Mangifera indica and *Mangifera zeylanica*: Perspectives on medicinal properties, therapeutic applications and potential uses as anticancer epigenetic drugs (Review)

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Abstract. Among the different types of mango species, *Mangifera indica* (MI) and *Mangifera zeylanica* (MZ) are well known for their therapeutic potential. MI is a pharmacologically and phytochemically diverse plant. Extracts prepared from different parts (bark, leaves, roots, seeds, flowers and fruits) of MI and major mango phytochemicals have been reported to exert a range of pharmacological effects. MZ is a plant endemic to Sri Lanka. The bark of MZ has been used in the Sri Lankan traditional medicine for the treatment of various ailments and conditions, including cancer. Recently, substantial efforts have been made to provide a scientific validation for its traditional use in the treatment of cancer. The present review article describes the pharmacological activities, including anti-inflammatory, antioxidant, anticancer, anti-microbial, anti-diabetic and anti-obesity properties of MI. Furthermore, the anticancer potential of MZ bark extracts and information on compounds isolated from MZ and their bio-activities are also described. The effects of major *Mangifera* compounds on epigenetic modifications have been widely studied. Therefore, the ability of *Mangifera* compounds to function as epigenetic drugs in the context of cancer drug discovery has become a promising area of investigation. However, an assessment of the clinical efficacy, and potential adverse and toxic effects of mango extracts is essential prior to their use in clinical practice.

Contents

1. Introduction

Mango is a fruit-bearing tree cultivated in tropical and sub-tropical regions of the world, with India being the largest producer (1). The genus *Mangifera* (family Anacardiaceae) comprises >70 species and 1,000 varieties (2). Among the various species, MI is the most widely found species across India, China, Mexico, Brazil, Pakistan, Thailand and The Philippines. MI is believed to have originated from the Indo-Burma region (2). The mango fruits are popular due to sensorial properties, such as a bright colour, luscious flavour and sweet taste (3). A large variety of phytochemicals with distinct chemical structures and a range of pharmacological properties have been reported in MI (1). Furthermore, various parts of MI have been used in the traditional medicines of South Asian and African countries. For example, extracts and decoctions prepared from different parts of MI are used in the treatment of various ailments and conditions, including anaemia, asthma, bronchitis, cough, diarrhoea, dysentery, haemorrhage, hypertension, leucorrhoea, piles and rheumatism, blisters and oral wounds, and animal bites (1). Images of *Mangifera indica* (MI) leaves, bark and fruits are presented in Fig. 1A (left panel, middle panel and right panel, respectively).

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Mangifera zeylanica (MZ), a species in the mango family, is a plant endemic to Sri Lanka. Similar to MI, MZ also bears edible fruits (4). The tree grows up to a height of 10-30 m and branches from a stout trunk. Compared with MI, MZ possesses smaller leaves (7-13 cm in length, dark green and shiny) and fruits (3-5 cm long and ripen fruits are yellow in colour) (Fig. 1B). The seed occupies a larger volume of the fruit than the fruit pulp (4). In Sri Lankan traditional medicine, the bark of MZ has been used in the treatment of various ailments and diseases, including cancer (1). According to the International Union for Conservation of Nature (IUCN), MZ has been classified as a vulnerable species (5). MZ leaves, bark and fruits are presented in Fig. 1B (left panel, middle panel and right panel, respectively).

Epigenetics modifications arise due to alterations in gene function that cannot be endorsed to DNA sequence modifications. Two key biological processes, DNA methylation and histone modifications (histone acetylation, deacetylation sumoylation and ubiquitylation) have been reported to largely contribute to such epigenetics modifications (6). In normal cells, it has been reported that the functions of a number of genes are highly regulated through DNA methylation and histone modifications (6). Given that epigenetic modifications tightly control gene expression, it is not surprising that any irregularity in the epigenetic modification is associated with aberrant gene functions (7). Notably, the dysregulation of epigenetics modifications have been reported in a range of human cancers (8). Several phytochemicals have been identified as promising drug candidates which can re-establish aberrant epigenetic profiles (9). The present review article discusses the biological and pharmacological effects of various extracts and phytochemicals of MI and MZ, as well as the effects of major mango bio-active compounds on epigenetic modifications.

