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Graviola: A Systematic Review on Its Anticancer Properties

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Abstract There has been an enormous interest in the literature that phyto-compounds have therapeutic and beneficial effects in various diseases including inflammatory associated arthritis, diabetes, hypertension, parasitic infections, and cancer. The leaves from the tropical tree Annona Muricata, also known as Graviola have been reported to have positive and effective properties against many of the above mentioned diseases. Cancer still remains the number one killer in the Western nations and most treatments for the disease rely on the use of chemotherapy that utilizes drugs that are also toxic against normal healthy cells. Thus, an alternative approach to anti-cancer therapies should involve the determination of novel drug targets that must be highly effective and specific against cancer development and growth. Additionally, the new generation novel drugs should be non-toxic to the host cells and affordable for the patients. This review summarizes the recent findings on the effects of Graviola tree extract as a novel anti-cancer agent for the treatment and prevention of cancers; a possible natural anti-cancer candidate agent in line with all the attributes pointed above.

Keywords: *cell death, apoptosis, necrosis, Graviola, anti-cancer agents, cancer, tumor*

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1. Natural Extracts against Cancer

Natural Plant extracts have been used for centuries by many cultures and civilizations as a basis for treating various diseases. More than 80% of the global population now depends on natural plant extracts through traditional therapies. [1,2,3] Recent investigators have focused on the progression, treatment and prevention of cancer with such compounds but room for improvement still remains.

To date, the use of conventional synthetic chemotherapeutic drugs lack the properties to be considered as effective therapeutic agents, with most of those associated with severe side effects and toxicity of the normal host cells. Whereas an alternative therapeutic approach that uses natural plant extracts is advantageous vs conventional therapy with limited side effects.

One of the first systematic approaches was carried out in 1950 with the vinca alkaloids (vinblastin and vincristine) discovery, isolated from the *Catharanthus roseus* G. Don. (Apocynaceae) followed by a number of effective extracts such as Triptolide (Tripterigium wilfordii), Amygdalin (B12), *Achyranthes aspera* Linn. (Family-Amaranthaceae) etc [4,5,6].

2. Graviola History

Graviola belongs to *Annonaceae* family, *Annona* genus and *muricata* species. Graviola is a fruit tree with many uses in traditional and alternative medicine. Graviola, soursop, guanábana, guanábano, guanavana, guanaba, corossol épineux, huanaba, toge-banreisi, durian benggala, nangka blanda, cachiman épineux are altering names for this evergreen plant that is mostly distributed in tropical and subtropical regions of the world. Graviola is a heart shaped edible fruit and together with its leaves, root and seeds is known to have beneficial properties in alternative medicine [7].

The fruits of Graviola are extensively used to make candies, syrups, ice creams, shakes and beverages. A wide range of ethno-medicinal activities in Africa and South America extensively use this plant in their conventional medicine. A number of laboratories have reported Graviola's for its benifical actions against anticonvulsant, antiparasitic, anti-arthritic, antimalarial, antidiabetic hepatoprotective and andicancer activities. Biological and chemical characterization studies indicate that annonaceous acetogenins are the main ingredients of Graviola [8,9,10].

Nowadays more than 100 annonaceous acetogenins that are generally characterized as a family of natural products with antitumor activities, from roots, leaves, barks, fruits and seeds of Graviola have been widely used in alternative medicine for many purposes. In the Peruvian Andes for example, the Graviola leaves are used to combat parasites and treat diabetes. In the Brazilian Amazon the leaves were used to treat liver problems and the leave – extracted oil is believed to help with rheumatism, neuralgia and arthritis. In the Eastern Andes and Jamaica, Haiti the juice of Graviola was used to stop diarrhea, used as muscle relaxant and lower the intestinal acidity [11-15].

Other reports have demonstrated that Graviola has a number of biological activities such as antifungal, anti-bacterial, anti-malarial and antioxidant. Furthermore, it has been showed to have anti-cancer properties on multi-drug resistant cancer cell lines. [16,17,18,19,20] The ability of Graviola to have selective growth inhibition against a variety of cancer cells including lung carcinoma cell lines, breast solid tumor lines, prostate adenocarcinoma, pancreatic carcinoma cell lines, colon adenocarcinoma cell lines, liver cancer cell lines, human lymphoma cell lines, and multi-drug resistant human breast adenocarcinoma will be discussed based on previously published data [21,22,23,24,25,26].

