

MINI-REVIEW

Anticancer Properties of *Psidium guajava* - a Mini-Review

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Abstract

Cancer is a complex disease caused by a progressive accumulation of multiple genetic mutations. Consumption of fruits is associated with lower risk of several cancers, which is mainly associated to their phytochemical content. The use of functional foods and chemopreventive compounds seems to contribute in this process, acting by mechanisms of antioxidant, anti-inflammatory, anti-angiogenic and hormonal. The *Psidium Guajava* has high potential functional related to pigments who are involved in the process of cancer prevention by having antioxidant activity. The aim of the present review is to expose some chemical compounds from *P. Guajava* fractions and their association with anti-carcinogenic function. The evidences supports the theory of anticancer properties of *P. Guajava*, although the mechanisms are still not fully elucidated, but may include scavenging free radicals, regulation of gene expression, modulation of cellular signalling pathways including those involved in DNA damage repair, cell proliferation and apoptosis.

Keywords: *Psidium guajava* - cancer - antioxidants - bioactive compound - functional foods

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Introduction

Psidium Guajava (*P. guajava*) is a plant native to tropical America and belongs to the family Myrtaceae. *P. guajava* is called “guayaba” in Spanish speaking countries and “goiaba” in Brazil. It is an important tropical fruit widely grown in Taiwan, Hawaii, Thailand, Philippines and Malaysia. All parts, including the fruits, leaves and barks have been traditionally used as the folkloric herbal medicines and exhibit many therapeutic uses including (Levy and Carley, 2012)

This plant is available in the South America, European, Africa and Asia. The common names of *Psidium Guajava* are guava (English), jambu batu (Malay), mansala (India) and gwaaba (Africa) (Sul’ain et al., 2012). Guava is a tree commonly used for shade or can be a shrub in door-yard gardens in the tropics (Vyas et al., 2010). Brazil is among the world’s top producers of guava and most of the country’s production is destined for the food industry to produce different products, like candies, juices, jams and frozen pulp.

The fruit process results in a discard of the leaves, seeds, part of the peel and pulp fraction not separated in the physical depulping process. These discard part hold important health properties. In ethno traditional medicine, extracts of the root, bark and leaves of *P. guajava* have been used to treat a wide range of illnesses (Levy and Carley, 2012). World Health Organization (WHO) also says that plants would be the best source for obtaining different types of medicines and drugs (Porwal et al., 2012).

In Guava, some of the ethnomedicinal uses includes the crushing of the leaves and the application of the liquids coming out from them on wounds, cuts, ulcers, boils, skin and soft tissue infectious site, rheumatic places and to date, phytochemical investigations have been reported on the tannins, flavonoids, essential oil, proteins, sesquiterpenoid alcohols and triterpenoid acids. Most of the researches performed so far focus on development of drugs to treat the cancer and *Psidium guajava* L. indicate the presence of cytotoxic compounds to treat different types of cancer (Begum et al., 2002; Deo and Shastri, 2003; Joseph and Priya, 2010)

Nutritional value

From a nutritional point of view, guava fruit yields 68 calories per 100 grams, is a good source of fiber, and contains four times the vitamin C content of oranges. Most of the vitamin C is found in the fruit’s skin that is usually not peeled before consumption. Guava’s vitamin C content is so high that a fruit puree was utilized by allied troops in World War II to fortify their rations (Sato et al., 2010). Furthermore, guava is rich in tannins, phenols, triterpenes, flavonoids, essential oils, saponins, carotenoids, lectins, vitamins, fiber and fatty acids, particularly lycopene, an important substance in the prevention of some types of cancer.

The fruit contains sugars, iron, calcium, phosphorus and vitamins A, B and (apart from C) in higher concentrations than most other fruits. Both articles (Sato et al., 2010; Joseph and R. 2011) demonstrated the nutritional

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Table 1. Nutritional Values of *P. Guajava* Estimated by Different Authors

