 69  | Murisolin         | Seed          | Acetogenin     | [50]  |
| 70  | Sabadelin         | Pulp          | Acetogenin     | [55]  |
| 72  | Solamin           | Leaf          | Acetogenin     | [50]  |
| 73  | Xylomaticin       | Seed          | Acetogenin     | [50]  |
| 74  | Apigenin-6-C-glucoside | Leaf     | Flavonoid     | [68]  |
| 75  | Argentinine       | Leaf          | Flavonoid      | [41]  |
| 76  | Catechin          | Leaf          | Flavonoid      | [41]  |
| 77  | Coumaric acid     | Pulp          | Flavonoid      | [69]  |
| 78  | Daidzein          | Leaf          | Flavonoid      | [68]  |
| 79  | Dihydrokaempferol-hexoside | Pulp  | Flavonoid     | [69]  |
| 80  | Epicatechin       | Leaf          | Flavonoid      | [41]  |
| 81  | Galloatechin      | Leaf          | Flavonoid      | [68]  |
| 82  | Genistein         | Leaf          | Flavonoid      | [68]  |
| 83  | Glycitein         | Leaf          | Flavonoid      | [68]  |
| 84  | Homoorientin      | Leaf          | Flavonoid      | [68]  |
| 85  | Isoferulic acid   | Leaf          | Flavonoid      | [68]  |
| 86  | Kaempferol        | Leaf,         | Flavonoid      | [41]  |
| 87  | Quercetin         | Leaf          | Flavonoid      | [41]  |
| 88  | Quercetin-3-O-glucoside | Leaf   | Flavonoid     | [41]  |
| 89  | Robinetin         | Leaf          | Flavonoid      | [68]  |
| 90  | Tangeretin        | Leaf          | Flavonoid      | [68]  |
| 91  | Rutin             | Leaf          | Flavonoid      | [21]  |
| 92  | Gallic acid       | Leaf          | Tannin         | [41,68]|
| 93  | Vitamin C         | Pulp, leaf    | Vitamin        | [36]  |
| 94  | Vitamin E         | Leaf, seed, pulp | Vitamin    | [36]  |
| 95  | Annoionol A       | Leaf          | Megastigmane   | [70]  |
| 96  | Annoionol B       | Leaf          | Megastigmane   | [70]  |
| 97  | Annoionol C       | Leaf          | Megastigmane   | [70]  |
| 98  | Annoiosonoside    | Leaf          | Megastigmane   | [70]  |
| 99  | N-p-coumaroyl tyramine | Leaf    | Amide         | [54]  |
| 100 | Annomuricatin A   | Seed          | Cyclopeptides  | [71]  |
| 101 | Annomuricatin B   | Seed          | Cyclopeptides  | [72]  |
| 102 | Annomuricatin C   | Seed          | Cyclopeptides  | [3]   |

5. Pharmacological Activities

5.1. Anticancer

The anticancer activity of *A. muricata* is related to its cytotoxic activity against cancer cells. Table 3 shows the effects of *A. muricata* against cancer cells.