2.1. Composition

Graviolas fruit flesh consists of 80% water, 1% protein, 18% carbohydrates and small amount of vitamins B, B2, C, potassium and dietary fiber. [27,28] The main group, annonaceous acetogenin, is a unique set of derivatives of C35 or C37 long chain fatty acids derived from the polyketide pathway (Figure 1). The annonaceous acetogenins found in Graviola include Annocatalin, annohexocin, annomonicin, annomontacin, annomuricatin A & B, annomuricin A thruE, annomutacin, annonacin, annonacinone, annopentocin A thru C, cis-annonacin, cis-corossolone,cohibin A thru D, corepoxylone, coronin, corossolin, corossolone, donhexocin, epomuricenin A & B,gigantetrocin, gigantetrocin A & B, gigantetrocinone, gigantetronenin, goniothalamicin, iso-annonacin, javoricin, montanacin, montecristin, muracin A thru G, muricapentocin, muricatalicin,muricatalin, muri-catenol, uricatetrocin A & B muricatin D, muricatocin A thru C muricin H,muricin I, muricoreacin, murihexocin 3, murihexocin A thru C, murihexol, murisolin, robustocin, rolliniastatin 1 & 2, saba-delin, solamin, uvariamicin I & IV, xylomaticin isolated from the leaves, root and stem barks of Graviola [29,30,31].

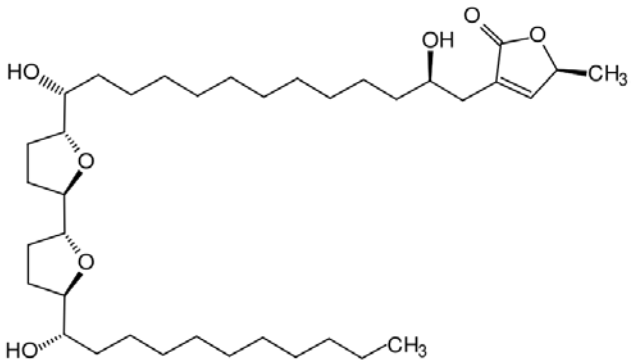

Figure 1. Bullatacin chemical structure, one out of the three main annonaceous acetogenin molecules including asimicin and bullatalicin that it is believed to be the one most bio-active anti-cancer molecule found in the Graviola extract

The essential oil of the fresh fruit pulp contains 2-hexenoic acid methyl ester (23.9%), 2-hexenoic acid ethyl ester (8.6%), 2-octenoic acid methyl ester (5.4%), 2-butenoic acid methyl ester (2.4%), β-caryophyllene (12.7%), 1,8- cineole (9.9%), linalool (7.8%), α-terpineol (2.8%), lialyl propionate (2.2%) and calarence (2.2%) [32].

Limited number of published data are found in literature for the anti-carcinogenic potential of Graviola natural extracts. Recent studies have suggested that Graviola also expresses analgestic and anti-inflammatory effects, promotes apoptosis (programmed cell death) and cytotoxicity on cancer cells that may result from the presence of alkaloids, essential oils and acetogenins. [11,33,34,35] These acetogenins demonstrated to be selective and toxic against various types of cancer cells without harming normal and healthy host cells [36,37,38].

2.2. Anticancer Characteristics

It has been previously reported that the Graviola extracts have significant anti-cancer effects in a number of cancer cell lines both *in vitro* and *in vivo.* [39] Studies revealed the Graviola extracts as having selective inhibition of breast cancer cells via EGFR downregulation. The epidermal growth factor receptor (EGFR) is an oncogene frequently overexpressed in breast cancer (BC), and its overexpression has been associated with poor prognosis and drug resistance. EGFR is therefore a rational target for BC therapy development. In addition, experiments showed that Graviola fruit extract (GFE) inhibit the growth of BC cells using xenografts mouse model studies. Moreover, GFE selectively inhibited the growth of EGFR-overexpressing human BC (MDA-MB-468) cells but not in non-tumorigenic human breast epithelial cells (MCF-10A). [39] These studies strengthen the evidence that Graviola has selective anti-growth effects between cancer and non-cancer cells.

Another study on breast cancer cells supported that Graviola promotes apoptosis in ER-related pathways. Moreover, Graviola decreased MCF-7 tumor growth while inhibiting ER-cyclin D1 and Bcl-2 protein expressions in nude mice. [40] In colon cancer cells, Graviola leaves also has significant effects on cell survival potential via mitochondrial-mediated apoptosis associated with the G1 cell cycle arrest. Graviola induces apoptosis by generating reactive oxygen species ROS and down-regulating the anti-apoptotic Bcl-2 protein, while up-regulating pro-apoptotic Bax protein. These processes subsequently lead to attenuation of mitochondrial membrane potential (MMP) and cytochrome c release. Release of cytochrome c activates apotosome and the intrinsic caspase cascade that triggers execution of apoptosis through DNA fragmentation. [41] Graviola has also been reported to have anti-proliferative effects of HL-60 cells via loss of cell viability, loss of MMP, G0/G1 phase cell arrest and morphological apoptotic changes. These results substantiate and confirm that Graviola does indeed have anti-proliferative and cytostatic activity in HL-60 cells [42].