Components		Sato et al., 2010	Joseph & Priya, 2011
Nutrient Units Value per 100g	Calories (Kcal)	68	77 - 86
	Protein (g)	2.55	0,1 - 0,5
	Fat (g)	0.95	0,43 - 0,7
	Carbohydrate (g)	14.32	9,1 - 17
	Fiber - total dietary (g)	5.4	0,9 - 1 (Crude fiber)
Minerals	Calcium - Ca (mg)	18	17,8 - 30
	Iron - Fe (mg)	0.26	200 - 400 (I.U.)
	Potassium - K(mg)	417	-
	Sodium - Na (mg)	2	-
	Zinc - Zn (mg)	0.23	-
	Selenium - Se (mcg)	0.6	-
	Vitamin C (mg)	228.3	-
Vitamins	Thiamin (mg)	0.067	0,03 - 0,04
	Riboflavin (mg)	0.04	0,6 - 1,068
	Niacin (mg)	1.084	40 (I.U.)
	Vitamin B3 (I.U)	-	35
	Vitamin B6 (mg)	0.11	-
	Folate (mcg)	49	-
	Vitamin A (I.U.)	624	0,046 (mg)
	Carotene beta (mcg)	374	-
	Vitamin E alpha-tocopherol (mg)	0.73	-
	Vitamin K phylloquinone (mcg)	2.6	-

Legend: "-": Not established values

values of guava (Table1).

Antioxidant Compounds

Guava, particularly its leaves, contains secondary plant metabolites with certain

polyphenols with potential intrinsic antioxidant, anti-inflammatory, and antiviral properties. Several guava components have been postulated as having anticancer effects *in vitro*, and the most frequently reported are ascorbic acid (vitamin C), flavonoids (apigenin), and lycopene. In guava composition, there are phenolic compounds, especially the flavonoids, both powerful antioxidants, of great importance in preventing the action of free radicals in the body and, therefore, able to prevent cancer and help to prevent premature skin aging (Deguchi et al. 1998; Ojewole 2006; Gutierrez et al., 2008; Peng et al., 2011; Luo et al., 2014).

Recently, scientists have found evidence that specific combinations of phytochemicals are more effective in protecting against diseases than the isolated compounds, pointing to a need to study the synergy among active compounds in plants, for example, by experimenting with plant extracts (Chiari et al., 2012).

The health-related properties possessed by phenolic compounds are based mainly on their antioxidant activity, particularly as free-radical scavenger and as metal chelators capable of catalyzing the peroxidation of lipids. It has been demonstrated that polyphenols (flavonoids and vitamin C) have the ability to counteract the toxicity, mutagenicity and carcinogenicity of various.

Thenmozhi and Rajan. (2015) also determinate the quantitative of bioactive compounds an ethanolic extract of *P. guajava* leaves. It contains high concentrations of phenol (9.33 mg/g), tannin (4.30 mg/g), flavonoids (6.42 mg/g) and saponin (3.67 mg/g) than the aqueous extract. The results of the study demonstrated that the ethanolic

extraction had a higher content of the phytochemicals than the aqueous extract. Begum et al. (2004) found five chemical constituents on *Psidium Guava* leaves, including one new. It has been identified pentacyclic triterpenoid guajanoic acid, β -sitosterol, uvaol, oleanolic acid, and ursolic acid.

According Qian and Nihorimbere (2004) the total phenolic content of ethanol guava leaf extracts was higher than water guava leaf extracts. The same results showed that ethanol guava leaf extraction (GLE) contained higher radical-scavenging activity than water GLE due to the higher amount of phenolic content, as represented by the Chiari et al. (2012) and Thenmozhi and Rajan (2015) studies. Mailoa et al. (2013) also determined that the ethanol is the best solvent compared to acetone for tannin extraction from guava leaves which ethanol extracts resulted in the amount of tannin 2.351 mg /g.

Since these compounds can be beneficial to human health, Chiari et al. (2012) improve the extraction procedure of secondary metabolites from guava fruits in order to increase the levels of phenolic compounds and flavonoid in the extract, assessing their contents by colorimetric assays associated with the study of its chromatographic profile and antioxidant activity. According to this study, total phenolic content results showed that the most effective solvent to extract phenolic compounds from the dried and powdered *P. guajava* L. was 70% (v/v) aqueous ethanol, followed by water and finally by 90% ethanol and absolute ethanol, these last two showing the same extraction efficiency chemical products. The qualitative analysis of ethanolic and aqueous extract of *Psidium guajava* leaves showed these contain tannin, phlobatannins, sapanoin, flavonoids, steroids, terpenoids, triterpenoids, carbohydrate, polyphenol and glycoside present in both extracts.