Extracts from several parts of *A. muricata* act as anticancer agents via several mechanisms. Reportedly, the extracts of the fruit, stems, seeds, and twigs of *A. muricata* administered to fibrosarcoma cells (HT1080) inhibited matrix metalloproteinases (MMPs) such as MMP-2 and MMP-9, which play important roles in cancer progression [17]. Extracts from the leaves, twigs, and roots inhibited the proliferation of the human leukemia cell line HL-60 by disrupting MMPs, reactive oxygen species (ROS) generation, and the G0/G1
cell cycle arrest that led to the inhibition of cancer cell growth [10] (Figure 5). Treatment of the A549 lung cancer cell line with the ethyl acetate extract of *A. muricata* leaves induced apoptosis via the upregulation of Bax and downregulation of Bcl-2 expressions. It has also been reported that apoptosis induced by the ethyl acetate extract of *A. muricata* leaf is related to cell cycle arrest at the G0/G1 phase [18]. The leaf extract induced apoptosis by enhancing the expression of caspase-3 in the colorectal cancer cell line COLO-205 [19] and the breast cancer cell line MDA-MB-231 [20]. Another study showed that the ethanol extract and ethyl acetate fractions of *A. muricata* leaves were active against MCF7 cells via an apoptosis mechanism mediated by decreased Bcl-2 expression and increased caspase-3 and caspase-9 expression [23]. Additionally, the presence of annonaceous acetogenins along with flavonoids in *A. muricata* leaves inhibited the proliferation of the human prostate cancer cell line PC-3 [21]. Several compounds isolated from *A. muricata* also show antiproliferative effects. Annomuricin E inhibited HT-29 cell growth by disrupting MMPs, causing leakage of cytochrome c from mitochondria, and activating the pro-apoptotic factors caspase-3, caspase-7, and caspase-9 [22]. Annonacin inhibited the proliferation of endometrial cancer cell lines ECC-1 and HEC-1A via annonacin-mediated apoptotic cell death, which was associated with an increase in caspase-3 cleavage and DNA fragmentation [24]. Another mechanism related to the anticancer activity of *A. muricata* is the modulation of antioxidant enzyme activities. A study reported that 50% ethanol extract of *A. muricata* leaves led to the upregulation of the expression of the antioxidant enzyme superoxide dismutase-1 (SOD1), which catalyzes the breakdown of superoxide into oxygen (O₂) and hydrogen peroxide (H₂O₂), preventing cellular damage [73].

![Figure 5. Anticancer mechanism of *A. muricata*.](image)

A study that administered 300 mg of *A. muricata* leaf water extract to patients with colorectal cancer in capsule form after breakfast reported the inhibition of colorectal cancer cell growth (DLD-1 and COLO 205). The *A. muricata* leaf water extract has selective inhibitory activity against colorectal cancer cells and does not inhibit normal cell growth. The inhibition of cancer cell growth is modulated by acetogenin activity in the complex I mitochondrial electron transport chain, hampering the process of ATP formation needed for cancer cell growth [22] (Figure 5). Other studies also showed the inhibitory effects of acetogenin against colon cancer cells. Consumption of 5 g of leaf extract powder and seeds of *A. muricata* three times per day accompanied by lifestyle modifications was shown to help the healing process in patients with colon cancer. Another study showed that one of the acetogenins in *A. muricata*, annoncherimolin, has cytotoxic potential against HT-29 colon cancer cells [74].
Table 3. IC\textsubscript{50} of several parts of *A. muricata* against cancer cell lines.

| Plant Parts                  | Cancer Cell Line                                      | IC\textsubscript{50} | Refs. |
|------------------------------|-------------------------------------------------------|-----------------------|-------|
| Leaf, twig, and root         | HL-60 human leukemia cell line                        | 6–49 µg/mL            | [10]  |
| Leaf                         | A-549 lung cancer cell line                           | 5.09 µg/mL            | [18]  |
|                              | Ethanol extract: 5.3 µg/mL; ethyl acetate fraction:    |                       |       |
|                              | 2.86 µg/mL; n-hexane fraction: 3.08 µg/mL; water      |                       |       |
|                              | fraction: 48.31 µg/mL                                 |                       |       |
| Leaf                         | MCF7 breast cancer cell line                          | 5.3 µg/mL             | [23]  |
|                              | Ethanol extract: 5.3 µg/mL                            |                       |       |
|                              | Ethyl acetate fraction: 2.86 µg/mL; n-hexane fraction:|                       |       |
|                              | 3.08 µg/mL; water fraction: 48.31 µg/mL              |                       |       |
| Annomuricin E from leaves    | PC-3 human prostate cancer cell line                  | 63 µg/mL              | [21]  |
| Annoniacin from seeds        | HT-29 colon cancer cell line                          | 1.62 µg/mL            | [22]  |
|                              | ECC-1 and HEC-1 human endometrial cancer cell lines   | 4.62–4.75 µg/mL       | [24]  |

5.2. Antiulcer

*A. muricata* contains a high concentration of flavonoids, tannins, and phenolic acids, which possess therapeutic effects due to their antioxidant, anti-inflammatory, and gastro-protective properties [25,75,76]. A survey revealed that the leaves and bark of *A. muricata* are popularly used to make tea to treat gastrointestinal problems such as gastritis and poor digestion [25].

