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REVIEW



Guava (*Psidium guajava* L.): a glorious plant with cancer preventive and therapeutic potential

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ABSTRACT

Guava (*Psidium guajava* L.) tree (Myrtaceae family) bears fruit rich in vitamins, fiber, and other nutrients. While native to Latin America, guava is grown in many tropical and subtropical regions across the globe where it has long been used in traditional medicine to treat a myriad of ailments. Guava has been shown to exhibit a number of biological and pharmacological activities, such as antioxidant, anti-inflammatory, immunomodulatory, antimicrobial, antidiabetic, and anticancer properties. Several parts of the plant, including the leaves, fruits, seeds, peels, pulp, bark, and oil, produce phytochemicals with medicinal properties. Emerging research has found that guava bioactive phytochemicals exert antitumorigenic effects against various human malignancies through multiple mechanisms. While there are numerous individual studies that document the anticancer effects of guava constituents, an up-to-date, comprehensive, and critical review of available research data has not been performed. Therefore, the purpose of this review is to present a complete analysis of the cancer preventive and anticancer therapeutic potential of guava-derived products and guava constituents, with a focus on the cellular and molecular mechanisms of action. The bioavailability, pharmacokinetics, and toxicity of guava as well as limitations, challenges, and future directions of research have also been discussed.

KEYWORDS

apoptosis; cancer; guava;
molecular mechanisms;
phytochemicals; prevention;
proliferation; *Psidium
guajava*; risk reduction

Introduction

Cancer, the second most common cause of death, is one the leading global health issues we face today (World Health Organization 2018). By the year 2035, the World Health Organization projects that there will be 24 million new cancer cases and 14.5 million cancer-related deaths per year (World Health Organization 2003). In order to combat this growing health problem, it is vital that novel therapeutic strategies are developed. Approximately, 30 to 40% of cancers are preventable by appropriate dietary and nutritional measures, physical activity, and maintenance of a healthy body weight (Glade 1999). Additionally, past research has postulated that consumption of a diet high in vegetables and fruits (more than 400 g/day) could prevent at least 20% of all cancers (Gullett et al. 2010). Over 60% of current anti-cancer drugs are derived from natural sources, including phytochemicals found in plants (Newman and Cragg 2012; Cragg and Pezzuto 2016). Furthermore, of the 94 plant species utilized in contemporary medicine, 80% have a modern pharmaceutical use that is related to their traditional and ethnomedicinal application (Fabricant and Farnsworth 2001). Thus, empirical investigation of the bioactive compounds and therapeutic potential of plants used in traditional medicine is of great importance to the discovery and

development of new disease preventive and therapeutic strategies.

Psidium guajava L., commonly known as guava, is a fruit-bearing tree belonging to the Myrtaceae family. It is a small shrub-like tree (reaching up to 10 meters tall) (Figure 1a) with a distinctive copper-colored bark (Figure 1b) that peels away to reveal an internal green layer (Morton 1987). The tree has shallow roots and a broadly spreading canopy that contains evergreen, oblong leaves (Figure 1c) which are fragrant when crushed (Morton 1987). The white flowers (Figure 1d) that bear its fruit have four to five petals and a tuft of around 250 white stamens with pale yellow anthers (Morton 1987). The guava fruit is round, oval, or pear-shaped (Figure 1e) with a size that ranges from 1 to 48 ounces and when ripe has a strong sweet and musky odor (Morton 1987). The outer peel is green or yellow and the flesh has a variety of colors, including white, yellow, pink, salmon, and red with numerous small hard white seeds (Morton 1987; Mercadante, Steck, and Pfander 1999). The fruit flavor also differs depending on the cultivar and can range from sweet to acidic (Morton 1987). *P. guajava*, or apple guava, is the guava species that is most commonly eaten and traded. Many cultivars of this species have been developed, selecting for traits, such as sweetness, aroma, color, and lack of seeds. Another species of guava, *P.*

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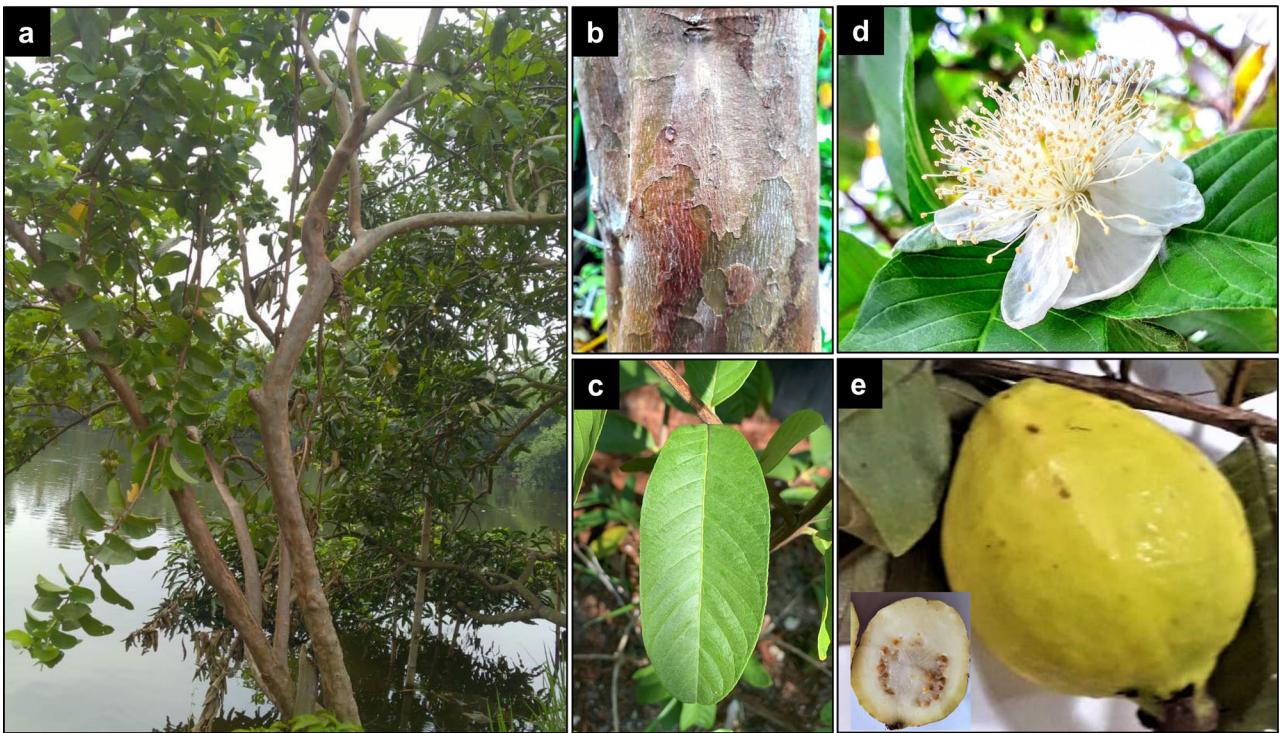


Figure 1. Various photographs of *P. guajava* depicting a tree (a), bark (b), leaf (c), flower (d), ripe whole fruit (e), and a cross section of fruit showing seeds (e, inset).

cattleyanum, produces edible yellow or red fruit, but is not commonly sold or consumed outside its cultivation areas (Courteau 2021). Although native to Brazil, it has become an invasive species in many tropic regions, such as Hawaii, where it poses a major environmental threat by preventing the growth of native species (US Forest Service 2009). The yellow fruit variety is *P. cattleyanum* var. *littorale*, which is more commonly known as lemon guava, yellow cherry guava, or yellow strawberry guava (USDA-ARS 2021). The red fruit variety is *P. cattleyanum* var. *cattleyanum*, also known as purple guava, red cattley guava, red strawberry guava, or red cherry guava (USDA-ARS 2021).

While native to the American tropics, *P. guajava* is well adapted to a diverse range of environmental conditions. It thrives in both dry and humid climates and grows in a wide variety of soil conditions. This hardiness has allowed it to grow and disperse across many tropical and subtropical countries across the world, including the Americas, Europe, Africa, and Asia (CABI 2019). Growing over 40% of the world's guava, India is the largest producer of guava, which is sold commercially for its juice and fruit as well as for other industrial applications, including the use of its wood for construction and leaves to create a black dye (Gutiérrez, Mitchell, and Solis 2008; TRIDGE 2020).

Due to its nutritional benefits, guava is placed among the "superfruits". It contains about 68 calories, 9 g of sugar, and 5.4 g of fiber per 100 g (raw) (USDA 2019). The vitamin C content is 4 times that of oranges, most of which is found within the peel (Correa, Couto, and Teodoro 2016). Accordingly, it is known as the "poor man's apple of the tropics" (Yadava 1997). Due to its high vitamin C content, guava fruit puree was utilized by allied troops during World

War II to fortify their rations (Lim and Khoo 1990). It also has comparatively high levels of iron, calcium, phosphorus, and vitamins A and B. Other compounds it contains include tannins, phenols, triterpenes, flavonoids, essential oils, saponins, carotenoids, and lectins. Guava fruits are utilized in the food industry to prepare various value-added products, such as juice, concentrate, sirup, nectar, beverages, jam, jelly, candies, ice cream, and confectioneries (Jiménez-Escríg et al., 2001; Sato et al. 2010).

In addition to its nutritional value, guava has numerous medicinal benefits. Many cultures have used various parts of *P. guajava*, including fruits, leaves, and bark, in folk medicine for the treatment of a variety of illnesses (Gutiérrez, Mitchell, and Solis 2008). Many countries in Latin America and the Caribbean as well as India, Bangladesh, Pakistan Kenya, Nigeria, Madagascar, Malaysia, Namibia, South Africa, Papua New Guinea, Thailand, and Indonesia have used guava-derived products to treat various communicable and non-communicable ailments, such as gastrointestinal disease, hepatic damage, bacterial and fungal infection, fever, rheumatism, respiratory illness, cough, diabetes, pain, wounds, mouth ulcers, uterine bleeding, blennorrhagia, menstrual disorders, amenorrhea, and as an emmenagogue (Gutiérrez, Mitchell, and Solis 2008; Barbalho et al. 2012; de Boer and Cotingting 2014; Díaz-de-Cerio et al. 2017; Daswani, Ghokar, and Birdi 2017). These therapeutic effects are thought to be due to the antioxidant, anti-inflammatory, antimicrobial, immunomodulatory, antihyperglycemic, and antihyperlipidemic effects of numerous phytochemicals present in *P. guajava* (Deguchi and Miyazaki 2010; Díaz-de-Cerio et al. 2017).

Most previous reviews of *P. guajava* provide a broad overview of ethnopharmacological uses, phytochemical

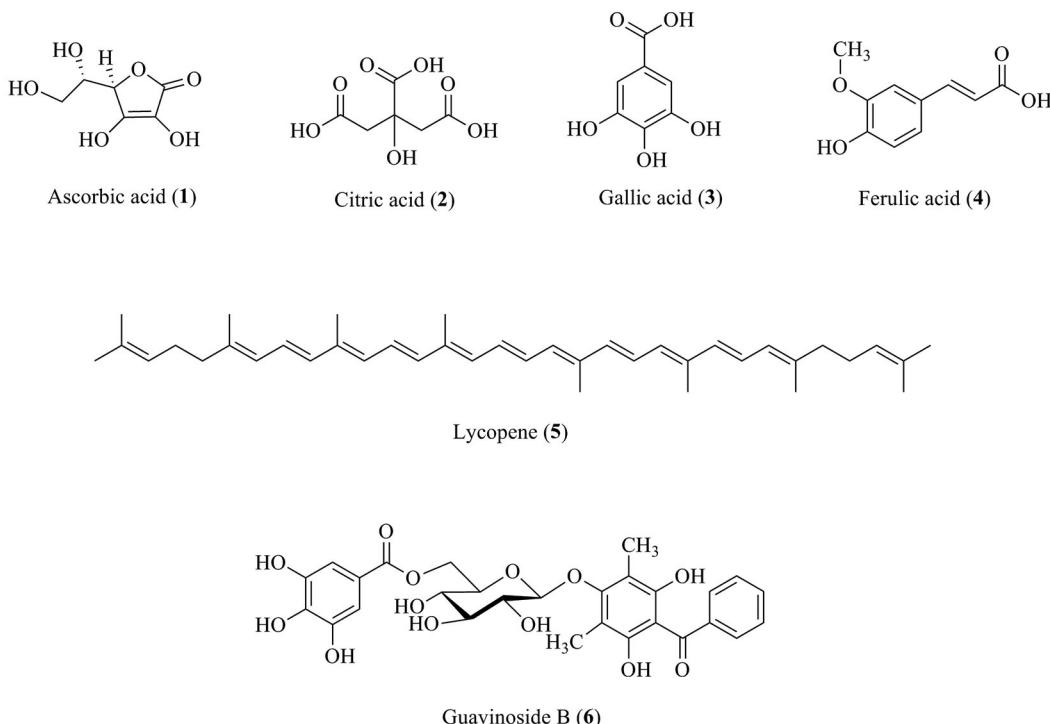


Figure 2. Chemical structures of several major bioactive compounds present in guava fruit.

compositions, pharmacological and biological properties, and therapeutic potential in the treatment of several diseases (Gutiérrez, Mitchell, and Solis 2008; Correa, Couto, and Teodoro 2016; Díaz-de-Cerio et al. 2017; Daswani, Ghokar, and Birdi 2017). Gutiérrez and coauthors (2008) published a review of *P. guajava*'s traditional uses, phytochemical profiles, and pharmacological effects. While this review did include some information about its anticancer potential, this was not the focus of the publication. Similarly, Daswani, Ghokar, and Birdi (2017) published a review of various medicinal uses of guava in rural India, but only a brief reference to its anticancer capabilities was included. Sato et al. (2010) and Correa, Couto, and Teodoro (2016) published reviews that did focus on the anticancer properties of *P. guajava*; however, the number of studies included was limited. Diaz-de-Cerio et al. (2017) published a review that summarized the results of studies investigating the health effects of guava leaves over the last decade. The limitation of this review was that it excluded other parts *P. guajava* that have bioactive properties and cancer was not a major focus. Currently, there are numerous individual reports on the anticancer effects of *P. guajava*, making it a promising potential resource for the development of novel agents for cancer prevention. However, an up-to-date, comprehensive, and critical review of available research data on the various components of the guava tree and its role in cancer prevention and intervention has not been published to the best of our knowledge. Therefore, the purpose of this review is to perform a critical analysis of the available literature and to provide a complete assessment of the cancer preventive and therapeutic potential of *P. guajava*, emphasizing its cellular and molecular mechanisms of action.

Phytochemical profiles of guava

The isolation and purification of minor and major phytochemicals from the different parts of guava involves a three to four step process, including collection, extraction, separation, and finally purification by various chromatography methods, such as thin-layer chromatography, vacuum liquid chromatography, flash column chromatography, traditional column chromatography, and high-performance liquid chromatography (HPLC) (Mercadante, Steck, and Pfander 1999; Arima and Danno 2002; Begum et al. 2002a; Begum, Hassan, and Siddiqui 2002b; Begum et al. 2004; Yang, Hsieh, and Liu 2008; Feng et al. 2015; Fu et al. 2010; Bagri et al. 2016). The gas chromatography (GC) coupled with mass spectrometry (GC-MS) is a very good technique for the identification of phytochemicals in the plant extracts (Khadhri et al. 2014; Chaturvedi et al., 2021; Weli et al. 2019). The GC-MS method has been used for the detection of volatile components in different guava extracts (Athikomkulchai et al. 2008; Jordan et al., 2003). The GC-MS analysis of essential oil of the leaves and stems of guava have reported the presence of various classes of chemical constituents (Khadhri et al. 2014; Chaturvedi et al., 2021; Weli et al. 2019). The high-performance liquid chromatography coupled with time-of-flight electrospray ionization mass spectrometry (HPLC-TOF-ESI/MS) method is very popular for the identification of flavonoid compositions in guava leaves (Wang et al. 2017). The semipreparative HPLC coupled with ultraviolet and diode array detection (UV/DAD) along with electrospray ionization-mass spectrometry (ESI-MS) is also a popular method to identify the bioactive flavonoid molecules of guava leaves (Eidenberger, Selg, and

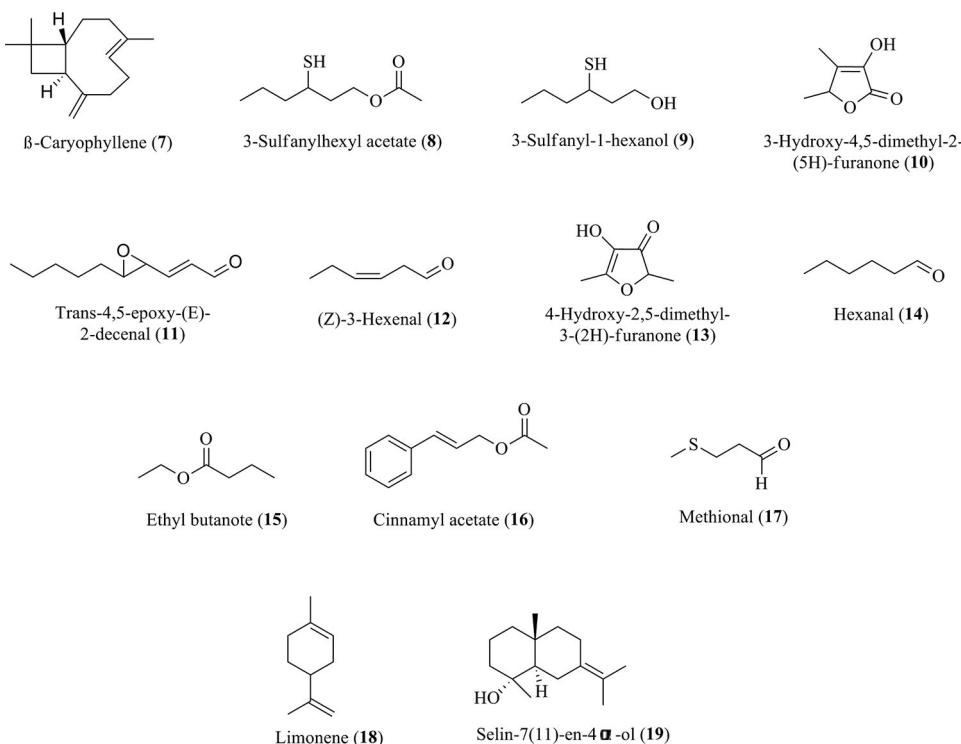


Figure 3. Chemical structures of various major essential oil and aroma-active constituents present in guava fruit.

Krennhuber 2013). The gas chromatography with flame ionization detection (GC-FID), GC-MS and gas chromatography-olfactometry (GC-O) are widely used for the identification and separation of aroma-active compounds in guava fruits (Steinhaus et al. 2008; Pino and Bent 2013). The HPLC-DAD-ESI coupled with quadrupole time of flight mass spectrometry (QTOF-MS) is commonly used for the identification of phenolic compounds in guava leaves (Díaz-de-Cerio et al. 2016). The solid phase microextraction, simultaneous distillation-extraction coupled with GC-FID, GC-MS, and aroma extract dilution analysis have been used for the quantification of odor-active volatile components of guava (Pino and Bent 2013). Finally, the stable isotope dilution assays have also been used for the quantification of aroma-active volatile components in guava (Steinhaus et al. 2009).

