

Review Article

**Pharmacological Activities of Graviola (*Annona muricata*):
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Abstract

Graviola (*Annona muricata*) is one major member of the plant family, *Annonaceae*. It is cultivated in the tropical zones, particularly in Central and South America. Graviola is worldwide known for its natural medicinal effects. In this regards, graviola extracts are used in the treatment of different kinds of cancers such as pancreatic, breast, prostate, lung, and blood cancers. The exact mechanisms behinds the anticancer effects of graviola are not clearly defined. However, it was assumed that graviola-induced apoptotic effects, necrosis, and modulation of the proliferation patterns of the cancer cells are major mechanistic effects of Graviola. Interestingly, graviola is also known for its other beneficial effects such as its antioxidant, anti-inflammatory, anti-rheumatic activities, and its wound healing effects. This mini review was undertaken to update and summarize the pharmacological activities of graviola.

KEYWORDS

Graviola, anticancer, antioxidant, mechanisms, pharmacological activities

INTRODUCTION

Graviola (*Annona muricata*) is one major member of the family, *Annonaceae*. It has several synonyms such as soursop, custard apple, guanabana, huanaba, guanabano, guanabana, and cachi-man epineux (Chang and Wu, 2001; Qazi *et al.*, 2018). Graviola is mainly cultivated in the tropical zones such as Peru, Columbia, Brazil, Cuba, and India (Sun *et al.*, 2014). Graviola fruit has a weight range of 0.4-4 kg. The fruit flesh and pulp are rich in various nutrients such as moisture (80%), carbohydrate (18%), vitamins (B1, B6, and B12), and minerals, with low protein content 1%. Therefore, graviola is extensively used in the food industry such as jams, ice-creams, candies, jelly, and nectar (Ribeiro de Souza *et al.*, 2009). Moreover, graviola has several therapeutic effects as it has antipyretic action, increases milk secretion in lactating mothers, treatment of gastrointestinal disorders such as dysentery, and diarrhea. Besides, it can be used in the treatment of diabetes, cystitis, rheumatism, insomnia, and other inflammatory conditions, and cancer (Gavamukulya *et al.*, 2014; Ishola, *et al.*, 2014; Asare *et al.*, 2015).

PHARMACOLOGICAL ACTIVITIES OF GRAVIOLA

Several *in vitro* and animal studies had investigated and reported several therapeutic effects of graviola. This mini review summarizes the recent reported pharmacological activities of graviola.

Anticancer activities of graviola

The number one killer in the USA and throughout the world, cancer continues to be one of the most serious health dangers. IARC, an organization dedicated to advancing cancer research, reported 14.1 million new cancer cases with 8.2 million fatalities global economy in 2012, with estimates of 21.7 and 13 million new Cancer incidence and mortality rates in 2030 (Ferlay *et al.*, 2015). The prognosis of patients with early malignancies has substantially improved, but patients with advanced cancers now have major co-morbidities due to the limited efficacy and accompanying toxicity of current medications. Although these restrictions led to the creation of synthetic chemicals for molecularly targeted therapies, the emergence of drug resistance has also reduced the usefulness of these treatments. One-third of the anticancer medications licensed by the US Food and Drug Administration (USFDA) have been made possible thanks to the identification of plant-based therapies over the previous several decades (Newman, 2008). Due to their demonstrated safety, low cost, and oral bioavailability, dietary phytochemicals offer numerous inherent advantages over manufactured substances (Greenlee, 2012). But only recently have scientists started to explain the molecular, cellular, and tissue levels of plant-derived medicines' modes of action (de Albuquerque *et al.*, 2011; Komlaga *et al.*, 2015). Numerous natural products have been thoroughly studied in recent years, and many of the chemicals have shown anticancer and other positive effects in controlled experiments. By influencing multiple mechanisms, including alteration of cellular prolifera-

tion, and differentiation, angiogenesis, apoptosis, and metastasis, the majority of anticancer natural compounds prevent the onset, development, and progression of cancer (Gupta *et al.*, 2010).