Researchers have suggested that guava's high antioxidant activity may interfere with cancers initiated

Table 2. Anticarcinogenic Activities of *P. guajava* Leaves Extracts in Different Cancer Cell Lines

Cancer type	Cell	Anticarcinogenic Activities	Compound	References
Cervical	HeLa	Cytotoxic effect by antioxidant compounds (tannin, saponins, alkaloids, phenols) – Complexes with proline-rich protein	Extracts of PG leaves	Joseph & Priya, 2010
Cervical	HeLa	Probable to regulate the apoptosis (alkaloids from essential oil)	Essential oil from PG leaves	Joseph et al., 2010
Metastatic prostate	DU 145	Suppressed the cell migration and the angiogenesis inhibit the expression of VEGF, IL-6 and IL-8 cytokines, and MMP-2 and MMP-9	Extracts of PG leaves	Peng et al., 2011
Human mouth	KB	Antitumoral or cytotoxic activities via inhibition of the NF-kB pathway	Extracts of PG leaves	Sato et al., 2010
Murine leukemia	P388	Antitumoral or cytotoxic activities via inhibition of the NF-kB pathway	Extracts of PG leaves	Sato et al., 2010
Metastatic prostate	DU 145	Antitumoral or cytotoxic activities via inhibition of the NF-kB pathway	Extracts of PG leaves	Sato et al., 2010
Murine fibrosarcoma	L929sA	Antitumoral or cytotoxic activities via inhibition of the NF-kB pathway	Extracts of PG leaves	Sato et al., 2010
Human breast	MCF7	Antitumoral or cytotoxic activities via inhibition of the NF-kB pathway	Extracts of PG leaves	Sato et al., 2010
Leukemia	AML (Kasumi-1)	Activation of the apoptotic pathway	Extracts of PG leaves	Levy & Carley, 2012
Cervical	HeLa	Apoptotic inducers interfere with cell cycle	Extracts of PG leaves	Sul'ain, Zazali & Ahmad, 2012
Human breast	MDA-MB-231	Antiproliferative activity	Extracts of PG leaves	Sul'ain, Zazali & Ahmad, 2012
Cell Madine Darby canine kidney	(MDCK).	Antiproliferative activity	Extracts of PG leaves	Sul'ain, Zazali & Ahmad, 2012
Oral	HSC-2	Significantly reduced the proliferation	Extracts of PG leaves	Alveolie et al., 2013
Human colon	HT-29	Induction of apoptosis via inhibition of cell cycle	Extracts of PG leaves	Lee & Park, 2010
Murine fibrosarcoma and human breast	L929sA, MDA-MB231 and MCF7	NFkappaB-inhibitory activity	Extracts of PG leaves	Kaileh et al, 2007
Human prostate	PC-3	Suppression of AKT/mTOR/S6K1 and MAPK signaling pathways	Extracts of PG leaves (hexane fraction)	Ryu et al, 2012
Metastatic prostate	DU-145	Suppression of the matrix metalloproteinases MMP-2 and MMP-9, and the upregulation of active caspase-3	Extracts of PG leaves	Chen et al, 2007
Ex vivo myeloid leukemia blasts	Acute myeloid leukemia (AML)	Induce apoptosis by caspase activation and p16, p21, Fas ligand (FASL TNF super-family, member 6), Bcl-2-associated agonist of cell death (BAD) and tumor necrosis factor receptor super-family, member 10b (DR5), overexpression	Extracts of PG pulp	Bomtempo et al., 2011

by oxidative and free radical damage to DNA and cell components. Leong and Shui (2002) measured the antioxidant capacity (AEAC, ascorbic acid equivalent antioxidant capacity) of selected fruits based on edible portion (wet weight) and guava (270 mg/100 g) showed high values of phenolic compounds and an important antioxidant activity compared to other selected fruits with lower values. On the other hand, other study reported that high phenolic content or antioxidant capacity did not relate to antiproliferative effect in cancer cells. Garcia-Solis et al. (2009) tested plant food extracts against the breast cancer cell line MCF-7. Although guava extract had the highest phenolic activity, only papaya extract had a significant antiproliferative effect when measured using the methylthiazolyldiphenyl-tetrazolium bromide assay.