2. Medicinal properties of MI

MI is one of the widely used medicinal plants. A number of pre-clinical investigations have reported a range of pharmacological effects of different MI extracts (1). MI is well known to possess polyphenolic compounds, which have been found to have diverse biological activities (1). Different parts of MI, including the leaves, stem, flowers, fruits and seeds possess essential nutrients, such as vitamins and minerals (10). The following sections describe some experimentally validated pharmacological effects (antioxidant, anti-inflammatory, anti-diabetic, anti-obesity and anti-microbial properties) of different parts (leaves, bark, seed and fruit peel and flesh) of MI.

Antioxidant properties. A number of studies have demonstrated the antioxidant properties of extracts prepared from different parts of MI. Dhital (11) demonstrated that the leaf methanol extract of MI exerts moderate free radical scavenging effects (12). In another study, among the aqueous bark extracts prepared from the Keitt, Kent, Honey (originally Ataulfo) and Tommy Atkins MI varieties, the aqueous bark extract of Kent was reported to possess the most pronounced antioxidant properties. Moreover, the Ataulfo extract was found to exert the most prominent cellular anti-oxidant effects (12). The leaf methanol extract of Mahajanaka, a mango variety found in Thailand, has been shown to exert potent free radical scavenging effects. The same leaf extract has also been shown to inhibit lipopolysaccharide-induced nitric oxide production in RAW264.7 cells (13). In another study by John *et al* 2012, exposure to an aqueous ethanol extract of MI stem bark increased the red blood cell count in Wistar strain albino rats, indicating its ability to enhance erythropoiesis and exert protective effects against oxidative damage. Furthermore, the increment of monocytes and neutrophils following exposure to the aqueous ethanol extract indicated its ability to enhance and modulate immunological activities (14). The leaf ethanolic extract of MI has been found to have antioxidant properties *in vivo*. In a previous study, the attenuation of cerebral oxidative status in rats was observed when the rats were fed various different doses of MI leaf ethanol extract. Moreover, increased levels of malondialdehyde, and reduced superoxide dismutase and glutathione peroxidase activities were observed in the hippocampus of the tested animals (15). The ethanolic extract of MI fruits has also been found to exert protective effects against cognitive impairment and oxidative stress (16). These observations indicate the ability of the MI plant extract to function as an antioxidant *in vitro* and *in vivo*.

Anti-inflammatory properties. The anti-inflammatory properties of mango peel, seed and pulp of Sri Lankan mango varieties have been investigated (17). Experiments conducted using the human red blood cell membrane stabilization assay demonstrated that the peel, pulp and seed ethyl acetate extracts of three different mango varieties (Willard, Vellaicolomban and Karthacolomban) exerted anti-inflammatory activities. Among these, the ethyl acetate extract of Karthacolomban seeds exhibited the highest anti-inflammatory activity (17). The ethanol leaf extract of MI was found to possess analgesic and anti-inflammatory effects *in-vivo* (18). Wistar Hannover rats treated with MI leaf ethanol extract have also been shown to exhibit diminished inflammatory activities induced by 4% formalin (19). In the study by Kim *et al* (20), polyphenolic derivatives of MI were shown to modulate dextran sulfate sodium (DSS)-induced colitis in rats, suggesting that MI polyphenolic derivatives can attenuate inflammatory responses. In another study, the methanol extract of MI stem bark was found to exert anti-inflammatory effects against DSS-induced colitis (21). Moreover, the administration of aqueous stem bark extracts of MI resulted in a reduction in the levels of thiobarbituric acid reactive substances, the expression of tumour necrosis factor-α (TNF-α), cyclooxigenase-2, inducible nitric oxide synthase and TNF receptor-2 in colonic tissue and, and in serum TNF-α and interleukin (IL)-6 levels (21). Collectively, these findings suggest that mango peel, seed and leaf extracts possess anti-inflammatory properties.