Lung cancers

Graviola leaf extract arrested cell cycle and promoted apoptosis, according to a recent in vitro experiment using A549 lung cancer cell line. The potential underlying molecular mechanism is the graviola-induced inhibition of the nuclear factor-B (NF-B) signaling, causing the production of reactive oxygen species (ROS), and increasing the Bax/Bcl-2 ratio-mediated attenuation of mitochondrial membrane potential, cytosolic cytochrome c, and caspase-3/9 activation (Moghadamtousi *et al.*, 2014a). Moreover, a quarter of lung cancer patients in Reunion treated by chemotherapy consume graviola regularly. The consequences of this intake were favorable (Moreau *et al.*, 2018).

Pancreatic cancer

It was reported that graviola had antiproliferative and anticancer effects in pancreatic cancer cells and subcutaneous xenografts; these effects included inducing cell cycle arrest coupled with apoptosis (Torres *et al.*, 2012). The flavonoid-rich hexane fraction of *A. muricata* leaves was found to have comparable antiproliferative properties (Rosdi *et al.*, 2015). The graviola reduced the motility and the invasion of the pancreatic cancer cell, possibly via downregulation of the mucin MUC4.

Prostate cancer

Prostate cancer was recorded in 164690 cases with 29430 deaths in the USA during 2018 (Siegel, 2018). As demonstrated by cytotoxicity assays such as MTT, a modest concentration (1 g/ml) of graviola extract exhibits strong antiproliferative activity in a panel of prostate cancer cell lines (22Rv1, LNCaP, and PC3) (Deep *et al.*, 2016). Additionally, they discovered that GPE had antiproliferative effects that were accompanied by decreased HIF-1 expression and NOX activity suppression (Deep *et al.*, 2016). The antiproliferative and apoptotic actions on prostate cancer PC-3 cells were attributed to the acetogenin derivatives (Sun *et al.*, 2014). Pure acetogenins that were extracted from graviola fruit exhibited similar anticancer properties (Sun *et al.*, 2014). Moreover, Yang *et al.* (2015) reported significant protection on prostate cancer, that was possibly due to the synergistic interactions among flavonoids and acetogenins in graviola leaves.

Breast cancer

Graviola's significant antiproliferative and anticancer properties have been demonstrated in breast cancer-related studies using breast cancer cell lines and xenograft mice models. According to these studies, graviola reduced the expression of the anti-apoptotic gene Bcl2 and the oestrogen receptor (ER), cyclin D1, and MCF-7 breast cancer cells' ability to grow (Ko *et al.*, 2011). Further studies revealed that graviola fruit extract did not influence the growth of healthy MCF-10A cells while it suppressed the proliferation and growth of xenograft tumors made of MDA-MB468 cells that overexpressed the EGFR (Dai *et al.*, 2011). Additionally, it was discovered that the proliferation of MDA-MB435S, HaCaT, and T47D breast cancer cells was inhibited by butanol and an aqueous extract of *A. muricata*. Additionally, it has been demonstrated that annosquacin B, which was extracted from *annona squamosa* seeds, modifies mitogen-activated protein kinase (MAPK) signaling and induces apoptosis in MCF-7/ADR cells (Yuan *et al.*, 2016).

Colon cancer

Natural products, such as graviola, have been extremely important in the treatment and prevention of colorectal carcinoma (CRC). The molecular mechanism of several *A. muricata* extracts' ability to treat CRC is currently being defined after extensive research. Additionally, *A. muricata* leaf extract enhanced the proapoptotic protein caspase-3 in COLO-205 cell line, demonstrating anticancer characteristics (Abdullah *et al.*, 2017). In CRC cell lines HT-29 and HCT-116, cell cycle arrest was demonstrated in the G1 phase as well as potent inhibition of migration, invasion, and apoptosis using the same extract (Moghadamtousi *et al.*, 2014a). Annomuricin A, B, C, E, and muricapentocin, among other phytochemical components from *A. muricata* leaves, also demonstrated cytotoxicity against CRC HT-29 cells (Kim *et al.*, 1998). ACG desacetyl uvaricin has also been demonstrated to cause DNA damage by inactivating the MAPK pathway and producing superoxides, which inhibits the development of SW480 cells (Xue *et al.*, 2014).

Cancer of head and neck

Recently, it was discovered that aqueous graviola leaf extract (AGLE) induces G2/M cell cycle arrest and has antiproliferative effects on the squamous cancer cell line SCC-25 (Magadi *et al.*, 2015). A poor dose of cisplatin given with graviola may have

Table 1. Examples of the anticancer activities of graviola reported in the current study.