The guava fruit contains low to moderate concentration of protein, fat, carbohydrate, calcium, iron, sodium, zinc, selenium, thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, vitamin A, vitamin C, vitamin E, and vitamin K (Sato et al. 2010; Correa, Couto, and Teodoro 2016). It is a good source of fiber and potassium and contains four times the vitamin C of oranges (Sato et al. 2010). Most of the vitamin C of guava is found in the fruit's skin (Sato et al. 2010; Correa, Couto, and Teodoro 2016). The flour of the guava fruits contains approximately 30% sugar, 20% total protein, 0.5% fat and a high level of crude fiber (Moreno et al. 2014). The percentage of water in guava fruit is very high (~85%) (Gutiérrez, Mitchell, and Solis 2008). The fruit yields 68 calories per 100 g (Sato et al. 2010).

Guava fruit is a rich source of various phytochemicals, such as polyphenols, flavonoids, isoflavonoids, tannins, phenolic acids, terpenoids, saponins, lectins, essential oils, and fatty acids (Shu, Chou, and Wang 2009; Sato et al. 2010; Moreno

et al. 2014; Ravi and Divyashree 2014; Correa, Couto, and Teodoro 2016). The major components of guava fruits are ascorbic acid (1) and citric acid (2) (Grover and Bala 1993) (Figure 2). Gallic acid (3) and ferulic acid (4) represent the major phenolic acid constituents in fruit extracts (Figure 2) (Chen and Yen 2007). Lycopene (5), a carotenoid compound, is the major component in raw guava fruits (Figure 2) (Sato et al. 2010). Phytochemical analysis revealed that the guava fruit is a rich source of triterpenoids and polyphenols and it is assumed that benzophenone glycosides are one of the main types of polyphenols present in guava (Gutiérrez, Mitchell, and Solis 2008; Li et al. 2020). Li et al. (2020) also reported the presence of five benzophenone glycosides in dried guava fruit extract, the most abundant being guavinoside B (6) (Figure 2). It is reported that the β -caryophyllene (7), a sesquiterpene, is the major constituent in fruits of guava (Figure 3) (El-Ahmady, Ashour, and Wink 2013). Sixteen carotenoids were reported to be present in the flesh of Brazilian ripe red guava (Mercadante, Steck, and Pfander 1999). A list of various major classes of phytochemicals present in different parts of guava is provided in Table 1.

The GC-MS analysis of aromatic profile of the commercial guava essence and fresh fruit puree revealed a total of 51 low molecular weight constituents with alcohols, esters, and aldehydes as the major components (Jordan et al., 2003). The major components in the fresh fruit puree of guava are 3-hydroxy-2-butanone, 3-methyl-1-butanol, ethyl butyrate, (Z)-3-hexen-1-ol, ethyl hexanoate, (Z)-3-hexenyl acetate, D-limonene, (Z)-ocimene, 2-phenylethyl alcohol, and 3-phenylpropanol (Jordan et al., 2003). A total of 141 volatile compounds were detected in guava fruit, and the major constituents are esters followed by terpenes, aldehydes, alcohols, acids, ketones, and furans (Pino and Bent

Table 1. Various major classes of phytochemicals present in different parts of guava (*P. guajava* L.).

Phytochemicals	Sources	References
<i>Phenolic compounds</i>		
1-O-Galloyl- β -D-glucose	Leaves	Fu, Luo, and Zhang 2009
2,6-Dihydroxy-3,5-dimethyl-4-O-(6''-O-galloyl- β -D-glucopyranosyl)-benzophenone	Leaves, fruits (ripe edible)	Shu, Chou, and Wang 2010b; Shu, Chou, and Wang 2012
2,6-Dihydroxy-3,5-dimethyl-4-O- β -D-glucopyranosyl-benzophenone	Fruits (ripe edible)	Shu, Chou, and Wang 2010b
2,6-Dihydroxy-3-formaldehyde-5-methyl-4-O-(6''-O-galloyl- β -D-glucopyranosyl)-diphenylmethane	Leaves	Shu, Chou, and Wang 2012
2,6-Dihydroxy-3-methyl-4-O-(6''-O-galloyl- β -D-glucopyranosyl)-benzophenone	Dried fruits	Shu, Chou, and Wang 2010b; Li et al. 2020.
2,6-Dihydroxy-3-methyl-4-O- β -D-glucopyranosyl-benzophenone	Dried fruits	Li et al. 2020.
3'-O-Methyl-3,4-methylenedioxylaglic acid 4'-O- β -D-glucopyranoside	Leaves	Shao et al., 2014
Abscisic acid	Fruits	Flores et al. 2015
Apigenin-7-O-glucoside	Leaves	Metwally et al. 2011
Catechin	Leaves	Díaz-de-Cerio et al. 2016
Chrysin 6-C-glucoside	Leaves	Shao et al., 2014
Cyanidin-3-O-glucoside	Fruits	Flores et al. 2015
Cypellocarpin C	Leaves	Li et al. 2019
Delphinidin 3-O-glucoside	Fruits	Flores et al. 2015
Ellagic acid	Leaves	Díaz-de-Cerio et al. 2016
Eucamalduside A	Leaves	Li et al. 2019
Galllic acid	Leaves	Begum et al. 2014; Díaz-de-Cerio et al. 2016
Gallocatechin	Leaves	Díaz-de-Cerio et al. 2016
Gallocatechin-(4 α -8)-catechin	Fruits	Flores et al. 2015
Gallocatechin-(4 α -8)-gallocatechol	Fruits	Flores et al. 2015
Garcimangosone D	Leaves	Ukwueze, Osadebe, and Okoye 2015
Gossypetin	Leaves	Shao et al., 2014
Guavin A	Leaves	Díaz-de-Cerio et al. 2016
Guavin B	Leaves	Díaz-de-Cerio et al. 2016
Guavin C	Leaves	Metwally et al. 2011
Guavin D	Leaves	Metwally et al. 2011
Guavinoside A	Leaves	Shao et al., 2014; Feng et al. 2015; Díaz-de-Cerio et al. 2016
Guavinoside B	Leaves	Shao et al., 2014; Feng et al. 2015; Díaz-de-Cerio et al. 2016
Guavinoside C	Leaves	Díaz-de-Cerio et al. 2016
Guavinoside D	Dried fruits, leaves	Li et al. 2020; Feng et al. 2015
Guavinoside E	Dried fruits, leaves	Li et al. 2020; Feng et al. 2015
Hyperin (Quercetin-3-O- β -D-galactoside)	Leaves, fruits	Fu, Luo, and Zhang 2009; Metwally et al. 2010; Shu, Chou, and Wang 2012; Feng et al. 2015; Díaz-de-Cerio et al. 2016; Flores et al. 2015
Iso-rhamnetin-3-O-galactoside	Fruits	Flores et al. 2015
Iso-rhamnetin-3-O-glucoside	Fruits	Flores et al. 2015
Kaempferol	Leaves	Shu, Chou, and Wang 2012; Shao et al., 2014; Wang et al. 2017
Luteolin-7-O-glucoside	Leaves	Metwally et al. 2011
Methyl ferulate	Leaves	Begum et al. 2014
Methyl p-E-coumarate	Leaves	Begum et al. 2014
Morin	Leaves	Díaz-de-Cerio et al. 2016
Morin-3-O-arabinoside	Leaves	Rattanachaikunsopon and Phumkhachorn 2010
Morin-3-O-lyxoside	Leaves	Rattanachaikunsopon and Phumkhachorn 2010
Morin-3-O- α -L-arabopyranoside	Leaves	Fu, Luo, and Zhang 2009
Myrciaphenone B	Leaves	Díaz-de-Cerio et al. 2016
Myricetin-3-O-arabinoside	Fruits	Flores et al. 2015
Myricetin-3-O-xyloside	Fruits	Flores et al. 2015
Myricetin-3-O- β -D-glucoside	Leaves, fruits	Fu, Luo, and Zhang 2009; Flores et al. 2015
Naringenin	Leaves	Díaz-de-Cerio et al. 2016
p-Hydroxy-benzoic acid	Leaves	Shao et al., 2014
Quercetin	Leaves	Fu, Luo, and Zhang 2009; Metwally et al. 2010; Rattanachaikunsopon and Phumkhachorn 2010; Shu, Chou, and Wang 2012; Shao et al., 2014; Díaz-de-Cerio et al. 2016; Wang et al. 2017;
Quercetin 3-O-gentibioside	Leaves	Metwally et al. 2011
Quercetin 3-O- β -D arabinopyranoside	Leaves	Metwally et al. 2011
Quercetin 4'-glucuronoid	Leaves	Metwally et al. 2011
Quercetin glucuronide	Leaves	Díaz-de-Cerio et al. 2016
Quercetin-3-O-arabinoside (Avicularin)	Leaves	Rattanachaikunsopon and Phumkhachorn 2010; Shu, Chou, and Wang 2012; Shao et al., 2014; Díaz-de-Cerio et al. 2016; Wang et al. 2017
Quercetin-3-O- α -D-arabinopyranoside	Leaves	Zhao et al. 2018
Quercetin-3-O- α -D-glucopyranoside	Leaves	Zhao et al. 2018
Quercetin-3-O- α -D-ribopyranoside	Leaves	Zhao et al. 2018

(continued)

Table 1. Continued.

Phytochemicals	Sources	References
Quercetin-3-O- α -D-xylpyranoside	Leaves	Zhao et al. 2018
Quercetin-3-O- α -L-arabinopyranoside (Guaijaverin)	Leaves, fruits	Shu, Chou, and Wang 2012; Shao et al., 2014; Flores et al. 2015; Ukwueze, Osadebe, and Okoye 2015; Díaz-de-Cerio et al. 2016; Wang et al. 2017
Quercetin-3-O- β -D-(2"-O-galloyl glucoside)-4'-O-vinylpropionate	Seeds	Michael, Salib, and Ishak 2002
Quercetin-3-O- β -D-glucopyranoside (Isoquercetin/Isoqueritrin)	Leaves, fruits	Fu, Luo, and Zhang 2009; Shu, Chou, and Wang 2012; Flores et al. 2015; Díaz-de-Cerio et al. 2016; Wang et al. 2017
Quercetin-3-O- β -D-xylopyranoside	Leaves	Wang et al. 2017
Quercitrin (Quercetin-3-O- β -L-rhamnoside)	Leaves	Shu, Chou, and Wang 2012; Díaz-de-Cerio et al. 2016; Wang et al. 2017
Reynoutrin	Leaves	Shu, Chou, and Wang 2012; Díaz-de-Cerio et al. 2016
Rutin	Leaves	Wang et al. 2017
Tamarixetin	Leaves	Shao et al., 2014
Turpinionoside	Fruits	Flores et al. 2015
Uralenneoside	Leaves	Díaz-de-Cerio et al. 2016
<i>Tannins</i>		
Acutissimin A	Barks	Tanaka et al. 1992
Acutissimin B	Barks	Tanaka et al. 1992
Amritoside (Ellagic acid 4-gentioside)	Leaves	Metwally et al. 2011
Eugenigrandin A	Barks	Tanaka et al. 1992
(+)-Gallocatechin	Barks	Tanaka et al. 1992
Isostrictinin	Leaves	Metwally et al. 2011
Mongolicain A	Barks	Tanaka et al. 1992
Mongolicain B	Barks	Tanaka et al. 1992
Pedunculagin	Leaves	Metwally et al. 2011
Pterocarinin A	Leaves	Díaz-de-Cerio et al. 2016
Stachyuranin A	Leaves	Díaz-de-Cerio et al. 2016
Stenophyllanin A	Barks, leaves	Tanaka et al. 1992; Díaz-de-Cerio et al. 2016
Stenophyllinin A	Barks	Tanaka et al. 1992
Strictinin	Leaves	Metwally et al. 2011
Vescalagin	Barks, leaves	Tanaka et al. 1992; Díaz-de-Cerio et al. 2016
<i>Triterpenoids</i>		
19 α -Hydroxylurs-12-en-28-oic acid-3-O- α -L-arabinopyranoside	Fruits	Shu, Chou, and Wang 2009
1 β ,3 β -Dihydroxyurs-12-en-28-oic acid	Fruits	Shu, Chou, and Wang 2009
20 β -Acetoxy-2 α ,3 β -dihydroxyurs-12-en-28-oic acid (Guavanoic acid)	Leaves	Begum et al. 2002a
2 α ,3 β ,19 α ,23 β -Tetrahydroxyurs-12-en-28-oic acid	Fruits	Shu, Chou, and Wang 2009
2 α ,3 β -Dihydroxy-24-p- <i>p</i> -coumaroyloxyurs-12-en-28-oic acid (Guavacumaric acid)	Leaves	Begum et al. 2002a
2 α ,3 β -Dihydroxyurs-12-en-28-oic acid	Fruits	Shu, Chou, and Wang 2009
2 α -Hydroxyoleanolic acid	Leaves	Fu, Luo, and Zhang 2009
2 α -Hydroxyursolic acid	Leaves	Begum et al. 2002a; Fu, Luo, and Zhang 2009
3 α ,19 α ,23,24-Tetrahydroxyurs-12-en-28-oic acid	Fruits	Shu, Chou, and Wang 2009
3 β ,13 β -Dihydroxyurs-11-en-28-oic acid	Leaves	Shao et al. 2012
3 β ,19 α ,23 β -Tri-hydroxyurs-12-en-28-oic acid	Fruits	Shu, Chou, and Wang 2009
3 β ,19 α -Dihydroxyurs-12-en-28-oic acid	Fruits	Shu, Chou, and Wang 2009
3 β ,23-Dihydroxy urs-12-en-28-oic acid	Fruits	Shu, Chou, and Wang 2009
3 β -Acetylursolicacid	Leaves	Shao et al. 2012
3 β -Hydroxyurs-11-en-28,13 β -olide	Leaves	Shao et al. 2012
3 β -O-cis-Coumaroyl-2 α -Hydroxy-urs-12-en-28-oic acid	Leaves	Shao et al. 2012
3 β -O-cis-ferulyl-2 α -Hydroxy-urs-12-en-28-oic acid	Leaves	Shao et al. 2012
3 β -O-cis-p-Coumaroyl Maslinicacid	Leaves	Shao et al. 2012
3 β -O-trans-ferulyl-2 α -hydroxy-urs-12-en-28-oic acid	Leaves	Shao et al. 2012
3 β -O-trans-p-coumaroyl maslinic acid	Leaves	Shao et al. 2012
6 β -Hydroxymaslinic acid	Leaves	Shao et al. 2012
Asiatic acid	Leaves, fruits	Begum et al. 2002a; Metwally et al. 2011; Shao et al. 2012; Flores et al. 2015
Arjunolic acid	Leaves	Shao et al. 2012
Betulinic acid	Leaves	Ghosh et al. 2010
Eucalyptolic acid	Leaves	Shao et al. 2012
Guajanoic acid (3 β -p-E-coumaroyloxy-2 α -methoxyurs-12-en-28-oic acid)	Leaves	Begum et al. 2004
Guajavolide (2 α ,3 β ,6 β ,23-tetrahydroxyurs-12-en-28,20 β -olide)	Leaves	Begum, Hassan, and Siddiqui 2002b
Guavenoic acid (2 α ,3 β ,6 β ,23-tetrahydroxyurs-12,20(30)-dien-28-oic acid)	Leaves , fruits	Begum, Hassan, and Siddiqui 2002b ; Flores et al. 2015
Ilelatifol D	Leaves	Begum et al. 2002a
Isoneriucoumaric acid	Leaves	Begum et al. 2002a

(continued)

Table 1. Continued.

Phytochemicals	Sources	References
Jacoumaric acid	Leaves	Begum et al. 2002a; Shao et al. 2012
Lupeol	Leaves	Ghosh et al. 2010
Madecassic acid	Fruits	Flores et al. 2015
Maslinic acid	Leaves	Metwally et al. 2011
Obtusol	Leaves	Begum et al. 2007
Oleanolic acid	Leaves	Begum, Hassan, and Siddiqui 2002b; Begum et al. 2004; Begum et al. 2007
Pedunculoside	Fruits	Flores et al. 2015
Pinfaensin	Fruits	Flores et al. 2015
Psidiumoic acid (2α -glycolyl- 3β -hydroxyolean-12-en-28-oic acid)	Leaves	Begum et al. 2007
Psiguanin A ($2\alpha,3\beta$ -dihydroxy-taraxer-20-en-28-oic acid)	Leaves	Shao et al. 2012
PsiguaninB ($2\alpha,3\beta,12\alpha,13\beta$ -tetrahydroxy-urs-28-oic acid)	Leaves	Shao et al. 2012
PsiguaninC ($2\alpha,3\beta,12\beta,13\beta$ -tetrahydroxy-urs-28-oic acid)	Leaves	Shao et al. 2012
PsiguaninD ($2\alpha,3\beta,12\beta,13\alpha$ -tetrahydroxy-urs-28-oic acid)	Leaves	Shao et al. 2012
Ursolic acid	Leaves, fruits	Begum et al. 2004; Begum et al. 2007; Shu, Chou, and Wang 2009; Fu, Luo, and Zhang 2009
Uvaol	Leaves	Begum et al. 2004
<i>Monoterpeneoids</i>		
1,8-Cineole	Essential oil of leaves	Cole and Setzer 2007
cis-Ocimene	Fruits (mature)	Soares et al. 2007
Humulene epoxide II	Essential oil of leaves	Chaturvedi et al., 2021
<i>Meroterpenoids</i>		
Diguajadial	Leaves	Yang, Hsieh, and Liu 2008
Ecallobusone E	Leaves	Li et al. 2019
Euglobal B1-1	Leaves	Li et al. 2019
Euglobal Ib	Leaves	Li et al. 2019
Euglobal Ic	Leaves	Li et al. 2019
Euglobal lib	Leaves	Li et al. 2019
Euglobal III	Leaves	Li et al. 2019
Euglobal Ivb	Leaves	Li et al. 2019
Euglobal V	Leaves	Li et al. 2019
Euglobal-lva	Leaves	Li et al. 2019
Guajadial	Leaves	Yang, Hsieh, and Liu 2007; Shao et al. 2010; Li et al. 2019
Guajadial C	Leaves	Li et al. 2019
Guajadial D	Leaves	Li et al. 2019
Guajadial E	Leaves	Li et al. 2019
Macrocarpal A	Leaves	Li et al. 2019
Psiguajadial H	Leaves	Li et al. 2019
Psiguajadial I	Leaves	Li et al. 2019
Psiguajadial J	Leaves	Li et al. 2019
<i>Sesquiterpenoids</i>		
(+)-Caryolane-1,9 β -diol	Leaves	Shao et al., 2014
(+)-Globulol	Leaves	Shao et al., 2014
2 β -Acetoxy clovan-9 α -ol	Leaves	Shao et al., 2014
cis-p-Bisabollene	Fruits (mature)	Soares et al. 2007
Clov-2-ene-9 α -ol	Leaves	Shao et al., 2014
Clovane-2 β ,9 α -diol	Leaves	Shao et al., 2014
ent-T-muurolol	Leaves	Shao et al., 2014
trans-p-Bisabollene	Fruits (mature)	Soares et al. 2007
β -Acoradiene	Fruits (mature)	Soares et al. 2007
β -Urcumene	Fruits (mature)	Soares et al. 2007
δ -Cadinene	Essential oil of leaves	Chaturvedi et al., 2021
Nerolidol	Essential oil of leaves	Cole and Setzer 2007
α -Selinene	Essential oil of leaves	Chaturvedi et al., 2021
Viridiflorene	Essential oil of leaves	Chaturvedi et al., 2021
α -Muurolol	Essential oil of leaves	Chaturvedi et al., 2021
<i>Sterols</i>		
β -Sitosterol	Leaves	Begum et al. 2004, 2007
β -Sitosterol xylopyranoside	Leaves	Bagri et al. 2016
β -Sitosterol-3-O- β -D-glucopyranoside	Leaves	Begum et al. 2002a
<i>Carotenoids</i>		
(13Z)-Lycopene	Flesh (ripe)	Mercadante, Steck, and Pfander 1999
(13Z)- β -Carotene	Flesh (ripe)	Mercadante, Steck, and Pfander 1999
(15Z)-Lycopene	Flesh (ripe)	Mercadante, Steck, and Pfander 1999
(15Z)- β -Carotene	Flesh (ripe)	Mercadante, Steck, and Pfander 1999
(9Z)-Lycopene	Flesh (ripe)	Mercadante, Steck, and Pfander 1999
(9Z)- β -Carotene	Flesh (ripe)	Mercadante, Steck, and Pfander 1999
(all-E)-Lycopene	Flesh (ripe)	Mercadante, Steck, and Pfander 1999
(all-E)- β -Carotene	Flesh (ripe)	Mercadante, Steck, and Pfander 1999
(all-E)- γ -Carotene	Flesh (ripe)	Mercadante, Steck, and Pfander 1999
(all-E,3R)-Rubixanthin	Flesh (ripe)	Mercadante, Steck, and Pfander 1999
(all-E,3R)- β -Cryptoxanthin	Flesh (ripe)	Mercadante, Steck, and Pfander 1999

(continued)

Table 1. Continued.

