Biomedical Effects of Graviola

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A member of the Annonaceae (Custard-apple family), Annona muricata, commonly known as soursop, graviola, paw-paw, or “guanabana”, is a tree native to Central America and West Indies that is abundant at altitudes lower than 900 m above sea level.

Keywords: Phytonutrients ; Phytochemicals ; Graviola ; Lipinski’s rule of 5 ; Veber’s rules ; Ghose filter ; Anticancer ; Antioxidant ; Antimicrobial ; Anti-inflammatory ; Immunomodulatory

1. Botanical Description

It is cultivated in tropical and subtropical climates in countries such as Angola, Brazil, Colombia, Costa Rica, Puerto Rico, India, and Venezuela [1]. The graviola tree is mainly appreciated for its edible fruit. Still, its parts (leaves, fruit, bark, root, etc.) have been commonly used in traditional pharmacopeia in the form of macerations, decoction, or as a topical medication [2][3]. While the graviola tree can grow in a large variety of soils, it prefers deep soils with good oxygenation [1]. Botanically speaking, its leaves are large and obovate to elliptically shaped, are green on top, and paler under the top with short petioles and a pungent smell. The tree produces yellow-greenish flowers and lags about two years in producing heart-shaped fruits. It usually bears fruits yearly from that point on (12–24 per year) and can produce up to 50 fruits from its fifth year [4].

2. Phytochemicals

More than two hundred (>200) bioactive compounds have been isolated from the leaves, seeds, root, bark, fruit, and fruit peel of the graviola tree [3]. Most frequently identified are alkaloids, phenolics, and terpenoids [5][6]. Acetogenins are considered the main bioactive compound in the *Annonaceae* family, with over 120 acetogenins identified from the root, leaves, stems, fruit pulp, and the seed of the family members [7][8]. Acetogenins are a particular class of secondary metabolites that could be considered part of the phenolics integrating polyketides and polyethers found exclusively in the plants of the *Annonaceae* family [9]. The structure of acetogenins is composed of a long carbon chain (35–38 carbons) as a fatty acid derivative. Graviola leaves contain key medically relevant polyphenolics compounds, including quercetin, rutin, and gallic acid [10][11][12]. The leaves of graviola also contain close to eighty (80) essential oils, including bioactive sesquiterpenes, and compounds such as potassium; calcium; zinc, phosphorus; magnesium; carbohydrates; vitamin A, B, and C; phytosterol; and calcium oxalate [13][14].

3. Biomedical Effects

3.1. Anticancer

Graviola anticancer activity has been extensively studied, and the cytotoxicity of graviola has been reported for several cancer types e.g., breast, colorectal, skin, head and neck, lung, liver, pancreatic, prostate cancer, and leukemia [1][15][16][17]. Most of the antiproliferative properties of the extracts are suggested to be mediated by the graviola acetogenins. The acetogenins exert an inhibitory activity on the NADPH mitochondrial complex 1, a component of the energy transport chain, which is crucial to the synthesis of high quantities of ATP in cancer cells [16][18][19]. Acetogenins have also been shown to target several critical cancer metabolic pathways by inhibiting the Na^+/K^+ ATPase pump and the hypoxic and glycolytic pathways, inducing apoptosis and cell cycle arrest [19][20][21].

3.2. Antioxidant

Studies conducted in vitro and in vivo suggest that graviola contains antioxidant compounds that act as free-radical scavengers and increase the activity of the antioxidant enzymes superoxide dismutase and catalase and downregulate the function of mitochondrial NADPH oxidase complex I [22][23][24]. The leaf and the fruit pulp of graviola are the parts of

the tree with the highest antioxidant properties [5]. The antioxidant activity of graviola is believed to be mediated by the following phenolic phytochemicals: quercetin, gallic acid, and graviola leaf polysaccharides [25][26].

3.3. Antimicrobial

3.3.1. Antiviral

It has been suggested that the phytochemicals polyphenolics in graviola exert some antiviral activity against RNA and DNA viruses [12][27]. A study by Wahab et al. showed that pretreating monkey kidney epithelial cells with a graviola leaf extract 24 h prior to infecting them with the dengue virus serotype 2 inhibited the virus replication. The treatment also increased the survival of the dengue-infected cells [28]. A recent clinical study conducted by Le Donne et al. investigated the antiviral properties of graviola on human papillomavirus (HPV)-infected patients who were supplemented with ellagic acid and graviola extract twice a day for six months. Results showed a 74% HPV clearance in treated patients compared to the 25% clearance for the placebo group [29]. Furthermore, recent in silico studies suggest that rutin, a phytonutrient abundant in graviola, could act as strong ligands and inhibit the function of proteins of the SARS-CoV and SARS-CoV-2 virus, thus suggesting potential therapeutic benefits against the COVID-19 infection [30][31].

