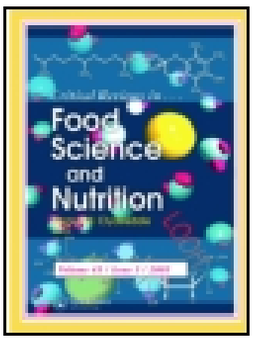

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REVIEW

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Mango (*Mangifera indica* L.): a magnificent plant with cancer preventive and anticancer therapeutic potential

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ABSTRACT

Mangifera indica L. (mango), a long-living evergreen plant belonging to the Anacardiaceae family, has been cultivated for thousands of years in the Indian subcontinent for its excellent fruits which represent a rich source of fiber, vitamin A and C, essential amino acids, and a plethora of phytochemicals. *M. indica* is extensively used in various traditional systems of medicine to prevent and treat several diseases. The health-promoting and disease-preventing effects of *M. indica* are attributed to a number of bioactive phytochemicals, including polyphenols, terpenoids, carotenoid and phytosterols, found in the leaf, bark, edible flesh, peel, and seed. *M. indica* has been shown to exhibit various biological and pharmacological activities, such as antioxidant, anti-inflammatory, immunomodulatory, antimicrobial, antidiabetic, antiobesity, and anticancer effects. There are a few studies conducted that have indicated the nontoxic nature of mango constituents. However, while there are numerous individual studies investigating anticancer effects of various constituents from the mango tree, an up-to-date, comprehensive and critical review of available research data has not been performed according to our knowledge. The purpose of this review is to present a comprehensive and critical evaluation of cancer preventive and anticancer therapeutic potential of *M. indica* and its phytochemicals with special focus on the cellular and molecular mechanisms of action. The bioavailability, pharmacokinetics, and safety profile of individual phytocomponents of *M. indica* as well as current limitations, challenges, and future directions of research have also been discussed.

KEYWORDS

Cancer; *in vitro*; *in vivo*; *Mangifera indica*; mango; phytochemicals; prevention; therapy

Introduction

Cancer is the second most common cause of death after cardiovascular disease and it represents a major health problem worldwide (Heron and Anderson 2016). Hence, novel therapeutic strategies to prevent and treat cancer are urgently needed to combat this global problem. Natural products, including fruits, vegetables, spices and herbs, have cancer preventive and therapeutic potential (Block et al. 2015; Bishayee and Sethi 2016; Kotecha, Takami, and Espinoza 2016). It has been estimated that high dietary consumption of vegetables and fruits (more than 400 g/day) could prevent at least 20% of all cancers (Gullett et al. 2010). Natural substances, including phytochemicals, are extensively used for new anticancer drug discoveries, and over 60% of the current anticancer drugs are derived from natural sources (Newman and Cragg 2012; Cragg and Pezzuto 2016).

Mangifera indica L., more commonly known as mango, is a plant of the Anacardiaceae family that is generally found in tropical and sub-tropical areas of the world. Although there are at least 69 different species belonging to the genus *Mangifera*, *M. indica* represents the most common species (Mukherjee 1972). *M. indica* is believed to have originated from India and Southeast Asia where it has been cultivated for more than 4000 years (Mukherjee 1953). Due to its widespread popularity, mango is the second most cultivated fruit following the banana, with an annual production of approximately 42 million tons (Galán Saúco 2004; Ediriweera, Tennekoon, and Samarakoon 2017). Although India has the highest production of the fruit, *M. indica* is also cultivated in more than 100 countries, including Pakistan, China, the Philippines, Thailand, Nigeria, Israel, Italy, Spain, Mexico, and Brazil (Galán Saúco 2004; Fowomola 2010; Lauricella et al. 2017). Mango, also known as "the king of fruits," is the national fruit of India and the Philippines, and it is the national tree of Bangladesh (Usman, Fatima, and Muhammad 2001). Both ripe and unripe mango fruits are processed into various value-added food products, such as juice, beverage (*panna*), pickles, chutney, sauce, puree, jam, cereal flakes, powder, nectar, and oils (Siddiq, Akhtar, and Siddiq 2012; Burton-Freeman, Sandhu, and Edirisinghe 2017). In addition to commercial processing, the use of mango is also increasing in various culinary preparations,

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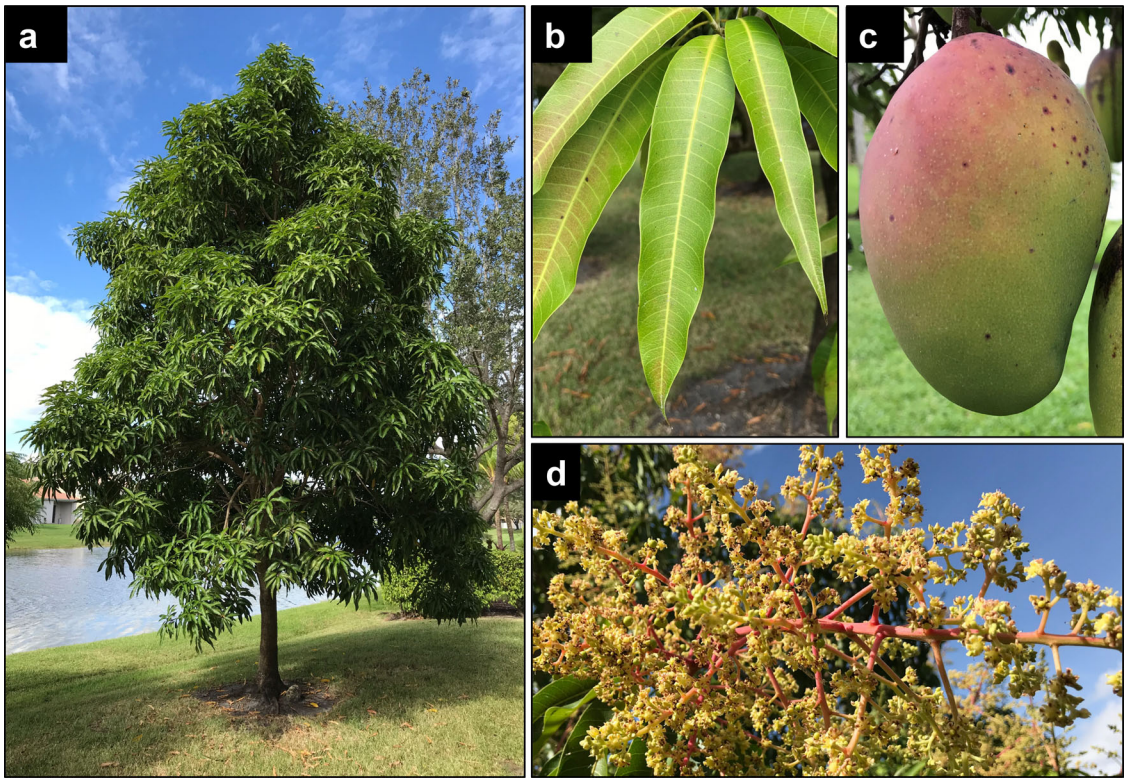

Figure 1. Various photographs of *M. indica* showing a whole tree (a), leaves (b), a fruit (c), and flowers (d).

including salads, salsa, ice-cream and various mango-flavored desserts (Tharanathan, Yashoda, and Prabha 2006). Mango kernel (seed) oil is used in the manufacturing of biscuits, muffins and also as a cocoa butter alternative (Abdel-Razik, Ashoush, and Yassin 2012).

M. indica is a medium to large evergreen tree (Figure 1a), the height of which can range from 10 to 45 m (Singh et al. 2013). The bark has been described as reddish to grayish-brown with a superficial cracked like appearance and the leaves are of variable size (Nandwani 2015). The leaves are broader at the base, although both ends taper to a point (Figure 1b). They are described as linear oblong and lanceolate-elliptical (Shah et al. 2010). There are about 3000 to 5000 small flowers in each panicles of the tree (Figure 1c), the color of which is whitish-red and yellowish-green with pots of red and purple on the petals (Shah et al. 2010; Nandwani 2015; Huda et al. 2015). The fruit (Figure 1d) is classified as a drupe with varying in size, weight, and color. The fruit has three components: (1) the exocarp is the smooth outer peel of the fruit which changes color as it ripens from green to yellow or orange-red; (2) the mesocarp, also referred to as the pulp of the mango, initially is dense, but softens as the fruit ripens to produce soft fibrils that are yellow-orange in color; and (3) the single oval shaped endocarp is also known as the mango seed or kernel (Lauricella et al. 2017).

Mango fruit in general has been a good source of carbohydrates, protein, fat, fiber, vitamins, minerals, and carotenoids (Jahurul et al. 2015; Lauricella et al. 2017). In addition to its sweet taste and nutritional value, various parts of *M. indica*, such as the bark, heartwood, leaf, fruit peel, pulp and seed, have ethnomedicinal use in indigenous and traditional systems of medicine (i.e. Ayurveda, Siddha and Unani) to treat a variety of human diseases (Khan et al. 2017). Countries such as Bangladesh, Benin, Brazil, the Canary islands, Cuba, Fiji, Ghana, Guyana, Haiti, India, Madagascar, Mali, Nicaragua, Nigeria, Pakistan, Peru, Senegal, Sri Lanka, Tanzania, and Tonga use mango constituents to treat various ailments and diseases, such as anemia, malaria, diarrhea, gastric disorders, hepatic disorders, cough, jaundice, anemia, hemorrhage, ulcers and diabetes (Ediriweera, Tennekoon, and Samarakoon 2017). The therapeutic effects of mango are possibly due to, but not limited to, antioxidant, anti-inflammatory, immuno-modulatory, antimicrobial, antibacterial, antiviral, antifungal, antiparasitic, antiallergic, antipyretic, antispasmodic, hypotensive, cardiotonic, hypolipidemic, antidiarrheal, gastroprotective, hepatoprotective, and antitumor properties of various phytochemicals present in *M. indica* (Shah et al. 2010; Ediriweera, Tennekoon, and Samarakoon 2017; Batool et al. 2018).

Most of the previous reviews provide a broad overview of various ethnopharmacological applications, diverse pharmacological properties, and multifaceted therapeutic potential of *M. indica* (Shah et al. 2010; Burton-Freeman, Sandhu, and Edirisinghe 2017; Ediriweera, Tennekoon, and Samarakoon 2017; Lauricella et al. 2017; Batool et al. 2018). Several articles focused on compounds from a particular anatomical part of the mango tree, e.g., seed (Nadeem, Imran, and Khalique 2016; Jin et al. 2019) or a specific phytochemical, e.g., mangiferin (Matkowski et al. 2013; Fomenko and Chi 2016; Gold-Smith, Fernandez, and Bishop 2016; Khurana et al. 2016; Núñez Sellés, Daglia, and Rastrelli 2016; Imran et al. 2017; Feng et al. 2019; Garrido-Suárez et al. 2020) or diseases linked to oxidative stress

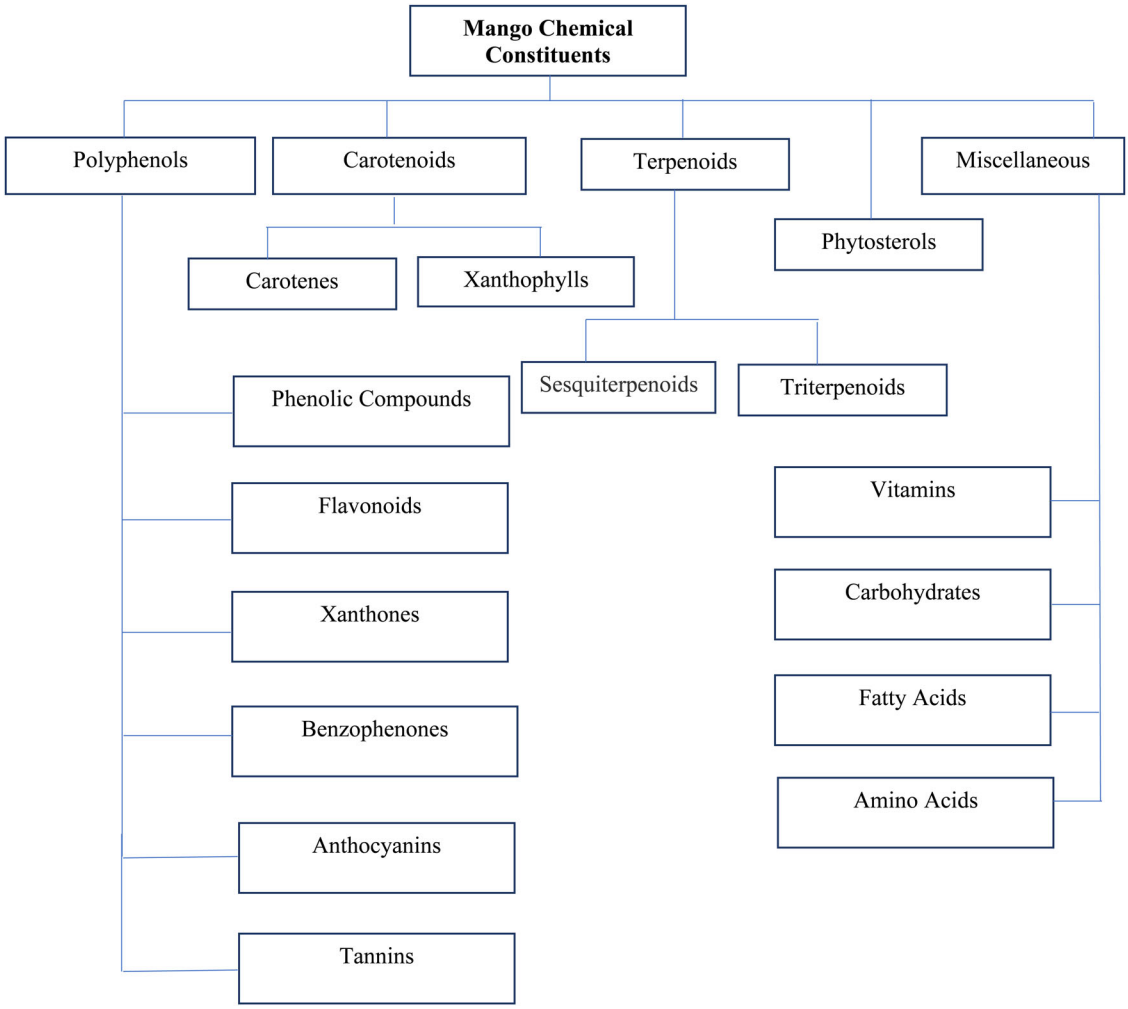

Figure 2. Overview of major classes of mango (*M. indica*)-derived phytochemicals.

(Sellés, Villa, and Rastrelli 2015). Although there are numerous individual experimental reports on anticancer effects of various constituents from the mango tree, an up-to-date, comprehensive and critical review of available research data on cancer prevention and intervention by various bioactive components of *M. indica* has not been performed according to our knowledge. The purpose of this work is to critically analyze the available literature to provide an exhaustive overview of cancer preventive and therapeutic potential of *M. indica* with an emphasis on molecular mechanisms of action.