Phytochemicals	Sources	References
(all-E,3R,3'R,6'R)-Lutein	Flesh (ripe)	Mercadante, Steck, and Pfander 1999
(all-E,3S,5R,6R,3'S,5'R,8'R)-Neochrome	Flesh (ripe)	Mercadante, Steck, and Pfander 1999
(all-E,3S,5R,6R,3'S,5'R,8'S)-Neochrome	Flesh (ripe)	Mercadante, Steck, and Pfander 1999
(all-E,3S,5R,8S)-Cryptoflavin	Flesh (ripe)	Mercadante, Steck, and Pfander 1999
Phytofluene (7,8,11,12,7',8'-Hexahydro- ψ , ψ -carotene)	Flesh (ripe)	Mercadante, Steck, and Pfander 1999
<i>Aliphatic compounds</i>		
11-Hydroxy-tricont-35-pentatriacontanoate	Leaves	Mehta et al. 2012
14,15-Dimethyl (cyclopropyl)-9-octadecyl-3-(4-hydroxyphenyl) propanoate	Leaves	Mehta et al. 2012
34-Octahexacontanol	Leaves	Mehta et al. 2012
Arachidic acid	Leaves	Bagri et al. 2016
Heptatriacont-8-ol	Leaves	Mehta et al. 2012
Hexaeicosan-16-ol	Leaves	Mehta et al. 2012
Nonacosan-23-ene-3-ol	Leaves	Mehta et al. 2012
Pentapentacont-17,31-diol	Leaves	Mehta et al. 2012
Pentatetracosan-10,25-diol	Leaves	Mehta et al. 2012
Tricosan-17-ene-5-ol	Leaves	Mehta et al. 2012
Untricontan-11,19-diol	Leaves	Mehta et al. 2012
<i>Aroma-active volatile compounds</i>		
(Z)-3-Hexenal	Fruit (ripening stage)	Sinuco et al. 2010
3-Hydroxy-4,5-dimethyl-2(5H)-furanone	Fruit (ripening stage)	Sinuco et al. 2010
3-Phenylpropyl-acetate	Fruits (mature)	Soares et al. 2007
3-Sulphanyl-1-hexanol	Fruit (ripening stage)	Sinuco et al. 2010
3-Sulphanylhexyl acetate	Fruit (ripening stage)	Sinuco et al. 2010
4-Hydroxy-2,5-dimethyl-3(2H)-furanone	Fruit (ripening stage)	Sinuco et al. 2010
4-Methoxy-2,5-dimethyl-3(2H)-furanone	Fruit (ripening stage)	Sinuco et al. 2010
Acetaldehyde	Fruits	Steinhaus et al. 2009
Cinnamyl acetate	Fruit (ripening stage)	Sinuco et al. 2010
Cinnamyl alcohol	Fruit (ripening stage)	Sinuco et al. 2010
Ethyl benzoate	Fruit (ripening stage)	Sinuco et al. 2010
Ethyl butanoate	Fruit (ripening stage)	Sinuco et al. 2010
Ethyl hexanoate	Fruits (mature)	Soares et al. 2007
Hexanal	Fruit (ripening stage)	Sinuco et al. 2010
Methional	Fruit (ripening stage)	Sinuco et al. 2010
Methyl (2R,3S)-2-hydroxy-3-methylpentanoate	Fruit (ripening stage)	Sinuco et al. 2010
Methyl (2S,3S)-2-hydroxy-3-methylpentanoate	Fruit (ripening stage)	Sinuco et al. 2010
Methyl benzoate	Fruit (ripening stage)	Soares et al. 2007; Sinuco et al. 2010
Methyl octanoate	Fruits (mature)	Soares et al. 2007
trans-4,5-Epoxy-(E)-2-decenal	Fruit (ripening stage)	Sinuco et al. 2010

2013). The major volatile components in guava fruits are ethyl acetate, (E)-2-hexenal, hexanal, 3-phenylpropyl acetate, (E)-cinnamyl acetate, ethyl hexanoate, β -caryophyllene, ethyl butanoate, ethyl octanoate, limonene, and ethyl (E)-cinnamate (Pino and Bent, 2013). Seventeen aroma-active compounds were considered in guava fruit, out of which the most typical aroma active compounds include (E)- β -ionone, ethyl hexanoate, ethyl butanoate, hexanal, (Z)-3-hexenal, hexyl acetate, (E)-2-hexenal, and limonene (Pino and Bent, 2013). The important aroma-active compounds in pink-fleshed Colombian guava include 4-methoxy-2,5-dimethyl-3(2H)-furanone, 4-hydroxy-2,5-dimethyl-3(2H)-furanone, 3-sulfanylhexyl acetate, and 3-sulfanyl-1-hexanol followed by 3-hydroxy-4,5-dimethyl-2(5H)-furanone, (Z)-3-hexenal, trans-4,5-epoxy-(E)-2-decenal, cinnamyl alcohol, ethyl butanoate, hexanal, methional, and cinnamyl acetate (Steinhaus et al. 2008). The principal aroma-active compounds of pink guavas include 3-sulfanylhexyl acetate (8), 3-sulfanyl-1-hexanol (9), 3-hydroxy-4,5-dimethyl-2(5H)-furanone (10), trans-4,5-epoxy-(E)-2-decenal (11), (Z)-3-hexenal (12), 4-hydroxy-2,5-dimethyl-3(2H)-furanone (13), hexanal (14), ethyl butanoate (15), cinnamyl acetate (16), and methional (17) (Figure 3) (Steinhaus et al. 2008; 2009).

The major chemical constituents of volatile oil of guava fruits are hexanal (65.9%), β -caryophyllene (24.1%), nerolidol

(17.3%), γ -butyrolactone (7.6%), (E)-2-hexenal (7.4%), 3-phenylpropyl acetate (5.3%), caryophyllene oxide [also known as β -caryophyllene oxide, CPO] (5.1%), (E,E)-2,4-hexadienal (2.2%), (Z)-3-hexenal (2.0%), (Z)-2-hexenal (1.0%), (Z)-3-hexenyl acetate (1.3%), and phenol (1.6%) (Paniandy, Ming, and Pieribattesti 2000). Other main compounds in the fruit oil of guava are limonene (18) and selin-7(11)-en-4 α -ol (19) (Figure 3), which belong to monoterpenoid group of compounds (El-Ahmady, Ashour, and Wink 2013). The concentrations of odor-active compounds in white- and pink-fleshed guavas, such as 3-sulphanylhexyl acetate and 3-sulphanyl-1-hexanol, decreased at the time of ripening, whereas the concentrations of aliphatic esters and furanones increased during this process (Sinuco et al. 2010).

The level of titratable acidity and sugars in immature and intermediate stage of maturation of guava fruits decreased, whereas the pH level and amount of vitamin C increased during the progress of maturation. The predominant volatile compounds in immature fruits and intermediate stage of maturation are (E)-2-hexenal and (Z)-3-hexenal, whereas in mature fruits the predominant volatile compounds are Z-3-hexenyl acetate, E-3-hexenyl acetate, caryophyllene, α -humulene, and β -bisabolene (Soares et al. 2007). The hot aqueous extracts of guava fruits reported water-soluble polysaccharides containing 2-O-methyl-L-arabinose, 2-O-acetyl-D-

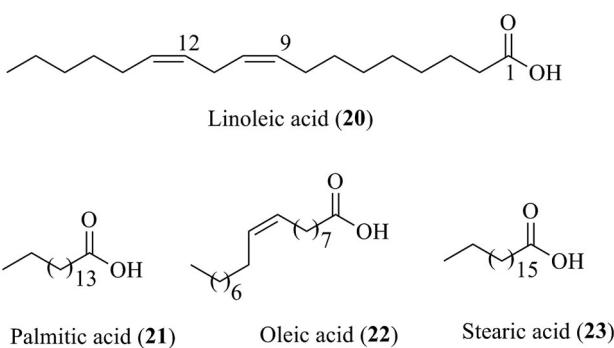


Figure 4. Chemical structures of the major fatty acid constituents present in the seeds from ripe guava.

galactose, and D-methyl galacturonate in a molar ratio of approximately 1:1:1 (Mandal et al. 2009). The guava pulp also contains various components, including ascorbic acid, β -carotene, and lycopene (Ravi and Divyashree 2014).

The guava seed contains glycosides, carotenoids, and phenolic compounds (Ravi and Divyashree 2014). The major fatty acid in ripe seeds of guava is linoleic acid (20) followed by palmitic acid (21), oleic acid (22), and stearic acid (23) (Figure 4) (Oppte 1978).

The leaves of guava are rich sources of phenolics, flavonoids, tannins, triterpenoids, and sesquiterpenoid-based meroterpenoids (Begum et al. 2002a; Shao et al. 2012; Díaz-de-Cerio et al. 2016). The important phenolic compounds in guava leaves are gallic acid, catechin, epicatechin, rutin, naringenin, and kaempferol (Ravi and Divyashree 2014). Gallic acid and ferulic acid also represent the major phenolic acid constituents in guava leaf extracts (Chen and Yen 2007). Various important phenolic constituents with the galloyl moiety, including 1-O-(1,2-propanediol)-6-O-galloyl- β -D-glucopyranoside, gallic acid, ellagic acid, ellagic acid-4-O- β -D-glucopyranoside, and quercetin-3-O-(6"-galloyl)- β -D-galactopyranoside, have been isolated from the aqueous ethanolic extract of guava leaves (Shu, Chou, and Wang 2010a). The HPLC analysis of guava leaf extracts detected the presence of seventy-two phenolic compounds (Díaz-de-Cerio et al. 2016) and the same analysis of fermented guava leaves extract revealed the presence of major polyphenolic compounds, including gallic acid (3) (Figure 2), chlorogenic acid (24), rutin (25), isoquercitrin (26), avicularin (quercetin-3-O- α -L-arabinofuranoside) (27), quercitrin (28), quercetin-3-O- β -D-xylopyranoside (29), kaempferol (30), and quercetin (31) (Figure 5) (Wang et al. 2016). The HPLC coupled with electrospray ionization and quadrupole time-of-flight mass spectrometry analysis of guava leaves revealed the presence of 72 phenolic compounds, which among them flavanols were the main class of phenolic compounds followed by flavan-3-ols, gallic and ellagic acid derivatives, and flavanones (Díaz-de-Cerio et al. 2016).

Five phenolic compounds, namely guavinoside C (32), quercetin (31), quercetin-3-O- α -L-arabinofuranoside (27), quercetin-3-O- α -L-arabinopyranoside (33), and guavinoside F (34), have been isolated from the leaves of guava (Figure 5) (Feng et al. 2015). The biologically important acylated phenolic glycosides, namely gujanoside A (35), gujanoside

B (36), gujanoside C (37), gujanoside D (38), gujanoside E (39), cypellogen A (40), cypellogen B (41), quercetin-3-O- β -D-(6"-O-p-coumaroyl)-galactopyranoside (42), and guavaric acid (43), have also been extracted from the leaves of guava (Figure 6) (Li et al. 2019).

Flavonoids are the main bioactive compounds in guava leaves. The flavonoid compositions in guava leaves were identified through the HPLC-TOF-ESI/MS method (Wang et al. 2017). The guava leaves contain two important bioactive flavonoids, namely quercetin and guajaverin (Ravi and Divyashree 2014). Four flavonoids, morin-3-O- α -L-lyxopyranoside, morin-3-O- α -L-arabopyranoside, quercetin-3-O-arabinoside, and quercetin, were reported from the leaves of guava (Arima and Danno 2002). The semipreparative HPLC of guava leaves isolated seven main flavonol-glycosides and out of that four compounds, namely peltatoside, hyperoside, isoquercitrin and guajaverin (quercetin-3-O- α -L-arabinopyranoside), have been unambiguously identified (Eidenberger, Selg, and Krennhuber 2013). A novel peptidoglycan, rhamnoallosan, has been isolated from the budding leaves of *P. guajava*. The hemicellulose rhamnoallosan consists of nine different monosaccharides as well as 14 amino acids. The predominant monosaccharides are rhamnose and allose followed by arabinose, tallose, xylose, fucose, glucose, mannose, and galactose. The principal amino acids are glycine, leucine, proline, and alanine followed by methionine, isoleucine, valine, histidine, tyrosine, phenylalanine, cysteine, aspartic acid, lysine, and glutamic acid (Chen et al. 2009).

Ten new aliphatic compounds were also reported from the ethanol extract of the leaves of *P. guajava* (Mehta et al. 2012). A new benzophenone glycoside, guajaphenone A, has been isolated from the methanol extract of leaves of *P. guajava* (Ukwueze, Osadebe, and Okoye 2015). The major chemical constituents of methanol, hexane, and chloroform extracts of leaves of guava included pyrogallol (35.18%), vitamin E (30.70%), and palmitic acid (30.73%), respectively (Ashraf et al. 2016).

A new triterpenoid, 6 β ,20 β -dihydroxy-12-ursen-28-oic acid, has been found to be present in the leaves of guava (Rao, Sahoo, and Rajesh 2012). The leaves of *P. guajava* are rich sources of lanostene-type triterpenoids (Bagri et al. 2016). Six new lanosterol-type triterpenoids, namely lanost-7-en-3 β -ol-26-oic acid, lanost-7-en-3 β , 12 β -diol-26-oic acid, lanost-7-en-3 β , 12 β , 29-triol-26-oic acid, lanost-cis-1,7,23-trien-3 β , 12 β ,18,22 α -tetraol-26-oic acid, lanosteryl-3 β -O-D-xylopyranosyl-2'-p-benzaldehyde, and lanost-7-en-3 β -ol-26-oic acid-3 β -D-glucopyranoside, were separated from the methanol extract of leaves of guava (Bagri et al. 2016). Five novel bioactive sesquiterpenoid-based meroterpenoids with unusual skeletons, such as psiguadial A (44), psiguadial B (45), psidial A (46), psidial B (47), and psidial C (48), were isolated from the leaves of *P. guajava* (Figure 7) (Shao et al. 2010; Fu et al. 2010).

The GC-MS analysis of guava leaf oil revealed the presence of 54 phytochemicals; the major constituents are isocaryophyllene (33.53%), veridiflorene (13.00%), farnesene (11.65%), *dl*-limonene (9.84%), δ -cadinene (1.75%), α -copaene (2.80%), α -humulene (3.74%), and τ -cadinol

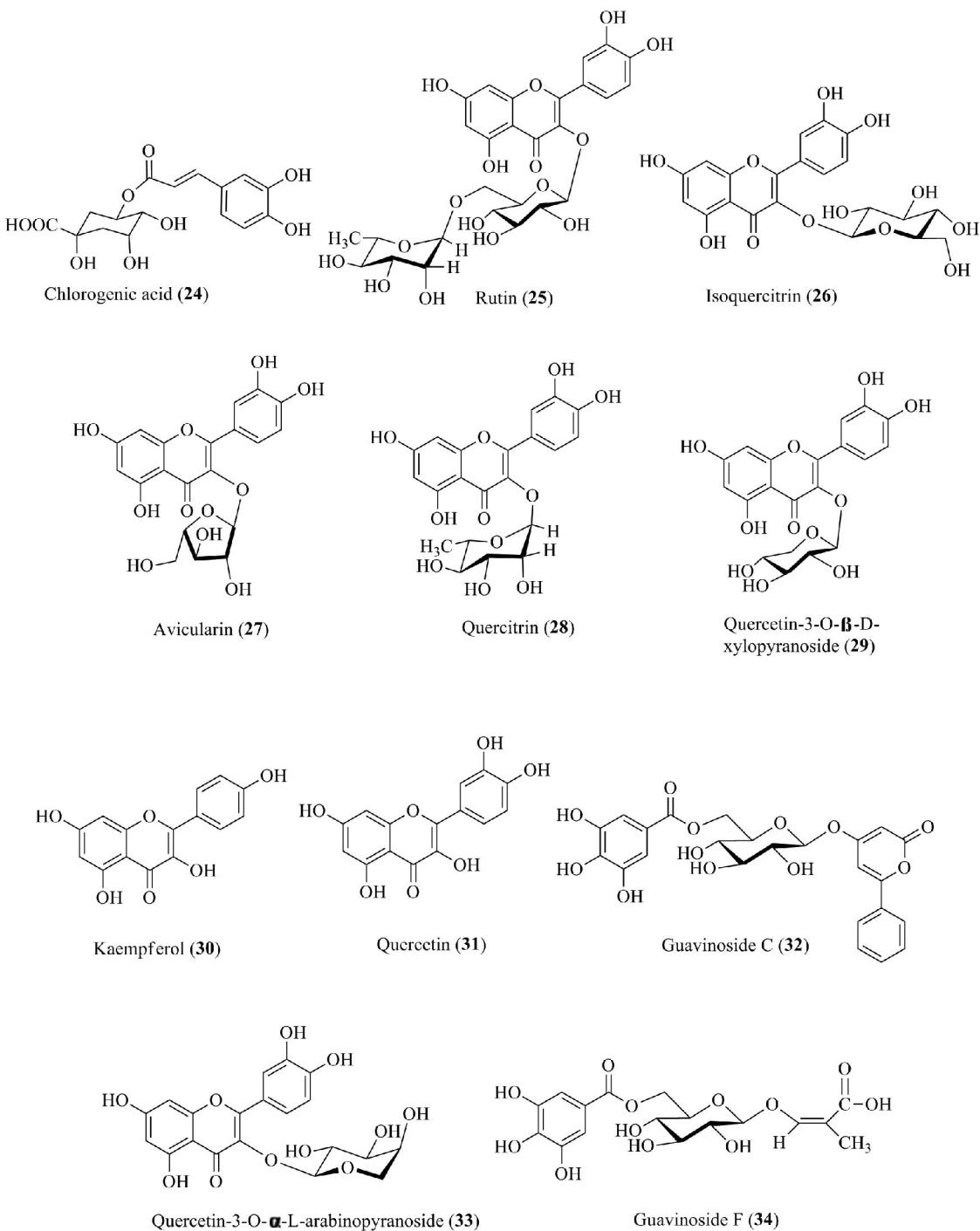


Figure 5. Chemical structures of several major bioactive phenolic constituents, as well as flavonoids, present in guava leaves.