Anti-diabetic and anti-obesity effects. The study by Perpétuo and Salgado (22) demonstrated the effects of diets containing mango flour on blood glucose levels in diabetic rats. Diabetic rats fed mango flour exhibited reduced blood glucose levels from the 10th day of feeding. Moreover, a 64% reduction in glycogen levels was observed compared to the control group (22). MI flavonoids have been reported to reduce blood glucose levels in Swiss albino mice with induced diabetes (23). Furthermore, MI leaf aqueous extract was found to increase high-density lipoprotein levels (23). The ethanol (95%)

Figure 1. (A) *Mangifera indica* leaves (left panel), bark (middle pane) and fruits (right panel). (B) *Mangifera zeylanica* leaves (left panel), bark (middle pane) and fruits (right panel).

extract of MI leaves and mangiferin modulated the endocannabinoid (CB) system and peroxisome proliferator-activated receptor-γ (*PPAR*γ) mRNA expression in cafeteria diet-fed rats, suggesting a possible role for MI in controlling obesity and metabolic syndrome (24). The endocannabinoid system has been reported to contribute to weight gain and glucose intolerance, while PPARγ is one the key regulators of adipose cell development and differentiation (24).

The peel acetone extract of MI possesses hypoglycaemic effects. The study by Gondi and Rao illustrated that the leaf extract of MI can be used against streptozotocin-induced diabetes in rats (25). Rats fed various doses of MI peel extracts were found to have lower levels of glycated haemoglobin (25). Narasimhan *et al* (26) also demonstrated that albino rats of the Wistar strain fed various doses of ferulic acid, a major compound found in mango, exhibited an enhanced glycogen synthesis, improved blood glucose tolerance and reduced gluconeogenic enzyme activities. Moreno *et al* (27) demonstrated that MI extracts inhibited the action of lipoprotein lipase and hormone sensitive lipase in male Wistar rats. Animals receiving stem bark and leaf extracts exhibited an inhibition of isoproterenol-stimulated glycerol release and an increment in faecal fat. Moreover, animals receiving MI leaf extract also exhibited an inhibition of pancreatic lipase (27). A study on lean and obese individuals identified that a mango supplementation decreased plasminogen activator inhibitor-1, glycated haemoglobin and inflammatory cytokine (IL-8 and monocyte chemoattractant protein-1) levels in obese individuals and controlled blood pressure, indicating a positive role of mango consumption against metabolic and obesity-related chronic diseases (28).

Anti-microbial properties. Acetone extracts of MI leaves have been shown to exhibit antibiotic activity against antibiotic-sensitive and multidrug-resistant bacteria, such as *Salmonella typhi*, *Staphylococcus aureus* and *Salmonella typhimurium* (29). Furthermore, a methanol extract of the seed kernal of MI has been found to exert inhibitory effects against *Staphylococcus aureus*, *Escherichia coli* and *Bacillus subtilis* (29). In the study by Manzur *et al* (30), aqueous and ethanolic extracts of MI leaves were found to exert inhibitory effects against *Stapylococcus* species isolated from cows. In another study, Mushore and Matuvhunye (31) demonstrated that an aqueous extract of stem bark of MI can reduce the growth of *S. aureus*. A recent study demonstrated that the hexane peel extract prepared from the Sindhura and Banisha mango varieties found in India exerted growth inhibitory effects against *Escherichia coli* (32). In addition, methanolic and ethyl acetate peel extracts was found to exert inhibitory effects against *Bacillus subtilis and Pseudomonas aeruginosa*, respectively (32). These findings suggest the potential use of MI extracts and by-products as anti-microbial agents. Further studies are required however, to elucidate anti-microbial mechanisms and to isolate active compounds.