In Vitro and *in vivo* model studies demonstrated the effect of Graviola extract in prostate cancer cell lines. These experiments showed that Graviola promotes necrosis in PC-3 cells through inhibition of tumor mobility and cellular metabolism. Further studies demonstrated downregulation of the expression of the hypoxia-related factors and glycolytic factors following treatment in PC cells with Graviola (i.e. HIF-1α, NF-κB, GLUT1, GLUT4, HKII, and LDHA) [26].

Follow up studies reported the *in vivo* Graviola leaf extract (GLE) pharmacokinetics and *in vitro* absorption kinetics resulting in inhibiting *in vitro* prostate cancer proliferation, viability and clonogenic colonies. Oral administration of 100mg/kg bw GLE showed tumor growth-inhibition in human prostate tumor in xenografts

studies. This study also demonstrated the synergy among the constituents of Graviola leaf extract (GLE) compared to its flavonoid-enriched (FEF) and acetogenin-enriched (AEF) fractions [43,54].

In another study Graviola also had effects on Lewis lung carcinoma (LLC) tumor cell lines that were examined both *in vivo* as well as *in vitro*. The study suggested that Graviola once again had antitumor activity by inhibiting the normal growth of the lung tumors. [47] Further studies also indicated the anti-cancerous and cytotoxic mechanisms of action of Graviola that affected NADH oxidase inhibition in cancer cell lines, downregulation of the P-glycoprotein pump via ATP depletion and Cell cycle arrest at S-phase progression [48,49,50,51].

A recently published study demonstrated also the preventive measure against 7,12-dimethylbenzeneanthracene DMBA-induced breast cell proliferation in the breast tissues of female albino mice. Once again, the study supported that the Graviola leaf extract could act as a cancer prevention agent [52].

3. Concluding Remarks

Overall, this mini review lists the existing knowledge about the natural plant extract agent, Graviola, and gives an insight on the important *in vitro* and *in vivo* studies that have been carried out based on its efficacy and functional characteristics. However, further studies are required to verify the exact properties and the mechanisms of action. Even though several reports demonstrated positive actions of Graviola, more robust and systematic clinical trials to test and verify its true validity and safety are necessary, in order to be confirmed as a therapeutic anti-cancer agent. Thus, well-designed, randomized, double blind trials are of major importance.

Concluding, the present review demonstrates the advantages of the possible use of Graviola for cancer treatment. Existing conventional cancer therapies are known to be highly toxic with severe side-effects that affect the quality of life of the patients and with no more than 6 months contribution of life expectancy [56,57]. Therefore, new drugs need to be developed that include bioactive natural molecules such as Graviola that do not have toxic side-effects and are selective in killing cancer cells but not the normal/physiological healthy host cells. Furthermore, pro-inflammatory responses and pathways are activated and suggested to play an important, primary role in tumourgenesis. Graviola with known strong anti-inflammatory effects can warrant a new in vivo study to determine whether one mechanism of action, could possibly be, through specifically inhibiting the site of inflammation in solid cancers [53,55].

Table 1. Scientific findings of previously published work on Graviola.

Trial type	Findings	Randomized	References
In Vivo	Graviola decreased MCF-7 tumor growth in nude mice.	No	Yu-Min Koa etal.(2011) [40]
In Vivo	Graviola has antitumor activity in lung cancer cells.	No	Wang, L. Q., et al (2002) [44] Woo, M. H., et al (1999) [45]
In Vivo	Graviola could act as a cancer prevention agent.	No	J.B. Minari *, U. Okeke (2014) [52]
In vitro	Graviola selectively inhibited the growth of EGFR-overexpressing human breast cancer cells.	*N/A	Dai Y, Hogan Set al. (2011) [39]
In vitro	Graviola induces apoptosis in colon cancer cells.	N/A	Soheil Zorofchian Moghadamtousi et al.(2014) [41]
In vitro	Graviola promotes necrosis in PC-3 cells.	N/A	Torres, M. P et al. (2012) [26] Yang C et al. (2015) [43]
In vitro	Graviola has antitumor activity in Lung cancer.	N/A	Kim, G. S., et al. (1998) [46] Zhao, G. X., et al. (1993) [47]

*N/A Not Applicable.

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