(0.08%) (Weli et al. 2019). The GC-flame ionization detection and GC-MS analysis of the essential oil of the senescent leaves of guava revealed the presence of forty-six constituents with the most abundant being sesquiterpenoids followed by monoterpenoids (Chaturvedi et al., 2021). The major constituents of the essential oil of guava leaves were limonene, β -caryophyllene (7) (Figure 3), caryophyllene oxide (49), caryophylla-4(12),8(13)-dien-5-ol (50), (E)-nerolidol (51), selin-7(11)-en-4 α -ol (19), α -cadinol (52), muurola-4,10(14)-dien-1- β -ol (53), 1,8-cineole (54), α -copaene (55), α -humulene (56), and α -pinene (57) (Figure 8) (Chen,

Hsieh, et al. 2007; Athikomkulchai et al. 2008; El-Ahmady, Ashour, and Wink 2013; Chaturvedi et al., 2021).

The GC-MS analysis of essential oils from the stems of guava reported humulene (10.93%), germacrene D (16.79%), and valerenol (10.62%) as the major constituents present in the oil of the stems (Khadhri et al. 2014). The bark of guava is a rich source of tannins, such as condensed, hydrolyzable, and complex tannins (Tanaka et al. 1992). Moreover, six new complex tannins, guajavin A, guajavin B, psidinin A, psidinin B, psidinin C, and psiguavin, have been isolated from the bark of guava (Tanaka et al. 1992).

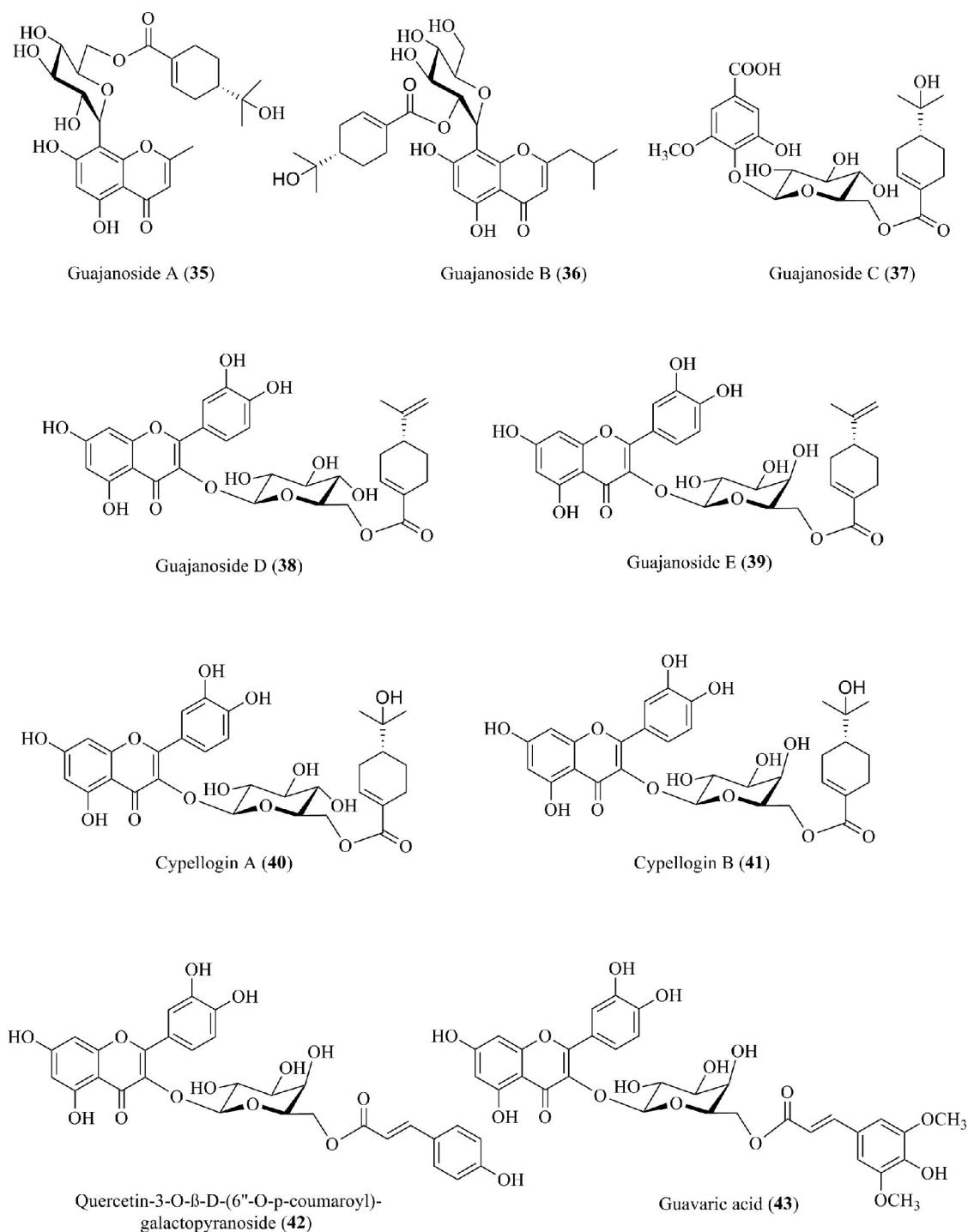


Figure 6. Chemical structures of some biologically important acylated phenolic glycosides present in guava leaves.

Literature search methodology

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria (Liberati et al. 2009) was followed for this work. The major databases used to search and collect primary literature for this review were PubMed, Scopus, and ScienceDirect. There were no time restraints on research articles that were published. The last search was performed in February 2021. Major keywords used in various combinations included: *Psidium guajava*, guava, phytochemicals, cancer, prevention, treatment, proliferation,

apoptosis, in vitro, in vivo, and clinical study. Initially, the abstracts of all publications were reviewed. Full-length articles were then collected, reviewed, and a decision was made regarding its incorporation for further analysis. Only reports published in the English language in peer-reviewed journals were included. Studies that evaluated the anticancer potential of a test item obtained from *P. guajava* using cancer cells or animal tumor models were considered. Available clinical studies pertaining to *P. guajava* and cancer were searched on clinicaltrials.gov. The methodological quality of each animal study was evaluated according to SYRCLE's

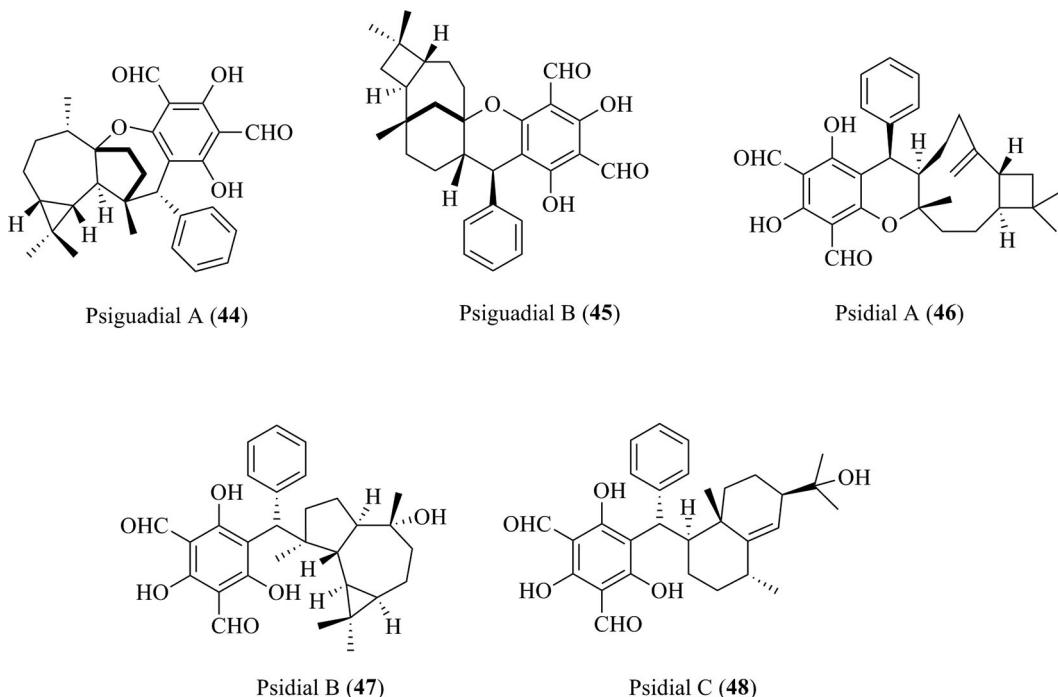


Figure 7. Chemical structures of various novel bioactive unusual sesquiterpenoid-based meroterpenoid skeletons present in guava leaves.

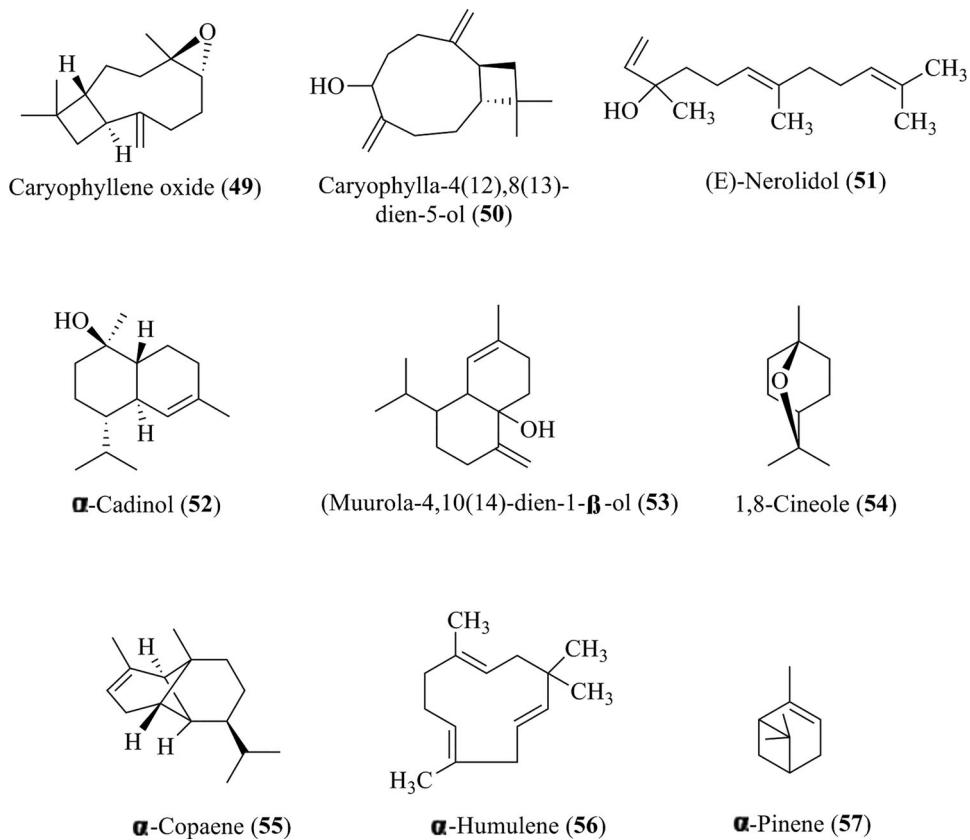


Figure 8. Chemical structures of various major essential oil and aroma-active constituents present in guava leaves.

RoB tool, an adapted version of the Cochrane RoB tool, that contains 10 items to investigate sources of bias (Hooijmans et al. 2014). Reference lists of collected articles were checked and previous reviews were examined for relevant publications. A total of 35 articles met the selection criteria. Figure 9 shows a scheme for literature search and study selection.

Guava extracts, fractions and pure compounds in cancer research

Breast cancer

The anticancer properties of *P. guajava* fruit, seed, leaf, and bark have been extensively investigated in vitro using several

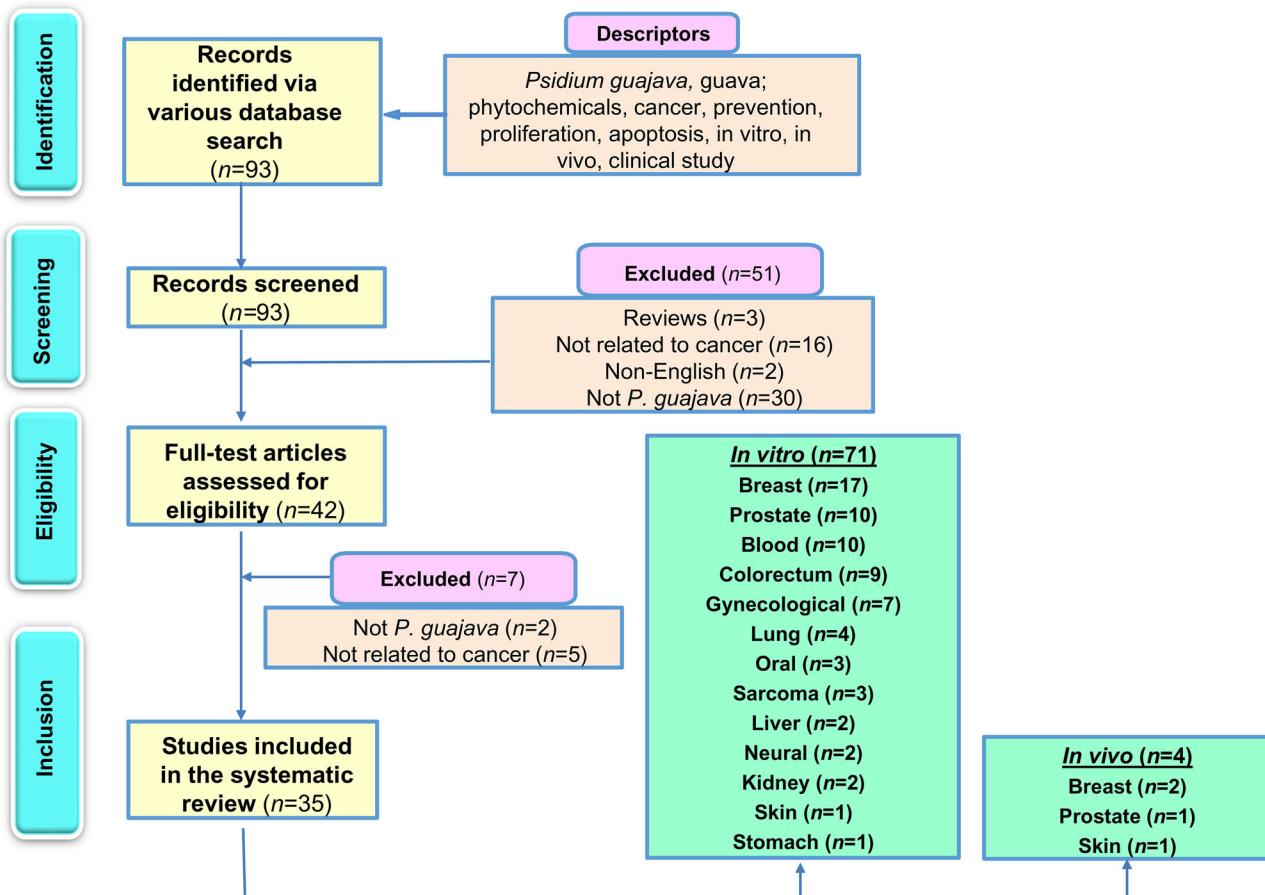


Figure 9. A PRISMA flow chart describing the process of literature search and study selection related to anticancer potential of *P. guajava*. The total number of in vitro and in vivo studies (75) is greater than the number of research publications included in our work (35) because several publications reported results from more than one organ-specific cancer or study type (in vitro or in vivo).

breast cancer cell lines. When *P. guajava* aqueous fruit extract was tested along with 13 other plant food extracts, the *P. guajava* extract was found to have the highest phenolic content and antioxidant capacity. However, when MCF-7, a breast cancer cell line positive for both estrogen receptor (ER) and progesterone receptor (PR), was treated with the *P. guajava* fruit extract, no antiproliferative effect was demonstrated (Table 2) (García-Solís et al. 2009). Bontempo et al. (2012) observed that *P. guajava* fruit and pulp extracts exerted antiproliferative effects and induced apoptosis in MDA-MB-231 cells, a triple-negative breast cancer (TNBC) cell line that lacks ER, PR, and human epidermal growth factor receptor 2 (HER2). In a subsequent study, the cytotoxic effect of a lycopene-rich *P. guajava* fruit extract (20% lycopene of dry weight) was tested on MCF-7 cells. The treated cells had increased cell cycle arrest at G1 and G2/M phases, DNA fragmentation, depolarization of the mitochondrial membrane potential, and morphologic changes, suggesting that the cytotoxic effects were via induction of a mitochondria-mediated apoptotic pathway (Dos Santos et al. 2018). Liu et al. (2020) tested *P. guajava* fruit extract against MDA-MB-231 and MDA-MB-468 cells (both TNBC cell lines). Cytotoxicity in both cell lines was induced through caspase-3 activation and increased poly ADP-ribose polymerase (PARP) cleavage signaling. In MDA-MB-231 cells, cell death resulted from the necrotic death pathway,

whereas cytotoxicity was induced via the apoptotic death pathway in MDA-MB-468 cells. The extract was also tested in combination with doxorubicin, a DNA topoisomerase II inhibitor used as chemotherapeutic drug for the treatment of TNBC, which yielded significantly increased anticancer activities. Additionally, when the *P. guajava* extract was combined with erlotinib and gefitinib, two epidermal growth factor receptor (EGFR) inhibitors, anticancer activity was again significantly increased. Recently, Correa et al. (2020) treated MDA-MB-435 (ER-negative breast cancer) and MCF-7 cell lines with *P. guajava* fruit pulp extract. In both cell lines, there was decreased cell viability, increased early and late phase apoptosis, and induction of cell cycle arrest. However, cell proliferation was only reduced in the MCF-7 cell line. Phytochemical characterization of the extract revealed the presence of lycopene, phenolics, and β-carotene. In another study, poly-ε-caprolactone lipid-core nanocapsules containing lycopene-rich *P. guajava* fruit extract exhibited superior cytotoxic effect against MCF-7 cells to that of the extract (Vasconcelos et al., 2020).

Lin and Lin (2020a) reported that guava seed polysaccharide fraction 3 (GSF3), an immunomodulatory polysaccharide from guava seed polysaccharide (GSPS), inhibited MCF-7 cell growth both directly and indirectly through immunomodulation. GSF3 direct action decreased B-cell lymphoma 2 (Bcl-2) and Bcl-2 associated X protein (Bax)

Table 2. Potential anticancer effects and mechanisms of action of guava-derived constituents based on in vitro studies.

