Phytochemistry and Pharmacological Effect of *Annona muricata*

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The Annonaceae family contains different types of bioactive chemical properties, such as alkaloids, acetogenins, flavonoids, terpenes, and essential oil, meaning the plants in this family are potential therapeutic agents. In vitro and in vivo studies have shown that *A. muricata* has the pharmacological effects of anti-cancer, anti-microbial, antioxidant, anti-ulcer, anti-diabetic, anti-hypertensive, and wound healing.

Annona muricata | pharmacology | Annona species | Phytochemistry

1. Introduction

Extensive phytochemical analyses on various parts of the *A. muricata* plant have revealed the presence of a variety of phytoconstituents and bioactive compounds. Thus, 212 compounds have been identified in this plant, with acetogenins being the most prevalent [1]. Other compounds that can be identified are alkaloids and phenolics. These compounds were analyzed through High-Performance Liquid Chromatography (HPLC), Nuclear Magnetic Resonance spectroscopy (NMR), Fourier-Transform Infrared spectroscopy (FTIR), Kedde's reagent, and HPLC coupled with a photodiode array detector (HPLC-DAD) [2][3][4].

Much research has been carried out on *A. muricata* to evaluate its pharmacological effect, in which a systematic review was conducted to incorporate the scientific studies published up to February 2017, deducing that only 2% had been conducted as clinical trials, 2% in silico modelling, 36% for in vivo studies, and most studies regarding this plant were carried out through in vitro studies [5]. The extract used was mainly based on organic solvents, as opposed to traditional preparations using water. The advantage of solvent extraction is due to the effectiveness in extracting most bioactive compounds [5]. The pharmacological effect of *A. muricata* is simplified in **Figure 1**, including in vivo and in vitro studies.