Phytochemical profiles of *M. indica*

The phytochemicals of mango differ depending on cultivar, region of planting, cultural practices as well plant nutritional conditions (Maldonado-Celis et al. 2019). Various anatomical parts of a mango tree, including fruits (flesh, peel, and seeds), flowers, leaves and stem bark, produce different types of phytochemicals. These phytochemicals can be broadly classified into polyphenols, terpenoids, carotenoids, sterols, carbohydrates, amino acids, fatty acids and vitamins (Figure 2). Polyphenols, including flavonoids, xanthones, and phenolic acids, are the most abundant compounds in *M. indica*. The major polyphenolic phytochemicals in mango plant and fruits are gallic acid, ellagic acid, propyl and methyl gallate, mangiferin, catechins, quercetin, kaempferol, rhamnetin, anthocyanins, benzoic acid, and protocatechuic acid (Figure 3) (Rymbai et al. 2013; Ediriweera, Tennekoon, and Samarakoon 2017; Kabir, Shekhar, and Sidhu 2017). The mango plant as well as its fruit contain other phytochemicals, such as triterpenoids (lupeol and friedelin), carotenoids (β-carotene and lutein), phytosterols (campesterol and β-sitosterol), fatty acids (stearic acid and oleic acid), amino acids (aspartic acid, proline, valine, cysteine, alanine, threonine, and tryptophan) and major nutrient, such as ascorbic acid (Figure 4) (Rai et al. 2007; Ajila, Rao, and Rao 2010; Anjaneyulu et al. 1999; Abdalla et al. 2007; Palafox-Carlos, Yahia, and González-Aguilar 2012; Ghosal, Biswas, and Chattopadhyay 1978). A detailed description of mango phytochemicals is provided elsewhere (Maldonado-Celis et al. 2019). A list of reported phytochemicals from different parts of mango (*M. indica*) is provided in Table 1.

The mango fruit contains several aroma-active compounds which confer the mango with an esthetic and sweet fragrance. At least 54 aroma-active compounds were reported from tree ripened fruits of five mango cultivars *viz.* Haden, White Alfonso, Praya Sowoy, Royal Special, and Malindi (Munafo et al. 2014). Mango fruits that are in green

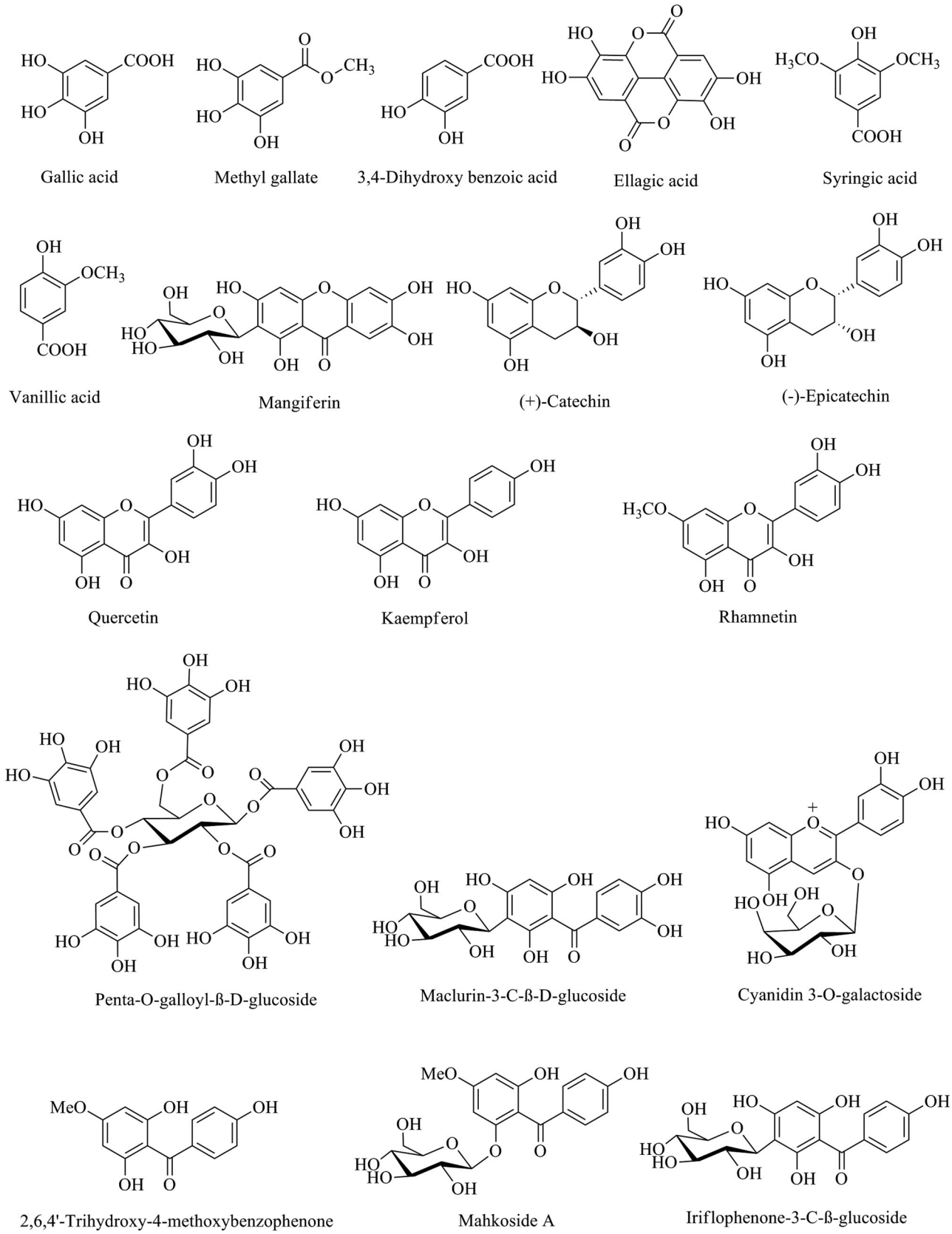

Figure 3. Chemical structures of major polyphenolic compounds present in mango (*M. indica*).

stage contain several amino acids, including aspartic acid, proline, valine, and cysteine (Figure 4) (Ghosal, Biswas, and Chattopadhyay 1978). A literature survey indicated that 372 volatile compounds were identified from 20 mango cultivars by gas chromatography (GC) and gas chromatography–mass spectrometry (GC-MS) analysis and terpene hydrocarbons were the major volatile compounds (Pino et al. 2005). There are several bioactive compounds, such as mangiferin,

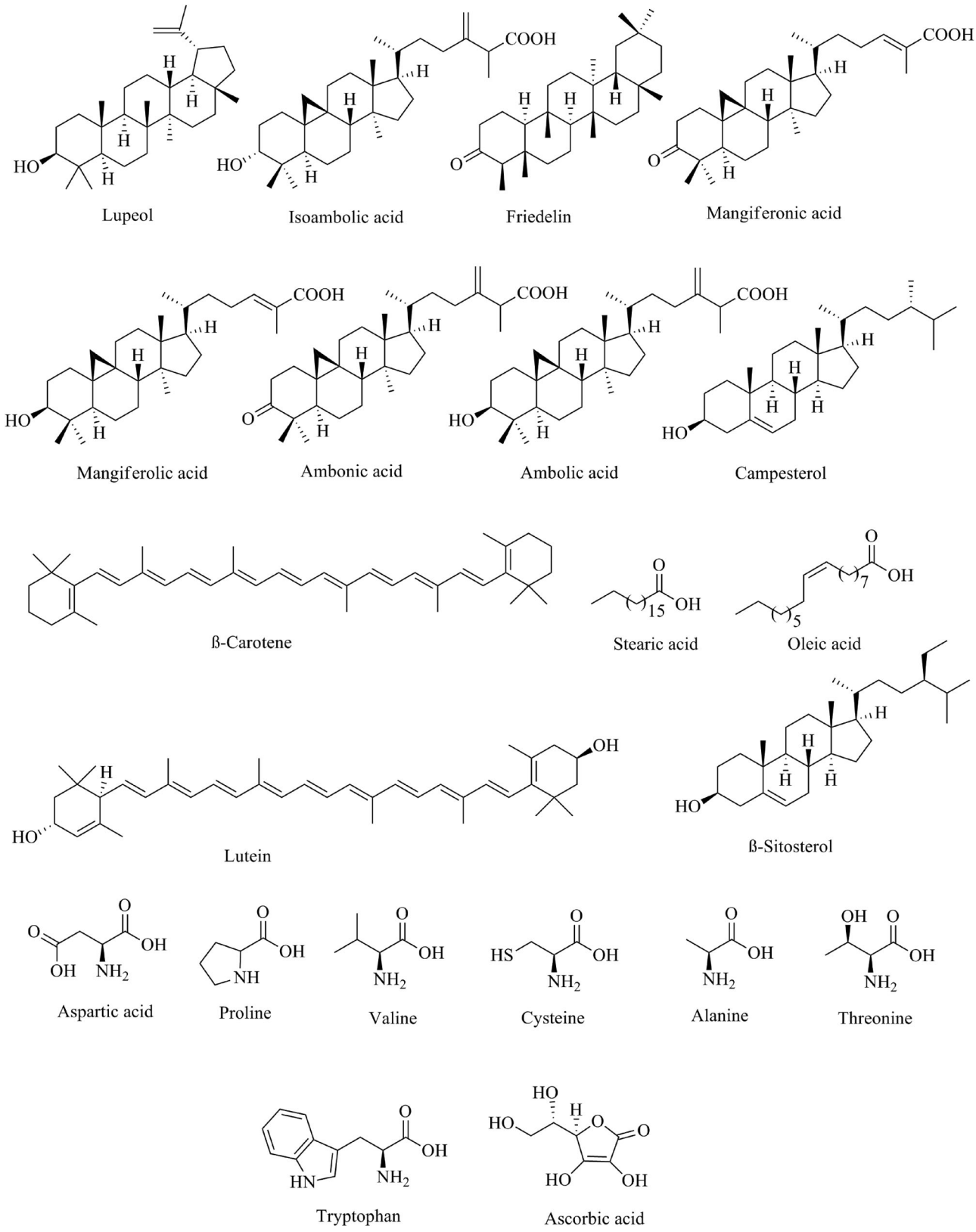

Figure 4. Chemical structures of major terpenoids, fatty acids and amino acids present in mango (*M. indica*).

α-amyrin, β-amyrin, homomangiferin, citric acid, quercetin, kaempferol, lupeol, myricetin, β-myrcene, α-pinene, β-pinene, and protocatechuic acid are present in mango fruit (Rai et al. 2007).

Raw and ripe mango fruits are a rich source of polyphenols and carotenoids (Ajila, Rao, and Rao 2010). The major phenolic compounds present in mango peel extract are syringic acid, quercetin, mangiferin, mangiferin pentoside, ellagic acid, protocatechuic acid, gentisic acid and gallic acid (Figure 3) (Ajila, Rao, and Rao 2010). Two resorcinol derivatives, namely 5-(11'*Z*-heptadecenyl)-resorcinol and 5-(8'*Z*,11'*Z*-heptadecadienyl)-resorcinol, were isolated from

Table 1. Phytochemicals extracted from various anatomical parts of mango tree (*M. indica* L.).

Compound name	Plant parts	References
Phenolic compounds		
(−)-Epicatechin	Stem bark, pulps	Núñez Sellés et al. 2002; Schieber, Ullrich, and Carle 2000
(+)-Catechin	Stem bark, leaves, flowers, pulps	Núñez Sellés et al. 2002; Ghosal, Biswas, and Chattopadhyay 1978; Schieber, Ullrich, and Carle 2000
1,2,3,4,6-Penta-*O*-galloyl-β-D-glucopyranose	Kernel	Nithitanakool, Pithayanukul, and Bavovada 2009
3-*C*-Gluco-Me-6-(*O*-triMegalloy)-2,4-dimethoxybenzoate	Flowers	Ghosal, Biswas, and Chattopadhyay 1978
5-(11′*Z*-heptadecenyl)-resorcinol	Peels	Knodler et al. 2008
5-(8′*Z*,11′*Z*-heptadecadienyl)-resorcinol	Peels	Knodler et al. 2008
Benzoic acid	Stem bark, leaves, pulps	Núñez Sellés et al. 2002; Elzaawely and Tawata 2010; Schieber, Ullrich, and Carle 2000
Benzoic acid propyl ester	Stem bark	Núñez Sellés et al. 2002
Caffeic acid	Kernel, pulps	Abdalla et al. 2007; Schieber, Ullrich, and Carle 2000
Chlorogenic acid	Fruits	Palafox-Carlos, Yahia, and González-Aguilar 2012
Cinamic acid	Kernel	Abdalla et al. 2007
Coumaric acid	Pulps	Schieber, Ullrich, and Carle 2000
Coumaric acid glycoside	Fruits	Krenek, Barnes, and Talcott 2014
Coumarin	Kernel	Abdalla et al. 2007
Ellagic acid	Flowers, peels, pulps	Ediriweera, Tennekoon, and Samarakoon 2017; Ajila, Rao, and Rao 2010; Schieber, Ullrich, and Carle 2000
Ester-mono-galloyl glucoside	Fruits	Krenek, Barnes, and Talcott 2014
Ethyl gallate	Leaves	Elzaawely and Tawata 2010
Ferulic acid	Leaves, pulps, kernel	Elzaawely and Tawata 2010; Schieber, Ullrich, and Carle 2000; Abdalla et al. 2007
Ferulic acid hexoside	Fruits	Krenek, Barnes, and Talcott 2014
Gallic acid	Stem bark, leaves, peels, kernel, fruits	Núñez Sellés et al. 2002; Ghosal, Biswas, and Chattopadhyay 1978; Elzaawely and Tawata 2010; Ajila, Rao, and Rao 2010; Nithitanakool, Pithayanukul, and Bavovada 2009; Krenek, Barnes, and Talcott 2014;Schieber, Ullrich, and Carle 2000
Gallic acid methyl ester	Stem bark, kernel	Núñez Sellés et al. 2002; Nithitanakool, Pithayanukul, and Bavovada 2009
Gallic acid propyl ester	Stem bark	Núñez Sellés et al. 2002
Gallocatechin	Leaves, flowers	Ghosal, Biswas, and Chattopadhyay 1978
Galloyl di-glucoside	Fruits	Krenek, Barnes, and Talcott 2014
Gentisic acid	Peels	Ajila, Rao, and Rao 2010
Gentisyl-protocatechuic acid	Peels	Ajila, Rao, and Rao 2010
Hepta-*O*-galloyl hexose	Peels	Ajila, Rao, and Rao 2010
Kinic acid	Stem bark	Singh et al. 2015
m-Coumaric acid	Pulps	Schieber, Ullrich, and Carle 2000
Me-6-(*O*-tri megalloyl)-2,4-dimethoxybenzoate	Flowers	Ghosal, Biswas, and Chattopadhyay 1978
m-Hydroxybenzoic acid	Pulps	Schieber, Ullrich, and Carle 2000
Mixture of 5-(12-*cis*-heptadecenyl)- and 5-pentadecyl-resorcinols	Fruits	Scartezzini and Speroni 2000
p-Hydroxy benzoic acid	Leaves, pulps, fruits	Elzaawely and Tawata 2010; Schieber, Ullrich, and Carle 2000; Krenek, Barnes, and Talcott 2014
Protocatechuic acid (3,4-dihydroxy benzoic acid)	Stem bark, leaves, peels, pulps, fruits	Núñez Sellés et al. 2002; Ghosal, Biswas, and Chattopadhyay 1978; Ajila, Rao, and Rao 2010; Schieber, Ullrich, and Carle 2000
Pyrogallol	Leaves	Elzaawely and Tawata 2010
Shikimic acid	Stem bark	Singh et al. 2015; Scartezzini and Speroni 2000
Sinapic acid	Fruits	Krenek, Barnes, and Talcott 2014
Sinapic acid hexoside	Fruits	Krenek, Barnes, and Talcott 2014
Sodium gallate	Peels	Ajila, Rao, and Rao 2010
Syringic acid	Leaves, peels	Elzaawely and Tawata 2010; Ajila, Rao, and Rao 2010
Syringic acid hexoside+	Peels	Ajila, Rao, and Rao 2010
Vanillic acid	Leaves, pulps, fruits	Elzaawely and Tawata 2010; Schieber, Ullrich, and Carle 2000; Palafox-Carlos, Yahia, and González-Aguilar 2012
Vanillin	Kernel	Abdalla et al. 2007
Flavonoids		
(–)-Epicatechin [2-(3,4-dihydroxyphenyl]-3,4-dihydro-2*H*-chromene-3,5,7-triol	Leaves	Kanwal et al. 2009
(–)-Epicatechin-3-O-β-glucopyranoside	Leaves	Kanwal et al. 2009
5-Hydroxy-3-(4-hydroxylphenyl) pyrano [3,2-g] chromene-4 (8*H*)-one	Leaves	Kanwal et al. 2009
6-(*p*-Hydroxybenzyl) taxifolin-7-O-β-D-glucoside (tricuspid)	Leaves	Kanwal et al. 2009
7-O-Methylquercetin-3-O-β-L-rhamnopyranoside	Leaves	Ge et al. 2011
Amentoflavone	Leaves	Ge et al. 2011
Apigenin	Pulps	Schieber, Ullrich, and Carle 2000
Eriodictyol-*O*-dihexoside	Fruits	Krenek, Barnes, and Talcott 2014
Eriodictyol-*O*-hexoside	Fruits	Krenek, Barnes, and Talcott 2014
Kaempferol	Flowers	Ghosal, Biswas, and Chattopadhyay 1978
Kaempferol-3-O-β-glucopyranoside	Peels, pulps, kernel	Berardini, Fezer, et al. 2005; Berardini, Knodler, et al. 2005; Schieber, Ullrich, and Carle 2000; Ribeiro et al. 2008
Kaempferol-hexose	Pulps	Schieber, Ullrich, and Carle 2000
Kaempferol-pentose	Pulps	Schieber, Ullrich, and Carle 2000
Myricetin	Flowers, pulps	Ghosal, Biswas, and Chattopadhyay 1978; Schieber, Ullrich, and Carle 2000

(*continued*)

Table 1. Continued.