Anticancer properties. Various extracts and compounds isolated from MI have been reported to exert anticancer effects *in vitro* and *in vivo*. Noratto *et al* (33) evaluated the anticancer effects of polyphenolic extracts prepared from five mango varieties (Haden, Francis, Honey, Kent and Tommy Atkins) in breast (MDA-MB-231), lung (A549), prostate (LNCaP), colon (SW-480) and leukaemia (Molt-4) cancer cell lines. The Ataulfo and Haden polyphenolic extracts exhibited cell growth inhibitory potential in all tested cancer cell lines in a dose-dependent manner. The Ataulfo extract exhibited the most potent inhibitory effects in the MDA-MB-231 cells, while the Haden extract displayed the most prominent inhibitory effects in the Molt-4 cells. Fitriasih *et al* (34) also demonstrated that the treatment of MCF-7 breast cancer cells with a methanol extract of MI leaves induced apoptosis by

decreasing *Bcl-2* expression and increasing *Bax* expression. In another study, when MDA-MB-231 cells were exposed to polyphenols extracted from MI pulp, cell growth was inhibited and the expression of PI3K signalling-associated miRNAs was modulated (35). Furthermore, Abdullah *et al* (36) reported that MI seed ethanolic extract induced the apoptosis of MCF-7 breast cancer cells.

Notably, major polyphenols, such as mangiferin, norathyriol and quercetin have been reported to exert inhibitory effects against P-glycoprotein, a member of the adenosine triphosphate binding cassette transporter superfamily responsible for multidrug resistance in human cancers (37). The PI3K/AKT/mTOR signalling pathway is a frequently activated signalling pathway in a range of human cancers (38). Banerjee *et al* (39) demonstrated that when BT474 breast cancer cells were exposed to MI pulp extracts, the expression of PI3K signalling-associated proteins, such as p-PI3K, p-AKT and AKT was reduced. Furthermore, female athymic BALB/c nude mice bearing BT474 tumours, exhibited a reduction in tumour size and PI3K signalling-associated proteins when fed the pulp extract (39). These findings indicate that MI extracts and phytochemicals may have potential for use in the development of drugs for cancer treatment. However, the possible toxic effects of mango extracts and compounds need to be determined and managed before using these as therapeutics for cancer in clinical practice.

3. Medicinal properties of MZ

Although MZ has been used in Sri Lankan traditional medicine against several diseases and conditions. including cancer, the scientific validation of its use for cancer treatments was only recently initiated (40). Hexane and chloroform extracts of MZ bark have been reported to exert anticancer effects in breast and ovarian cancer cells *in vitro* (40,41). Moreover, two new halogenated compounds and a new resorcinolic lipid were isolated from the bark of MZ (41,42). The scientific evidence related to the anticancer effects of MZ extracts and compounds is briefly discussed below.

Anticancer properties exerted by various MZ extracts and isolated compounds. Two new halogenated compounds (chloromangiferamide and bromomangiferic acid), quercetin and catechin (41), as well as a new resorcinolic lipid (42) were isolated from the bark of MZ. Of these compounds, chloromangiferamide have been shown to exert selective anticancer effects in MDA-MB-231 triple-negative breast cancer cells with less cytotoxicity to MCF-10A normal mammary epithelial cells. Furthermore, experiments performed using qPCR assays revealed that chloromangiferamide regulated the expression of genes associated with the cell cycle, apoptosis, topoisomerases, drug metabolism, receptor tyrosine kinase signalling, histone deacetylases (HDAC1-4, 6-8 and 11), protein kinases, phosphatases, growth factors and PI3K signalling in MDA-MB-231 cells (41). The isolated new resorcinolic lipid has been shown to exert potent cytotoxic effects through a mechanism related to oxidative stress in MCF-7 oestrogen receptor positive breast cancer cells (42).