Cancer type	Observation	Reference
Lung cancers	Graviola leaf extract arrested cell cycle and promoted apoptosis in A549 lung cancer cell line	Moghadamtousi <i>et al.</i> (2014)
Pancreatic cancer	Graviola reduced the motility and the invasion of the pancreatic cancer cell, possibly via downregulation of the mucin MUC4	Rosdi <i>et al.</i> (2015)
Prostate cancer	Graviola peeled extract had antiproliferative effects on prostate cancer PC-3 cells	Sun <i>et al.</i> (2014)
Breast cancer	Graviola reduced the expression of the anti-apoptotic gene Bcl2 and the oestrogen receptor (ER), cyclin D1, and MCF-7 breast cancer cells' ability to grow	Ko <i>et al.</i> (2011)
Colon cancer	Graviola arrested cell cycle in the colon cancer cell lines, HT-29 and HCT-116	Moghadamtousi <i>et al.</i> (2014) and Kim <i>et al.</i> (1998)
Cancer of head and neck	Graviola had antiproliferative effects on the squamous cancer cell line SCC-25	Magadi <i>et al.</i> (2015)
Blood cancer	Graviola has antiproliferative and apoptotic effects on human leukemia HL-60 cells	Pieme <i>et al.</i> (2014)

considerable antitumor effects in head and neck cancers since cisplatin alone is not an effective treatment for cancer of head and neck.

Blood cancer

Between 4% and 9% of all cancer diagnoses worldwide and in the USA are hematological malignancies, such as B-cell chronic lymphocytic leukemia (CCL), acute myeloid leukemia (AML), multiple myeloma, or non-Hodgkin's lymphoma (Siegel, 2018). Studies have shown that graviola has antiproliferative and apoptotic effects on human leukemia HL-60 cells (Pieme et al., 2014). Mechanistic studies revealed that cell cycle arrest and MMP depletion were linked to antiproliferative and apoptotic effects (Pieme et al., 2014). Additionally, it was discovered that *A. muricata*'s ethanolic leaf extract (ELE) and methanolic leaf extract (MLE) caused apoptosis in the multidrug resistant subline CEM/ADR5000 cells, CCRF-CEM, and chronic myelogenous K562 leukemia cells, respectively (Kuate et al., 2016).

The exact mechanisms behind the anticancer activities of graviola are still need extensive investigations. However, most of the published reports had concluded that graviola could induce apoptosis, cytotoxicity, prevent initiation, development, and progression of cancer by modulating various mechanisms including cellular proliferation, differentiation, apoptosis, angiogenesis, and metastasis (Rady et al. 2018). In this minireview, we will summarize the most established mechanisms behind anticancer activities of graviola.

Apoptosis

In the majority of multicellular organisms, apoptosis, or programmed cell death, is essential for healthy growth and tissue homeostasis (Tait et al., 2010). Apoptosis is essential for eliminating cells that are selectively unneeded or that pose a harm to an organism's integrity, which prevents the growth and/or spread of cancer (Rady et al., 2017). However, the gene(s) controlling apoptosis are frequently defective in malignancies, which results in unchecked growth (Indovina et al., 2015). Finding an effective natural product as an anticancer treatment depends on its capacity to cause cellular apoptosis in tumor tissue (Goldar et al., 2015). There have been several investigations into graviola anticancerous qualities. Apoptosis was observed to be induced by muricata extracts. Breast MDAMB-468 cancer cells undergo apoptosis when exposed to leaf extracts of *A. muricata* (Kuate et al., 2016). Similar to this, *A. muricata* fruit extract causes breast T47D cancer

cells to undergo apoptosis (Rachmani et al., 2012). By increasing proapoptotic caspase-3 marker activity in COLO-205 colon cancer cells, an ethanolic extract of *A. muricata* leaves causes apoptosis (Eggadi et al., 2014). Analogously, anomuricin E produced from *A. muricata* leaves promoted apoptosis in HT-29 colorectal cancer cells by activation of caspases 3/7 and 9 and overexpression of BAX and downregulation of BCL-2 at the mRNA and protein levels (Zorofchian Moghadamtousi et al., 2015). According to a terminal deoxynucleotidyl transferase-mediated dUTP nick-end labelling (TUNEL) experiment, an ethanolic leaf extract dramatically increased caspase3 activity to cause death in K562 leukemia cancer cells (Ezirim et al., 2013). Apoptosis was brought on by the treatment of colorectal cancer cells HT-29 and HCT-116 with an ethyl acetate extract of leaves. This caused MMP to be disrupted, cytochrome c to leak, the initiator and executioner caspases to be activated, Bax to be upregulated, and Bcl-2 to be downregulated. Similar to this, an ethyl acetate extract from the leaves of *A. muricata* caused lung cancer cell A549 to undergo apoptosis by increasing ROS production. This was followed by the reduction of MMP through the overexpression of Bax and the downregulation of Bcl-2 (Moghadamtousi et al., 2014a).