Compound name	Plant parts	References
Quercetin	Flowers, peels, pulps, kernel	Ghosal, Biswas, and Chattopadhyay 1978; Ajila, Rao, and Rao 2010; Schieber, Ullrich, and Carle 2000; Ribeiro et al. 2008
Quercetin 3-O-arabinofuranoside	Peels, kernel	Schieber, Berardini, and Carle 2003; Ribeiro et al. 2008
Quercetin 3-O-arabinopyranoside	Peels, pulps	Berardini, Fezer, et al. 2005; Berardini, Knodler, et al. 2005; Schieber, Ullrich, and Carle 2000
Quercetin 3-O-galactoside (hyperin)	Peels, leaves, pulps, kernel	Schieber, Ullrich, and Carle 2000; Ribeiro et al. 2008; Ge et al. 2011
Quercetin 3-O-xyloside	Peels, seed-kernel	Berardini, Fezer, et al. 2005; Berardini, Knodler, et al. 2005; Ribeiro et al. 2008
Quercetin-3-O-α-glucopyranosyl-(1-2)-β-glucopyranoside	Leaves, peels	Kanwal et al. 2009; Berardini, Fezer, et al. 2005; Berardini, Knodler, et al. 2005
Quercetin-3-O-β-glucopyranoside	Leaves, peels, pulps, kernel	Ge et al. 2011; Schieber, Ullrich, and Carle 2000; Ribeiro et al. 2008
Quercetin-3-O-β-L-rhamnopyranoside	Leaves, peels, pulps, kernel	Ge et al. 2011; Berardini, Fezer, et al. 2005; Berardini, Knodler, et al. 2005; Schieber, Ullrich, and Carle 2000; Ribeiro et al. 2008
Rhamnetin 3-O-β-galactopyranoside	Peels	Berardini, Fezer, et al. 2005; Berardini, Knodler, et al. 2005
Rhamnetin-3-O-β-D-glucopyranoside	Leaves, peels,	Ge et al. 2011, Berardini, Fezer, et al. 2005; Berardini, Knodler, et al. 2005
Fatty acids and dicarboxylic acids		
Arachidonic acid	Kernel	Abdalla et al. 2007
Eicosatrienoic acid	Stem bark	Rymbai et al. 2013
Estearic acid	Stem bark	Rymbai et al. 2013
Linoleic acid	Stem bark, kernel, fruits	Rymbai et al. 2013; Abdalla et al. 2007
Linolenic acid	Seed-kernel, fruits	Abdalla et al. 2007
Malonic acid	Stem bark	Rymbai et al. 2013
Myristic acid	Stem bark, kernel	Rymbai et al. 2013; Abdalla et al. 2007
n-Pentacosanol	Fruits	Ediriweera, Tennekoon, and Samarakoon 2017
Oleic acid	Kernel, fruits	Abdalla et al. 2007
Palmitic acid	Stem bark, kernel	Rymbai et al. 2013, Abdalla et al. 2007
Stearic acid	Kernel	Abdalla et al. 2007
Succinic acid	Stem bark	Rymbai et al. 2013
Sesquiterpenoids		
Aromandrene	Stem bark	Rymbai et al. 2013
Hinesol	Stem bark	Rymbai et al. 2013
α-Guaiene	Stem bark	Rymbai et al. 2013
β-Elemene	Stem bark	Rymbai et al. 2013
β-Eudesmol	Stem bark	Rymbai et al. 2013
β-Selinene	Stem bark	Rymbai et al. 2013
Triterpenoids		
23-Epimeric 3β,23-dihydroxycycloart-24-en-26-oic acid	Stem bark	Anjaneyulu et al. 1999
23-Hydroxymangiferolic acid	Stem bark	Nguyen et al. 2016
23-Hydroxymangiferonic acid	Stem bark	Nguyen et al. 2016
24(*R*)-3-oxo-24-methylenecycloartan-26-ol	Stem bark	Anjaneyulu et al. 1999
24-Methylenecycloartane-3β,26-diol/24-Methylencycloartan-3,26-diol	Stem bark, fruits	Anjaneyulu et al. 1989; Anjaneyulu et al. 1999; Scartezzini and Speroni 2000; Ediriweera, Tennekoon, and Samarakoon 2017; Nguyen et al. 2016
27-Hydroxymangiferolic acid	Stem bark	Nguyen et al. 2016
27-Hydroxymangiferonic acid	Stem bark	Nguyen et al. 2016
29-Hydroxymangiferonic acid (3-oxo-29-hydroxycycloart-24E-en-26-oic acid)	Stem bark	Anjaneyulu et al. 1985
2α,3β,23-Trihydroxyurs-12,20(30)-dien-28-oic acid	Leaves	Pan et al. 2016
30-Desmethyl-urs-3-on-20-ol (Mangiferdesmethylursanone)	Stem bark	Gupta and Ali 1999
3-Ketodammar-24E-ene-20S,26-diol	Stem bark	Anjaneyulu et al. 1985
3-oxo-23(R or S)-hydroxycycloart-24-en-26-oic acid	Stem bark	Anjaneyulu et al. 1999
3-oxo-Taraxastane-20-(R or S)-ol [Ψ-taraxastanonol]	Stem bark	Anjaneyulu et al. 1999
3α,22(R or S)-Dihydroxycycloart-24*E*-en-26-oic acid	Stem bark	Anjaneyulu et al. 1989; Anjaneyulu et al. 1999
3α,27-Dihydroxycycloart-24*E*-en-26-oic acid	Stem bark	Anjaneyulu et al. 1989
3β,22(R or S)-dihydroxycycloart-24*E*-en-26-oic acid	Stem bark	Anjaneyulu et al. 1989
3β,23(R or S)-Dihydroxycycloart-24*E*-en-26-oic acid	Stem bark	Anjaneyulu et al. 1989; Anjaneyulu et al. 1999
3β-Hydroxycycloart-24-en-26-al	Stem bark, fruits	Anjaneyulu et al. 1989; Scartezzini and Speroni 2000; Ediriweera, Tennekoon, and Samarakoon 2017
8,26-Cyclo-urs-21-en-3β,20β-diol	Leaves	Pan et al. 2016
Actinidic acid	Leaves	Pan et al. 2016
Ambolic acid	Stem bark	Anjaneyulu et al. 1999; Nguyen et al. 2016
Ambonic acid	Stem bark	Anjaneyulu et al. 1999; Nguyen et al. 2016
Arjunolic acid	Leaves	Pan et al. 2016
C-24 Epimer of cycloart-25-ene-3β,24,27-triol	Stem bark	Anjaneyulu et al. 1989; Anjaneyulu et al. 1985
C-24 Epimer of cycloart-25-ene-3β,24-diol	Stem bark, fruits	Anjaneyulu et al. 1989; Scartezzini and Speroni 2000; Ediriweera, Tennekoon, and Samarakoon 2017
C-24 Epimer of cycloartane-3β,24,25-triol	Stem bark	Anjaneyulu et al. 1989; Anjaneyulu et al. 1985
Cycloart-23-ene-3β,25-diol	Stem bark	Anjaneyulu et al. 1989
Cycloart-24-ene-3β,26-diol	Stem bark	Anjaneyulu et al. 1989; Anjaneyulu et al. 1985
Cycloartane-30-ol	Stem bark	Khan et al. 1994
Cycloartane-3β,30-diol	Stem bark	Khan et al. 1994
Cycloartane-3β,25-diol	Stem bark	Anjaneyulu et al. 1989
Cycloartenol	Stem bark, fruits	Anjaneyulu et al. 1989;Scartezzini and Speroni 2000; Ediriweera, Tennekoon, and Samarakoon 2017

(*continued*)

Table 1. Continued.

Compound name	Plant parts	References
Dammarenediol-II	Stem bark, fruits	Anjaneyulu et al. 1985; Anjaneyulu et al. 1985; Scartezzini and Speroni 2000; Ediriweera, Tennekoon, and Samarakoon 2017
epi-Ψ-Taraxastane-3β,20-diol	Stem bark, fruits	Anjaneyulu et al. 1989; Scartezzini and Speroni 2000; Ediriweera, Tennekoon, and Samarakoon 2017; Anjaneyulu, Babu, and Connolly 1994
Friedelan-3α-ol	Roots	Anjaneyulu, Babu, and Connolly 1994
Friedelan-3β-ol	Roots	Rai et al. 2007; Anjaneyulu, Babu, and Connolly 1994
Friedelin	Leaves, roots	Rai et al. 2007; Anjaneyulu, Babu, and Connolly 1994; Scartezzini and Speroni 2000
Glochidonol	Flowers	Ghosal, Biswas, and Chattopadhyay 1978
Hopane/lupane-1β,3β,22-triol	Stem bark	Anjaneyulu et al. 1989
Hydroxymangiferolic acid	Stem bark	Anjaneyulu et al. 1989
Indicoside A	Stem bark	Khan et al. 1993
Indicoside B	Stem bark	Khan et al. 1993
Isoambolic acid	Stem bark	Nguyen et al. 2016
Isomangiferolic acid	Stem bark	Anjaneyulu et al. 1989
Lupenone	Flowers	Ghosal, Biswas, and Chattopadhyay 1978
Lupeol	Leaves, flowers	Pan et al. 2016; Ghosal, Biswas, and Chattopadhyay 1978; Scartezzini and Speroni 2000
Mangiferolate A	Stem bark	Nguyen et al. 2016
Mangiferolate B	Stem bark	Nguyen et al. 2016
Mangiferolic acid	Stem bark	Nguyen et al. 2016; Anjaneyulu et al. 1989
Mangiferonic acid	Stem bark	Nguyen et al. 2016; Anjaneyulu et al. 1989
Methyl ambonate	Stem bark	Nguyen et al. 2016
Methyl ambulate	Stem bark	Nguyen et al. 2016
Methyl mangiferonate	Stem bark	Anjaneyulu et al. 1985
Ocotillol II	Stem bark, fruits	Anjaneyulu et al. 1985;Scartezzini and Speroni 2000; Ediriweera, Tennekoon, and Samarakoon 2017
Olean-11-one-13(18)-ene (mangiferoleanone)	Stem bark	Gupta and Ali 1999
Taraxerone	Stem bark	Anjaneyulu et al. 1989
Urs-3-one (mangiferursanone)	Stem bark	Gupta and Ali 1999
Ursolic acid	Flowers	Ghosal, Biswas, and Chattopadhyay 1978
α-Amyrin	Stem bark, fruits	Anjaneyulu et al. 1989;Scartezzini and Speroni 2000; Ediriweera, Tennekoon, and Samarakoon 2017
β-Amyrin	Stem bark, fruits	Anjaneyulu et al. 1989; Scartezzini and Speroni 2000; Ediriweera, Tennekoon, and Samarakoon 2017
Phytosterols		
Δ-Avenasterol	Kernel	Abdalla et al. 2007
5α-Stigrnastane-3β,6α-diol	Stem bark	Anjaneyulu, Babu, and Connolly 1994
6β-Hydroxycampest-4-en-3-one	Stem bark	Anjaneyulu, Babu, and Connolly 1994
6β-Hydroxystigmast-4-en-3-one	Stem bark	Anjaneyulu, Babu, and Connolly 1994; Anjaneyulu et al. 1999
6β-Hydroxystigmasta-4,22-dien-3-one	Stem bark	Anjaneyulu, Babu, and Connolly 1994
Campesterol	Stem bark, kernel	Anjaneyulu et al. 1989; Abdalla et al. 2007
Stigmasterol	Kernel	Abdalla et al. 2007
β-Sitosterol	Stem bark, kernel, fruits	Anjaneyulu, Babu, and Connolly 1994; Anjaneyulu et al. 1989; Abdalla et al. 2007; Scartezzini and Speroni 2000
β-Sitosterol-3β-arachidate	Stem bark	Anjaneyulu, Babu, and Connolly 1994
Xanthones		
1,3,6,7-Tetraoxygenated xanthone	Flowers	Ghosal, Biswas, and Chattopadhyay 1978
1,3,5,6,7-Pentaoxygenated xanthone	Flowers	Ghosal, Biswas, and Chattopadhyay 1978
Isomangiferin	Peels, pulps	Berardini, Fezer, et al. 2005; Berardini, Knodler, et al. 2005; Ribeiro et al. 2008
Isomangiferin gallate	Peels, pulps	Berardini, Fezer, et al. 2005; Berardini, Knodler, et al. 2005; Ribeiro et al. 2008
Mangiferin pentoside	Peels	Ajila, Rao, and Rao 2010
Mangiferin	Stem bark, leaves, flowers, peels, pulps, kernel	Nguyen et al. 2016; Zhang et al. 2011; Ge et al. 2011; Berardini, Fezer, et al. 2005; Berardini, Knodler, et al. 2005; Schieber, Ullrich, and Carle 2000; Ribeiro et al. 2008
Mangiferin gallate	Peels, pulps	Berardini, Fezer, et al. 2005; Berardini, Knodler, et al. 2005; Ribeiro et al. 2008
Methyl mangiferonate	Fruits	Scartezzini and Speroni 2000
Methyl isomangiferolate	Fruits	Scartezzini and Speroni 2000
Benzophenone derivatives		
2,4,4′,6-Tetrahydroxy benzophenone-3-C-β-D-glucoside	Leaves	Pan et al. 2016
2,4,4′,6-Tetrahydroxy-3′-methoxybenzophenone-3-C-β-D-glucopyranoside	Leaves	Pan et al. 2016
2,4,4′,6-Tetrahydroxybenzophenone-3-C-(6-O-*p*-hydroxybenzoyl)-β-D-glu-copyranoside	Leaves	Pan et al. 2016
2,4′,6-Trihydroxy-4-methoxybenzophenone	Leaves	Pan et al. 2016
2,4′,6-Trihydroxy-4,3′-dimethoxybenzophenone-3-C-β-D-glucopyranoside	Leaves	Pan et al. 2016
2,4′,6-Trihydroxy-4-methoxybenzophenone-2-O-glucoside	Leaves	Ge et al. 2011; Pan et al. 2016
2,4′,6-Trihydroxy-4-methoxybenzophenone-3-C-β-D-glucopyranoside	Leaves	Pan et al. 2016

(*continued*)

Table 1. Continued.