Materials tested	Cell lines used	Concentration	Anticancer effects	Mechanisms	References
<i>Breast cancer</i>					
Aqueous fruit extract	MCF-7	0-24 µg GAE/mL	Did not show antiproliferative activity		García-Solís et al. 2009
Total acetone fruit and pulp extract	MDA-MB-231	1.5 mg/mL	Reduced proliferation	↑Apoptosis	Bontempo et al. 2012
Ethanolic fruit extract	MCF-7	6.25-1600 µg/mL	Reduced proliferation	G1 and G2/M phase cell cycle arrest; ↑DNA fragmentation; ↑depolarization of mitochondrial membrane potential	Dos Santos et al., 2018
Fruit extract	MDA-MB-231 and MDA-MB-468	50-100 µg/mL	Induced cytotoxicity and decreased cell viability	↑Apoptosis; ↑necrotic cell death; ↑cells at sub-G1 cell cycle; ↑caspase-3; ↑PARP	Liu et al. 2020
Fruit pulp extract	MCF-7 and MDA-MB-435	15-5000 µg/mL	Reduced proliferation (MCF-7 only) and decreased cell viability	↑Apoptosis; alterations in cell cycles	Correa et al. 2020
Poly-ε-caprolactone lipid-core nanocapsules containing fruit extract and free fruit extract	MCF-7	6.25-200 µg/mL	Decreased cell viability		Vasconcelos et al., 2020
Seed polysaccharide fraction 3	MCF-7	8-200 µg/mL	Inhibited cell growth and decreased cell viability	↑Bax; ↓Bcl-2; ↑Fas	Lin and Lin 2020a
Seed polysaccharides	MCF-7	8-200 µg/mL	Inhibited cell growth	↑M1 (IL-1β + IL-6 + TNF-α)/M2 (IL-10) cytokine secretion ratio	Lin and Lin 2020b
Seed acetone extract and two isolated compounds	Ehrlich ascites carcinoma	0.5-100 µg/mL	Inhibited cell growth		Salib and Michael 2004
Leaf	MCF-7 and MDA-MB-231	IC ₅₀ : 820 µg/mL (MCF-7)	Induced cytotoxicity (MCF-7) Did not show cytotoxic effect (MDA-MB-231)	↓NF-κB (MCF-7)	Kaileh et al. 2007
Petroleum ether, methanolic and aqueous leaf extracts	MDA-MB-231	IC ₅₀ : 4.23-55.69 µg/mL	Induced cytotoxicity and reduced proliferation		Sul'ain et al., 2012
Leaf extract (DCE) and its various fractions	MCF-7	TGI: 8-61 µg/mL	Exhibited growth inhibition		Rizzo et al., 2014
Leaf extract (DCE) F _{FINAL} (obtained from DCE)	MCF-7, MCF-7 BUS and MDA-MB-231	TGI: 64.61 µg/mL TGI: 2.27-8.86 µg/mL	Reduced proliferation Reduced proliferation	↑G1-phase; ↓S-phase; ↓G2/M-phase (MCF-7 BUS)	Bazioli et al. 2020 Bazioli et al. 2020
Guajavodial A, B, and C (from leaf)	MCF-7	IC ₅₀ : 14.54-22.28 µM	Induced cytotoxicity		Qin et al. 2016
CPO (from leaf)	MCF-7	30 or 50 µg/mL	Reduced proliferation	↑Apoptosis; ↓PI3K/Akt/mTOR/S6K1; ↑p-ERK; ↑p-JNK; ↑p38 MAPK	Park et al., 2011
CPO (from leaf)	MDA-MB-231 MDA-MB-231-pcDNA3 and MDA-MB-231-BCRP	10 or 30 µM IC ₅₀ : 27.24-62.64 µg/mL	Reduced proliferation Induced cytotoxicity	↓p-STAT3 (Ser727)	Kim et al., 2014 Mbaveng et al. 2018
<i>Gastrointestinal tract and associated cancers</i>					
Leaf oil	KB (Mouth epidermal carcinoma)	0.019-4.962 mg/mL	Induced cytotoxicity		Manosroi, Dhumtanom, and Manosroi 2006
Ethanolic leaf extract	HSC-2 (Oral squamous cell carcinoma)	15.625-500 µg/mL	Reduced proliferation	↑Apoptosis	Pakpahan et al. 2013
Leaf extracts (methanol, hexane, and chloroform)	SCC4 (Tongue squamous carcinoma)	10, 25, 50 and 100 mg/mL	Induced cytotoxicity	↑Antioxidant activity	Ashraf et al. 2016
Guavinoside C and F, and quercetin (from leaves)	SGC-7901 (Gastric cancer)	IC ₅₀ : 3.729-7.878 µg/mL	Induced cytotoxicity	↑Antioxidant activity	Feng et al. 2015
Psigujavodial A and B (from fruit)	HCT116 (Colorectal cancer)	IC ₅₀ : 7.60-21.6 µM	Induced cytotoxicity	↑Apoptosis; ↓TOP1	Qin et al. 2017
Ethanolic leaf and stem extract	RKO-AS45-1 (Colorectal carcinoma)	IC ₅₀ : 21.2 µg/mL	Induced cytotoxicity		Braga et al. 2014

(continued)

Table 2. Continued.

Materials tested	Cell lines used	Concentration	Anticancer effects	Mechanisms	References
Ethanol leaf extract	COLO320DM (Colon adenocarcinoma)	100 mg/mL	Reduced cell growth	↓PGHS isoform activity ↓PGE ₂ ↓DNA synthesis	Kawakami et al. 2009
Leaf extract (DCE) and its various fractions	HT29 (Colon cancer)	TGI: 5-43 µg/mL	Reduced proliferation		Rizzo et al., 2014
Leaf extract (DCE) and F _{FINAL} (obtained from DCE)	HT29 (Colon cancer)	TGI: 6.65-101.78 µg/mL	DCE did not show cytotoxicity; F _{FINAL} induced cytotoxicity		Bazioli et al. 2020
Guajavodial A-C (from leaves)	SW-480 (Colon adenocarcinoma)	IC ₅₀ : 13.07-18.97 µM	Induced cytotoxicity		Qin et al. 2016
Guavinoside B, guavinoside E, and 3,5-dihydroxy-2,4-dimethyl-1-O-(6'-O-galloyl-β-D-glucopyranosyl)-benzophenone (from leaves)	HT29(Colon cancer)	20-100 µM	Reduced cell growth		Zhu et al. 2019
Guavinoside B, guavinoside E, and 3,5-dihydroxy-2,4-dimethyl-1-O-(6'-O-galloyl-β-D-glucopyranosyl)-benzophenone (from leaves)	HCT116 (Colon cancer)	20-100 µM	Reduced cell growth, suppressed colony formation	↑Apoptosis; ↑p53; ↑p-ERK1/2; ↑p-JNK; ↑caspase-8 cleavage; ↑caspase-9 cleavage	Zhu et al. 2019
Acetone branch extract	HT29 (Colon cancer)	50, 100, and 250 µg/mL	Induced cytotoxicity	↑Apoptosis; ↑chromatin condensation; ↑sub G1 cells;	Lee and Park 2010
Bark extract	HCT116 p53+/+ and HCT116 p53-/-(Colon cancer)	IC ₅₀ : 18.63, 40.63 µg/mL	Induced cytotoxicity		Mbaveng et al. 2018
Seed oil	HepG2 (Hepatocellular carcinoma)	6.25-200 µg/mL	Did not exhibit cytotoxicity		Prommaban et al. 2019
Guajavodial A-C (from leaves)	SMMC-7721 (Hepatocellular carcinoma)	IC ₅₀ : 3.54-5.05 µM	Induced cytotoxicity		Qin et al. 2016
<i>Gynecological cancers</i>					
Methanolic leaf extract	HeLa (Cervical cancer)	10% crude concentration	Induced cytotoxicity		Joseph and Priya, 2010
Petroleum ether, methanolic and aqueous leaf extracts	HeLa (Cervical cancer)		Did not exhibit cytotoxicity		Sul'ain et al., 2012
Ethanol leaf and stem extract	HeLa(Cervical cancer)	IC ₅₀ : 15.6 µg/mL	Induced cytotoxicity		Braga et al. 2014
Guavinoside C and F and quercetin (from leaves)	HeLa(Cervical cancer)	IC ₅₀ : 3.246-10 µg/mL	Induced cytotoxicity	↑Antioxidant activity	Feng et al. 2015
Hexane leaf extract	OV2008 (Ovarian cancer)	100-500 µg/mL	Decreased cell viability		Levy and Carley 2012
Leaf extract (DCE) and its various fractions	NCI/ADR-RES (Resistant ovarian cancer) and OVCAR-3 (Ovarian cancer)	TGI: 0.64-61 µg/mL	Reduced proliferation		Rizzo et al., 2014
Leaf extract (DCE) and F _{FINAL} (obtained from DCE)	OVCAR-3 and NCI-ADR/RES	TGI: 2.66-50.51 µg/mL	Reduced proliferation		Bazioli et al. 2020
<i>Hematological cancers</i>					
Acetone total fruit and pulp extracts	NB4 (Acute promyelocytic leukemia)	0.1-3.0 mg/mL	Reduced proliferation and induced differentiation	↑Apoptosis; ↓G1 cell cycle; ↑p21; ↑p16; ↑caspase-8; ↑caspase-9; ↓FLIP-L (pulp only); ↑granulocytic differentiation	Bontempo et al. 2012
Seed oil	K562 (Human erythroleukemia)	6.25-200 µg/mL	Inhibited proliferation		Prommaban et al. 2019
Seed acetone extract and two isolated compounds	P388 (Leukemia)	0.5-100 µg/mL	Induced cytotoxicity		Salib and Michael 2004
Leaf essential oil	P388 (Leukemia)	0.02-0.08 mg/mL	Reduced proliferation		Manosroi, Dhumtanom, and Manosroi 2006
Hexane leaf extract	Kasumi-1 (Leukemia)	100-500 µg/mL	Induced cytotoxicity		Levy and Carley 2012
Leaf extract (DCE) and its various fractions	K562 (Leukemia)	TGI: 0.78-32 µg/mL	Reduced proliferation		Rizzo et al., 2014

(continued)

Table 2. Continued.

Materials tested	Cell lines used	Concentration	Anticancer effects	Mechanisms	References
Leaf extracts (methanol, hexane, and chloroform)	KBM5 (Chronic myelogenous leukemia)	10-100 mg/mL	Induced cytotoxicity	↓NF-κB activation; ↑antioxidants	Ashraf et al. 2016
Guajavadiol A-C (from leaves)	HL-60 (Leukemia)	IC ₅₀ : 3.38-6.49 μM	Induced cytotoxicity		Qin et al. 2016
Bark extract	CCRF-CEM (Drug-sensitive leukemia) and CEM/ADR5000 (Drug-resistant leukemia)	IC ₅₀ : 1.29-6.35 μg/mL	Reduced proliferation	↑Apoptosis; ↑caspase activation; ↑G0/G1 cell cycle arrest; ↑ROS production	Mbaveng et al. 2018
Acetone total fruit extract	U937 (Histiocytic lymphoma)		Did not show antiproliferative activity		Bontempo et al. 2012
Leaf extracts (methanol, hexane, and chloroform)	U266 (Multiple myeloma)	10-100 mg/mL	Induced cytotoxicity		Ashraf et al. 2016
CPO (from leaf)	U266 and MM1.S (Melphalan-sensitive multiple myeloma)	10 or 30 mM	Reduced proliferation	↓STAT3; ↓c-Src; ↓JAK1/2; ↓cyclin D1; ↓c-Myc; ↓B-catenin; ↑p21; ↑SHP-1; ↑BAX; ↑caspase-3; ↑PARP cleavage; ↓VEGF; ↓PLAUR; ↓IL-8; ↓MET; ↓cathepsin B	Kim et al., 2014
<i>Kidney cancer</i>					
Leaf extract (DCE) and its various fractions	786-0 (Kidney cancer)	TGI: 28-44 μg/mL	Reduced proliferation		Rizzo et al., 2014
Leaf extract (DCE) and F _{FINAL} (obtained from DCE)	786-0	TGI: 7.69-62.88 μg/mL	Inhibited proliferation		Bazioli et al. 2020
<i>Lung cancer</i>					
Leaf extract (DCE) and its various fractions	NCI-H460	TGI: 5-64 μg/mL	Reduced proliferation		Rizzo et al., 2014
Leaf extract (DCE) and F _{FINAL} (obtained from DCE)	NCI-H460	TGI: 2.79-57.82 μg/mL	Reduced proliferation		Bazioli et al. 2020
Guavinoside C and F and quercetin (from leaves)	A549	IC ₅₀ : 7.011 - >10 μg/mL	Induced cytotoxicity	↑Antioxidant activity	Feng et al. 2015
Guajavadiols A-C	A-549	IC ₅₀ : 5.62-5.78 μM	Induced cytotoxicity		Qin et al. 2016
<i>Neural cancer</i>					
Leaf extract (DCE) and F _{FINAL} (obtained from DCE)	U251 (Glioblastoma)	TGI: 3.90-61.5 μg/mL	Reduced proliferation		Bazioli et al. 2020
Bark extract	U87MG and U87MG.ΔEGFR (Glioblastoma)	IC ₅₀ : 28.84-39.86 μg/mL	Induced cytotoxicity		Mbaveng et al. 2018
<i>Prostate cancer</i>					
Seed polysaccharides	PC-3	1.6-200 μg/mL	Inhibited cell growth and decreased cell viability	↓(IL-6 + TNF-α)/IL10 ratio	Lin and Lin 2016
Aqueous leaf extract	DU-145	0.1-1.0 mg/mL	Reduced cell viability, colony forming ability, and cell migration	↑Apoptosis; ↑caspase-3; cell cycle arrest at G ₀ /G ₁ ; ↓MMP-2; ↓MMP-9	Chen, Hsieh, et al. 2007
Rhamnoallosan (from leaf extract)	DU-145	1 mg/mL	Decreased cell viability		Chen et al. 2009
Aqueous leaf extract	LNCaP	0.1-1.0 mg/mL	Induced cytotoxicity and reduced proliferation	↑Apoptosis; ↓Bcl-2/Bax ratio; cell cycle arrest at G ₀ /G ₁ ; ↑p53; ↓AR; ↓PSA; ↓p-Akt; ↑p-p38; ↑p-Erk1/p-Erk2	Chen et al. 2010
Aqueous leaf extract	DU-145	0.1-1 mg/mL	Decreased cell viability and inhibited cell migration	↓VEGF; ↓IL-6; ↓IL-8; ↓MMP-2; ↓MMP-9; ↑TIMP-2	Peng et al. 2011
Leaf extracts and a hexane fraction	PC-3	50-100 μg/mL	Exerted cytotoxicity	↑Apoptosis; ↓Bcl-2; ↓Bcl-xL; ↓survivin; ↓IAP-1; ↓IAP-2; ↓cyclin D1; ↓COX-2; ↓VEGF; ↓ERK; ↓JNK; ↑caspase-3; ↓Akt/mTOR/S6K1; ↓MAPK	Ryu et al. 2012

(continued)

Table 2. Continued.

Materials tested	Cell lines used	Concentration	Anticancer effects	Mechanisms	References
Leaf extract (DCE) and its various fractions	PC-3	TGI: 12-29 µg/mL	Displayed growth inhibition		Rizzo et al., 2014
Leaf extract (DCE) and FFFINAL (obtained from DCE)	PC-3	TGI: 3.70-39.94 µg/mL	Reduced proliferation		Bazioli et al. 2020
CPO (from leaf)	PC-3	30 or 50 µg/mL	Reduced proliferation	↑Apoptosis; ↑cells at sub-G ₁ ; ↓Bcl-2; ↓Bcl-xL; ↓survivin; ↓IAP-1; ↓IAP-2; ↓c-PARP; ↑cyt. c; ↓cyclin D1; ↓COX-2; ↓VEGF/p38 MAPK; ↑caspase-3; ↑p53; ↑p21; ↑ROS; ↑ERK; ↑JNK; ↓PI3K/Akt/mTOR/S6K1;	Park et al., 2011
CPO (from leaf)	DU145	10 or 30 µM	Reduced proliferation and suppressed invasion	↑Apoptosis; ↓c-Src; ↓JAK1/2; ↓SHP-1; ↓p-STAT3	Kim et al., 2014
<i>Sarcoma</i>					
Pulp, seed and peel extracts	U2OS (Osteosarcoma)	1.5 mg/mL	Did not show cell death or cell cycle alteration		Bontempo et al. 2012
Petroleum ether, methanolic and aqueous leaf extracts	MG-63 (Osteosarcoma)	IC ₅₀ : 5.42-61.88 µg/mL	Induced cytotoxicity and reduced proliferation		Sul'ain et al., 2012
Leaf extract	L929sA (Murine fibrosarcoma)	IC ₅₀ : 55 µg/mL	Induced cytotoxicity	↓NF-κB expression	Kaileh et al. 2007
<i>Skin cancer</i>					
Leaf extract (DCE) and its various fractions	UACC-62 (Melanoma)	TGI: 0.31-65 µg/mL	Reduced proliferation		Rizzo et al., 2014

Abbreviations: AML, acute myeloid leukemia; Bax, Bcl-2 associated X apoptosis regulator; Bcl-2, B-cell lymphoma 2; Bcl-xL, Bcl-2 extra-large; CD11c, integrin sub-unit α X; COX-2, cyclooxygenase-2; CPO, β -caryophyllene oxide; c-Src, c-terminal Src kinase; DCE, dichloromethane crude extract; ECE, ethanolic crude extract; ERK, extracellular signal-regulated kinase; FAS, fas cell surface death receptor; FLIP, CASP8 and FADD-like apoptosis regulator; GAE, gallic acid equivalent; GBF, butanol fraction of guava leaf extract; JAK, janus kinase; JNK, c-jun NH₂-terminal kinase; IAP-1, inhibitor of apoptosis protein-1; IC₅₀, half-maximal inhibitory concentration; IL-1 β , interleukin-1 β ; MAPK, p38 mitogen-activated protein kinase; MCM, macrophage-conditioned media; MET, MET proto-oncogene receptor tyrosine kinase; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-κB; PARP, poly ADP-ribose polymerase; PI3K, phosphatidylinositol 3-kinase; PLAUR, plasminogen activator urokinase receptor; ROS, reactive oxygen species; S6K1, ribosomal protein S6 kinase B1; SAPK, stress activated protein kinase; SHP-1, protein tyrosine phosphatase non-receptor type 6; STAT3, signal transducer and activator of transcription 3; TGI, total growth inhibition; TIMP-2, TIMP metallopeptidase inhibitor 2; TNF- α , tumor necrosis factor- α ; TOP1, DNA topoisomerase I; uPAR, urokinase-type plasminogen activator receptor; VEGF, vascular endothelial growth factor.

mRNA expression and increased Bax/Bcl-2 mRNA expression ratios in treated cells, suggesting a pro-apoptotic effect. To evaluate the indirect immunotherapeutic action of GSF3, MCF-7 cells were treated with splenocytes conditioned media (SCM) or macrophages conditioned media (MCM) cultured with and without GSP3. Both the SCM and MCM cultured with GSF3 demonstrated significantly decreased cell viability. Finally, the SCM cultured with GSF3 increased the expression of Fas mRNA in MCF-7 cells. Another study conducted by the same group (Lin and Lin 2020b) compared the anti-inflammatory and anticancer effects of GSP3 with lipopolysaccharide (LPS)-induced macrophages on MCF-7 cells. GSP3 significantly increased M1 [interleukin 1 β (IL-1 β)+IL-6 + tumor necrosis factor- α (TNF- α)]/M2 (IL-10) cytokine secretion ratios by macrophages in the absence of LPS, which negatively correlated with MCF-7 cell viability, suggesting that increased M1 macrophages may inhibit MCF-7 cell growth. Salib and Michael (2004) prepared an acetone extract from dried guava seeds from which they isolated two novel phenylethanoid glycosides. The acetone seed extract had moderate growth-inhibitory activity against Ehrlich ascites carcinoma (EAC) cells, whereas the two isolated compounds, 1-O-3,4-dimethoxy-phenylethyl-4-O-3,4-dimethoxy cinnamoyl-6-O-cinnamoyl-b-D-glucopyranose

and 1-O-3,4-dimethoxyphenylethyl-4-O-3,4-dimethoxy cinnamoyl-b-D-glucopyranose, showed substantial growth inhibitory activity against EAC cells. However, the underlying mechanisms of action were not studied.