MODULATION OF CELLULAR PROLIFERATION

Cancer formation and progression are characterized by proliferation, which is evidenced by altered expression and/or activity of proteins connected to the cell cycle. The normal cell cycle is hampered in cancer, leading to unchecked cell growth, proliferation, and tumor progression. It has been demonstrated that AGEs and *A. muricata* extracts control the cell cycle machinery, causing cell cycle arrest and preventing cell proliferation. Anomuricin E produced from *A. muricata* leaves has been shown to inhibit cell proliferation in the HT-29 colorectal cancer cell line by arresting the cell cycle at the G1 phase (Moghadamtousi et al., 2014a). Hepatic Hep G2 and breast MCF-7 and MDA-MB-231 cancer cell proliferation was strongly inhibited by extracts of hexane, ethyl acetate, and methanol (Moghadamtousi et al., 2015). In PC-3 colorectal cancer cells, a hexane leaf extract dramatically inhibited cell growth (Sun et al., 2016). *A. muricata* extracts in hexane and methanol inhibited the growth of A549 (Moghadamtousi et al., 2015), lung cancer cells as well as HT-29 and HCT-116 colorectal adenocarcinoma cells (Moghadamtousi et al., 2014a). After being treated with methanol pericarp extract, NCI-H292 cancer lung cells shown antiproliferative and cytotoxic activity (Gomes de Melo et al., 2010). Inhibition of growth by G0/G1 cell cycle

Table 2. Examples of the other pharmacological activities of graviola reported in the current study

Cancer type	Observation	Reference
Antioxidant activity	Graviola leaf extract (GLE) scavenges peroxy and nitrogen radicals and lowers ROS production generated by H ₂ O ₂ .	Son et al. (2016)
	GLE increased the expression of antioxidant enzymes like SOD1 and Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2)	
Anti-inflammatory activity	Graviola suppressed proinflammatory cytokines such as tumor necrosis factor (TNF) and IL-1 in rats with arthritis	Foong and Hamid (2012)
Wound healing	Graviola upregulated heat shock protein 70, a crucial protein for wound healing that also plays a role in cell proliferation	Moghadamtousi et al. (2015)
Antimicrobial activity	Graviola extracts exert significant antibacterial activities against <i>Staphylococcus aureus</i> , <i>Streptococcus pyogenes</i> , <i>Bacillus subtilis</i> , <i>Escherichia coli</i> , <i>Proteus vulgaris</i> , <i>Salmonella typhimurium</i> , <i>Klebsiella pneumoniae</i> , and <i>Enterobacter aerogenes</i> .	Coria-Télez et al. (2018)

arrest was achieved in leukaemia HL-60 cancer cells by ethanol extracts of roots, fruits, or leaves (Moghadamtousi *et al.*, 2014b). Capan-1 cells from pancreatic cancer decreased cell proliferation when treated with hexane or DMSO (Rosdi *et al.*, 2015).

NECROSIS AND OTHER RELATED EFFECTS

Caspase activity is not necessary for necrotic cell death, in contrast to its counterpart, apoptosis. Contrary to apoptosis, chemotherapy-induced necrosis results in a breach of the plasma membrane, which causes the contents of the cell to leak out and activate the immune system. Through the downregulation of hypoxia-related factors in pancreatic FG/COLO357 and CD18/HPAF cancer cells, this inhibits cellular metabolism and causes additional necrosis (Torres *et al.*, 2012). Important roles in cancer metastasis are also played by cancer cell invasion, migration, and motility (Matsuoka and Yashiro, 2014). Therefore, blocking cancer cell invasion, migration, or motility prevents metastasis, which accounts for more than 90% of patient fatalities (Zhou *et al.*, 2014). The motility of cancer cells was reduced after treatment with leaf extracts in pancreatic FG/COLO357 and CD18/HPAF cancer cells (Torres *et al.*, 2012). More strikingly, treatment of colorectal cancer cells HT-29 and HCT-116 with an ethyl acetate leaf extract clearly prevented cancer cell invasion and migration (Moghadamtousi *et al.*, 2014b). A portion of these effects have also been shown in a clinical model system in addition to the preclinical investigations using cell lines mentioned above (Hansra *et al.*, 2014).