Compound name	Plant parts	References
2,6,4′-Trihydroxy-4-methoxybenzophenone	Stem bark	Nguyen et al. 2016
4,4′,6-Trihydroxybenzophenone-2-O-α-L-arabinofuranoside	Leaves	Pan et al. 2016
4′,6-Dihydroxy-4-methoxybenzophenone-2-O-(2″), 3-C-(1″)-1″-desoxy-α-L-fructofuranoside	Leaves	Pan et al. 2016
Aquilarinoside A	Leaves	Pan et al. 2016
Foliamangiferoside A	Leaves, stem bark	Zhang et al. 2011; Nguyen et al. 2016
Foliamangiferoside A1	Stem bark	Nguyen et al. 2016
Foliamangiferoside A_1	Leaves	Zhang et al. 2011
Foliamangiferoside A_2	Leaves	Zhang et al. 2011
Foliamangiferoside A_3	Leaves	Zhang et al. 2013
Foliamangiferoside A_4	Leaves	Zhang et al. 2013
Foliamangiferoside B	Leaves	Zhang et al. 2011
Foliamangiferoside C_1	Leaves	Zhang et al. 2011
Foliamangiferoside C_2	Leaves	Zhang et al. 2011
Foliamangiferoside C_3	Leaves	Zhang et al. 2011
Foliamangiferoside C_4	Leaves	Zhang et al. 2013
Foliamangiferoside C_5	Leaves	Zhang et al. 2013
Foliamangiferoside C_6	Leaves	Zhang et al. 2013
Foliamangiferoside C_7	Leaves	Zhang et al. 2013
Iriflophenone 3-C-(2-*O*-p-hydroxybenzoyl)-β-D-glucoside	Leaves	Pan et al. 2016; Zhang et al. 2011
Iriflophenonehexoside	Peels	Ajila, Rao, and Rao 2010
Iriflophenone-2-O-β-D-glucopyranoside	Leaves	Pan et al. 2016
Iriflophenone-3-*C*-(6-*O*-*p*-hydroxybenzoyl)-*O*-β-glucoside	Leaves	Ge et al. 2011
Iriflophenone-3-*C*-β-glucoside	Leaves	Zhang et al. 2011; Ge et al. 2011
Maclurin hexoside	Peels	Ajila, Rao, and Rao 2010
Maclurin-3-C-β-D-glucoside, 2,4′,6-Trihydroxy-4-methoxybenzophenone-2-O-β-D-glucopyranoside	Leaves	Zhang et al. 2011
Maclurin-3-*C*-β-glucoside	Leaves	Ge et al. 2011
Maclurin-tri-O-galloyl hexoside	Peels	Ajila, Rao, and Rao 2010
Mahkoside A	Stem bark	Nguyen et al. 2016
Amino acids		
Alanine	Stem bark, flowers, kernel	Ediriweera, Tennekoon, and Samarakoon 2017; Rai et al. 2007; Abdalla et al. 2007; Singh et al. 2015
Arginine	Kernel	Abdalla et al. 2007
Aspartic acid	Kernel, fruits	Abdalla et al. 2007; Ghosal, Biswas, and Chattopadhyay 1978
Cysteine	Fruits	Ghosal, Biswas, and Chattopadhyay 1978
Glutamic acid	Kernel	Abdalla et al. 2007
Glycine	Stem bark, kernel	Ediriweera, Tennekoon, and Samarakoon 2017; Abdalla et al. 2007; Singh et al. 2015
Histidine	Kernel	Abdalla et al. 2007
Isoleucine	Kernel	Abdalla et al. 2007
Leucine	Kernel	Abdalla et al. 2007
Lysine	Kernel	Abdalla et al. 2007
Methionine	Kernel	Abdalla et al. 2007
Phenylalanine	Kernel	Abdalla et al. 2007
Proline	Kernel, fruits	Abdalla et al. 2007; Ghosal, Biswas, and Chattopadhyay 1978
Serine	Kernel	Abdalla et al. 2007
Threonine	Flowers, kernel	Rai et al. 2007; Abdalla et al. 2007
Tryptophan	Flowers	Rai et al. 2007
Tyrosine	Kernel	Abdalla et al. 2007
Valine	Flowers, kernel, fruits	Rai et al. 2007; Abdalla et al. 2007; Ghosal, Biswas, and Chattopadhyay 1978
γ-Aminobutyric acid	Stem bark	Ediriweera, Tennekoon, and Samarakoon 2017; Singh et al. 2015
Long-chain hydrocarbons		
9,12-Tetradecadiene-1-ol-acetate	Stem bark	Singh et al. 2015
N-tetracosane	Stem bark	Singh et al. 2015
N-triacontane	Stem bark	Singh et al. 2015
Polyalcohols		
Myo-inositol	Stem bark	Rymbai et al. 2013
Sorbitol	Stem bark	Rymbai et al. 2013
Xylitol	Stem bark	Rymbai et al. 2013
Free sugars		
Arabinose	Stem bark, flowers	Rymbai et al. 2013; Rai et al. 2007
Galactose	Stem bark, flowers	Rymbai et al. 2013; Rai et al. 2007
Glucose	Stem bark, flowers	Rymbai et al. 2013; Rai et al. 2007
Alicyclic glycoside		
10-nonylcyclohex-12-ene-11-glucoside	Root bark	Gupta and Ali 1999
Anthocyanins		
Anthocyanidin hexoside	Peels	Berardini, Fezer, et al. 2005
Cyanidin 3-*O*-galactoside	Peels	Berardini, Fezer, et al. 2005
Carotenoids		
9- or 9′-*cis*-Lutein	Pulps	Chen, Tai, and Chen 2004
All-*trans*-β-carotene	Pulps	Chen, Tai, and Chen 2004
cis-β-Carotene	Pulps	Chen, Tai, and Chen 2004

(*continued*)

Table 1. Continued.

Compound name	Plant parts	References
Lutein	Peels	Ajila, Rao, and Rao 2010
Luteoxanthin	Peels, pulps	Chen, Tai, and Chen 2004
Neochrome	Peels, pulps	Chen, Tai, and Chen 2004
Neoxanthin/*cis*-Neoxanthin	Peels, pulps	Chen, Tai, and Chen 2004
Violaxanthin/*cis*-Violaxanthin	Peels, pulps	Ajila, Rao, and Rao 2010; Chen, Tai, and Chen 2004
Zeaxanthin	Peels, pulps	Chen, Tai, and Chen 2004
β-Carotene	Peels	Ajila, Rao, and Rao 2010
Apocarotenoids		
Abscisic acid	Fruits	Krenek, Barnes, and Talcott 2014
Abscisic acid glucoside	Fruits	Krenek, Barnes, and Talcott 2014
Dihydrophaseic acid glucoside	Fruits	Krenek, Barnes, and Talcott 2014
Dihydrophaseic acid glucoside	Fruits	Krenek, Barnes, and Talcott 2014
Vitamins		
Ascorbic acid	Pulps, kernel, fruits	Munafo et al. 2014; Maldonado-Celis et al. 2019; Palafox-Carlos, Yahia, and González-Aguilar 2012; Scartezzini and Speroni 2000
α-Tocopherol	Kernel, fruits	Abdalla et al. 2007; Scartezzini and Speroni 2000
Υ-tocopherol	Kernel	Abdalla et al. 2007
Tannins		
Hepta-*O*-galloylglucoside	Kernel	Engels et al. 2009
Hexa-*O*-galloylglucoside	Kernel	Engels et al. 2009
Penta-*O*-galloylglucoside/Gallotannin	Kernel, pulps	Engels et al. 2009; Schieber, Ullrich, and Carle 2000

mango peel extract (Knodler et al. 2008). The major flavonoids present in ripe mango peel extract are quercetin, rhamnetin, kaempferol and its glycosides (Figure 3) (Schieber, Ullrich, and Carle 2000; Berardini, Fezer, et al. 2005; Berardini, Knodler, et al. 2005). The major carotenoids present in mango peel extract are β-carotene, lutein (Figure 4) and violaxanthin (Ajila, Rao, and Rao 2010). Mango peel in the ripeness stage contains higher concentrations of anthocyanins, such as cyanidin 3-*O*-galactoside and an anthocyanidin hexoside (Figure 3) (Rymbai et al. 2013; Berardini, Fezer, et al. 2005). During ripening the lipid compositions of mango, mainly omega-3 and omega-6 fatty acids, are increased. Carotenoids and chlorophylls (*a* and *b*) are the significant pigments of mango fruit. The acidic nature of mango fruit is due to the presence of important organic acids, namely citric and malic acids (Maldonado-Celis et al. 2019). Mango pulp is a rich source of polyphenolic compounds, such as *m*-hydroxybenzoic acid, vanillic acid, *p*-hydroxybenzoic acid, *m*-coumaric acid, coumaric acid, ferulic acid, catechins, epicatechin, ellagic acids, benzoic acid, protocatechuic acid, gallotannin, mangiferin, isomangiferin, apigenin, myricetin, quercetin, kaempferol and its glycosides (Figure 3) (Schieber, Ullrich, and Carle 2000; Ribeiro et al. 2008). Ascorbic acid is the major nutrient in ripe mango pulp (Figure 4). (Munafo et al. 2014; Maldonado-Celis et al. 2019; Palafox-Carlos, Yahia, and González-Aguilar 2012). The mango kernel is a rich source of essential and non-essential amino acids. The essential amino acids include leucine, isoleucine, methionine, phenylalanine, lysine, threonine, tyrosine and valine and non-essential amino acids include aspartic acid, glutamic acid, serine, proline, glycine, alanine, histidine, and arginine (Abdalla et al. 2007). The mango kernel extract is also a good source of polyphenols, sesquiterpenoids, phytosterols, and microelements, such as selenium, copper, and zinc (Schieber, Berardini, and Carle 2003). The important phenolic compounds of the mango kernel include 1,2,3,4,6-penta-*O*-galloyl-β-D-glucopyranose, methyl gallate, and gallic acid (Nithitanakool, Pithayanukul, and Bavovada 2009). Several important tannins, such as penta-*O*-galloylglucoside (1,2,3,4,6-penta-*O*-galloyl-β-D-glucopyranose), hexa-*O*-galloylglucoside, and hepta-*O*-galloylglucoside, have also been extracted from the mango kernel (Figure 3) (Engels et al. 2009). The mango kernel contains stearic acid as a major saturated fatty acid and oleic acid as a major unsaturated fatty acid in all lipid classes. The mango kernel also contains various vitamins (Abdalla et al. 2007).

Mango leaves contain high amounts of phenolic and flavonoid compounds (Elzaawely and Tawata 2010). The ethyl acetate (EtOAc) fraction of mango leaves yielded a number of important phenolic compounds, such as benzoic acid, *p*-hydroxy benzoic acid, pyrogallol, vanillic acid, syringic acid, ferulic acid, ethyl gallate, gallic acid, protocatechuic acid, catechin, and gallocatechin (Figure 3) (Elzaawely and Tawata 2010; Ghosal, Biswas, and Chattopadhyay 1978). From methanolic extract of mango leaves, five flavonoid compounds, namely (–)-epicatechin-3-*O*-β-glucopyranoside; 5-hydroxy-3-(4-hydroxylphenyl) pyrano [3,2-g] chromene-4 (8H)-one; 6-(*p*-hydroxybenzyl) taxifolin-7-*O*-β-D-glucoside (tricuspid), quercetin-3-*O*-α-glucopyranosyl-(1-2)-β-glucopyranoside, and (–)-epicatechin [2-(3,4-dihydroxyphenyl)-3,4-dihydro-2*H*-chromene-3,5,7-triol], have been isolated (Kanwal et al. 2009). Several triterpenoids, such as arjunolic acid and actinidic acid, and benzophenone derivatives, namely 2,4,4′,6-tetrahydroxy-3′-methoxybenzophenone-3-*C*-β-D-glucopyranoside, iriflophenone 3-C-(2-*O*-p-hydroxybenzoyl)-β-D-glucoside, 2,4,4′,6-tetrahydroxybenzophenone-3-C-(6-*O*-p-hydroxybenzoyl)-β-D-glu-copyranoside, 4,4′,6-trihydroxybenzophenone-2-*O*-α-L-arabinofuranoside, iriflophenone-3-C-β-glucoside, maclurin-3-C-β-D-glucoside, and 2,4′,6-trihydroxy-4-methoxybenzophenone, have been isolated from mango leaf extracts (Figure 3) (Pan et al. 2016; Zhang et al. 2011; Zhang et al. 2013).

Mango stem bark is the rich source of triterpenoids and polyphenolic compounds. From the methanolic extract of *n*-hexane fraction of mango stem bark several important cycloartane-type triterpenoids, such as mangiferolate B, isoambolic acid, mangiferolate A, mangiferonic acid,

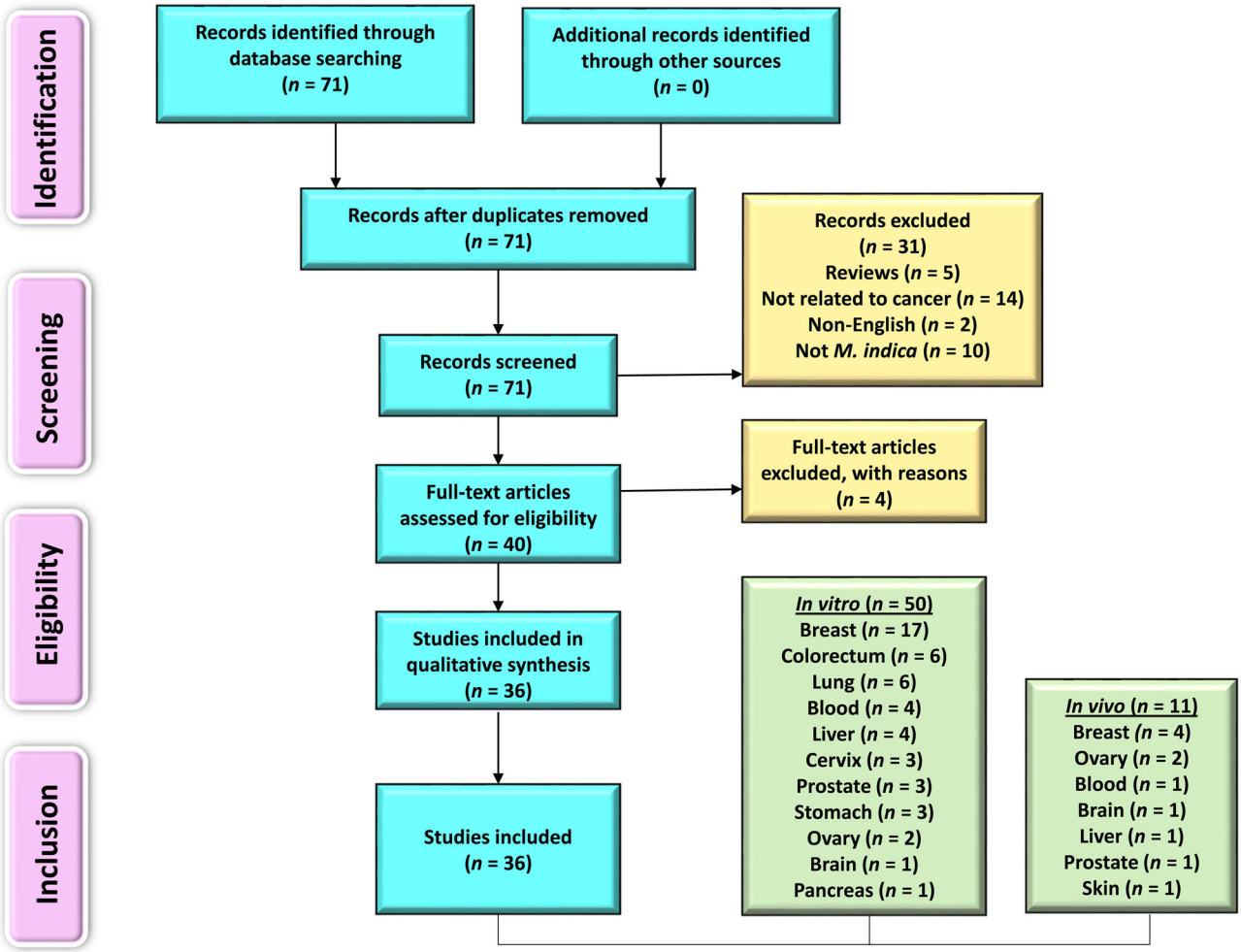

Figure 5. PRISMA flow chart describing the process of literature search and study selection related to anticancer potential of *M. indica*. The total number of *in vitro* and *in vivo* studies (61) is greater than the number of studies included in our work (36) because several publications reported results from more than one organ-specific cancer or study (*in vitro* or *in vivo*) type.