In several studies, *A. muricata* has been reported to improve gastric lesions. A study that used a hydroalcoholic extract of *A. muricata* leaves to treat ulcers in absolute or acidified methanol- or indomethacin-induced gastric lesions in rats showed that the extract reduced the ulceration process by activating prostaglandin synthesis as a gastro protector and suppressed aggressive factors of the gastric mucosa [25]. In another study, *A. muricata* ethyl acetate extract showed antiulcer activity via ROS-scavenging and gastric wall damage protection in rats with ethanol-induced gastric injury. Additional mechanisms of *A. muricata* antiulcer activity include the upregulation of Hsp70 and the downregulation of Bax, which are involved in gastric injury suppression [26]. The minimal inhibitory concentration of *A. muricata* leaf extract against *H. pylori* is 20 mg/mL [77]. *A. muricata* also showed antiulcer activity by downregulating the expressions of Bax and MDA and upregulating the expressions of catalase (CAT), superoxide dismutase (SOD), glutathione (GSH), nitric oxide (NO), PGE2, glycogen, and Hsp70 [27]. *A. muricata* also inhibited inflammatory mediators such as IL-1β, TNF-a, and IL-6 [78] (Figure 6).

![Figure 6. Antiulcer mechanisms of A. muricata.](image-url)
5.3. Antidiarrhea

Diarrhea is a common gastrointestinal disorder caused by bacterial infections. It is characterized by abdominal pains, watery stools, and increased bowel movement frequency [79]. Antibiotics have been used as antidiarrhea drugs; however, disadvantages such as bacterial resistance and adverse side effects limit their usefulness [80]. Traditional plants are also widely used to treat diarrhea. The bark and fruit of *A. muricata* are widely used by West Africans to treat diarrhea, and their antidiarrhea effects have been reported [81,82]. The fruit of *A. muricata* showed antidiarrhea activity at a dose of 400 mg/kg body weight in mice with castor oil-induced diarrhea. Flavonoids, triterpenoids, and saponins of *A. muricata* play a role in its antidiarrhea activity by inhibiting intestinal motility and secretions that cause diarrhea [28].

5.4. Antidiabetic

*A. muricata* also exhibits antidiabetic activity. It contains flavonoids that inhibit α-glucosidase activity through hydroxylation bonding and substitution at the b-ring. This inhibition suppresses carbohydrate hydrolysis and glucose absorption and inhibits carbohydrate metabolism into glucose [83].

*A. muricata* fruit extracts were reported to exert antioxidant and antidiabetic effects by inhibiting key enzymes relevant to type 2 diabetes mellitus, such as α-amylase and α-glucosidase, in vitro. A study showed that the pericarp of *A. muricata* has the highest inhibitory enzyme and antioxidant properties [33]. The fruit pulp and leaf extract also showed high abilities to inhibit α-amylase and α-glucosidase and minimize the rate of glucose assimilation into the blood after feeding compared with the standard drug [84]. The aqueous extract of *A. muricata* shows antidiabetic effects via antioxidant mechanisms. *A. muricata* leaf extract given to streptozotocin-induced diabetic mice induced a decrease in lipid peroxidation processes, which are a sign of oxidative stress, and indirectly affected insulin production and endogenous antioxidants [12].

*A. muricata* seed oil also showed potential antidiabetic activity against type 1 diabetes induced by streptozotocin. The study showed that an experimental model treated with *A. muricata* seed oil had significantly reduced blood glucose levels compared with the control group. The preserved area of the pancreatic islets was also improved compared with that in the control group [85]. Another study indicated that diabetic rats treated with *A. muricata* had significantly reduced blood glucose levels. That study also reported that daily intraperitoneal administration of 100 mg/kg *A. muricata* extracts to diabetic rats for 15 consecutive days resulted in a statistically significant increase in body weight despite a decrease in food and fluid intake, which is an indicator of improved glycemic control [86].