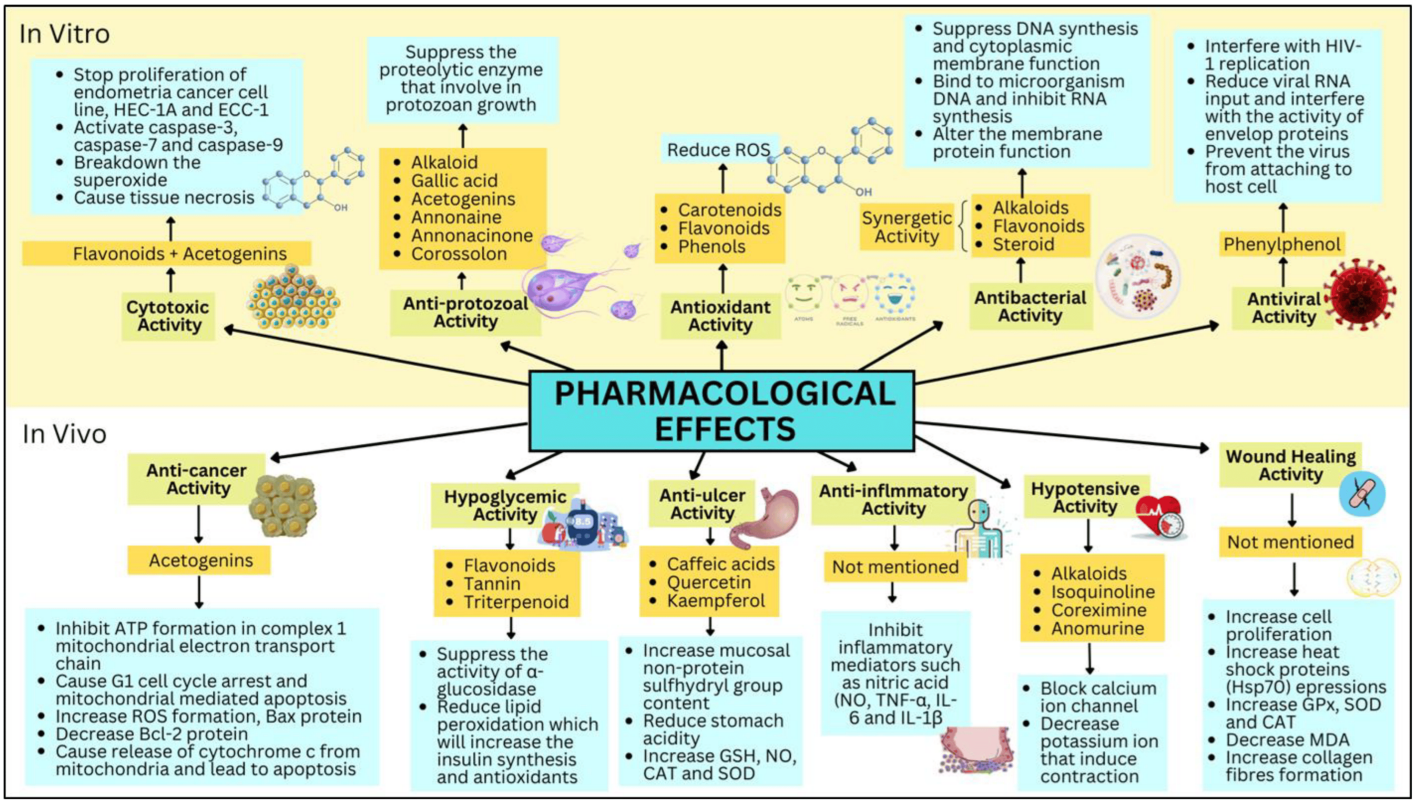

Figure 1. Pharmacological effects of *A. muricata* along with its bioactive compounds and mechanism.

2. Phytochemistry and the Pharmacological Effect of *A. muricata*

2.1. In Vitro Studies

2.1.1. Cytotoxic Activity

Many investigations have been carried out to study the anti-cancer properties *of A. muricata*. The cytotoxic activity of this plant occurs due to the presence of acetogenin, which is the most-abundant chemical family in various parts of *A. muricata.* Acetogenins and flavonoids contained within the leaves can hinder human prostate cancer cell line PC-3 proliferation. This effect occurs as they promote necrosis by inhibiting cellular metabolism and tumor mobility [6]. Annonacin compounds showed the ability to mediate apoptotic cell death by increasing DNA fragmentation and cleavage of caspase-3. This process stops the proliferation of endometrial cancer cell lines, including HEC-1A and ECC-1. The cellular damage can also be prevented using ethanol extract leaves by up-regulating the expression of superoxide dismutase-1 of antioxidant enzyme expression [5]. This expression leads to a breakdown of superoxide, allowing the cell to function. Other than that, annomuricin E is capable of inhibiting HT-29 cell growth. Annomuricin causes cytochrome c to leak from the mitochondria by disturbing the matrix metalloproteinases (MMPs). Thus, pro-apoptotic factors, such as caspase-3, caspase-7, and caspase-9, will be activated [6].

On the other hand, the application of *A. muricata* extracts on fibrosarcoma cells (HT1080) can suppress the MMP-2 and MMP-9, hindering cancer progression. The proliferation of human leukemia cell line HL-60 can be suppressed using extracts from *A. muricata* leaves, roots, and twigs [6]. This effect is due to the reduction in reactive oxygen species (ROS) generation, a halt in G0/G1 cell cycle, and a disruption in MMPs. Meanwhile, the administration of ethyl acetate extract and ethanol extract can increase caspase-3 and caspase-9 expression while decreasing Bcl-2 expression. This process activates MCF7 cell apoptosis. Ethyl acetate extract from leaves alone can enhance the expression of caspase-3 in colorectal cancer cell line COLO-205 and breast cancer lines. *A. muricata* extract also has selective action on breast cancer by inducing apoptosis to up-regulate the Bax, down-regulate the expression of Bcl-2, and inhibit the cell cycle at the G0/G1 phase [7].