27-hydroxymangiferonic acid, 23-hydroxymangiferonic acid, mangiferolic acid, 27-hydroxymangiferolic acid, 23-hydroxy-mangiferolic acid, ambonic acid, methyl ambonate, ambolic acid, methyl ambulate, and 24-methylencycloartan-3,26-diol, were isolated (Figure 4) (Nguyen et al. 2016). Different phenolic compounds, such as gallic acid, benzoic acid, 3,4-dihydroxy benzoic acid (protocatechuic acid), gallic acid methyl ester, gallic acid propyl ester, mangiferin, (+)-catechin, (−)-epicatechin, and benzoic acid propyl ester, are also reported from mango stem bark (Núñez Sellés et al. 2002). Mangiferin is a xanthone class of phenolic compound and it is found in different parts of *M. indica*, such as stem bark, flowers, and different parts of the fruits (e.g., peels, pulps, and seeds). Several important phytosterols and benzophenone derivatives are also found in mango stem bark. The important benzophenone derivatives include 2,6,4′-trihydroxy-4-methoxybenzophenone, mahkoside A, foliamangiferoside A, and foliamangiferoside A1 (Figure 3) (Nguyen et al. 2016) and phytosterols include campesterol, β-sitosterol, β-sitosterol-3β-arachidate, 6β-hydroxystigmast-4-en-3-one, 6β-hydroxycampest-4-en-3-one, 6β-hydroxystigmasta-4,22-dien-3-one, 5α-stigrnastane-3β,6α-diol, and 6β-hydroxystigmast-4-en-3-one (Anjaneyulu et al. 1989; Anjaneyulu, Babu, and Connolly 1994; Anjaneyulu et al. 1999). Existing literature also indicate that in mango stem bark, other classes of compounds, such as fatty acids, sesquiterpenes, polyalcohols, free sugars and alicyclic glycoside, are also present (Rymbai et al. 2013; Gupta and Ali 1999).

Mango flowers are a rich source of amino acids, including threonine, alanine, valine, and tryptophan (Figure 4) (Rai et al. 2007). The GC-MS analyses confirm that monoterpene hydrocarbons represent a major portion of the mango flowers. The constituents of essential oils in mango flowers are extracted by both microwave-assisted hydrodistillation and hydrodistillation techniques and the major constituents are terpinolene, δ-3-carene, limonene, α-terpinene, and *p*-cymen-8-ol (Wang et al. 2010). The GC-MS analysis of ethanolic extract of ethyl acetate fraction of mango flowers indicates the presence of several fatty acids, such as (7-methyl-octyl)-benzene, 21-methoxy-henicosan-4-ol, 20-hydroxy-tricosanoic acid, 4-hydroxy-oconic acid ethyl ester, hentriaconta-1,5-diene, icos-2-ene, nonadeca-1,5,9-triene and icosanic acid ethyl ester (Karumanchi and Mehta 2016).

Literature search methodology

The Preferred Reporting Items for systematic reviews and meta-analysis (PRISMA) criteria (Liberati et al. 2009) which is recommended for reporting systematic reviews were followed for this work. The major databases used to find primary literature were PubMed, ScienceDirect, and Scopus. There were no time restraints on research articles that were published. The last search was performed in January 2020. Various combinations of keywords that were used included: *Mangifera indica*; mango; chemopreventive; chemotherapeutic; *in vivo*, *in vitro*; cancer; tumor; prevention; treatment, proliferation, apoptosis, and clinical studies. Initially, the abstracts of all publications were reviewed to determine the next step, i.e., collection of full-length articles. Once a full article was reviewed, a decision was made regarding its incorporation for further analysis. Only reports published in English language were included. Book chapters and conference abstracts were excluded. No anticancer clinical studies pertaining to *M. indica* were found on clinicaltrials.gov. The searches were also performed by reviewing the bibliography sections of published papers. The literature search was independently conducted by two individual researchers (BM and MA) and disagreements were resolved through discussions and upon consultation with a third researcher (AB), whenever necessary. Figure 5 shows a scheme for literature search and study selection.

Mango extracts and pure compounds in cancer prevention and therapy

Breast cancer

In one of earliest studies, polyphenolics extracted from fruit pulps of Ataulfo and Haden mango cultivars (both from Mexico) were tested for anticancer effects against MDA-MB-231 human breast cancer cell line. Mango polyphenols from both cultivars showed cell growth suppression in a concentration-dependent manner with the phytochemicals from the Ataulfo variety demonstrating superior effects. However, the underlying mechanism of action of the aforementioned effect was not reported (Noratto et al. 2010) (Table 2). In a subsequent study, Banerjee et al. (2015) prepared a polyphenol-rich extract using mango pulp of Keitt cultivar (Mexico) which showed cytotoxic activity against BT474 human ductal carcinoma cells. Mechanistically, mango polyphenolics suppressed the mRNA expressions of phosphoinositide 3-kinase (PI3K), Akt (also known as protein kinase B), hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF) as well as protein levels of Akt, phospho-Akt (pAkt), phospho-PI3K (pPI3K), VEGF and nuclear factor-κB (NF-κB) and increased the expression of miR-126 in BT474 cells. Nemec et al. (2016) investigated the antiproliferative effects of a low molecular weight faction of mango polyphenols and their metabolites (gallic acid, methylgallate and pyrogallol) using an in situ breast cancer cell line (MCF10DICS.COM). Although both polyphenolic fraction and pyrogallol were unable to decrease cell viability following a 48-h exposure, they significantly diminished cellular proliferation. The mango polyphenols and pyrogallol significantly reduced the mRNA expressions of mammalian target of rapamycin (mTOR) and HIF-1α and protein expressions of insulin receptor (IR), insulin-like growth factor type 1 receptor (IGF-1R), Akt, mTOR and P70S6K. The results of this study indicate that mango polyphenols and absorbable microbial metabolite pyrogallol (derived from non-absorbable gallotannins) exert antiproliferative effect in ductal carcinoma in situ breast cancer at physiologically-relevant concentration through regulation of Akt/mTOR signaling axis. In an extension of the previous study, the same research group (Nemec et al. 2017) showed that the mango pulp extract and pyrogallol arrested MCF10DICS.COM cells at S-phase via elevation of reactive oxygen species (ROS). Additionally, *in silico* analysis revealed that pyrogallol has the potential to bind to the allosteric site of AMP-activated protein kinase (AMPK) and cause its activation (Nemec et al. 2017).

Wilkinson et al. (2011) investigated the effects of mango peel and flesh ethanolic extracts in MCF-7 breast cancer cells. Various extracts effectively decreased the proliferation and reduced the viability of MCF-7 cells accompanied by a decrease in the peroxisome proliferator-activated receptor-γ (PPAR-γ) activity in comparison with the control cell line (Cos-7). This study has suggested that combinations of various chemical constituents may be responsible for the observed bioactivities of mango fractions and purification and activity profiling of individual phytocomponents could be challenging to relate to the whole fruit effects. In another study, exposure of MCF-7 cells to an ethanolic extract prepared using mango peel, decreased cell viability in a concentration-dependent manner with simultaneous inhibition of the activity as well as expression of aromatase. The results of this study underscore the potential of mango peel extract (containing various phenolics, flavonoids, alkaloids and triterpenoids) as a tissue-specific aromatase inhibitor which could be valuable for the therapy of estrogen receptor-positive breast cancer (Shaban et al. 2016).

The mango kernel (seed) is generally considered a waste product which contains various bioactive phytochemicals. Abdullah et al. (2014) conducted research on the potential benefits of varying concentrations of ethanolic mango (Water lily, Malaysia) seed extract (5–50 µg/mL) on MCF-7 and MDA-MB-231 breast cancer cells. Based on (3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay, neutral red uptake assay, trypan blue dye-exclusion assay and lactate dehydrogenase release assay, the extract was found to induce significant cytotoxicity against both cell lines and low toxicity toward MCF10 noncancerous mammary epithelial cells. Phytochemical characterization of the extract revealed presence of butylated hydroxytolune, a potent antioxidant, as the most abundant phytocompound. Subsequent studies by the same research group found that the seed extract produced time- and concentration-dependent increases in oxidative stress markers, namely ROS and malondialdehyde (MDA), elevated pro-apoptotic factors, such as Bcl-2-like protein 4 (Bax), cytochrome c (cyt. c), p53, caspase-7, caspase-8 and caspase-9, and decreased pro-

survival markers, such as Bcl-2 and glutathione (GSH) in MCF-7 and MDA-MB-231 cells (Abdullah, Mohammed, Rasedee, et al. 2015; Abdullah, Mohammed, Abdullah, et al. 2015). Castro-Vargas et al. (2019) explored the anticancer potential of agroindustrial waste from two Colombian mango cultivars, namely "Sugar Mango" and "Tommy Atkins." The phenolic extracts of "Sugar Mango" seed coat and seed kernel exhibited antiproliferative activity against MDA-MB-231 cells. The seed kernel extract containing mangiferin and several galloyl glucoside possessed significant antioxidant properties. A homo-polysaccharide isolated from the seed kernel of "Kottukonam" variety of *M. indica* demonstrated cytotoxicity against MCF-7 and Ehrlich ascites carcinoma (EAC), a spontaneous murine mammary adenocarcinoma, possibly via execution of programed cell death pathways (Varghese et al. 2019).

An ethanolic extract from the *M. indica* leaf also has an antiproliferative potential against breast cancer *in vitro*. Cytotoxic activity was observed when BT474 human ductal carcinoma cells were treated with the crude ethanolic leaf extract from Okrong mangos from Thailand. However, mango phytochemical mangiferin did not affect breast cancer cell survival (Ganogpichayagrai, Palanuvej, and Ruangrungsi 2017). Fernandez-Ponce et al. (2017) also demonstrated the antitumor effect of pressurized leaf extracts from *M. indica* (Kent cultivar from Spain) on breast cancer cell lines, MCF-7 (minimally invasive) and MDA-MB-231 (highly invasive) and nontoxic effects on MCF10 cells. The leaf extract with homomangiferin and methyl gallate demonstrated greater cytotoxic potential against MDA-MB-231 cells, whereas the extract rich in gallotannins was more effective against MCF-7 cells. The pressurized leaf extracts also reduced the levels of ROS generation in tested cell lines. The observed cytotoxic effect of mango leaf extract could be attributed to a synergistic effect of various phytochemicals rather than mangiferin which is the predominant constituent of mango leaves.

Vimang, a standardized extract of stem bark of selected varieties of *M. indica*, has been used to complement cancer therapies in Cuba (Guevara et al. 2001). Vimang and its phytoconstituents, glucosyl xanthone, mangiferin and indanone gallic acid, were tested against highly aggressive and metastatic breast cancer cell line MDA-MB-231. Vimang and gallic acid resulted in a significant inhibition of cell proliferation and/or cytotoxicity, whereas mangiferin had no inhibitory effect. All three test substances suppressed the activation of NF-κB by IKKα/β kinase, resulting in impairment of IκB degradation, NF-κB translocation and binding of NF-κB to DNA. Moreover, gallic acid hindered additional NF-κB pathways involved in survival of cancer cells and therapy resistance, such as mitogen-activated protein kinase 1 (MEK1), c-Jun N-terminal kinase 1/2 (JNK1/2), mitogen- and stress-activated kinase 1 (MSK1), and ribosomal s6 kinase (p90RSK) and also inhibited NF-κB target genes, namely interleukin-6 (IL-6) and IL-8, C-X-C chemokine receptor type 4 (CXCR-4), cyclooxygenase-2 (COX-2), Bcl-2, X-linked inhibitor of apoptosis (XIAP) and VEGF (García-Rivera et al. 2011). All results indicate gallic acid as an active constituent of vimang extract.

Several investigators used pure compounds isolated from mango and evaluated their anticancer efficacy against breast cancer *in vitro*. In one study, MCF-7 cells previously exposed to short-term (10 days) doxorubicin (a cancer chemotherapeutic drug) were treated with mangiferin at 10, 25 or 50 µM for 96 h. Exposure of high concentration of mangiferin with previous doxorubicin treatment was found to significantly reduce the viability of MCF-7 cells by decreasing the mRNA expression of P-glycoprotein (P-gp), indicating re-sensitization of previously resistant breast cancer cells to doxorubicin (Louisa, Soediro, and Suyatna 2014). Deng, Tian, and Liang (2018) treated MCF-7 and MDA-MB-231 breast cancer cells with mangiferin, which resulted in a concentration-dependent inhibition of cell growth and viability. Mangiferin also caused marked inhibition of MDA-MB-231 cell migration and invasion by impairing Ras-related C3 botulinum toxin substrate 1 (Rac1)/Wiskott-Aldrich syndrome protein-family verprolin-homologous protein 2 (WAVE2) signaling as evidenced from a decrease in actin-related protein 2 (Arp2), Arp3, WAVE2, Rac1/Cdc42, and phospho-Rac1/Cdc42. Wilkinson et al. (2015) examined the potential anti-breast cancer activity of various mango-derived compounds, such as mangiferin, quercetin and norathyriol (aglycone form of mangiferin). It was found that while mangiferin had no effect on the viability of MCF-7 cells, quercetin and norathyriol did decrease the viability. Only norathyriol activated both estrogen receptor-α (ER-α) and ER-β (both are involved in breast cancer cell proliferation), whereas mangiferin and quercetin were able to activate ER-α. The results of this study indicate that the bioactive polyphenolic components of *M. indica* may have very specific targets in breast cancer.

Unlike numerous *in vitro* investigations, there are only few attempts to explore *in vivo* chemopreventive and therapeutic effects of mango constituents in breast cancer. García-Solís, Yahia, and Aceves (2008) completed a study using Ataulfo mango puree pulp in which female Sprague-Dawley rats subjected to N-methyl-N-nitrosurea (MNU)-induced mammary carcinogenesis were fed with 0.02–0.06 g puree/mL of water for 3 or 24 weeks. The study showed that short-term or long-term mango consumption at physiological levels did not prevent mammary carcinogenesis in rats (Table 3). This null result illustrated that the phytochemicals present in Ataulfo cultivar specifically do not possess the properties to inhibit mammary carcinogenesis or increase plasma antioxidant capacity in MNU-treated rats. However, rats that were not treated with MNU but were given mango puree in their water for a long period of time did show an increased plasma antioxidant level.

Oral administration of a mango pulp extract, containing benzoic acid and cinnamic acid, reduced xenografted BT474 tumor volume by 73% in female athymic BALB/c nude mice compared to control animals. Mechanistic study revealed that mango polyphenolics decreased the expression of NF-κB (p65), pPI3K, pAkt, mTOR, HIF-1α and VEGF as well as modulated various miRNAs associated with regulation of

cell proliferation and tumor growth (Banerjee et al. 2015). Nemec et al. (2017) compared antiproliferative effects of a mango polyphenol-rich extract with pyrogallol using female athymic BALB/c nude mice xenografted with MCF10DDCIS.com cells. The mice were given 100 µg of the extract (0.8 GAE/day) or pyrogallol (0.2 mg/day) for 4 weeks beginning one week after the MCF10DCIS.com cells were implanted. Mango polyphenols and pyrogallol significantly reduced tumor volume (more than 50%) compared to the control by decreasing the phosphorylated protein levels of IR, IRS1, IGF-1R, increasing the protein levels of Sestrin2 and Beclin and reducing the mRNA levels of mTOR and ERK. Finally, polysaccharides isolated from *M. indica* seed (PSM001) significantly reduced tumor volume and number of viable tumor cells in mice transplanted with EAC cells via unknown mechanisms (Varghese et al. 2019).