OTHER POTENTIAL HEALTH-RELATED BENEFITS

Graviola extracts had significant therapeutic properties for other conditions that affect people, such wounds, inflammatory and oxidative diseases, microbial and parasitic diseases, in addition to their chemopreventive and chemotherapeutic effects on cancer. In addition to being utilized as herbal remedies for liver illnesses, headaches, hypertension, cystitis, and diabetes, graviola organs also contain antidiarrheal, anti-inflammatory, and antispasmodic properties (De Sousa *et al.*, 2010). In addition to the previously mentioned advantages, graviola components have also been shown to have anticancer, antidepressant, gastroprotective, antimalarial, and wound healing properties (Moghadamtousi *et al.*, 2015).

Antioxidant activity

Various graviola extracts exert antioxidant activities as reported in several studies. It's noteworthy that *A. muricata*'s butanolic leaf extract (BLE) and aqueous leaf extract (ALE) exhibited potent antioxidative properties that shielded normal cells from hydrogen peroxide (H₂O₂)-induced DNA damage (George *et al.*, 2015). Another *in vivo* investigation revealed that ALE has protective effects in rats given diabetes (Ojewole and Adewole, 2009). Additionally, it has been demonstrated that graviola leaf extract effectively scavenges peroxy and nitrogen radicals and lowers ROS production generated by H₂O₂. They also demonstrated that GLE increased the expression of antioxidant enzymes like SOD1 and Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) (Son *et al.*, 2016).

Anti-inflammatory activity

Numerous studies have demonstrated that oral administra-

tion of ethanolic leaf extract (ELE) of *A. muricata* at various doses greatly reduced the edema that carrageenan-induced in rats' paws. Interestingly, there was a corresponding decline in leukocyte migration and exudate volume due to this anti-inflammatory activity of ELE of *A. muricata* (De Sousa *et al.*, 2010). Additionally, it was demonstrated that LE of graviola (10-300 mg/kg BW) has a potent anti-inflammatory effect in rat models of arthritis and mice with xylene-induced ear edema (Foong, and Hamid, 2012). They also demonstrated that rats with arthritis caused by CFA had considerable suppression of proinflammatory cytokines such as tumor necrosis factor (TNF) and IL-1 (Foong and Hamid, 2012).

Wound healing

Researchers have found that an ethyl acetate extract of *A. muricata* leaves has wound-healing properties against wounds in rats. After using the extract topically for 15 days, investigations using a macroscopic and microscopic lens showed that there had been significant healing. Additionally, immunohistochemistry analysis showed that heat shock protein 70, a crucial protein for wound healing that also plays a role in cell proliferation, was up regulated during the healing process. By increasing the levels of catalase, glutathione peroxidase, and superoxide dismutase, the antioxidant potential of *A. muricata* leaves also enhanced wound healing (Cu, Zn-SOD) (Moghadamtousi *et al.*, 2015).

Antimicrobial activity of graviola

Graviola extracts exert significant antibacterial activities against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Bacillus subtilis*, *Escherichia coli*, *Proteus vulgaris*, *Salmonella typhimurium*, *Klebsiella pneumonia*, and *Enterobacter aerogenes*. The extract had substantial antibacterial action against *Pseudomonas aeruginosa* and *S. aureus*, and the ethanolic extract had antibacterial efficacy against *S. aureus* and *Vibrio cholera* (Coria-Téllez *et al.*, 2018).

CONCLUSION

This minireview summarizes the anticancer activities of graviola extracts against various organs cancers such as pancreatic, lung, breast, colon, and prostate cancers. Graviola extracts are of particular importance as basic and supportive treatment of cancers. The mechanism behind such anticancer activities of graviola needs further investigation. However, induction of apoptosis, necrosis, and modulation of proliferation pattern of the cancer cells are suggested mechanisms. Graviola also of importance as antioxidants and in the treatment of several bacterial diseases, diabetes, and wound healing.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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