2.1.2. Anti-Protozoal Activity

A. Muricata also exhibits therapeutic potential against protozoans that caused amebiasis diseases, chagas, schistosomiasis, malaria, and leishmaniasis [1]. The most-effective part of *A. muricata* in anti-protozoal activity is the seed, as it contains annonacinone, acetogenins, and corossolone [6]. A study showed that the extract from leaves of *A. muricata* can inhibit the growth of *Plasmodium* but is less effective against *Toxoplasma*. This concluded that *A. muricata* has an anti-protozoal effect and the degree of effectiveness varies [8].

2.1.3. Antioxidant Activity

Many diseases (i.e., cardiovascular diseases, arthritis, and cancer) arise due to reactive oxygen species (ROS). Studies showed that *A. muricata* contains vitamins, carotenoids, flavonoids, and phenolic acids, all of which have antioxidant properties. The flavonoids, such as gallocatechin, kaempferol, quercetin, rutin, and argentinine, that are abundant in the leaf part may contribute to its potent antioxidant effect and improve other conditions caused by high ROS levels by donating hydrogen [6]. Another study also stated that the ethanolic extract of *A. muricata* is more effective compared to the aqueous extract of the plant since ethanolic extract sustains more secondary metabolites compared to aqueous extract [9]. The content of antioxidant compounds depends on the solvents used for the extraction, in which more compounds can be extracted in polar solvents compared to non-polar solvents [9].

2.1.4. Anti-Viral Activity

Regarding anti-viral bioactivity, *A. muricata* extracts exhibit virucidal activity by interfering with HIV-I replication early in the infection. The plant extracts reduce the risk of viral particle transmission by lowering viral RNA input and interfering with the function of envelope proteins during virus entry into the host cell [1]. In addition, it also prevents the virus from attaching to the host cell. The stem and bark of *A. muricata* ethanolic extract showed in vitro anti-viral effects against the herpes simplex virus, in which the minimum inhibitory concentration was 1 mg/mL. Moreover, the acidified ethanolic extract reduced viral multiplication after 1 h of contact. This plant's anti-viral properties are due to phenolics [6]. It is reported that rutin is the most-abundant component that inhibits viral replication. Furthermore, flavonoid glycosides, quercetin, and naringenin inhibit the spread of SARS-CoV-2 by targeting angiotensin-converting enzymes (ACEs). Meanwhile, studies have shown that quercetin and vanillin have a herpesvirus effect [10].

2.2. In Vivo Study

2.2.1. Anti-Cancer Activity

A randomized control trial on colorectal patients administrated with 300 mg of *A. muricata* extract containing 0.36% acetogenins after breakfast showed suppression in colorectal cancer cell growth [11]. In addition, G1 cell cycle arrest causes mitochondria-mediated apoptosis [6]. Acetogenins induce apoptosis by increasing ROS formation, ann pro-apoptotic Bax protein, and down-regulating antiapoptotic Bcl-2 protein. These processes impair the mitochondrial membrane potential and then cause the release of cytochrome c. This cytochrome c activates apoptosomes and the intrinsic caspase cascade initiates DNA fragmentation, resulting in apoptosis execution. Annocherimolin, an acetogenin, has cytotoxic activity against HT-29 colon cancer cells [5].

On the other hand, the acetogenin compound in *A. muricata* is capable of inhibiting NADH oxidase, which will affect the production of ATP later on. ATP is crucial for cancer cells as it helps them to proliferate [6]. In addition, it also blocks the production of adenosine triphosphate (ADP), which is used by this molecule to activate the pump for cancer drug removal. Hence, acetogenins have been suggested to make chemotherapy more effective. Some studies also proposed that acetogenins have chemotherapeutic potential, especially in cancer cells that have developed resistance to medications [5].