Gastrointestinal tract and associated cancers

Mango peel extracts exhibited significant and concentration-dependent antiproliferative effects against AGS human gastric adenocarcinoma cells regardless of ripeness, whereas mango flesh extracts registered modest effects. The observed antiproliferative effects of both extracts correlated with their phenolic and flavonoid contents (Kim et al. 2010). Vimalraj, Ashokkumar, and Saravanan (2018) prepared gold nanoparticles (AuNPs) using an aqueous extract of *M. indica* seeds and found that this formulation at 25 µg/mL suppressed the growth of AGS gastric cancer cells without being nontoxic to normal cells. In the chick chorioallantoic membrane model, AUNPs significantly inhibited the angiogenic process as evident from decreased blood vessel size, length, and junctions which could be mediated through downregulation of Ang-1/Tie2 pathway. An ethanolic extract of *M. indica* leaf at 200 µg/mL exhibited cytotoxic potential against Kato-III human gastric carcinoma cells similar to that of mangiferin (Ganogpichayagrai, Palanuvej, and Ruangrungsi 2017).

Noratto et al. (2010) tested polyphenolic extracts of fruit pulp of several mango varieties against SW-480 human colon adenocarcinoma cells. Polyphenolics extracted from five cultivars, namely Ataulfo, Haden, Kent, Francis, and Tommy Atkins, in the order of decreasing efficacy, induced concentration-dependent growth suppression of SW-480 cells. The Ataulfo and Haden polyphenols inhibited cancer cell growth via cell cycle arrest, increased mRNA expression of pro-apoptotic and cell cycle regulatory biomarkers and decreased generation of ROS. Velderrain-Rodríguez et al. (2018) treated LS180 human colon adenocarcinoma cells with "Ataulfo" mango peel polyphenolic extracts and individual components results were analyzed via MTT reduction assay. An alkaline fraction of mango peel extract and gallic acid showed the most antiproliferative activity against the colon cancer cells. The antiproliferative capacity of gallic acid was found to be related to its antioxidant property. Lauricella et al. (2019) designed a study to explore anticancer effects of mango peel extract on three different human colorectal cancer cell lines, namely Caco-2, HCT116, and HT-29. The extract reduced cancer cell viability, imparted morphological changes and inhibited clonogenic survival of all cell lines. As regards to mechanism, the extract triggered DNA fragmentation and apoptotic cell death associated with production of ROS, activation of JNK and ERK1/2, and elevation of manganese super oxide dismutase (MnSOD) and nuclear factor erythroid 2-related factor 2 (Nrf2). Finally, mango peel extract activated a stress-induced DNA damage response as evidenced by phosphorylation of H2A histone family member X (γH2AX) and ataxia-telangiectasia mutated (ATM) kinase and upregulation of p53. The phytochemical characterization of the extract revealed the presence of organic acids, gallates and gallotannins, xanthones and benzophenone derivatives that could be responsible for the observed effects. In another study, phenolic extracts of "Sugar Mango" seed coat and seed kernel displayed moderate antiproliferative activity against HT-29 cells, possibly due to antioxidant activity (Castro-Vargas et al. 2019). Ramos et al. (2014) exposed HT-29 human colorectal adenocarcinoma cell line with essential oils obtained from hydrodistillation of *M. indica* cultivars Rosa and Espada. Major terpenes found in the essential oils from these cultivars include α-pinene, β-pinene and terpinolene (in Rosa), and terpinolene and δ-3-carene (in Espada). Of these constituents, β-pinene showed potent cytotoxic activity against HT-29 cells as determined by cell viability assay. Similar cytotoxic effects were observed with an ethanolic extract of *M. indica* Okrong leaves and mangiferin against another human cancer cell line, SW 620 (Ganogpichayagrai, Palanuvej, and Ruangrungsi 2017). Vimang, a standardized extract of stem bark of *M. indica*, elicited a modest inhibitory effect on the survival of Caco2 human colorectal adenocarcinoma cells in a concentration-dependent manner (García-Rivera et al. 2011).

Extracts prepared using ripe and unripe mango peels displayed superior antiproliferative activities against HepG2 human hepatocellular carcinoma cells to those of ripe and unripe mango flesh (Kim et al. 2010). Mango (Okrong cultivar) ethanolic leaf extract also showed cytotoxic potential against HepG2 cells; however, the result was less pronounced than that of mangiferin (Ganogpichayagrai, Palanuvej, and Ruangrungsi 2017). However, an methanolic extract of *M. indica* bark did not exhibit cytotoxicity against HepG2 cells up to a maximum concentration of 250 µg/mL (Hiraganahalli et al. 2012). Using another human hepatocellular cell line (MHCC97L), Tan et al. (2018) found that 48 h incubation with mangiferin at a concentration of 120 µg/mL reduced cell proliferation, possibly by halting cells in G1 phase, without affecting cell viability. Additionally, mangiferin reduced the invasive and migratory properties of MHCC97L cells in a concentration- and time-dependent manner. Finally, polymerase chain reaction array coupled with gene ontology analysis revealed that Wnt signaling pathway was the most predominant target of mangiferin and *LEF1* was the most downregulated gene in this pathway.

At least one investigation reports the effect of mangiferin in PANC-1 human pancreatic cancer cells which have an altered metabolism, enabling them to withstand and survive under extreme conditions of nutrient deprivation. In a study

conducted by Nguyen et al. (2016), a methanol extract of *M. indica* bark displayed strong preferential cytotoxicity against PANC-1 human pancreatic cancer cells maintained in nutrient-deprived medium (NDM), without apparent toxicity to cells that were cultured in normal nutrient-rich medium (DMEM). The results were reported as preferential cytotoxicity (PC_{50}) values, which is 50% cancer cell death in NDM without toxicity in DMEM. Phytochemical profiling of the extract led to the isolation of 19 compounds, in which mangiferolate B and isoambolic acid exhibited the most cytotoxic potential against PANC-1 cells with PC_{50} values of 11.0 and 4.8 μM, respectively. The cytotoxic effect of isoambolic acid was further investigated using a live cell imaging system. It was found that isoambolic acid inhibited cell mobility and gradually induced plasma membrane blebbing, leading to a drastic change in PANC-1 cell morphology followed by cell death.

Expanding on *in vitro* results as described earlier, Tan et al. (2018) explored *in vivo* antitumor effects of mangiferin using an orthotopic implantation hepatocellular carcinoma (HCC) mouse model with luciferase-tagged MHCC97L cells. After 5 weeks of oral treatment with 50 mg/kg mangiferin, the tumor cell-derived bioluminescence signal was significantly lower in mangiferin-treated animals compared to control, indicating tumor regression. Oral administration of mangiferin also reduced the tumor size, suppressed intratumor proliferative activity (Ki-67), invasiveness and microvessel density (CD-31) as well as downregulated *LEF1* gene expression. The results of this study in connection with previous *in vitro* findings indicate that mangiferin is a potent inhibitor of Wnt that targets *WT1/LEF1*-mediated activation of Wnt for the treatment of HCC.

Gynecological cancers

Kim et al. (2010, 2012) investigated potential anticancer activity of ethanolic extracts of mango peel and flesh and pure compounds, quercetin and mangiferin, against HeLa human cervix adenocarcinoma cells. A significant antiproliferative activity was observed in a time- and concentration-dependent manner following exposure to the mango peel extract and quercetin. The extract induced death of HeLa cells through induction of apoptosis as evidenced by DNA fragmentation accompanied by downregulation of Bcl-2 expression, degradation of poly ADP-ribose polymerase (PARP) protein, and activation of caspase-3, caspase-7, caspase-8 and caspase-9. The phytochemical analysis of the mango peel extract revealed the presence of various constituents, including quercetin-3-*O*-galactoside, quescetin-3-*O*-arabinopyranoside, mangiferin, mangiferin gallate, isomangiferin gallate, oleic acid, linoleic acid and ethyl linoleate. In another study, Nagajyothi et al. (2016) synthesized barium carbonate nanoparticles ($BaCO_3$ NPs) using aqueous extract of *M. indica* seed and tested its anticancer potential against cervical carcinoma *in vitro*. $BaCO_3$ NPs inhibited the growth of HeLa cells and promoted apoptosis by increasing the expression and activity of caspase-3.

Mangiferin was found to reduce the viability of OVCAR3 human ovarian adenocarcinoma cells and remarkably increase the sensitivity of these cells to anticancer drug cisplatin. Mangiferin also activated caspase-dependent apoptosis and downregulated Notch expression in OVCAR3 cells (Zou et al. 2017). A subsequent study reported that mangiferin reduced the proliferation and induced apoptosis of human ovarian cancer (OVCAR8) cells with concurrent downregulation of YAP expression. Additionally, mangiferin decreased the migration and invasion of OVCAR8 cells and sensitized these cells to cisplatin, and all these effects were abrogated by YAP overexpression (He et al. 2019).

The anti-ovarian cancer effects of mangiferin as observed *in vitro* have been extended to *in vivo* xenograft tumor models. In one study conducted by Zou et al. (2017), OVCAR3 cells were xenografted in nude mice and the animals were subjected to mangiferin treatment (10–100 mg/kg body weight) for 14 days. Mangiferin at a dose of 50 or 100 mg/kg significantly decreased the tumor growth and increased the survival of tumor-bearing animals compared to control. A combined treatment with mangiferin (50 mg/kg) and cisplatin (10 mg/kg) produced similar results with regards to tumor growth inhibition compared to 100 mg/kg mangiferin, suggesting that mangiferin may increase the sensitivity of ovarian cancer cells to standard chemotherapy drug cisplatin. A similar effect was observed in another xenograft model (OVCAR8) in which a treatment with mangiferin in combination with cisplatin resulted in better antitumor effect compared to cisplatin monotherapy (He et al. 2019). Interestingly, an overexpression of YAP in this tumor model abrogated the therapeutic benefit of a combined treatment, indicating that mangiferin potentiated the effect of cisplatin via regulation of YAP signaling pathway.

Hematological cancers

Percival et al. (2006) measured the anticancer effect of whole juice and juice extracts of *M. indica* on human promyelocytic leukemia cell line (HL-60) by examining the cell cycle kinetics. Incubation of the cells with whole juice and juice extract for 24 h resulted in an inhibition of cell cycle in the G_0/G_1. A mango juice fraction with low peroxyl radical scavenging activity was found to be the most effective in arresting cells in the G_0/G_1 phase. In another study that utilized the same cancer cell line, essential oils from different *M. indica* varieties (Rosa and Espada) and individual phytocomponents, demonstrated considerable cytotoxic activities (Ramos et al. 2014). Noratto et al. (2010) tested the efficacies of polyphenolic extracts from different varieties of *M. indica* pulp against Molt-4 acute lymphoblastic leukemia cells. Although polyphenolics from Ataulfo and Haden varieties exhibited antiproliferative activities, the underlying mechanisms of action were not understood. An aqueous extract of *M. indica* fruit reduced the viability of cancerous B-lymphocytes isolated from chronic lymphocytic leukemia patients in a concentration-dependent manner without affecting normal B-lymphocytes. Mechanistic studies revealed that the extract directly and selectively targeted

mitochondria of neoplastic cells and induced cancer cell death via ROS-mediated mitochondrial pathway characterized by mitochondrial swelling, reduction of mitochondrial membrane potential ($\Delta\Psi m$), inhibition of succinate dehydrogenase (SDH), cyt. c release and caspase-3 activation (Ayatollahi et al. 2019). In Dalton's ascites lymphoma, a spontaneous and highly invasive T-cell murine lymphoma model, polysaccharides isolated from *M. indica* seed (PSM001) significantly suppressed tumor volume and reduced the number of viable tumor cells (Varghese et al. 2019).

Lung cancer

Noratto et al. (2010) studied the effects of polyphenolics prepared from mango pulp extract (from Ataulfo and Haden cultivars) on lung cancer cell line A549 and found that the phytochemicals induced cell growth suppression in a concentration-dependent manner. The IC_{50} values were found to be 13.2 mg/L and 8.3 mg/L when tested against Ataulfo and Haden cultivars, respectively. Bai et al. (2018) investigated phytochemical composition, antioxidant and cytotoxic effects of an extract derived from mango peel. The extract and its components, such as caffeic acid, chlorogenic acid, gallic acid, procyanidin B_2, oleanolic acid and vanillic aldehyde, demonstrated considerable antioxidant activities which may contribute to their cytotoxic effects against A549 cells. While gallic acid possessed the strongest antioxidant property, oleanolic acid exhibited the most antiproliferative activity comparable to that of positive control 5-fluorouracil. A seed kernel extract of Colombian "Sugar Mango" inhibited the proliferation of A549 cells (Castro-Vargas et al. 2019). Various essential oils from *M. indica*, and their chemical constituents, including α-pinene, β-pinene and terpinolene, were found to inhibit the growth of NCI-H292 human lung mucoepidermoid carcinoma and HEp-2 human larynx carcinoma cells with unknown mechanisms (Ramos et al. 2014).

An ethanolic extract of *M. indica* leaves as well as mangiferin conferred similar cytotoxic activities against Chago K-1 human bronchogenic carcinoma cells (Ganogpichayagrai, Palanuvej, and Ruangrungsi 2017). In another study, zinc oxide nanoparticles (ZnO NPs) were prepared utilizing an aqueous extract of *M. indica* leaves and tested for their ability to inhibit the proliferation of A549 cells. Using the MTT assay, the investigators found that percent of viable cells were indirectly proportional to the concentration of ZnO NPs in a concentration-dependent manner. The observed cytotoxic property of ZnO NPs was comparable to that of a standard drug cyclophosphamide. It is possible that ZnO NPs show their cytotoxic effect via penetration of cell membrane through ion channels and interaction with nitrogenous bases of DNA and intracellular proteins (Rajeshkumar et al. 2018).

Neural cancers

Mu et al. (2018) investigated the role of mangiferin in radiosensitivity of glioblastoma cells. A decreased proliferation and increased DNA damage were observed when U-87 and U-118 human glioblastoma cells were pretreated with mangiferin (25 µg/mL) and exposed to ionizing radiation (5 Gy). Additional experiments revealed that mangiferin inhibited the non-homogenous end-joining DNA double-strand break repair pathway with a simultaneous inhibition of the phosphorylation of serine-protein kinase ATM, TP53-binding protein 1 and γH2AX as well as the number of γH2AX foci in glioblastoma cells following irradiation.

The aforementioned investigators also evaluated the anticancer effects of mangiferin alone or in combination with radiotherapy using xenografted U-118 tumor in nude mice. The tumor-bearing animals were treated with mangiferin at 5 mg/kg only or exposed to 25 Gy ionizing radiation in addition to mangiferin treatment. Although mangiferin alone had marginal effect, a smaller tumor volume, decreased tumor weight and prolongation of life span of tumor-bearing animals were observed in the group treated with mangiferin following irradiation (Mu et al. 2018). The results clearly indicate that mangiferin may increase the sensitivity of glioblastoma to radiotherapy.

Prostate cancer

A study by Noratto et al. (2010) showed growth-inhibitory activities of polyphenolics derived from mango pulp (Ataulfo and Haden varieties) against human prostate carcinoma cell line (LNCaP) in a concentration-dependent manner with Haden variety exhibiting better results. In another prostate cancer cell line (PC-3), phenolic extracts of "Sugar Mango" seed coat and seed kernel showed moderate antiproliferative activity (Castro-Vargas et al. 2019). Prasad, Kalra, and Shukla (2008) detected the presence of lupeol in the aqueous extract of fresh mango pulp. The same investigation also found that lupeol demonstrated concentration- and time-dependent inhibition of LNCaP cell proliferation with an IC_{50} value of 75 μM at 48 h post-treatment. Lupeol also resulted in a loss of mitochondrial membrane potential and DNA fragmentation of LnCaP cells.