Some aspects are questionable in the antioxidant activity of these compounds. Several authors inquire

whether or not findings from these in vitro chemical antioxidant activity assays were reflected in vivo as chemical antioxidant activity assays, generally, use non-physiological temperature and/or pH, and do not account for bioavailability, uptake, or metabolism of compounds of interest. While others claim the antioxidant capacity measured reflects closer the in vivo action of the antioxidants.

Cancer

Cancer is a global health problem with high morbidity and mortality and poses both economic and psychological challenges. Cancer cure and prevention therefore remain a high priority for the scientific and medical community across the world. These complex disease are caused by endogenous and exogenous factors leading to the

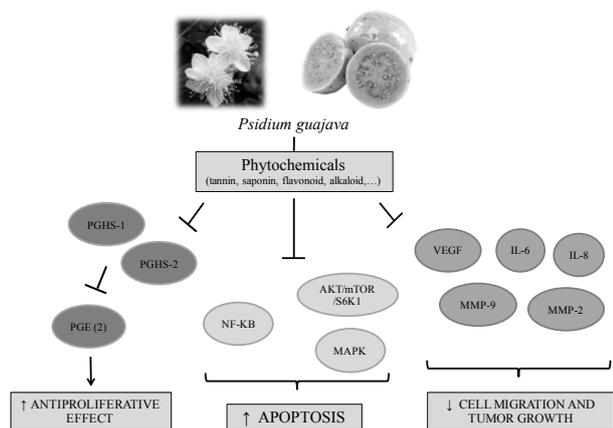


Figure 1. Potential Mechanisms of Anti-cancer Activity of *P. guajava*

sequential accumulation of genetic alterations, a scenario known as multi-step oncogenesis (Lee and Park, 2010).

The past two decades have witnessed a paradigm shift in tumor biology, from the reductionist dogma that tumors are masses of malignant cells that acquire certain cell-autonomous properties, to the evolving view that tumors are aberrant organs in which transformed cells along with other recruited normal cell types conspire to foster tumor growth and metastasis (Liu et al., 2016). Cancer can occur as the result of a disruption of this balance, due to either an increase in cell proliferation or a reduction in cell death or both. Cancer cells are characterized by unregulated growth, as well as insufficient and inappropriate vascular supply. Moreover, a core of cells was subjected to micro environmental stress conditions, and has decreased apoptotic potential through genetic alterations, thereby resulting in resistance to apoptosis (Lee and Park, 2010).

Cancer imposes a heavy societal burden worldwide, in terms of both epidemiology and costs. The introduction of more sophisticated imaging and diagnostic techniques and advanced drugs that specifically target tumor cells is leading to increasingly expensive treatments, which may be affordable only for few patients. Prevention, and particularly primary prevention, is an effective way of addressing the challenging issue of cancer, since between a third and a half of cancers could be prevented on the basis of our current knowledge of risk factors. Moreover, prevention is cost-effective, its effects are not limited to high-risk subjects but extend to the entire population, and it is not dependent on socioeconomic status (Valle et al., 2015).

Chemotherapy is the treatment of disease, especially cancer, using chemical substances. These chemicals are capable of destroying cancer cells, keeping them from growing and spreading, shrinking the size of tumor or relieving the cancer symptoms. However, chemotherapy can destroy or slow down the growth of normal cells, including cells of the hair, mouth, digestive system, as well as those of blood. Therefore, oncologists are still searching for new anticancer drugs with more potent inhibitory and less side effects. It is conceivable that effective plant-derived chemoprevention agents might target molecules that regulate the cell cycle, cellular senescence, and apoptosis (Pakpahan et al., 2013).

The inhibition capacity of a compound or food to cancer cells proliferation is a desirable factor in the progression of cancer. The function of antioxidant nutrients in the etiology of cancer remains controversial, since these nutrients have an important structural function and act as cofactors in several enzymes (Bargellini et al., 2003).

Development of new anti-cancer agents are vital because cancer has been the second major cause of death around the world population. The number will be expected to rise to 9 million in 2015 with a further arise of more than 11 million deaths in 2030 (Sul'ain et al., 2012). The limitations of these current conventional therapies used in the treatment of cancers have in recent years contributed to a significant increase in the targeted screening of plant materials for cytotoxic activities. Such limitations include the severe unwanted effects, drug resistance and relapse that usually accompanies chemotherapy of cancer and the postulation that ethnopharmacologically derived therapies might represent a safer modality of treatment. The search for anticancer agents from natural sources has been successful worldwide. Ethnopharmacological knowledge is a helpful lead in the search for plants with potential cytotoxic activity (Levy and Carley, 2012).