5.5. Antiprotozoal

Diseases caused by parasitic protozoa such as toxoplasmosis, trypanosomiasis, leishmaniasis, and malaria are the most common protozoal diseases worldwide [30]. The lack of treatment options for parasitic protozoal infections implies the importance of developing therapies for protozoal diseases by utilizing the potential of medicinal plants.

Several studies have been conducted to determine the antiprotozoal activity of *A. muricata*. A study reported that *A. muricata* ethanol leaf extract showed antiprotozoal activity against *Toxoplasma gondii* with an IC$_{50}$ of 113.3 µg/mL [29]. Another study reported that *A. muricata* ethyl acetate leaf extract showed antiprotozoal activity against *Leishmania* spp. and *Trypanosoma cruzii* with IC$_{50}$s of < 2.5 µg/mL [30]. Moreover, some studies detected antiprotozoal activities in several compounds isolated from *A. muricata*. Two acetogenins, annonacinone and corossolone, that were isolated from the seeds of *A. muricata* showed antileishmanial activity, with an IC$_{50}$ ranging from 13.5 to 37.6 µg/mL [87]. *A. muricata* ethanol leaf extract also has antiprotozoal activity against *Plasmodium falciparum* with an IC$_{50}$ of 46.1 µg/mL [29]. Additionally, the dichloromethane fractions and subfractions of *A. muricata* bark and roots showed antiprotozoal activity against *P. falciparum*, with IC$_{50}$ values ranging from 0.07 to 3.46 µg/mL. Furthermore, gallic acid compounds isolated
from the bark and roots of *A. muricata* showed activity against *P. falciparum* with an IC$_{50}$ of 3.32 µg/mL [32].

5.6. **Antibacterial**

*A. muricata* extracts showed antibacterial activity against Gram-positive and Gram-negative bacteria compared with the standard antibiotic streptomycin. However, the solvent used for extraction can affect the bioactive efficacy of the extracts. The combination of *A. muricata* ethanolic extract and antibiotic treatment decreased the potential of antibiotic multidrug-resistant *Escherichia coli* and *Staphylococcus aureus* strains [88–90]. Another study reported that the bioactive compounds in *A. muricata*, such as alkaloids (annonaine, asimilobine, liriodenirine, normuciferine, etc.), attack the bacterial membrane (plasma and outer membrane), resulting in broad-spectrum antibacterial activity [34].

5.7. **Antiviral**

*A. muricata* extract has been reported to possess antiviral activity, for example by interfering with the replication process of HIV-I. In another study, ethanolic extracts from the stem and bark of *A. muricata* showed in vitro antiviral activity against herpes simplex virus [91,92]. Another study showed that acidified ethanolic extract of *A. muricata* decreased viral replication after 1 h of contact time. This activity may be due to the presence of phenolic compounds such as rutin [93]. Acetogenins such as annomuricin a, annomuricin b, annomuricin c, muricatocin c, muricatacin, cis-annonacin, annonacin-10-one, cis-goniothalamicin, arianacin, and javoricin were shown to possess good inhibitory activity against SARS-CoV-2 spike proteins (in silico). Cis-annonacin had a low binding energy and greater hydrogen bond formation ability, which indicated that it was the most potent among the acetogenins tested in the study. This result shows that annonaceous acetogenins can be viewed as potential anti-SARS-CoV-2 agents and should be studied in vitro and in vivo [94].

5.8. **Antihypertensive**

Research has revealed that *A. muricata* fruit extracts exhibit antioxidant and antihypertensive properties through angiotensin-I-converting enzymes in vitro [33]. *A. muricata* leaf extract was also shown to show antihypertensive activity in normotensive rats. The suggested hypotensive mechanism of action of *A. muricata* extract is via the blockage of calcium ion channels, which lowers blood pressure [35]. Another study showed that *A. muricata* aqueous extract had antihypertensive properties; combinations of *A. muricata* and other plants, such as *Persea americana*, also exhibited antihypertensive activity, providing a safe and effective solution for hypertension prevention and treatment [95].