Prasad, Kalra, and Shukla (2008) also investigated prostate cancer chemopreventive effects of mango pulp extract and lupeol using male Swiss albino mice injected with testosterone (5 mg/kg) for 14 consecutive days. Both the extract and lupeol supplementation resulted in abrogation of prostate enlargement in testosterone-exposed animals. Additional findings include a significantly high percentage of apoptotic cells, loss of mitochondrial transmembrane potential, DNA laddering, downregulation of Bcl-2 and upregulation of Bax and caspase-3 in the prostate tissue of animals treated with mango-derived products.

Skin cancer

There is at least one study that investigated anti-skin cancer potential of *M. indica* using an *in vivo* model. Administration of mango seed-derived polysaccharides (PSM001) alone or in combination with the anticancer drug vincristine suppressed the metastasis of B16F10 murine melanoma cells to the lungs in mice (Varghese et al. 2019).

However, the underlying mechanism of the observed antimetastatic effect was not reported.

Bioavailability and pharmacokinetics of mango constituents

Bioavailability and bioaccessibility are two terms used to describe the pharmacokinetics of phytochemicals and other compounds. Bioavailability is described as the fraction of a dose of a photochemical that remains in the systemic circulation in its unaltered form (Stahl et al. 2002). Bioaccessibility, however, relates to the ability of the gastrointestinal system to absorb the active components of a phytochemical (Stahl et al. 2002). These are important topics that must be discussed since phytochemicals are only useful if they can be made available and absorbed in the systemic circulation. Mangos possess two major forms of phytochemicals. These chemicals include polyphenols, which are soluble in water, and carotenoids, which are soluble in fat (Burton-Freeman, Sandhu, and Edirisinghe 2017). The metabolism of these compounds depends on a variety of circumstances, such as the level of ripeness, the variety of mango, how the mango is processed (juice, dried, or fresh) and if the mango is eaten with any other food items.

The major carotenoid compounds found in mango include α-carotene, β-carotene, cryptoxanthin, and zeaxanthin (Gouado et al. 2007). Gouado et al. (2007) studied the bioavailability of carotenoids in human participants when given three forms of mango (fresh, juice, and dried). The results of their study showed that fresh mango had the greatest bioavailability and dried mango had the least. Another study examined β-carotene content in mango varieties and found the measure of β-carotene is least in the Malgea variety of mango and it is the greatest in the Badami variety of mango (Veda, Platel, and Srinivasan 2007). However, the bioaccessibility of this compound was greatest in the Rasprui mango variety (39.1%) and the lowest was in the Badami variety (24.5%) (Veda, Platel, and Srinivasan 2007). The content and bioaccessibility were found to be independent of one another. In addition, the bioaccessibility was correlated to the amount of organic acid present in the mango with the highest organic content having the greatest bioaccessibility (Veda, Platel, and Srinivasan 2007). Additionally, by adding milk to mango the bioaccessibility of β-carotene was increased to a great extent (Veda, Platel, and Srinivasan 2007). β-Carotene content was also found to depend on the level of ripeness of the mango with higher ripeness correlating to increased β-carotene content (Ornelas-Paz et al. 2008). Researchers further found that the bioaccessibility of β-carotene content in mango is related to the ability of the compound to locate into micelles in the digestion process, and therefore bioaccessibility can be accelerated with the co-administration of dietary fat (Ornelas-Paz et al. 2008).

When quantitative analysis of phenolic compounds in mango was conducted, it was found that mango stem bark contained seven phenolic compounds with mangiferin making up the greatest percentage (7%) (Núñez Sellés et al. 2002). Numerous studies have shown that mangiferin, a major component of mango, has poor oral bioavailability and several studies cite the first pass metabolism of the liver, low permeability, or low solubility to be the cause (Han et al. 2010; Hou et al. 2012). An *in vivo* study in rats conducted by Tian et al. (2016) found that liver metabolism had only slightly contributed to the poor bioavailability since mangiferin did not reach a concentration that could be detected in the liver over a period of 48 h. The same investigators indicated that passive transport was the primary mechanism of transport into the liver and that there was poor permeability of mangiferin in the liver. Han et al. (2010) also cited the poor bioavailability (1.2%) of mangiferin when administered orally to rats. Another study conducted on human subjects found that mangiferin's peak plasma concentration was 38.64 ng mL^{-1}1h following an oral dose of 0.9 g (Hou et al. 2012). The researchers attributed this low bioavailability to the first pass effect of the liver (Hou et al. 2012). Since mangiferin has low bioavailability, the goal of various researchers was to discover what can increase the bioavailability. When mangiferin is put in a complex with soya phospholipid *in vivo* there was a 9.75-fold increase in the bioavailability of mangiferin compared to mangiferin used alone (Bhattacharyya et al. 2014).

According to one study, the mango peel contains two major phenolic compounds: chlorogenic acid and vanillic acid (Blancas-Benitez et al. 2015). Mango pulp paste contains phenolic compounds, such as hydroxycinnamic acid, gallic acid and hydroxybenzoic acid (Blancas-Benitez et al. 2015). The bioaccessibility of these compounds were determined to be 40.53% in the peel and 38.67% in the pulp (Blancas-Benitez et al. 2015). These phenolic compounds are thus able to be effectively absorbed from the intestines. *In vitro* and *in vivo* studies were conducted to assess the bioavailability of specific mango kernel seed extra components: methyl gallate, pentagalloyl glucopyranose, and gallic acid (Jiamboonsri et al. 2015). The study demonstrates the low bioavailability of each compound. The absorptive permeability was lowest in pentagalloyl glucopyranose followed by gallic acid and then methyl gallate. The low oral bioavailability was attributed to the compounds breakdown at alkaline pH, enzymatic breakdown by the gut, and the poor absorption of the compounds. Quirós-Sauceda et al. (2017) conducted a randomized crossover pilot clinical trial to evaluate the matrix effect (raw flesh vs. juice) of "Ataulfo" mango on the bioavailability of its phenolic compounds (gallic acid, chlorogenic acid, and p-coumaric)and indicated that the bioavailability of major phenolicsare preserved and may increase when the flesh is processed into juice. A further study conducted on human participants by Barnes et al. (2019) found that the metabolism of the mango gallotannin metabolites depended on the body mass index of those who consumed it.

Additional, human and animal *in vivo* studies need to be conducted to further our knowledge regarding the bioavailability and bioaccessibility of the phytochemicals found in mango. Most of the aforementioned studies demonstrate that poor bioavailability, especially that of mangiferin,

Table 2. Anticancer effects and mechanisms of action of *M. indica* based on *in vitro* studies.

Materials tested	Cell lines used	Concentration	Effects	Mechanisms	References
Breast cancer					
Polyphenolic extract of fruit pulp	MDA-MB-231	IC_{50}: 1.2–8.3 mg GAE/L	Displayed cell growth suppression		Noratto et al. 2010
Polyphenolic extract of fruit pulp	BT474	2.5–20 mg GAE/L	Induced cytotoxicity	↓PI3K; ↓Akt; ↓HIF-1α; ↓VEGF; ↓pAkt, ↓pPI3K; ↓NF-κB; ↑miR-126	Banerjee et al. 2015
Polyphenolic extract of mango mesocarp and pyrogallol	MCF10DIS.COM	1–10 mg GAE/L	Inhibited cell proliferation	↓mTOR; ↓HIF-1α; ↓IGF-1R; ↓IR; ↓Akt; ↓P7056K	Nemec et al. 2016
Polyphenolic extract of fruit pulp and pyrogallol	MCF10DIS.COM	1–20 mg/L	Arrested cells at the S-phase	↑ROS generation; ↑AMPK	Nemec et al. 2017
Flesh and peel extracts	MCF-7		Inhibited proliferation and reduced viability	↓PPAR-γ	Wilkinson et al. 2011
Ethanolic peel extract	MCF-7	1–50 μg/mL	Decreased cell viability	↓Aromatase gene expression, ↓aromatase activity	Shaban et al. 2016
Ethanolic seed extract	MCF-7 and MDA-MB-231	5–50 μg/mL	Exhibited selective cytotoxicity toward cancer cells	↑ROS; ↑MDA; ↑Cyt. c; ↑p53; ↑Bax; ↑caspase-7; ↑caspase-8; ↑caspase-9; ↓Bcl-2; ↓GSH	Abdullah et al. 2014; Abdullah, Mohammed, Rasedee, et al. 2015; Abdullah, Mohammed, Abdullah, et al. 2015
Phenolic extracts of seed coat and seed kernel	MDA-MB-231	1.25–125 μg/mL	Displayed antiproliferative activities	Antioxidant activity	Castro-Vargas et al. 2019
Homo-polysaccharide from seed kernel (PSM001)	MCF-7 and EAC (murine mammary adenocarcinoma cells)	0.001–1000 μg/mL	Exhibited cytotoxicity	↑Apoptosis	Varghese et al. 2019
Ethanolic leaf extract	BT474	0.02–200 μg/mL	Exhibited antiproliferative activity		Ganogpichayagrai, Palanuvej, and Ruangrungsi 2017
Leaf extract	MCF-7 and MDA-MB-231	0.01–100 μg/mL	Reduced cancer cell survival	Antioxidant activity	Fernandez-Ponce et al. 2017
Stem bark extract (vimang) and gallic acid	MDA-MB-231	1.25–800 μg/mL	Inhibited cell proliferation	↓IL-6; ↓IL-8; ↓COX-2; ↓CXCR4; ↓XIAP; ↓Bcl-2; ↓VEGF; ↓NF-κB; ↓MEK1; ↓JNK1/2; ↓MSK1; ↓p90RSK	García-Rivera et al. 2011
Mangiferin + doxorubicin	MCF-7	50 μg/mL	Reduced cell viability	↓P-gp	Louisa, Soediro, and Suyatna 2014
Mangiferin	MDA-MB-231	2–10 μM	Inhibited cell migration and invasion	↓Arp2; ↓Arp3; ↓WAVE2; ↓Rac1/Cdc42; ↓pRac1/Cdc42	Deng, Tian, and Liang 2018
Querectin and norathyriol	MCF-7	100 μM	Reduced cell viability	↓ER-α; ↓ER-β	Wilkinson et al. 2015
Gastrointestinal tract and associated cancers					
Ethanolic peel and flesh extracts	AGS (human gastric cancer cells)	125–1000 μg/mL	Inhibited cancer cell growth		Kim et al. 2010
Mango seed-AuNP	AGS (human gastric cancer cells)	10–100 μg/mL	Suppressed cell proliferation and angiogenesis	↓Ang-1; ↓Tie2	Vimalraj, Ashokkumar, and Saravanan 2018
Ethanolic leaf extract; mangiferin	Kato-III (human gastric carcinoma cells)	0.02–200 μg/mL	Displayed cytotoxic activity		Ganogpichayagrai, Palanuvej, and Ruangrungsi 2017
Polyphenolic extract of fruit pulp	SW-480 (human colon adenocarcinoma cells)	IC50: 1.6–27.3 mg GAE/L	Suppressed cancer cell growth	⊥G2/M; ↑Bax; ↑Bim; ↑p21; ↑caspase-8; ↑PKMYT1; ↓ROS	Noratto et al. 2010
Polyphenolic peel extract; gallic acid	LS180 (human colon adenocarcinoma cells)	IC50: 94–137 μg/mL	Exhibited antiproliferative activity	↑Apoptosis; antioxidant activity	Velderrain-Rodríguez et al. 2018
Hydro-alcoholic extract of peel	Caco-2, HCT116, HT-29 (human colorectal carcinoma cells)	15–600 μg/mL	Induced cytotoxic effects and inhibited colony formation	↑Apoptosis; ↓PCNA; ↓pro-caspase-9; ↓pro-caspase-3; PARP cleavage; ↑ROS; ↑pJNK; ↑pERK1; ↑Mn-SOD; ↑pNrf2; ↑γH2AX; ↑pATM; ↑p53	Lauricella et al. 2019
Phenolic extracts of seed coat and seed kernel	HT-29 (human colorectal adenocarcinoma cells)	1.25–125 μg/mL	Exhibited antiproliferative effects	Antioxidant activity	Castro-Vargas et al. 2019
Essential oils from fruit; α-pinene, β-pinene and terpinolene	HT-29 (human colon adenocarcinoma cells)	IC50: 6.6–28.7 μg/mL	Induced cytotoxicity		Ramos et al. 2014

Ethanolic leaf extract; mangiferin	SW-620 (human colon adenocarcinoma cells)	0.02–200 μg/mL	Showed cytotoxic potential		Ganogpichayagrai, Palanuvej, and Ruangrungsi 2017
Stem bark extract (vimang)	Caco2 (human colorectal adenocarcinoma cells)	25–800 μg/mL	Inhibited cell survival		García-Rivera et al. 2011
Ethanolic peel and flesh extracts	HepG2 (human hepatocarcinoma cells)	125–1000 μg/mL	Inhibited cancer cell proliferation		Kim et al. 2010
Ethanolic leaf extract; mangiferin	HepG2 (human hepatocarcinoma cells)	0.02–200 μg/mL	Exhibited cytotoxic potential		Ganogpichayagrai, Palanuvej, and Ruangrungsi 2017
Methanolic bark extract	HepG2 (human hepatocarcinoma cells)	31.25–250 μg/mL	Did not affect cell viability		Hiraganahalli et al. 2012
Mangiferin	MHCC97L (human hepatocellular carcinoma cells)	50, 120 μg/mL	Reduced proliferation, invasion and migration	⊥G1; ↓*LEF1*; ↓Wnt pathway	Tan et al. 2018
Methanol bark extract; mangiferolate A and isoambolic acid	PANC-1 (human pancreatic cancer cells)	PC_{50}: 15.5 μg/mL; 4.8–11 μM	Inhibited cell survival	Novel cell death	Nguyen et al. 2016
Gynecological cancers					
Ethanolic peel and flesh extracts	HeLa (human cervical cancer cells)	62.5–1000 μg/mL	Showed antiproliferative activity	↑Apoptosis; ↓Bcl-2; ↑caspase-3; ↑caspase-7; ↑caspase-8; ↑caspase-9; ↓PARP	Kim et al. 2010, 2012
$BaCO_3$ NPs of aqueous extract of mango seed	HeLa	0.001–2 mg/mL	Caused cell growth inhibition	↑Apoptosis; ↑caspase-3	Nagajyothi et al. 2016
Mangiferin	OVCAR3 (human ovary cancer cells)	12.5–100 μg/mL	Inhibited cell viability	↑Apoptosis; ↑Bax; ↑Bid; ↓Bcl-2; ↓Bcl-xL; ↑caspase-3 activity; ↑cyt. c; ↓Notch 3; ↓cyclin D1; ↓β-catenin	Zou et al. 2017
Mangiferin	OVCAR8 (human ovary cancer cells)	25 μg/mL	Inhibited cell proliferation, migration and invasion	↑Apoptosis; ↓YAP; ↓TEAD4	He et al. 2019
Hematological cancers					
Whole juice and juice extracts	HL-60 (human acute promyelocytic leukemia cells)	0.5%–2%	Induced cell cycle arrest at G0/G1 phase		Percival et al. 2006
Essential oils from fruit; α-pinene, β-pinene and terpinolene	HL-60 (human acute promyelocytic leukemia cells)	3.6–28.8 μg/mL	Inhibited tumor cell growth		Ramos et al. 2014
Polyphenolic extracts from fruit pulp	Molt-4 (acute lymphoblastic leukemia cells)	1.6–27.3 μg/mL	Caused cell cycle arrest	↑Apoptosis; ↓NF-κB; ↑mRNA expression of pro-apoptotic proteins	Noratto et al. 2010
Aqueous fruit extract	B-lymphocytes (human chronic lymphocytic leukemia cells)	100–2000 μg/mL	Reduced viability	↑Apoptosis; ↑caspase-3; ↓SDH; ↑ROS; ↓ΔΨm; ↑cyt. c.	Ayatollahi et al. 2019
Lung cancer					
Polyphenolic extracts from fruit pulp	A549 (human lung carcinoma cells)	1.6–27.3 μg/mL	Caused cell cycle arrest	↑Apoptosis; ↓NF-κB; ↑mRNA expression of pro-apoptotic proteins	Noratto et al. 2010
Mango peel extract and oleanolic acid	A594	4.7–15 μg/mL (IC_{50})	Showed cytotoxic activities	Antioxidant activity	Bai et al. 2018
Phenolic extract of seed kernel	A549	1.25–125 μg/mL	Inhibited cell proliferation	Antioxidant activity	Castro-Vargas et al. 2019
Essential oils from fruit, α-pinene, β-pinene and terpinolene	HEp-2 (human laryngeal carcinoma), NCI-H292 (human mucoepidermoid pulmonary carcinoma cells)	3.6–12.3 μg/mL	Induced cytotoxicity		Ramos et al. 2014
Leaf extract	Chago K-1 (human bronchogenic carcinoma cells)	0.02–200 μg/mL	Reduced cell viability		Ganogpichayagrai, Palanuvej, and Ruangrungsi 2017
ZnO NPs of leaf extract	A594	1–100 μg/mL	Displayed cytotoxicity	Antioxidant activity	Rajeshkumar et al. 2018
Neural cancers					
Mangiferin	U-87 and U-118 (human glioblastoma cells)	25 μg/mL	Increased the sensitivity of cells toward radiation	↑DNA damage; ↓pATM; ↓p53BP1; ↓pγH2AX; ↓pγH2AX foci	Mu et al. 2018
Prostate cancer					
Polyphenolic extracts from fruit pulp	LNCaP (human prostate carcinoma cells)	1.6–27.3 μg/mL	Registered antiproliferative effects		Noratto et al. 2010

(*continued*)

Table 2. Continued.