Possible Anticancer Guava Components

In several years, the increasing study on anti-cancer agent based on traditional used of medicinal plant has become quietly extensive in anti-cancer research. This reason can be supported by the recent studies which showed that many plants, including their components can be function effectively as tumor suppressor as well as apoptosis inducers in cancer cells. Generally, the tumor suppressing activity arises from the medicinal plants will interfere with cell cycle, thus enhance the immune activity and suppress tumor angiogenesis (Sul'ain et al., 2012).

Guava contains secondary plant metabolites with certain polyphenols with potential intrinsic antioxidant, anti-inflammatory, and antiviral properties. Several guava components have been postulated as having anticancer effects in vitro, and the most frequently reported ascorbic acid (vitamin C), flavonoids (apigenin), and lycopene (Sato et al., 2010).

Several studies demonstrated results of anti-carcinogenic activities of *P. guajava* leaves. Joseph and Priya (2010) reported in the first time that Guava leaf methanol extract possesses a cytotoxic effect on HeLa cells. The cytotoxic activity may depend on the phytochemicals such as tannin, saponin, flavonoid and alkaloid, for example. They also reported that the tannin may do irreversible form complexes with proline-rich proteins, resulting in the inhibition of cell protein synthesis. Further, the concentrate oil detained cell growth to less 50, 4%, probably with effects on apoptosis regulation (dose-dependent starting from 150µgm/mL). The authors also determined major compounds of essential oil, as cryptonine alkaloid, dihydrobenzophenanthridine (cytotoxic, antitumor alkaloid), prenol (terpene) and flavone.

According to Peng et al. (2011) the aqueous extract of

guava bears an extremely high content of polyphenolic and isoflavonoids and the IC_{50} to suppress the cell viability is 0.57 mg/ml. Furthermore, guava can effectively inhibit the expression of VEGF, IL-6 and IL-8 cytokines, and MMP-2 and MMP-9, important factors that affect the cell migration and a tumor growth. They conclude that *P. guajava* potentially possesses a strong anti-prostate cancer effect.

It has been suggested that certain components in the guava leaves have anticancer activity in terms of inhibiting the proliferation of selected cancer cell lines (Sato et al., 2010). It was found a molecular evidence that cytotoxic activities of guava may act by inhibition of the nuclear factor-kappaB (NF- κ B) pathway (Kaileh et al., 2007). Another study followed examining the effect of fermented guava leaf extract on liposaccharide (LPS)-induced NF- κ B activation. The guava leaf extract is also involved in the inhibition of nitric oxide synthase (iNOS) and COX-2 via the down-regulation of NF- κ B pathway, revealing a partial molecular basis for the anti-inflammatory properties of guava leaf extract (Ryu et al., 2012).

Prostaglandin endoperoxide H synthase (PGHS) is a key enzyme for the synthesis of prostaglandins (PGs), which play important roles in inflammation and carcinogenesis. Guava leaf extract inhibited the PGE(2) synthesis and also suppressed the DNA synthesis rate in the PGHS-1- and PGHS-2-expressing cells. These results demonstrate the antiproliferative effect of guava leaf extract may be partially due to the inhibition of PGHS isoform catalytic activity (Kawakami et al., 2009).

Levy and Carley, (2012) also demonstrated *P. guajava* extract has a significant cytotoxic activity in the Kasumi-1 leukemia cancer cells. The IC_{50} of 200 μ g/ml obtained was comparable to the IC_{50} of 250 μ g/ml obtained by (Chen et al., 2007) in human prostate carcinoma cell line (DU-145) treated with aqueous *P. guajava* extract. It has been suggested that this anti-cancer activity may be due to the presence of polyphenolic compounds such as gallic acid and flavonoids in the extract. Gallic acid and flavonoids, such as quercetin and kaempferol, have also been identified in hexane extracts of *P. guajava* leaves. Therefore, the cytotoxic activity of *P. guajava* extract against Kasumi-1 cells could be attributed to the presence of these compounds.