An extract of shade-dried and ground parts (leaves) of *P. guajava*, obtained using a mixture of dichloromethane and methanol, was investigated for its anticancer effects against the MCF-7 and MDA-MB-231 breast cancer cell lines. While significant cytotoxicity occurred with treated MCF-7 cells, no such effect was observed with treated MDA-MB-231 cells, indicating a cell type-dependent activity. The anti-cancer mechanism of the extract in MCF-7 cells has been proposed to be due to inhibition of NF-κB reporter gene expression (Kaileh et al. 2007). Aqueous, methanolic, and petroleum ether extracts of *P. guajava* leaf induced cytotoxicity and reduced proliferation in MDA-MB-231 cells. The petroleum extract yielded the lowest half maximal inhibitory concentration (IC₅₀) value, although the mechanism was not indicated (Sul'ain et al. 2012). Rizzo et al. (2014) evaluated antiproliferative effects of *P. guajava* leaf dichloromethane crude extract (DCE) and its various fractions, namely PG.(F2-F3), PG.(F2-F3).(F6-F9), and PG.(F2-F3).(F6-F9).(F4), against MCF-7 cells. All test materials exhibited growth inhibition with a maximum effect was achieved with

Table 3. Potential anticancer effects and mechanisms of action of guava-derived constituents based on in vivo studies.

Materials tested	Animal tumor models	Anticancer effects	Mechanisms	Dose (route)	Duration	References
<i>Breast cancer</i>						
Seed acetone extract and two isolated compounds	Female Swiss albino mice bearing EAC cells	Increased survival time				Salib and Michael 2004
A fraction derived from leaf extract (DCE)	Female BALB/c mice inoculated with Ehrlich ascites tumor cells	Reduced tumor growth and increased uterus proliferation	↑Estrogen-like effects	10, 30 and 50 mg/kg (i.p.)	Once every 3 days for 21 days	Rizzo et al., 2014
<i>Prostate cancer</i>						
Aqueous leaf extract	Nude mice xenografted with LNCaP cells	Reduced tumor size and decreased PSA		1.5 mg/mouse/day (oral)	6 weeks	Chen et al. 2010
<i>Skin cancer</i>						
Aqueous leaf extract	Female B6 mice inoculated with B16 melanoma cells	Failed to prevent tumor growth		20 µg/mouse/day (oral)	3 consecutive days; B16 cells were injected 5 days after the last treatment	Seo et al. 2005
Ethanolic leaf, bark, and root extracts	Female B6 mice inoculated with B16 melanoma cells	Prevented tumor growth	↓Tr cell activity; ↑T1/T2 ratio	20 µg/mouse/day (oral)	3 consecutive days; B16 cells were injected 5 days after the last treatment	Seo et al. 2005
Aqueous leaf extract; Ethanolic leaf, bark, and root extracts	Female B6 mice inoculated with B16 melanoma cells	Did not reduce the growth of existing tumors		20 µg/mouse/day (oral)	3 consecutive days; B16 cells were injected one week before the first treatment	Seo et al. 2005

Abbreviations: DCE, dichloromethane crude extract; EAC, Ehrlich ascites carcinoma; PSA, prostate-specific antigen.

PG.(F2-F3).(F6-F9).(F4) fraction. It has been suggested that guajadial, psidial A and psiguajadial A and B are the major components of the most active fraction PG.(F2-F3).(F6-F9).(F4).(F7). Most recently, Bazioli et al. (2020) investigated the effects of DCE and a fraction (named F_{FINAL}) obtained from DCE that contains guajadial and psidial A. While DCE exhibited a weak antiproliferative activity against MCF-7 cells, F_{FINAL} showed a potent activity against MCF-7, MCF-7 BUS (ER-overexpressing breast cancer cell), and MDA-MB-231 breast cancer cell lines. Additionally, there was an increase in G1-phase population and reduction in both S- and G2/M-phase populations amongst MCF-7 BUS cells following a treatment with F_{FINAL}.

Qin et al. (2016) tested guajavadiol A, B, and C, isolated from *P. guajava* leaf, for antitumor effects against MCF-7 cells. Although the compounds induced cytotoxicity, the underlying mechanism of action was not reported. In a separate investigation, a hexane fraction (GHF) of *P. guajava* leaf extract was used to obtain pure compound CPO. In CPO-treated MCF-7 cells, there was reduced cell proliferation, increased apoptosis, cell cycle arrest, and elevated phosphorylation of c-Jun NH₂-terminal kinases (JNK) and p38 mitogen-activated protein kinases (MAPK). Furthermore, CPO inhibited the phosphatidylinositol 3-kinase (PI3K)/serine/threonine protein kinase B (Akt)/mammalian target of rapamycin (mTOR)/ribosomal S6 kinase β-1 (S6K1) signaling cascade and activated extracellular signal-regulated kinases (ERK) (Park et al. 2011). A subsequent study published from the same research group demonstrated that CPO reduced cell proliferation in MDA-MB-231 cells in a concentration- and time-dependent manner. Additional

experiments showed that CPO inhibited constitutive STAT3 phosphorylation at serine727 (Kim et al. 2014).

The cytotoxicity of a *P. guajava* bark (PGB) extract was investigated against various cell lines, namely MDA-MB-231-pcDNA3 and its resistant subline MDA-MB-231-breast cancer resistance protein (BCRP). MDA-MB-231-BCRP exhibits resistance to chemotherapeutic agents, such as 7-ethyl-10-hydroxycamptothecin (SN-38), mitoxantrone, and topotecan, by pumping them out of cells (Imai et al. 2005). The results demonstrated that PGB exerted greater cytotoxic effect against MDA-MB-231-BCRP cells compared to MDA-MB-231-pcDNA3 cells. However, the underlying mechanism was not investigated (Mbaveng et al. 2018).

There are at least two studies that investigated the anti-cancer potential of *P. guajava* using an in vivo breast cancer models. Extending their in vitro study as mentioned earlier, Salib and Michael (2004) found that oral administration of a crude acetone extract of *P. guajava* seeds and its two glycosidic compounds increased survival time of mice bearing EAC cells compared to control animals via unspecified mechanisms (Table 3). In solid Ehrlich murine breast adenocarcinoma, there was significant inhibition of tumor growth at 10, 30, and 50 mg/kg of a fraction [PG.(F2-F3).(F6-F9)] derived from DCE in comparison to the control group. Furthermore, the three doses of the fraction were equally effective as doxorubicin, an anthracycline antibiotic, in inhibiting tumor growth, and were significantly less toxic than doxorubicin. Additionally, the fraction stimulated the growth of uterus in experimental animals, indicating its action as a selective estrogen receptor modulator (Rizzo et al. 2014).

Gastrointestinal tract and associated cancers

Overall, the gastrointestinal tract (GIT) is responsible for more cases of cancer and cancer-associated deaths than any other organ system in the body (Bjelakovic et al. 2008). There have been many studies on the effects of guava components in various GIT and related cancers.

Manosroi et al. (2006) found that the oil extracted from *P. guajava* leaves displayed high cytotoxicity against human mouth epidermal carcinoma (KB) cells with an IC₅₀ value of 0.0379 mg/mL, which was higher than that of the positive controls 5-fluorouracil (5-FU), a chemotherapeutic drug commonly used in colon cancer, and vincristine, a plant-derived chemotherapeutic drug (1.77 and 0.166 mg/mL respectively). The underlying mechanism was not investigated. An ethanolic extract of *P. guajava* leaves was found to reduce cell proliferation and induce apoptosis in HSC-2 oral squamous cell carcinoma cells (Pakpahan et al. 2013). Ashraf et al. (2016) compared the cytotoxicity of methanol, hexane, and chloroform extracts of *P. guajava* leaf against human tongue squamous carcinoma (SCC4) cells. It was found that while all the extracts decreased cell growth, the hexane extract showed the most cytotoxicity. The antioxidant activities were also assessed using fluorescence recovery after photobleaching (FRAP) and 2,2,1-diphenyl-1-picrylhydrazyl (DPPH) assays, and it was found that the ascending order of activity was hexane, chloroform, and methanol. Despite its high antioxidant activity, the methanol extract had the least in vitro anticancer activity, whereas hexane had the most. Due to this finding, the authors proposed that various components found in the hexane extract, such as tetracosane, a-copaene, g-sitosterol, vitamin E and squalene, may play a role in its antitumor activity.

Feng et al. (2015) isolated 10 compounds from *P. guajava* leaves which included four new compounds, namely guavinoside C, D, E and F, and six known compounds, quercetin, quercetin-3-O- α -L-arabinofuranoside, quercetin-3-O- α -L-arabinopyranoside, quercetin-3-O- β -D-galactopyranoside, guavinoside A, and guavinoside B. A 3-[4, 5-dimethylthiazol-2-yl]-2, 5 diphenyl tetrazolium bromide (MTT) assay performed on human gastric cancer (SGC-7901) cells showed that guavinoside C, guavinoside F, and quercetin had significant cytotoxic effects. Notably, these three compounds were shown to have strong antioxidant activity based on DPPH, FRAP, and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) assays (higher than vitamin C control), suggesting a relationship between their cytotoxic and antioxidant effects.

Qin et al. (2017) extracted 16 meroterpenoids from guava fruit, including two novel compounds, psiguajavadial A and B. It was found that all 16 meroterpenoids exhibited significant cytotoxicity against human colorectal cancer (HCT116) cells and a DNA topoisomerase I (Top1)-mediated cleavage assay suggested inhibition of Top1 as a mechanism of action. Top1 is an enzyme that can form single stranded breaks in DNA, as well as double stranded breaks if strands are affected sequentially. Additionally, inhibition of Top1 is the mechanism of action of the frequently used chemotherapy drugs topotecan, irinotecan, and belotecan. Immunofluorescence of phosphorylated histone H2AX

(λ H2AX), a marker of double stranded DNA damage, was not detected when compared to the control in HCT116 cells treated with psiguajavadial A and B, further supporting that guava phytoconstituents have an antagonizing effect on Top-mediated DNA breaks.

Ethanolic leaf and stem extract showed significant cytotoxicity against colorectal carcinoma (RKO-AS45-1) cells; however, no mechanism of action was investigated (Braga et al. 2014). Prostaglandin endoperoxide H synthase (PGHS) is an enzyme involved in the synthesis of prostaglandins (PG), which play important roles in inflammation and carcinogenesis. It was found that human colon adenocarcinoma (COLO320DM) that overexpress PGHS-1 and PGHS-2 have an increased rate of DNA synthesis compared to COLO320DM cells that do not express those isoforms. When the overexpressing COLO320DM cells were treated with ethanolic guava leaf extract, the rate of DNA synthesis was brought down to that of non-overexpressing cells. Additionally, guava leaf extract inhibited PGE₂ synthesis and suppressed cell growth rate by inhibiting the PGHS isoforms (Kawakami et al. 2009). Rizzo et al. (2014) tested the cytotoxic effects of *P. guajava* leaf DCE and its various fractions [PG.(F2-F3), PG.(F2-F3).(F6-F9), and PG.(F2-F3).(F6-F9).(F4)] against HT-29 colon cancer cells. A total growth inhibition (TGI) assay showed that DCE and its three fractions had considerable antiproliferative effects. Similarly, Bazioli et al. (2020) prepared DCE from guava leaves which was fractionated to yield a fraction referred to as F_{FINAL}, which contained 49% guajadial. The antiproliferative activities of DCE and F_{FINAL} were tested using a TGI assay. DCE was found to be inactive against HT29 cells (TGI = 101.78 μ g/mL), but F_{FINAL} had moderate cytotoxic activity (TGI = 6.65 μ g/mL), which was even greater than the doxorubicin control (TGI = 10.34 μ g/mL). The authors proposed that the high levels of guajadial in F_{FINAL} are likely the reason for the difference in antiproliferative activity between the two guava leaf fractions.

Qin et al. (2016) isolated three novel meroterpenoids from *P. guajava* leaves, namely guajavadial A, B, and C, and found them to have significant cytotoxicity against human colon adenocarcinoma (SW-480), with IC₅₀ values greater than the cisplatin (a chemotherapy drug) control. From guava leaves, Zhu et al. (2019) isolated three compounds, namely, guavinoside E, guavinoside B, and 3,5-dihydroxy-2,4-dimethyl-1-O-(6'-O-galloyl- β -D-glucopyranosyl)-benzophenone. All three compounds had significant anticancer activity against human colon cancer cell lines HCT116 and HT29. Guavinoside B, the most active compound, concentration-dependently inhibited cell growth in HCT116 cells more strongly than in HT29 cells. Notably, guavinoside B did not show toxicity against normal colon cells (CCD-18Co), unlike 5-FU. Further testing against the HCT116 cell line showed suppression of colony formation and induction of apoptosis following guavinoside B treatment. Mechanistic studies showed both guavinoside B and 3,5-dihydroxy-2,4-dimethyl-1-O-(6'-O-galloyl- β -D-glucopyranosyl)-benzophenone increased the expression of p53, an inducer of apoptosis, and cleaved caspase-8. However, only guavinoside B

treatment increased p-ERK1/2 and p-JNK proteins (known to promote MAPK-induced apoptosis) and cleaved both caspase-8 and caspase-9 (regulators of apoptosis), suggesting that these pathways are related to the guavinoside B's stronger anticancer bioactivity.

Acetone extract of guava branch (GBA) caused concentration-dependent cytotoxicity and reduced cell viability by 30–70% in human colon cancer (HT29) cells as compared to control cells. Mechanistic studies found an increase in cells in the sub-G1 phase of the cell cycle as well as chromatin condensation and sharking, both of which are characteristics of apoptosis. The results indicate that the cytotoxic action of GBA is mediated through the induction of apoptosis via inhibition of the cell cycle (Lee and Park 2010).

Mbaveng et al. (2018) tested the cytotoxicity of a bark extract (PGB) against colon cancer HCT116 p53^{+/+} cells and its knockout clone HCT116 p53^{-/-}. It is well-known that p53 is a tumor suppressor gene that is activated in response to stressors, such as DNA damage and oxidative shock, where it plays a vital role in cell cycle regulation, apoptosis, and genomic stability (Woods and Vousden 2001). PGB had significant cytotoxic effects against HCT116 p53^{+/+} but not against HCT116 p53^{-/-}, which had a degree of resistance (IC_{50} ratio of resistant to sensitive line) of 2.18. The resistance of the knockout line suggests that the activity of p53 plays a role in PGB's cytotoxic effects.

Guava seed oil was not toxic (cell viability >80%) to human hepatocellular carcinoma (HepG2) cells 24 or 48 h following the treatment (Prommaban et al. 2019). Qin et al. (2016) found that guajadial A, B, and C, isolated from *P. guajava* leaves, had significant cytotoxicity against human hepatocellular carcinoma (SMMC-7721) cells. Guajadial C was the most potent, but all three had IC_{50} values less than the cisplatin control.

Gynecological cancers

The cytotoxicity of various *P. guajava* extracts and pure compounds have been evaluated against several gynecological cancers, including cervical and ovarian cancers.

According to a study conducted by Joseph and Priya (2010), a methanolic extract of *P. guajava* leaf showed pronounced cytotoxic activity against HeLa cervical epithelial adenocarcinoma cell line. Although no anticancer mechanistic pathway was investigated, the phytochemical characterization of the extract revealed the presence of several compounds, including tannins, alkaloids, saponins, terpenoids, flavonoids, cardiac glycosides, phenol, and carbohydrates. In a subsequent study, various *P. guajava* leaf extracts tested against HeLa cell line did not demonstrate significant cytotoxicity or antiproliferative activity (Sul'ain et al. 2012). In contrast, Braga et al. (2014) utilized an ethanolic extract on *P. guajava* leaves and the results showed significant cytotoxic activity via unknown mechanisms.

Feng et al. (2015) isolated four new compounds in addition to six known ones from *P. guajava* leaves to test against HeLa cells. Guavinoside C and guavinoside F had strong inhibitory activity, while quercetin had moderate

cytotoxicity. The observed antioxidant activity has been suggested as a possible anticancer mechanism of the compounds. Interestingly, the remaining compounds, guavinoside A, guavinoside B, guavinoside D, guavinoside E, quercetin-3-O-a-L-arabino-furanoside, quercetin-3-O-a-L-arabinopyranoside, and quercetin-3-O-b-D-galactopyranoside did not demonstrate significant cytotoxicity.

A hexane extract of *P. guajava* leaves demonstrated decreased viability of OV2008, an ovarian cancer cell line, via an unknown mechanism (Levy and Carley 2012). Rizzo et al. (2014) reported antiproliferative activity of guava leaf DCE and various fractions against OVCAR-3 (ovarian cancer) and NCI/ADR-RES (resistant ovarian cancer) cells. However, no mechanism of action was indicated. Another study investigated DCE and a guajadial-enriched fraction (F_{FINAL}) against OVCAR-3 and NCI/ADR-RES cells. DCE showed weak antiproliferative activity against OVCAR-3 ($TGI = 27.23 \mu\text{g/mL}$), while F_{FINAL} had potent activity ($TGI = 2.66 \mu\text{g/mL}$) similar to that of the doxorubicin control ($TGI = 2.12 \mu\text{g/mL}$). Likewise, in the NCI/ADR-RES cells, DCE had weak activity ($TGI = 50.51 \mu\text{g/mL}$) while F_{FINAL} had potent activity ($TGI = 6.19 \mu\text{g/mL}$) (Bazioli et al. 2020). The superior antiproliferative activity of F_{FINAL} fraction to that of DCE may be attributed to its high level of active compound guajadial.

Hematological cancers

Bontempo et al. (2012) prepared an acetone extract from the whole fruit and found that it decreased cell proliferation, increased apoptosis, and promoted cell differentiation in human acute promyelocytic leukemia (NB4) cells. However, in primary acute myeloid leukemia (AML) blast cells the effects of whole acetone fruit extract were limited to increased apoptosis and in AML (U937) it had no effects on the cell cycle or apoptosis at all. The antiproliferative effects on the NB4 cells were found to be due to a G1 cell cycle blockage of up to 80% and cell differentiation was due to an upregulation of granulocytic differentiation. To isolate which part of the fruit contributed the most to the antineoplastic activity against NB4 cells, extracts of the pulp, seeds, and peel were created. It was found that the pulp was mostly responsible for cell cycle arrest and apoptosis, the peel had the strongest cell differentiation induction activity, and the seeds were the weakest component showing only marginal inhibition of cell cycle progress. The total fruit and pulp extract showed increased levels of caspase-8 and caspase-9 activity and an overexpression of p21, p16, death receptor 5 (DR-5), Fas ligand (FASL), and Bcl-2-associated agonist of cell death (BAD), which are all mediators of apoptosis. Additionally, only the pulp extract showed a significant reduction in the cellular FLICE-like inhibitory protein long form, a strong inhibitor of caspase-8-mediated apoptosis, which provided a possible mechanism for its stronger activity.

Prommaban et al. (2019) used hexane extraction method to obtain guava seed oil (GSO) containing linoleic acid and antioxidants. GSO was found to inhibit the proliferation of

human erythroleukemia (K562) cells in a concentration-dependent manner. However, the underlying mechanism of antiproliferative effect was not reported. An aqueous acetone extract prepared from dried guava seeds showed moderate cytotoxicity whereas two isolated compounds, 1-O-3,4-dimethoxy-phenylethyl-4-O-3,4-dimethoxy cinnamoyl-6-O-cinnamoyl-b-D-glucopyranose and 1-O-3,4-dimethoxy-phenylethyl-4-O-3,4-dimethoxy cinnamoyl-b-D-glucopyranose, showed low toxicity against murine leukemia (P388) cells (Salib and Michael 2004).