Materials tested	Cell lines used	Concentration	Effects	Mechanisms	References
Phenolic extracts of seed coat and seed kernel	PC-3 (human prostate adenocarcinoma cells)	1.25–125 µg/mL	Exhibited antiproliferative effects	Antioxidant activity	Castro-Vargas et al. 2019
Lupeol	LNCaP (human prostate carcinoma cells)	10–125 µM	Inhibited cell proliferation	↑Apoptosis	Prasad, Kalra, and Shukla 2008

presents a barrier to accessing mango's therapeutic effects. Additional research must be conducted in order to truly find the cause of low bioavailability of the phytochemicals found in mango and more studies must be conducted on ways to improve their bioavailability and bioaccessibility so that mango can be utilized for its chemopreventive and chemotherapeutic effects.

Toxicity studies

In addition to the bioavailability and pharmacokinetics of a bioactive compound, it is imperative to take into account the toxicity of that compound. Since mangiferin is unique to mangos, considerable toxicity studies have taken place on this xanthone derivative more than any other phytochemical constituent. Mango as a fruit is safe to consume, but concerns arise when leaf and bark extracts are used in antitumor studies. Mangiferin, being a natural compound, shows minimal toxicity to humans and it is considered nontoxic (Gold-Smith, Fernandez, and Bishop 2016). An *in vitro* study performed by Rodeiro, Delgado, and Garrido (2014) showed that neither mango stem bark extract nor mangiferin reduced viability of human peripheral lymphocytes or cells of the lymphoblastoid line upon treatment with 1000 μg/mL for 1 h. However, in a study conducted by Prado et al. (2015), oral administration of mangiferin in rodents exhibited low acute toxicity, and intraperitoneal application of this xanthone at the highest concentration of 2000 mg/kg caused death of one male and one female rat. Their research also showed that at a concentration of 1000 mg/kg, mangiferin induced apoptosis and necrosis of acinar cells of the pancreas as observed in histopathological studies. This illustrated that the pancreas was the primary target for mangiferin toxicity. In another study by Jagetia and Baliga (2005), mangiferin's intraperitoneal median lethal dose (LD50) in DBAxC57BL mice was 400 mg/kg, since it resulted in 50% mortality among tested mice. Stem bark extract from *M. indica* has only shown toxicity in animals when injected intraperitoneally and after acute exposure (Rodeiro, Delgado, and Garrido 2014). Mango leaf extract, at >200 μg/mL, also exhibited toxicity on lung fibroblast (Wi-38) while the extract increased percent survival of skin fibroblast (Ganogpichayagrai, Palanuvej, and Ruangrungsi 2017). Another study conducted about mango leaf extract with 60% mangiferin, concluded that the highest dose tested, 2000 mg/kg of body weight, was the "no observed adverse effect level" in rats *in vivo* (Reddeman et al. 2019). The researchers also reported no mutagenic effects in the Ames test, but did, however, find clastogenic effects in a chromosomal aberration test *in vitro* (Reddeman et al. 2019). This is in contrast to studies that found no DNA damaging potential of mangiferin when used in *E. coli* chromotest (Rodeiro et al. 2012) and no genotoxic effects in erythrocytes in bone marrow and liver cells as well as no embryo toxicity in rats given stem bark extract of mangiferin (González et al. 2007). Since mangiferin has a polyphenolic structure, it likely undergoes biotransformation in the liver,

Table 3. Chemopreventive and anticancer therapeutic action of *M. indica* based on *in vivo* studies.

Materials tested	Animal tumor models	Effects	Mechanisms	Dose (route)	Duration	References
Breast cancer						
Mango purée pulp	MNU-induced mammary carcinogenesis in female Sprague-Dawley rats	Did not prevent mammary carcinogenesis; did not increase plasma antioxidant capacity		0.02–0.06 g mango/mL of drinking water (p.o.)	3 or 24 weeks	García-Solís et al. 2008
Polyphenolic extract from mango fruit pulp	Female athymic BALB/c nude mice xenografted with BT474 cells	Suppressed tumor volume	↓NF-κB (p65); ↓pPI3K; ↓pAkt; ↓mTOR; ↓HIF-1α; ↓VEGF; ↑miR-126	100 µL of extract (0.8 GAE/day) (p.o.)	35 days	Banerjee et al. 2015
Polyphenolic extract from mango fruit pulp and pyrogallol	Female athymic BALB/c nude mice xenografted with MCF10DCIS.COM cells	Inhibited tumor size	↓pIR; ↓pIRS1; ↓pIGF-1R; ↑Sestrin2; ↑Beclin; ↓mTOR; ↓ERK	100 µg of extract (0.8 GAE/day) or pyrogallol (0.2 mg/day)	4 weeks	Nemec et al. 2017
Homo-polysaccharide from seed kernel (PSM001)	Female BALB/c mice transplanted with EAC cells	Exhibited antitumor effects		200 mg/kg	13 days	Varghese et al. 2019
Gynecological cancers						
Mangiferin; mangiferin + cisplatin	Female BALB/c nude mice xenografted with OVCAR3 cells	Reduced tumor weight, volume and increased survival		50–100 mg/kg (i.p.)	2 weeks	Zou et al. 2017
Mangiferin + cisplatin	Female BALB/c nude mice xenografted with OVCAR3 cells	Decreased tumor weigh and increased survival		50 mg/kg (i.p.)	2 weeks	He et al. 2019
Hematological cancers						
Homo-polysaccharide from seed kernel (PSM001)	Female BALB/c mice transplanted with DLA cells	Exhibited antitumor effects		200 mg/kg	13 days	Varghese et al. 2019
Liver cancer						
Mangiferin	Athymic BALB/c-nu/nu mice with orthotopic MHCC97L tumor	Reduced growth, proliferation, invasiveness and angiogenesis of tumors	↓Ki-67, ↓CD31; ↓*LEF1*; ↓Wnt	50 mg/kg/2 days (p.o.)	5 weeks	Tan et al. 2018
Neural cancers						
Mangiferin	BALB/c nude mice injected with U-118 cells	Reduced tumor volume, decreased tumor weight, and prolonged survival		5 mg/kg (i.p.)		Mu et al. 2018
Prostate cancer						
Aqueous pulp extract; lupeol	Male Swiss albino mice exposed to testosterone	Suppressed prostate enlargement and proliferation	↑Apoptosis; ↑Bax; ↑caspase-3; ↓Bcl-2; ↓ROS	Extract: 1 mL/mouse (p.o.); Lupeol: 1 mg/mouse (p.o.)	2 weeks	Prasad, Kalra, and Shukla 2008
Skin cancer						
Homo-polysaccharide from seed kernel (PSM001); PSM001 + vincristine	Male C57BL/6 mice injected with B16F10 cells	Inhibited metastasis of tumor cells		PSM001: 200 mg/kg; Vincristine: 0.065 mg/kg (i.p.)	10 days	Varghese et al. 2019

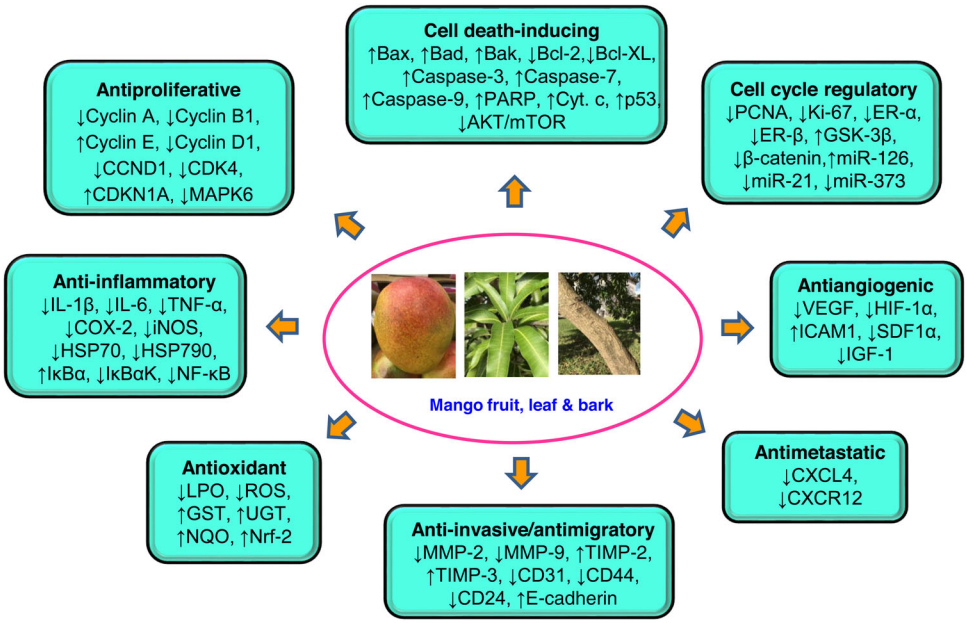

Figure 6. Major anticancer mechanisms and molecular targets of *M. indica*-derived constituents based on preclinical (*in vitro* and *in vivo*) experimental findings.

and due to this reason, further research into the safety of mangiferin metabolites may be required (Tolosa et al. 2013).

Conclusion and future research directions

M. indica is a magnificent plant which has been cultivated and utilized for thousands of years for its nutritional and medicinal values. In this review, we have provided a systematic analysis of *in vitro* and *in vivo* studies that examined the chemopreventive and chemotherapeutic actions of *M. indica* and its phytochemicals as well as the pharmacokinetics and toxicity of individual active components. Although the mango fruit (including flesh, juice, peel, seeds and oil) have been extensively studied, other parts of mango tree, including leaf and bark, have also been utilized in anticancer research. In addition to various extracts and fractions of *M. indica,* numerous phytoconstituents, such as mangiferin, gallic acid, quercetin, norathyriol, α-pinene, *β*-pinene, terpinolene, mangiferolate A, isoambolic acid, oleanolic acid, and lupeol, have been shown to possess cancer preventative and anticancer therapeutic potential. These phytochemicals have been shown to kill cancer cells and/or suppress tumor growth through antiproliferative, pro-apoptotic, cell cycle-regulatory, anti-inflammatory, antioxidant, anti-invasive, antimetastatic, and antiangiogenic effects (Figure 6). The anticancer effects of *M. indica* phytochemicals are exerted through regulation of diverse biomolecular and cellular mechanisms and signaling pathways. Such mechanisms include, but are not limited to, decreasing pro-inflammatory cytokines (IL-6, TNF-α, COX-2, and NF-*κβ*), angiogenic factors (VEGF, IGF-1, SDF1α, and HIF-1α), proliferative factors (cyclins, cyclin-dependent kinases, and MAPK6) and metastatic factors (CXCL4 and CXCR12). Additionally, *M. indica*-derived phytocompounds have been found to upregulate various proteins involved in cell death (Bax, Bad, Bak, caspases, and p53), prevent cellular oxidative stress as well as regulate the cell cycle (Figure 6).

The majority of the current literature on antineoplastic effects of *M. indica* is limited to *in vitro* studies. Examples of cancer types that are impacted by *M. indica* phytochemicals include gastric cancer, colon cancer, liver cancer, pancreatic cancer, lung cancer, breast cancer, ovarian cancer, uterine cancer, prostate cancer, neural, skin, and hematological cancers. The literature examined in this review shows the promise of utilizing *M. indica* for chemotherapy for various cancer subtypes. However, the effects of *M. indica* phytochemicals on breast cancer have been investigated most thoroughly in both *in vitro* and *in vivo* studies. Further *in vivo* experiments on other cancer types need to be conducted since the limited number of available studies do show great potential for mango bioactive constituents in various cancer subtypes.

The limitation to *M. indica's* therapeutic utilization includes low bioavailability and bioaccessibility of some of its phytochemical components, particularly mangiferin. Most studies attributed the poor bioavailability and bioaccessibility to the first pass effect by the liver, poor intestinal absorption, and low solubility. The bioavailability and accessibility are also dependent on various factors, such as mango processing and variety. The limited bioavailability of many mango phytochemicals may limit its therapeutic effect.

The limited toxicity studies conclude that *M. indica* and its major component mangiferin are safe. *M. indica*, with its limited toxicity, may present as an alternative to traditional cancer chemotherapy which are associated with undesirable adverse effects. Nevertheless, at least one study showed clastogenic effects of mangiferin *in vitro*. Hence, further research needs to be conducted to determine if the same toxicity applies in human subjects and uncover which other mango phytochemicals and metabolites may have the potential to be mutagenic.

Future research directions have been identified by our comprehensive research and analysis of limitations. Since mangiferin is unique to *M. indica,* it is the primary phytochemical examined in anticancer research. However, further studies should be conducted to explore anticancer potential of additional major phytochemicals of *M. indica*. In addition, more *in vivo* studies should be conducted since the majority of research is limited to *in vitro* analysis. Moreover, the chemical synergy of *M. indica* phytochemicals warrants further research due to the fact that current literature mostly examines phytochemicals individually. Although, many studies presented in this article indicate that the mango phytochemicals may have a synergistic effect in inhibiting cancer proliferation and growth. Although several mechanisms of anticancer action of *M. indica* phytochemicals have been proposed by different investigators, further research must be conducted to completely understand the molecular targets affected by these bioactive phytocompounds as well as their metabolites in various organ systems. Although some research has been conducted, additional research must oversee the development of a better delivery system and formulation for *M. indica*-derived phytochemicals to increase their bioavailability and bioaccessibility. Perhaps additional studies utilizing micelles, liposomes, and emulsions should be investigated to increase the bioavailability of *M. indica*. Supplementary research studies must be conducted to determine the amount of mango that needs to be consumed in order to optimize its chemopreventive effect. The *in vitro* results found in cancer cells should be replicated by *in vivo* studies in order to confirm antitumorigenic effects and underlying molecular mechanisms. Considering the impressive antineoplastic results presented in this review, randomized clinical trials utilizing *M. indica* phytochemicals should be conducted. The possibility for utilizing *M. indica* bioactive constituents in combination with traditional chemotherapy to adjuvant its effects must also be determined. Based on our in-depth analysis of current research, *M. indica*-derived phytoconstituents have the potential to be developed as a valuable pharmaceutical for cancer prevention as well as multitargeted agent for pharmacotherapy of cancer.

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Disclosure statement

The authors have declared that there is no conflict of interest.

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