5.9. **Wound Healing**

*A. muricata* is also known for its wound healing activity. Two doses of *A. muricata* ethyl acetate extract showed significant wound healing activity in both macroscopic and microscopic analyses of wounds. Wound treatment with an ointment containing *A. muricata* ethyl acetate extract caused a significant increase in antioxidant levels and a decrease in the MDA level in wound tissues compared with those in the vehicle control [96]. *A. muricata* bark and leaf extracts also showed wound healing effects compared with that in untreated wounds [97].

6. **Toxicology**

Several studies have been conducted to determine the toxicity of *A. muricata*. The level of toxicity of *A. muricata* depends on the part of the plant as well as the solvent. A study showed that *A. muricata* aqueous extract had an LD$_{50}$ > 5 g/kg, whereas that of the ethanolic extract was >2 g/kg [14]. Another study reported an LD$_{50}$ of >211 mg/kg for *A. muricata* leaf aqueous extract, which is higher than the recommended daily consumption limit for humans. The aqueous extract of *A. muricata* with doses of >1 g/kg can cause
hypoglycemic conditions and hyperlipidemia, and doses of >5 g/kg can cause damage to the kidneys [98].

A study reported that acetogenin in A. muricata is a neurotoxin that has the potential to cause neurodegenerative disorders [99]. Acetogenin causes an increase in tau phosphorylation, which is associated with neurodegenerative tauopathy [100]. In addition, some alkaloids in A. muricata are believed to have an influence on nerve cells [1]. Annonacin, the most abundant acetogenin in A. muricata, as well as some types of alkaloids, such as reticuline, solamin, and coreximine, disrupt the energy formation process in dopaminergic cells [4]. In murine model tests, annonacin was demonstrated to penetrate the brain barrier, decrease ATP levels in brain cells, and damage the basal ganglia [101]. In mice, annonacin caused a decrease in ATP levels in the striatum and disrupted energy production by mitochondria, resulting in the disruption of tau cells, which led to symptoms of neurodegenerative disease [99].

Although some compounds in A. muricata have been reported to play a role in neurodegenerative disorders, the doses that produced negative effects were equivalent to consuming one fruit every day for 1 year [102]. Research on the neurotoxicity of annonacin showed that neurodegenerative conditions caused by these compounds arise due to continuous exposure or consumption. Thus, to avoid the occurrence of neurodegenerative conditions that may occur due to compounds present in A. muricata, continuous excessive consumption is not recommended [103].

7. Conclusions

A. muricata is widely used as a traditional medicine. Parts of the A. muricata plant, such as the leaves, fruit, seeds, bark, and roots, have pharmacological properties. From the 49 research articles that we obtained, it was reported that its pharmacological properties included anticancer (25%), antiulcer (17%), antidiabetic (14%), antiprotozoal (10%), antidiarrhea (8%), antibacterial (8%), antiviral (8%), antihypertensive (6%), and wound healing properties (4%) (Figure 7), because of the various compounds contained in A. muricata. Meanwhile, from 35 reference articles, 101 single compounds of A. muricata were reported. The main active compounds in A. muricata are acetogenins (49%), alkaloids (26%), flavonoids (19%), and others (6%), which are reported to be responsible for the pharmacological activities listed above (Figure 8). However, not all secondary metabolites of A. muricata have been identified.

Figure 7. Distribution of pharmacological activities of A. muricata.

Many studies on A. muricata were conducted in the past three decades; however, no preparations produced from A. muricata have been tested and approved by the FDA or EMA. Acetogenins, which are the main active compounds, are difficult to obtain because they are thermolabile, creating challenges for the scale-up and production of stable raw
materials. Thus, developing drug preparations is difficult, despite the empirical evidence regarding the bioactivity of acetogenin compounds. Moreover, high doses of acetogenins can be neurotoxic and may cause neurodegenerative disorders. Some alkaloids present in *A. muricata* are also believed to affect nerve cells. However, research on the neurotoxicity of annonacin states that neurodegenerative conditions caused by these compounds arise due to continuous exposure or consumption. Further research on the toxicity of *A. muricata* and clinical trials testing the pure compounds are needed to fully elucidate its pharmacological activities and ensure the safety of *A. muricata* as a potential drug for various diseases.

**Figure 8.** Proportions of phytochemical compounds in *A. muricata*.

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