2.2.2. Anti-Ulcer

Gastric ulcers are caused by excessive amounts of gastric acid secreted in the stomach and a decrease in gastric-wall mucus. Moreover, ROS also contributes to this damage. *A. muricata* plants possess gastroprotective properties, most probably due to antioxidant compounds. These compounds can increase the mucosal nonprotein sulfhydryl group content and improve gastric lesions. *A. muricata* extract can reduce stomach acidity and significantly reverse the loss of gastric-wall mucosa, similar to the effects of proton pump inhibitors, such as omeprazole. The *A. muricata* extract improves the amount of several enzymes that can lower cellular ROS, including nitric oxide (NO), glutathione (GHS), catalase (CAT), prostaglandin E2 (PGE-2), superoxide dismutase (SOD), as well as malondialdehyde (MDA) [1].

According to a survey, *A. muricata* leaves and bark are frequently brewed as tea to cure digestive issues, such as gastritis and poor digestion. Other preparations of *A. muricata* using ethyl acetate showed anti-ulcer activity by protecting stomach-wall damage and scavenging ROS in rats with ethanol-induced gastric injury. The inhibition of gastric damage is accomplished by up-regulating Hsp70 and down-regulating Bax, which are crucial mechanisms in anti-ulcer action [6].

2.2.3. Anti-Inflammatory Activity

Several studies have shown that *A. muricata* has anti-inflammatory effects, with the leaf being the most commonly studied. *A. muricata* leaf extract inhibits inflammatory mediators, such as nitric oxide (NO), TNF-α, IL-6, and IL-1β; hence, they have the potential to treat inflammation [7]. Oral administration of *A. muricata* ethanolic leaf extracts

(10, 30, 100, and 300 mg/kg) significantly reduced carrageenan-induced paw edema, demonstrating the plant's anti-inflammatory properties. Leukocyte migration and exudate volume were reduced along with this anti-inflammatory action. The same extract, administered orally to mice, significantly reduced abdominal contortions generated by acetic acid (0.6% *v/v*), displaying a potent anti-nociceptive effect [12].

2.2.4. Hypotensive Activity

According to research results, *A. muricata* exhibits hypotensive action, which can reduce blood pressure by blocking calcium ion channels rather than engaging endothelium- and nitric-oxide-dependent mechanisms. Ca+ antagonism during this mechanism tones down the high activity of K+ that can induce contractions [12]. Another study stated that this mechanism did not affect the heart rate but did affect the blood pressure. Administration of *A. muricata* leaf extract to normotensive rats showed significantly declined dose-dependent blood pressure. In addition, the combination of *A. muricata* with *Persea americana* showed a positive result for anti-hypertensive activity [6]. *A. muricata*'s hypotensive effect could be attributed to the alkaloid compounds found in the plant's leaves. Isoquinoline, coreximine, and anomurine, alkaloids, have been shown to have a transient depressive effect on blood pressure [13].

2.2.5. Wound Healing

This plant showed a compromising wound-healing activity, especially from the leaf and bark extract [12]. A wound heals in four stages: coagulation, inflammation, proliferation, and maturation [1]. Several of these phases are accelerated by the administration of *A. muricata* extract. Heat-shock proteins (Hsp70) expressed during the inflammatory phase are crucial for healing due to their role in cell proliferation, and *A. muricata* caused a significant increase in Hsp70 [12]. A large amount of the cytokines and free radicals produced during this phase by the inflammatory cells might cause lipid peroxidation in the wound. Tissues treated with *A. muricata* extract showed enhanced glutathione peroxidase (GPx), SOD, and CAT activity, which protects tissue from oxidative damage and speeds up the healing process. Furthermore, ethyl acetate leaf extract of *A. muricata* reduces MDA, a lipid peroxidation biomarker that can damage collagen, fibroblast, and endothelial cell metabolism, which are critical for wound healing [14]. This was supported by a study on ethyl acetate extract at a low dose of 5%*w/w* and a high dose of 10%*w/w* against a wound created on the neck. During the maturation phase, collagen accumulated and fibroblasts multiplied. According to a histological study, *A. muricata* extracts increased the number of collagen fibers deposited in the wound [14].

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