Studies conducted with MZ bark extracts have also demonstrated notable scientific findings, which support its traditional use in cancer treatment. The hexane extract of MZ bark was previously reported to exert cytotoxic effects in breast (MCF-7 and MDA-MB-231) and ovarian (SKOV-3) cancer cells through the induction of apoptosis. The gas chromatography-mass spectrometry (GC-MS) analysis of the hexane extract of MZ bark identified certain unknown compounds, which indicated the presence of new phytochemicals in the bark of MZ (40). Furthermore, the chloroform extract of MZ fruit peel induced the apoptosis of MCF-7 breast cancer cells through a mechanism related to oxidative stress, suggesting the potential use of MZ fruit peel as a cost-effective source for anticancer compounds (43). However, in order to elucidate the complete anticancer mechanisms exerted by MZ extracts and isolated compounds, *in vivo* investigations are necessary to determine the *in vivo* anticancer efficacy and toxic effects of the MZ extracts.

Preliminary investigations conducted in the authors' laboratories identified that extracts prepared from MZ leaves exerted anticancer effects in breast and lung cancer cells *in vitro* (unpublished data). *In vitro* investigations performed using MI and MZ extracts are summarized in Table I, while *in vivo* investigations performed using various MI extracts are listed in Table II. The chemical structures of the compounds present in MI and MZ are illustrated in Fig. 2. In addition, the pharmacological activities of various compounds isolated from MI and MZ are summarised in Table III. A comparison of the anticancer activities of various MI and MZ extracts is presented in Table IV. Furthermore, the potential efficacy of chloromangiferamide to target HDAC genes in MDA-MB-231 triple-negative breast cancer cells is illustrated by the schematic diagram in Fig. 3.

4. Epigenetic modifications in human cancer

Epigenetic modifications can be defined as heritable alterations of gene expression levels which are independent of DNA sequences (6). Apart from the DNA methylation and histone modifications, microRNAs (miRNAs/miRs) also contribute to the epigenetic regulation of gene expression (78). It has been reported that the regulation of epigenetic processes is largely controlled by the environmental conditions, lifestyle, developmental stages, pathological conditions and diet (79,80). During the development and cellular differentiation of an organism, cell type-specific epigenetic patterns developed define normal pattern of gene functions in each cell type (80). Furthermore, it has been reported that epigenetic modifications play a key role in the development of a number of diseases, including cancer, autoimmune diseases, neurodegenerative diseases and psychiatric disorders (81,82). Therefore, understanding the role of epigenetics in human diseases and identification potential drug targets which can target aberrant epigenetic alterations will be extremely beneficial.

Chromatin structure. Nucleic acid material of eukaryotes consists of DNA and histone proteins (83). Histone proteins are found as octamers and are wrapped by 1.65 turns of DNA. These octamers consist of two copies of histone subunits known as H2A, H2B, H3 and H4. The N-terminal tails of these subunits contain higher amounts of lysine resulting in an overall positive charge. The chromatin structure functions as a

Table I. *In vitro* and *in vivo* studies conducted with different extracts/parts of *Mangifera indica* and *Mangifera zeylanica*.