Manosroi, Dhumtanom, and Manosroi (2006) found that guava leaf essential oil displayed potent cytotoxicity against P388 cells, and the observed effect was greater than the positive control vincristine, but not 5-FU. In a separate study, guava leaf hexane extract showed a concentration-dependent cytotoxic effect on AML (Kasumi-1) cells (Levy and Carley 2012). Based on TGI assay, DCE and its various fractions exhibited a strong growth inhibitory effect on leukemia (K562) cells with the most active fraction being PG.(F2-F3).(F6-F9) (Rizzo et al., 2014). Ashraf et al. (2016) found that methanol, hexane, and chloroform guava leaf extracts showed significant concentration-dependent cytotoxicity against human chronic myelogenous leukemia (KBM5) cells with a maximum effect of the hexane extract. The hexane extract also completely inhibited TNF- α -induced NF- κ B activation at a concentration of 25 mg/mL, but had little effect on cell viability. The investigators attributed the hexane fraction's strong cytotoxicity to its high content of vitamin E and caryophyllene, which are known for their strong anti-inflammatory properties.

Qin et al. (2016) found that novel guava leaf compounds, guajavadiol A, B, and C, had strong cytotoxicity against leukemia (HL-60) cells (IC_{50} =4.73, 6.49, 3.38 μ M respectively). However, this activity was found to be of lesser magnitude than cisplatin (IC_{50} =2.01 μ M).

Mbaveng et al. (2018) tested PBG against a drug-sensitive acute lymphocytic leukemia (ALL) cell line (CCRF-CEM) and found that it displayed considerable cytotoxicity. Mechanistic studies showed that PBG induced cell cycle arrest in the G0/G1 phase and increased cell necrosis. Additionally, PBG increased apoptosis by activating caspase-3, caspase-7, caspase-8, and caspase-9, depleting mitochondrial membrane potential, and increasing the production of reactive oxygen species (ROS). The same study also tested PBG against the ALL subline, CEM/ADR5000, which over-expresses P-glycoprotein, a cell membrane protein that pumps out foreign substances allowing cancer cells to be resistant to multiple drugs. It was found that PBG displayed significant cytotoxic effect against the CEM/ADR5000 cells which was greater than the doxorubicin control, suggesting its potential for treating drug resistant hematological malignancies.

There is at least one study that evaluated the anticancer effects of guava-derived products against lymphoma. However, an acetone total fruit extract did not show any antiproliferative activity in histiocytic lymphoma (U937) cells (Bontempo et al. 2012).

Ashraf et al. (2016) found that methanol, hexane, and chloroform guava leaf extracts showed significant concentration-dependent cytotoxicity in human multiple myeloma (U266) cells. The hexane and chloroform extracts had the better cytotoxic profiles compared to methanol extract.

Kim et al. (2014) tested CPO against U266 cells and found that it induced apoptosis and decreased the proliferative potential of the tumor cells. Mechanistic studies revealed that CPO time- and concentration-dependently suppressed signal transducer and activator of transcription 3 (STAT3) activation through the induction of SHP-1 tyrosine phosphatase. Furthermore, it was found that this STAT3 inhibition was mediated through the upstream downregulation of c-Src and JAK 1 and JAK 2. CPO also led to downregulation of proliferative markers cyclin D1, c-Myc, and β -catenin and upregulation of cell cycle inhibitor p21. The same study also found that CPO induced apoptosis in U266 cells and increased Bax, caspase-3, and PARP-cleavage (which is consistent with a pro-apoptotic phenotype). CPO also reduced the invasive potential of U266 cells by downregulating VEGFA, PLAUR, IL-8, MET, and cathepsin B. Additionally, by using melphlan-sensitive MM1.S cells (which lack active STAT3 and Src), the researchers found that CPO inhibited IL-6-induced STAT3 and Src activation.

Kidney cancer

A guava leaf extract (DCE) and its various fractions have been found to exert cytotoxic activities against 786-0 kidney adenocarcinoma cells (Rizzo et al., 2014). In an extension of this study, Bazioli et al. (2020) found that a guajadial-rich fraction (F_{FINAL}) exhibited more potent antiproliferative activity against 786-0 cells compared to DCE.

Lung cancer

Rizzo et al. (2014) evaluated antiproliferative effects of a guava leaf extract (DCE) and various fractions derived from it against NCI-H460 lung cancer cells. Although all test materials exerted growth inhibition, a potent activity was achieved with the fraction PG.(F2-F3).(F6-F9).(F4). In a subsequent study, Bazioli et al. (2020) reported that a guajadial-enriched fraction (F_{FINAL}) obtained from DCE showed a promising anticancer activity in NCI-H460 cells via unknown mechanisms.

Guavinoside C, guavinoside F and quercetin extracted from guava leaf had significant cytotoxic effects against A549 lung cancer cells which were thought to be mediated by antioxidant activity (Feng et al. 2015). Furthermore, novel guava leaf compounds, guajavadiol A, B, and C, had strong cytotoxic effects against A549 cells with IC_{50} values (5.62-5.78 μ M) lower than the cisplatin control (13.71 μ M) (Qin et al. 2016).

Neural cancer

In glioblastoma (U251) cells, DCE was found to have no cytotoxic activity, whereas its guajadial-rich fraction had

potent activity (Bazioli et al. 2020). The cytotoxicity of a guava bark extract (PGB) was tested against glioblastoma (U87MG) cells and the resistant subline U87MG. Δ EGFR. It was found to have weak cytotoxic effects against both cell lines (Mbaveng et al. 2018).

Prostate cancer

Numerous investigators used various guava-derived products and explored their efficacies against different prostate cancer models. Lin and Lin (2016) treated PC-3 cells with *P. guajava* seed polysaccharides (GSPS) with and without macrophage-conditioned media (MCM). It was found that GSPS alone did not inhibit PC-3 cell viability as compared to a paclitaxel control. However, MCM cultured with GSPS showed a concentration-dependent increased inhibition of PC-3 cell growth compared to MCM alone. A possible explanation for this finding is the negative correlation between PC-3 viability and the ratio of IL-6 plus TNF- α to IL-10 level [(IL-6 + TNF- α)/IL10] within the MCM.

Chen, Hsieh, et al. (2007) investigated the anticancer capabilities of *P. guajava* aqueous leaf extract on human prostate cancer (DU-145) cells compared to normal human prostate epithelial (PZ-HPV-7) cells. Treated DU-145 cells had decreased cell viability, reduced colony formation, and induced apoptosis in contrast to PZ-HPV-7 cells. A possible mechanism for the increased apoptosis may be the induction of active caspase-3. Additionally, the leaf extract suppressed the migration of DU-145 cells with simultaneous inhibition of the expression of matrix Metalloproteinase-2 (MMP-2) and MMP-9. Phytochemical analysis from the same laboratory revealed that *P. guajava* leaf extract contained a large amount of soluble polyphenolics (SP), including gallic acid (348 mg/g), catechin (102 mg/g), epicatechin (60 mg/g), rutin (100 mg/g), and quercetin (102 mg/g). However, when reconstituted, the SP components had only 40% of the original bioactivity of *P. guajava* leaf extract, suggesting that the soluble carbohydrate portion was responsible for the remaining 60% of bioactivity (Hsieh et al. 2007). Subsequently, a novel peptidoglycan named rhamnoallosan was isolated from the leaf extract, demonstrating strong antiproliferative activity against DU-145 cells complementary to the coexisting soluble polyphenolics. Finally, the same research group (Chen et al. 2010) examined the bioactivity of *P. guajava* leaf extract on LNCaP cells with and without the synthetic androgen R1881. In both experimental conditions, the leaf extract elicited cytotoxicity, inhibited cell proliferation and downregulated the expression of androgen receptor (AR) and prostate-specific antigen (PSA). Additionally, there was increased cell cycle arrest in the G0/G1 phase with a concentration-dependent increase in apoptosis. The molecular mechanisms of action of the leaf extract to induce apoptosis in LNCaP cells involved decreased Bcl-2/Bax ratio, upregulation of p53, inactivation of phospho-Akt (p-Akt), activation of phospho-p38 (p-p38), and elevation of phospho-Erk1 (p-Erk1) to phospho-Erk2(p-Erk2) ratio,

Peng et al. (2011) found that a *P. guajava* aqueous leaf extract suppressed viability and migration of DU-145 cells. Mechanistic studies found that the extract suppressed vascular endothelial growth factor (VEGF), IL-6, IL-8, MMP-2, and MMP-9, while it activated TIMP. The anticancer property of the extract was thought to be due to its high levels of polyphenolic and isoflavanoid compounds. Another study by Ryu et al. (2012) found that various *P. guajava* leaf extracts and a hexane fraction exhibited cytotoxic effects against PC-3 cell. The guava leaf hexane fraction (GHF) induced apoptotic effects and downregulated various proteins that mediate cell proliferation, cell survival, metastasis, and angiogenesis in PC-3 cells and arrested cells in the sub G1 phase through suppression of Akt and its downstream proteins mTOR and S6K1. GHF also decreased the activation of ERK, JNK, and p38 in PC-3 cells through downregulation of MAPK. Phytochemical characterization of GHF identified 60 compounds, including β -eudesmol, α -copaene, phytol, α -patchoulene (3.76%), CPO, caryophylla-3(15),7(14)-dien-6-ol, (*E*)-methyl isoeugenol, α -terpineol, and octadecane.

Rizzo et al. (2014) tested the antiproliferative activity of a guava leaf extract (DCE) and various fractions against PC-3 cells. Although the various test materials had exhibited considerable growth inhibitory effects, no mechanism of action was indicated. Most recently, DCE demonstrated a weak antiproliferative activity against PC-3 cells compared to a potent antiproliferative activity exerted by a guajadial-enriched fraction (FFINAL) (Bazioli et al. 2020).

Park et al. (2011) studied the cytotoxic effects of CPO extracted from *P. guajava* leaf on PC-3 cells. Their results demonstrated suppression of cell proliferation, increased apoptosis, and cell cycle arrest following CPO treatment. CPO not only inhibited the PI3K/Akt/mTOR/S6K1 signaling cascade, but also activated ERK, JNK, and p38 MAPK. CPO induced increased ROS generation from mitochondria, loss of mitochondrial membrane potential, release of cytochrome c, activation of caspase-3, and cleavage of PARP. Moreover, CPO downregulated the expression of various downstream gene products that mediate cell proliferation (cyclin D1), survival [Bcl-2, Bcl-xL, survivin, inhibitor of apoptosis-1 (IAP-1), and IAP-2], metastasis (cyclooxygenase-2), angiogenesis (VEGF), and increased the expression of p53 and p21. Interestingly, when CPO was employed in combination with the pharmacological PI3K/Akt inhibitor wortmannin and Akt inhibitor IV, the cytotoxic and PARP cleavage effects were further potentiated. The same research group (Kim et al., 2014) tested the anticancer properties of CPO against DU145 cells and found that it induced apoptosis and decreased the invasive and proliferative potential of the tumor cells. CPO inhibited STAT3 (but not STAT5) activation, through the induction of SHP-1 tyrosine phosphatase, mediated by upstream suppression of c-Src, JAK1, and JAK2. CPO was also found to reduce STAT3 translocation into the cell nucleus.

There is at least one *in vivo* study that showed that oral administration of *P. guajava* aqueous leaf extract (1.5 mg/mouse/day) demonstrated significant reduction of tumor

size with diminished serum PSA levels in LNCaP xenograft mouse tumor model. The tumor size of the control group increased 5.8-fold, while the leaf extract-treated group's tumor size increased only 3.7-fold by week 6. However, the mechanism of action of the observed in vivo antitumorigenic effect of the extract was not elucidated (Chen et al. 2010).

Sarcoma

Several studies evaluated the potential anticancer effect of *P. guajava* against sarcoma, which are connective tissues cancers. *P. guajava* fruit pulp, seed and peel extracts did not display cell death or cell cycle-regulatory activity in osteosarcoma (U2OS) cells (Bontempo et al. 2012). Sul'ain et al. (2012) created three different extracts from *P. guajava* leaves and found that petroleum ether extract showed superior antiproliferative activity against osteosarcoma (MG-63) cells to that of the methanolic and aqueous extract. Moreover, *P. guajava* leaf extract was found to exhibit cytotoxicity against murine fibrosarcoma L929sA cells (Kaileh et al. 2007). Mechanistic studies investigating the effects on NF- κ B were performed by transfecting L929sA fibroblasts with NF- κ B-dependent reporter gene constructs. A clear inhibition of NF- κ B reporter gene expression was observed with the extract. However, TNF-activated NF- κ B/DNA binding was not affected. These results indicate that the repression of NF- κ B by the leaf extract may be at the NF- κ B transactivation level.

Skin cancer

There is at least one study that investigated the anti-skin cancer potential of *P. guajava* using an in vitro model. Rizzo et al. (2014) tested the cytotoxic effects of DCE and its various fractions on melanoma (UACC-62) cells and found that the most active fraction was PG.(F2-F3).

One study investigated the in vivo effects of *P. guajava* against a mouse model of skin cancer. Seo et al. (2005) prepared three ethanolic extracts using *P. guajava* leaves, roots, and bark, as well as an extract prepared by boiling the *P. guajava* leaves in water. When female B6 mice were treated orally with various extracts and then inoculated subcutaneously with B16 melanoma cells, it was found that pretreatment with various ethanolic extracts reduced the growth of B16 tumor, whereas the aqueous leaf extract showed no protective effect against B16 tumor growth. Interestingly a maximum protective effect was achieved with the ethanolic leaf extract. However, the aforementioned extracts had no inhibitory effect in mice with existing tumors which indicates that their effects are preventative and not therapeutic. Mechanistic studies revealed that pretreatment with the ethanolic leaf extract downregulated the T regulatory (Tr) cell activity which leads to an increase in Th1 cells which likely mediates the prophylactic effect against B16 tumor cell growth.

Bioavailability and pharmacokinetics of guava constituents

Guava contains numerous phytochemicals that possess anti-cancer potential. Given the variety of components, the bioavailability and pharmacokinetic characteristics may differ. The bioavailability is the fraction of the ingested compound that reaches the systemic circulation and is able to be utilized, while bioaccessibility is the quantity that is released from the food matrix in the GI tract that becomes available for absorption.

Flavonoids are a common component of *P. guajava* that have demonstrated anticancer activities. Apigenin and quercetin are two such flavonoids studied extensively for their bioavailability and pharmacokinetic characteristics. In a study by Tang et al. (2017), apigenin was characterized by poor systemic availability due to its low lipid and water solubility. The main part of the ingested apigenin is either excreted unabsorbed or rapidly metabolized after absorption. In an attempt to resolve this issue, new technologies and formulations have been used to improve its bioavailability. Apigenin dissolution from the carbon nanopowder-apigenin system after 60 min was improved by 275% when compared with that of pure apigenin, and the relative oral bioavailability was enhanced by approximately 183% (Ding et al. 2014). Apigenin nanocrystals prepared by supercritical antisolvent process displayed more rapid dissolution velocity with a higher cumulative amount than coarse powder in vitro (Zhang et al. 2013). Additionally, a self-microemulsifying drug delivery system may improve the solubility and dissolution of apigenin, as it could increase the solubility of apigenin in water about 7500-fold (Zhao et al., 2013)

Historically, flavonoids were believed to be scarcely absorbed by the intestines and instead excreted into feces. However, more recent studies have shown that quercetin is absorbed by both the small and large intestine and subsequently converted to its conjugated metabolites (Terao, Kawai, and Murota 2008). Once ingested, intestinal bacteria exert glycosidase activity and hydrolyze the sugar unit to release quercetin in its aglycone form (Tamura et al. 1980). The quercetin aglycone is then further absorbed via the stomach or small intestine (Crespy et al. 1999; Crespy et al. 2002). This is mediated by either passive diffusion or organic anion transporting polypeptide-mediated absorption (Nait Chabane et al. 2009). Absorbed quercetin aglycone is then metabolized into other pharmacologically-active derivative forms in human plasma (Moon et al. 2000). Murota et al. (2002) demonstrated that oral administration of quercetin was partly absorbed via the body's lymphatic system, implying that the efficacy of absorption is improved with fat-soluble components in the diet.

Prolonged consumption of dietary quercetin resulted in low levels of quercetin metabolites being rapidly distributed amongst various organs (Shimoi et al. 2001). When long-term use of quercetin was studied in vivo, the quercetin and quercetin metabolites were widely distributed in rat tissues, with the highest concentrations in lungs and the lowest concentrations in the brain, white fat, and spleen. In a short-term in vivo pig study, the liver and kidney contained the highest concentrations of quercetin and quercetin metabolites, whereas the brain, heart, and spleen had the lowest

concentrations (de Boer et al. 2005). Research on the pharmacokinetics of quercetin in humans revealed that upon ingestion, the amount measured in human plasma is in the high nanomolar (100–200 nM) or low micromolar (0.5–1.5 μM) range (Spagnuolo et al. 2012; Notoya et al. 2004; Bulzomi et al. 2012; van der Woude et al., 2003). Supplementation with 1 g/day of quercetin for 28 days increased plasma concentration to 1.5 μM (Conquer et al. 1998; Manach et al. 2005). Additional research has found that the elimination half-life of quercetin is around 25 h, which indicates that a diet rich in quercetin could easily maintain a high plasma quercetin level (Hannum 2004; Michaud-Levesque, Bousquet-Gagnon, and Bélieau 2012; Katalinić et al. 2010; Jaramillo et al. 2010; Watjen et al., 2005). Therefore, chronic intake of polyphenols is necessary to obtain bioeffective concentrations of quercetin (Dajas 2012; Damianaki et al., 2000; Hempstock et al., 1998).

Lycopene is a lipophilic compound and its absorption from dietary sources is low and highly variable. Dietary intake of lycopene-rich foods is poorly correlated with plasma concentrations of lycopene. The extent of intestinal lymphatic transport and the bioavailability of lycopene were evaluated in a mesenteric lymph duct cannulated anesthetized rat model; however, a low bioavailability of $1.85 \pm 0.39\%$ was found (Faisal, O'Driscoll, and Griffin 2010). In the GI tract, specifically the small intestine, lycopene is packaged into micelles formed from bile salts and lipids and then passively absorbed. Once incorporated into chylomicrons, lycopene is transported from the intestinal mucosa to the general circulation via lymphatics. In the blood, low-density lipoprotein is the primary carrier of lycopene (van Breemen et al. 2002). The primary sites of lycopene accumulation in vivo are the liver, seminal vesicles, and prostate tissue (Gajic et al. 2006). Additionally, Liu et al. (2006) found that lycopene can be selectively accumulated by androgen-sensitive prostate cells and localized to the nuclear membrane and nuclear matrix, suggesting a possible role for a lycopene receptor or transporter. Nagarajan et al. (2019) developed a facile extraction process to isolate lycopene from pink guava decanter. The lycopene-pectin complex formation was measured and fitted against three different models, a first-order kinetic model, a second-order kinetic model, and a Peleg model. The two-site kinetic model demonstrated the best fitting using two separate rate constants, one for the fast phase ($k_f = 0.229\text{min}^{-1}$) and one for the slow phase ($k_s = 0.001\text{min}^{-1}$) of extraction.

While the bioavailability and pharmacokinetics of several phytochemicals that are found in guava have been studied, there is limited research on other guava-derived phytochemicals. Additional animal and human studies are needed to augment our knowledge regarding the bioavailability and bioaccessibility of the phytochemicals present in guava to understand their full therapeutic potential.

as safe" for human consumption per the Food and Drug Administration (GRAS 2021). The toxicity and safety of guava constituents were reviewed previously (Deguchi and Miyazaki 2010; Morais-Braga et al. 2016; Daswani, Ghokar, and Birdi 2017). Current literature on the toxicity of *P. guajava* and its components based on in vitro and in vivo studies is summarized in the following sections.