3.3.2. Antibacterial

Graviola leaf extracts have been shown to exert in vitro antibacterial activity against oral pathogenic strains such as *S. mutants*, *S. mitis*, *P. gingivalis*, *P. intermedia*, *P. intermedia*, and *C. albicans* [32][33]. An in vivo study conducted in albino rats demonstrated the efficiency of graviola unripe fruit extracts to inhibit the growth of *S. typhi* [34]. Furthermore, aqueous leaf extract and fruit-skin ethanolic graviola extracts showed a strong antibacterial effect against *K. pneumoniae*, *S. aureus*, and *P. aeruginosa* bacteria, i.e., the pathogens responsible for respiratory infections in the human immunodeficiency virus (HIV/AIDS) patients [35].

3.3.3. Antifungal

Researchers did not find studies testing the antifungal activity of any graviola extract. However, researchers found studies evaluating this property in some of graviola's phytochemicals. In 2017, a research group found that gallic acid has in vitro antifungal activity against dermatophyte strains (between 43.75 and 83.33 µg/mL), and Candida strains (*C. albicans* MIC = 12.5 µg/mL, and *Trichophyton rubrum* MIC = 43.75 µg/mL) by inhibiting the ergosterol synthesis. They also confirmed this activity after in vivo studies administrating 80 mg/kg d of gallic acid [36]. In another study, researchers found that quercetin induces apoptosis in *Candida albicans* through mitochondrial dysfunction by increasing intracellular magnesium [37].

3.4. Anti-Inflammatory

The anti-inflammatory properties of graviola have been extensively studied in vitro and in vivo [38]. Cercato et al. reported that a topical application of a graviola leaf extract (0.3, 1, or, 3 mg/ear) significantly reduced ear edema and myeloperoxidase activity in Swiss mice with 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced ear inflammation. The authors were also able to show that the anti-inflammatory effect of the extract was associated with a reduction in the total amount of hydroperoxides and with modulation of catalase antioxidant activity [39]. While studying the anti-inflammatory response in lipopolysaccharide (LPS)-stimulated murine macrophage cell line RAW264.7 treated with graviola ethanolic leaf extracts, Laksmitawati et al. reported a downregulation in pro-inflammatory protein markers, such as tumor necrosis factor-alpha (TNF-α), interleukin-1β, interleukin-6, in the treated macrophages cells compared to untreated controls [40]. Furthermore, graviola aqueous extract suppresses nitric oxide production [41]. Similarly, an in vivo study conducted in rodents by Ishola et al. showed that the administration of a lyophilized graviola fruit extract inhibits the activity of the pro-inflammatory biomarkers cyclooxygenase (COX)-1 and COX-2 in a dose-dependent manner [42].

3.5. Immunomodulatory

As previously described, the specific bioactive constituents responsible for the major antioxidant, anti-inflammatory, and antimicrobial properties of graviola include different classes of annonaceous acetogenins (metabolites and products of the polyketide pathway), alkaloids, flavonoids, and sterols. Several studies have reported that graviola possesses immunomodulatory properties. For example, a study conducted in rodents by Umayra et al. shows that administration of an ethanolic graviola leaf extract boosts the immunological response through the activation of phagocytic cells [43]. Furthermore, an immune-enhancing activity of graviola leaf extracts has been observed in RAW 264.7 macrophage cells in vitro, a phenomenon which is believed to be mediated by the activation of the mitogen-activated protein kinase (MAPK) pathways [44].

3.6. Predicted gastrointestinal absorption (GIA)

The physicochemical properties for the main six bioactive phytochemicals in graviola (benzylisoquinoline, annonacin/acetogenin, cinnamic acid, coumaric acid, caffeic acid and rutin) were calculated based on the combination of Lipinski's, Ghose's, and Veber's rules (L-Ro5, GF, VR). The range of pharmacokinetics data for the molecules are summarized as follow: molecular weight (160-500 Da); hydrogen bond donors ≤5; hydrogen bond acceptors ≤10; molar refractivity (40-130); lipophilicity (-0.4–5.6); rotatable bonds ≤ 10: polar surface area <140; the total number of atoms (20-70), lipophilicity considering ionizable groups at pH 7.4 [LogD] (1-5) [45],[46],[47],[48]. 50 % of the graviola's bioactive phytochemicals (benzylisoquinoline, coumaric acid, caffeic acid) comply with all of the "drug-likeness" rules. The remaining 50% (annonacin/acetogenin, cinnamic acid, and rutin) violate most of the parameters of the L-Ro5, GF and VR. Accordingly, rutin is predicted to have the lowest GIA, followed by annonacin/acetogenin and then, cinnamic acid.

4. Contraindications

Studies from patients of the French West Indies, whose diet is rich in graviola, showed the development of a type of Parkinsonism resistant to the common anti-parkinsonism drug to treat tremors, levodopa [15]. This observation must lead scientists to further study if the acetogenins and alkaloids present in the graviola fruit could be toxic to brain cells, specifically dopaminergic neurons, which are the main cells affected in Parkinson's disease. In general, patients with neurological ailments should avoid the consumption of graviola supplements. Given that graviola is already widely used in traditional medicine, it could potentially be used against many health conditions if properly tested in further clinical studies. In conclusion, the benefits and side-effects of graviola should be carefully evaluated on a case-by-case basis.

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