Plant	Plant part and extract	Disease/condition	Cell line/s used	Pathway/s	(Refs.)
Mangifera indica	Ethanol and PBS extracts of peel	Colorectal cancer	HT29, Caco-2 and HCT116	γH2AX-mediated genotoxicity and apoptosis	(44)
	Ethanol extract of seed kernel	Breast cancer	MDA-MB-231 and MCF-7	Increments in neutral red uptake and lactate dehydrogenase release and enhanced cytotoxicity	(45,46)
	Aqueous extract of fruits	Leukaemia	B-lymphocytes from patients	Intrinsic pathway of apoptosis and induction of oxidative stress	(47)
	Ethanol extract of seed	Breast cancer	MCF-7	Upregulation of *Bax*, cytochrome c, *p53* and caspases,	(36)
				Reduction of GSH and Bcl-2 levels and induction of oxidative stress	(36)
	Ethanol (80%) extract of pomace	Malignant tumours	HepG2, MCF-7, A549, HeLa, A2780, HCT-116 and BGC-823	Induction of apoptosis	(48)
	Ethanol (80%) extract of peel	Breast cancer	MCF-7	Downregulation of CYP19A1 leading to decreased aromatase activity	(49)
	Methanol extract of peel	Breast cancer	MCF-7	Inhibitory effects on Ca^{2+} channels	(50)
			BT474	Suppression of the PI3K/AKT pathway	(39)
				Modulation of the miR-126 expression	(39)
	Mango beverage	Inflammation in intestinal colitis	CCD-18Co	Modulation of the miR-126/PI3K/AKT/mTOR axis	(51)
Mangifera zeylanica	Peel chloroform extract	Breast cancer	MCF-7	Induction of oxidative stress	(43)
	Hexane extract of bark	Breast and ovarian cancer	MCF-7, MDA-MB-231 and SKOV-3	Induction of apoptosis	(42)

protective mechanism for genetic information and regulatory mechanism to control the access to enzymes and proteins necessary for DNA replication and gene expression (84).

DNA methylation and its role in human cancers. DNA methylation exclusively takes place in the cytosine bases of CpG dinucleotides in the human genome (85). Short CpG contents (0.5-4 kb), referred to as CpG islands, are commonly found in the human gene promoter regions (86). The epigenetic silencing of tumour suppressor genes (for example *CDKN1C, CDKN2A, RUNX3, WT1, FOXA2, DAPK, TMS1, BCL2, HOXD11, GPC3, LAMA3* and *LKB1*) due to the hypermethylation of CpG islands is frequently observed in human cancers (86). Several oncogenes are upregulated through promoter hypermethylation (6). For example, the promoter of the gene *SOSTDC1*, which encodes for a bone morphogenetic protein, is frequently upregulated through hypermethylation (85,86). The *FLT4* gene, that encodes a tyrosine kinase receptor for vascular endothelial growth factors C and D, is frequently upregulated through promoter hypermethylation. *CYBA*, a gene that encodes for cytochrome B light chain is also upregulated through DNA hypermethylation (86). *APC* is a tumour suppressor gene known to regulate the Wnt signalling pathway. In colorectal cancer the hypermethylation of the *APC* gene promoter induces the down-regulation of *APC* (87). The *RASAL2* gene that encodes for Ras-GTPase-activating protein 2 is also upregulated through promoter hypomethylation in distinct human cancers (88). DNA methyl transferase inhibitors are useful drugs in cancer treatments. Deoxycytidine is one of the very first drugs which undergoes a series of phosphorylation steps and incorporates into CpG sites of DNA, leading to the formation of covalent bonds between DNA methyl transferase 1 (DNMT1) catalytic sites (89,90). 5-Aza-2'-deoxycytidine is a Food and Drug Administration (FDA)-approved DNMT inhibitor used in the treatment of myelodysplastic syndromes (91).

Histone modifications in cancer. Histone acetylation is another major epigenetic modification event, which involves