At least three studies investigated the in vitro toxicity of *P. guajava*. One of the earliest toxicity studies found no statistically significant alterations in the cell cycle or the number of chromosome alterations in cultured human peripheral lymphocytes after treatment with water infused with *P. guajava* leaves (tea) at 2.62 mg/mL, which is 10 times the concentration found in brewed tea (Teixeira et al. 2003). This finding supports that guava leaf tea is not toxic or mutagenic at high concentrations. In another study, the aqueous extract of guava leaves was tested for toxicity against human skin fibroblast cells and it was found that the median lethal concentration, defined as 50% cellular mitochondrial activity, was 3.5 mg/mL. Additionally, the results showed a high cell viability rate of 93% using an MTT assay, indicating low toxicity (Suwanmanee, Kitisin, and Luplertlop 2014). Guavinoside E, guavinoside B, and 3,5-dihydroxy-2,4-dimethyl-1-O-(6'-O-galloyl-β-D-glucopyranosyl)-benzophenone, isolated from guava leaf extract, showed no significant growth inhibition on CCD-18Co normal colon cells up to a concentration of 100 μM, indicating nontoxic characteristics (Zhu et al. 2019).

Several studies investigated the in vivo toxicity of guava and its components. Six Wistar rats were treated by intra-peritoneal (i.p.) injection with 26.2 mg/100 g body weight of tea made by infusing water with *P. guajava* leaves, which was ten times the concentration of brewed tea. After 24 h, it was found that there were no significant alterations in the cell cycle or chromosome number in the rat bone marrow cells, indicating that there are no toxic or mutagenic effects at this dose (Teixeira et al. 2003). Attawish et al. (1995) investigated the effects of tea made from fresh *P. guajava* leaves when administered orally to rats daily at 0.2, 2 and 20 g/kg of body weight per day (equivalent to 1, 10 and 100 times the therapeutic dose for treatment of diarrhea). After six months, symptoms of hepatotoxicity and renal disorders, such as hydronephrosis in males and nephrocalcinosis and pyelonephritis in females, were observed. No changes in weight or mortality were observed in Wistar rats 72 h after oral administration of 10–50 mg/100 g body weight of aqueous *P. guajava* leaf extract, indicating low toxicity (Etuk and Francis 2003). Ojewole, Awe, and Chiwororo (2008) determined that *P. guajava* leaf aqueous extract had a median lethal dose (LD₅₀) value of $1,534 \pm 69$ mg/kg body weight after mice were administered the extract i.p. at graded doses (50–3200 mg/kg body weight), supporting its low levels of toxicity. Uboh, Okon, and Ekong (2010) monitored the hepatic damage biomarkers, namely aspartate aminotransferase (AST), alanine aminotransaminase (ALT) and alkaline phosphatase (ALP), total protein, and albumin, after aqueous *P. guajava* leaf extract (200 mg/kg body weight) was administered to rats orally for 30 days. There were no significant changes in any

Toxicity and safety profiles of guava-derived agents

Guava has been used for both nutritional and medicinal purposes for thousands of years and is "generally recognized

of the hepatic biomarkers or signs of physical damage observed upon histopathological analysis of the liver tissues, indicating there was no hepatotoxicity. However, in the same experiment, a significant increase in red blood cell count, hematocrit, and hemoglobin concentration was found in the rats, indicating that aqueous *P. guajava* leaf extract did affect the hemopoietic system. Ekaluo et al. (2013) administered aqueous guava leaf extract to male rats at a dose of 100–300 mg/kg body weight for 70 days and found significant dose-dependent increases in the levels of luteinizing hormone, follicle stimulating hormone and testosterone as well as an increase in conception and litter size. No visible signs of acute toxicity or mortality were observed 24 h after Wistar male rats were orally administered aqueous *P. guajava* leaf extract at a dose range of 50–5000 mg/kg body weight, indicating low toxicity (Shekins and Dorothy 2014).

Chen, Hsieh, et al. (2007) confirmed that guava leaf extract at a dose of 2000 mg/kg body weight, *per os*, for 28 days was nontoxic. Moreover, no signs of acute toxicity or mortality were observed in rats after an oral dose of 2000 mg/kg body weight of *P. guajava* leaf ethanolic extract, indicating low toxicity (Dutta and Das 2010). Bazioli et al. (2020) treated 15 Swiss female mice orally with a guajadial-enriched DCE fraction (100 and 200 mg/kg body weight) and then monitored them during the first 4 h post-treatment as well as for 14 days for signs of toxicity. During the first 4 h both doses of the guava fraction showed treatment-induced piloerection, abdominal writhing, and lethargy, with the highest dose having more obvious effects. However, after 24 h, all the animals recovered and there were no deaths.

The acute toxicity of GSO (10 mg/kg body weight, *per os*) was tested on mice which were observed over 14 days (Prommaban et al. 2019). None of the mice showed any adverse effects or macroscopic organ abnormalities after necropsy, suggesting that the oral LD₅₀ of GSO was greater than 10 mg/kg body weight and it is relatively nontoxic to animals at this dosage. The same investigators also tested the subchronic toxicity on Wistar rats (6 groups each containing 5 males and 5 females) who were administered with different doses of GSO over 90 days. It was found that even at the highest dose (30 g linoleic acid equivalent GSO/kg body weight) no significant adverse effects or changes in liver, kidney, and hematological biomarkers were noted. Upon necropsy, no significant gross abnormalities were observed in all internal organs, including the heart, liver, kidneys, adrenal glands, intestines, uterus, testes, ovaries, spleen, lungs, and pancreas (Prommaban et al. 2019). Thus, GSO appears to be safe without negative short- or long-term effects when administered orally at this dosage.

There have also been several studies that investigate the toxicity of pure compounds of *P. guajava*. Zucco et al. (2002) found that betulinic acid did not display cytotoxicity against human normal dermal fibroblasts or human peripheral blood lymphocytes. In a 90-day oral chronic toxicity study of lycopene, the “no-observed-adverse-effect level” (NOAEL) was found to be 586 and 616 mg/kg body weight daily in male and female Wistar rats, respectively, which was the highest dose tested (Jonker et al. 2003). This finding is congruent with the European Food Safety Authority

recommendation that the acceptable daily intake of lycopene for humans is 0.5 mg/kg body weight/day (EFSA 2008). In a separate study, rats treated with high doses of morin (300–2400 mg/kg body weight) daily for 13 weeks showed a significant elevation in hepatic damage biomarkers as well as an increase in liver and kidney size. Using these results, the NOAEL level for morin was calculated to be approximately 299 and 365 mg/kg body weight for male and female mice, respectively (Cho et al. 2006). While numerous in vitro studies demonstrate that quercetin induces mutagenicity, in vivo studies with mice, rats, and rabbits show that quercetin is not carcinogenic and support that it is safe for consumption (Harwood et al., 2007). Lupeol has not been found to cause systemic toxicity in mice and rats at doses ranging from 30 to 2000 mg/kg body weight (Siddique and Saleem 2011). When apigenin was administered i.p. to mice at doses ranging from 25 to 200 mg/kg body weight, doses of 100 and 200 mg/kg body weight were found to raise the hepatic biomarkers ALT, AST, and ALP, as well as the ratio of oxidized/reduced glutathione and the level of lipid peroxides (Singh et al. 2012).

Overall, the literature available supports that *P. guajava* and its components are safe to use at therapeutic doses. However, some of the compounds were tested for toxicity using the maximum dose used for treatment, so there should be further investigation into the effects of larger doses. Additionally, more in vivo animal studies and human clinical trials are needed to confirm its nontoxicity and to determine its safety for use in humans.

Conclusion, challenges, and future perspectives

P. guajava is a glorious plant that has been utilized for centuries across many cultures for its nutritional and medicinal properties. In this review, we have provided a systemic analysis of *P. guajava*'s anticancer potential, which includes in vitro and in vivo studies that examined its chemopreventive and chemotherapeutic actions, as well as its phytochemicals, pharmacokinetics, and toxicity. Various parts of the guava tree, including the leaves, fruits, seeds, peels, pulp, bark, stem, and oil, have been studied. Additionally, specific phytochemicals, including CPO, 3,5-dihydroxy-2,4-dimethyl-1-O-(6'-O-galloyl-β-D-glucopyranosyl)-benzophenone, guajadial, guajavadial A-C, guavinoside B, C, E, and F, psidial A, psiguajadial A-B, quercetin, and rhamnoallosan, have been isolated and evaluated for anticancer efficacy. Various guava extracts, fractions, and isolated phytochemicals have been shown to exhibit antineoplastic effects through antiproliferative, pro-apoptotic, cell cycle regulatory, anti-inflammatory, antioxidant, anti-invasive, antimetastatic, and antiangiogenic effects (Figure 10). All these guava-derived products kill cancer cells and/or suppress tumor growth by regulating several diverse oncogenic and oncosuppressive molecules and signaling pathways (Figure 11). These anti-cancer pathways include, but are not limited to, decreasing proliferative factors (cyclin D1, c-Myc, MAPK, and β-catenin), pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, and NF-κB), metastatic factors (MMP-2, MMP-9, and ERK1/2),

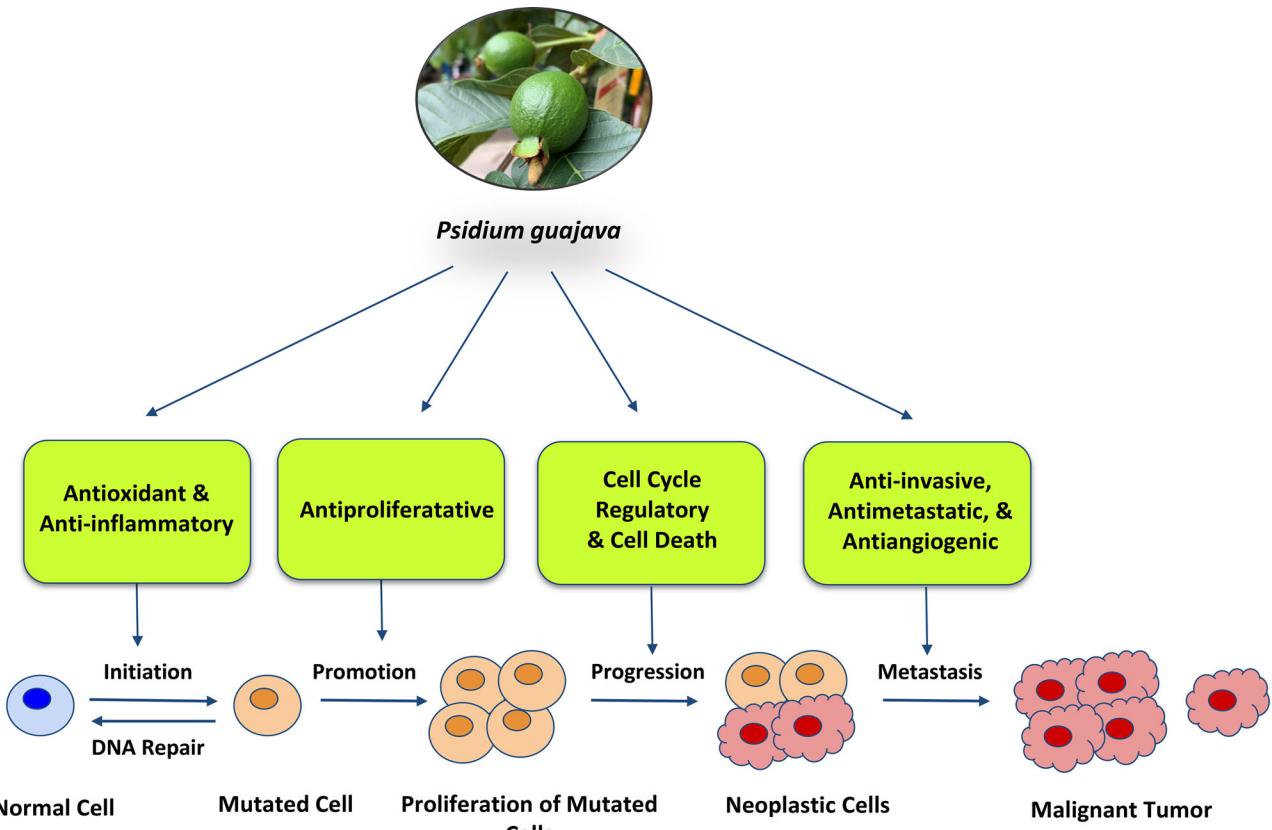


Figure 10. *P. guajava* constituents exert anticancer effects in different stages of cancer initiation, promotion, progression, and metastasis. Antioxidant and anti-inflammatory compounds prevent the initiation stage of cancer and promote DNA repair. Antiproliferative components inhibit the promotion stage. Cell cycle regulatory and cell death promoting constituents prevent the progression of mutated cells into neoplastic cells. Anti-invasive, antimetastatic, and antiangiogenic compounds inhibit metastasis which prevents the spread of malignancy.

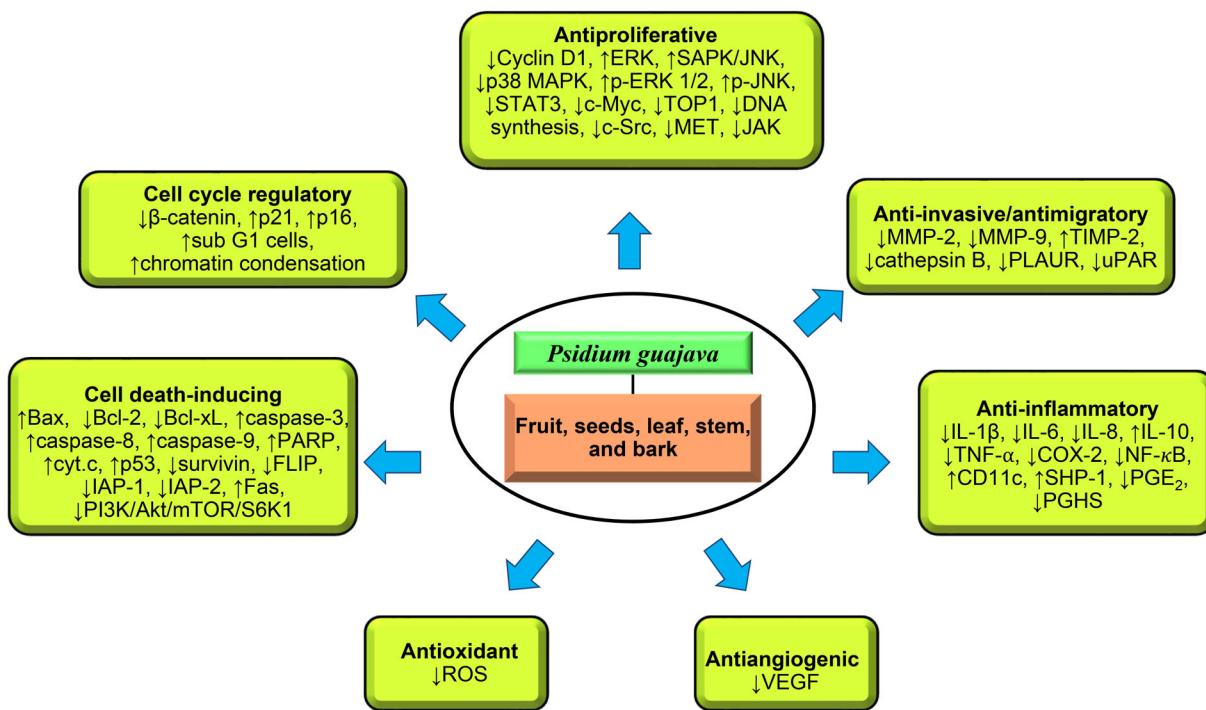


Figure 11. Overview of antitumor mechanisms and molecular targets of *P. guajava*-derived constituents based on in vitro and in vivo studies.

invasive factors (VEGF, PLAUR, IL-8, MET, and cathepsin B), and angiogenic factors (VEGF). Moreover, guava constituents also upregulate proteins involved in programmed cell

death (Bax, caspases, p53, DR-5, FASL, and BAD), prevent cellular oxidative stress (ROS), and regulate the cell cycle (p16, p21, and β -catenin).

The literature reviewed in this article demonstrates the potential of using *P. guajava* for the prevention and intervention of various cancer subtypes including breast, gastrointestinal, genitourinary, neurological, pulmonary, hematological, renal, and skin cancer. The vast majority of the current literature is limited to in vitro studies, as there were 71 in vitro versus 4 in vivo (Figure 9). The literature examined in this review shows the promising potential of guava phytoconstituents for specific cancer subtypes. Mammary, gastrointestinal, hematological, and prostatic cancers have been the most extensively investigated in vitro, while the in vivo studies involve mammary, prostatic, and skin cancer. The 4 in vivo studies achieved an average score quality of 27.5% based on SYRCLE's RoB tool, as several protocol details were not reported.

Limitations to *P. guajava*'s therapeutic utilization include the sparse research on its bioavailability and pharmacokinetics, in addition to the limited clinical research that has been conducted. While there is strong evidence of the bioavailability of certain nonspecific *P. guajava* phytochemicals, such as quercetin and lycopene, research on guava-specific phytochemicals is lacking. More studies on this topic should be conducted to better understand the metabolism and appropriate dosing of guava and its constituents to obtain desired cancer preventative and anticancer therapeutic effects. Several toxicity studies have been conducted and the majority have supported that *P. guajava* is safe at therapeutic doses.

Etminan et al. (2004) performed a meta-analysis of human studies on healthy males and found that dietary lycopene (12.7 mg per day), consumed through tomatoes, reduced the risk of prostate cancer (pooled relative risk = 0.90). However, the authors concluded that the effect was too modest to recommend lycopene supplements for prostate cancer prevention and that the inconsistent results in the literature require more research. There are 5.204 mg of lycopene per 100 g of guava so to intake 12.7 mg one would have to consume approximately 244 g of guava, which is about 4.5 fruits per day (Sato et al. 2010). Due to the conflicting evidence and lack of studies that use guava as a source of dietary lycopene, more research must be done before we can conclude that dietary guava can prevent cancer. Furthermore, the high amount of fruit required to achieve the chemopreventive levels of lycopene may not be practical. Clinical research using extracts that contain concentrated amounts of the active guava phytochemicals may produce better results and be more realistic for optimizing the cancer preventive potential of guava.

In our analysis, we have also identified several future research directions. Since guajadial is unique to *P. guajava*, it is the primary phytochemical examined in anticancer research. However, further studies should be conducted to explore the anticancer potential of additional guava phytochemicals as well as the chemical synergy of *P. guajava* phytochemicals, given that current literature mostly examines the phytochemicals individually. There is dire need for further in vivo and clinical studies, as the research shows guava has considerable promise as a chemotherapeutic agent. Although several mechanisms of *P. guajava* anticancer effects have been proposed by different investigators, further research must be

conducted to completely understand the molecular targets affected by these phytocompounds in various organ systems.

The bioavailability of guava must be further investigated in order to deduce the delivery system, formulation, and quantity of *P. guajava* that needs to be consumed to observe its anticancer effects. The in vitro results found in cancer cells should be replicated by in vivo studies to confirm anti-tumorigenic effects and underlying molecular mechanisms. Additionally, in order to conclude its safety in humans, in vivo animal studies with larger doses and clinical trials with human subjects must be conducted. Randomized clinical trials utilizing *P. guajava* should be conducted, as well as studies combining *P. guajava* phytochemicals with traditional chemotherapy to potentiate its effects. Considering the impressive and encouraging anticancer results presented in this in-depth review, *P. guajava*-derived products and phytoconstituents present a significant promise as cancer preventive and antineoplastic agents to combat human cancers.

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Disclosure statement

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