Different organic extracts of *P. guajava* showed no anti-proliferative activity on HeLa cells, according to Sul'ain et al. (2012). However, petroleum ether leaves extract showed the most effective anti-proliferative activity followed by methanol extract and water extract to MDA-MB-231. Petroleum ether extract also showed similar effects on MG-63 followed by methanol extract and water extract. The petroleum ether leaf extract also showed the most anti-proliferative activity towards MDCK.

Pakpahan et al. (2013) reported an effect of *Psidium guajava* L. leaves in anticancer activity against HSC-2 cell line of human oral cancer. The results suggests that guava has cytotoxic effects based on anti-proliferative and apoptosis assays. Lee and Park (2010) assessed the cytotoxic effects of acetone extracts of guava branch (GBA) against colon cancer cell line (HT-29) and

subsequently have a proposed mechanism responsible for its cell death activity. GBA promoted reduction (30 - 70%) in cell viability as compared to the control, in a dose-dependent manner. As they showed, after 24h of incubation with various concentrations of acetone extracts of guava branch, many of the cells showed cytoplasmic shrinkage and loss of normal nuclear architecture, became detached and found floating in the medium.

Ryu et al. (2012) set out to determine whether the anticancer effects of guava leaves are related with their ability to suppress constitutive AKT/mammalian target of rapamycin (mTOR)/ribosomal p70 S6 kinase (S6K1) and mitogen-activated protein kinase (MAPK) activation pathways in human prostate cancer cells. They found that guava leaf hexane fraction (GHF) was the most potent inducer of cytotoxic and apoptotic effects in PC-3 cells. The molecular mechanism or mechanisms of GHF apoptotic potential were correlated with the suppression of AKT/mTOR/S6K1 and MAPK signaling pathways. This effect of GHF correlated with down-regulation of many proteins that mediate cell proliferation, cell survival, metastasis, and angiogenesis. Analysis of GHF identified 60 compounds, including β -eudesmol, α -copaene, phytol, α -patchoulene, β -caryophyllene oxide (CPO), caryophylla-3(15),7(14)-dien-6-ol, (E)-methyl isoeugenol, α -terpineol, and octadecane. These findings suggest that guava leaves can interfere with multiple signaling cascades linked with tumorigenesis and provide a source of potential therapeutic compounds for both the prevention and treatment of cancer.

The aqueous extract of *Psidium guajava* L. (PE) inhibited prostate cancer cell line (DU-145) in a dose- and time-dependent manner. At 1.0 mg/mL, PE reduced the viability of PCa (the androgen independent PCa cells) and DU-145 to 36.1 and 3.59%, respectively. Besides, they observe the colony forming capability of DU-145 cells was apparently lowered. Suppression of the matrix metalloproteinases (MMP-2 and MMP-9) and the upregulation of active caspase-3 at 0.10 to 1.0 mg/mL in DU-145 were also effected in a dose-dependent manner by PE at 0.25 to 1.0 mg/mL, implicating a potent anti-metastasis power of PE. They also ascribe the anticancer activity of PE to its high polyphenolic (165.61 \pm 10.39 mg/g) and flavonoid (82.85 \pm 0.22 mg/g) contents (Chen et al., 2007).

Bontempo et al. (2012) in their study confirmed selective activity against certain types of tumour. Ex vivo myeloid leukaemia blasts use corroborated that *P. guajava* was able to induce cell death but did not exhibit anti-cancer effects on all malignant cells investigated. *P. guajava* itself and its pulp-derived extract were found to induce apoptosis accompanied by caspase activation and p16, p21, Fas ligand (FASL TNF super-family, member 6), Bcl-2-associated agonist of cell death (BAD) overexpression.

Conclusion

The treatment of cancer has made substantial improvements since the early years of modern anti-tumour drug research. A relevant field of application of natural compounds is cancer chemoprevention since these

compounds may inhibit specific processes involved in carcinogenesis.

This review found that guava could inhibit cancer cell proliferation and induce cancer cell apoptosis in part through oxidant-mediated mechanisms. However, additional studies are necessary to investigate which mechanisms and signal transductions are responsible for the regulation of cell cycle and apoptosis after treatment with guava and are required to clarify the mechanisms and to evaluate the bioavailability and metabolism of guava components before it can be determined that intake can reduce cancer risk. It is important to emphasize that only rigorous preclinical and clinical studies along with a precise understanding of the pharmacology of new compounds may assure the selection of active and safe anticancer and chemopreventive drugs, including guava compounds.

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