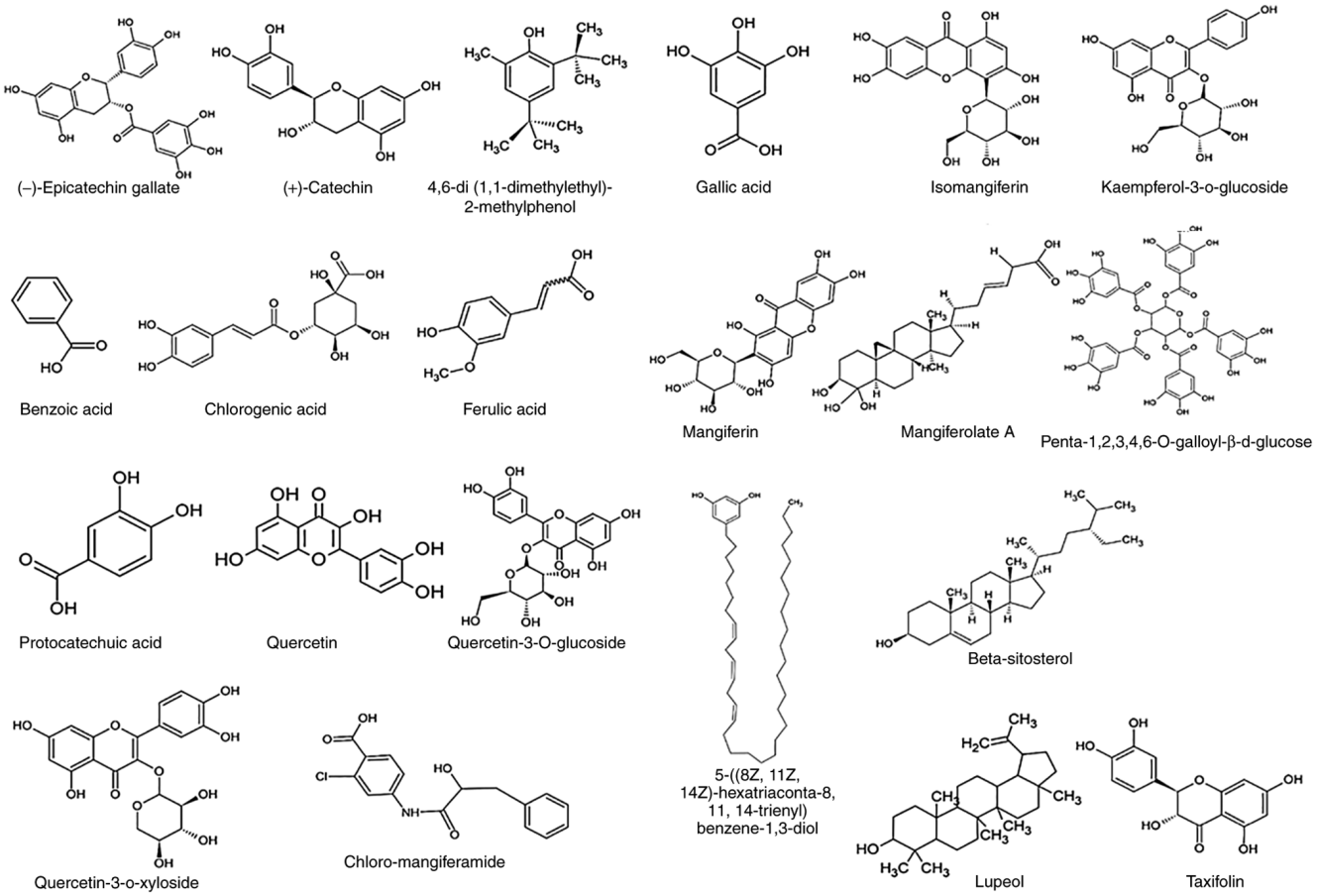

Figure 2. Chemical structures of various compounds found in *Mangifera indica* and *Mangifera zeylanica*.

Table II. *In vivo* pharmacological activities of various extracts/major compounds of *Mangifera indica*.

Extract	Disease/condition	Test animals	Effects	(Refs.)
Aqueous extract of leaves	Diabetics	Wistar rat	Increment of insulin sensitivity and levels in diabetic animals	(52)
Ethanol extract of leaves	Obesity	Wistar rat	Modulation of endocannabinoid system and PPARγ expression leading to the control of metabolic syndrome and obesity	(24)
Mango polyphenols	Anti-tumorigenic properties	Female athymic BALB/c nude mice	Suppression of the PI3K/AKT pathway; modulation of miR-126 expression	(39)
Stem bark extract and leaf extract (ethanol)	Obesity	Male Wistar rats	Inhibition of pancreatic lipase and lipoprotein lipase led to reduce the lipid uptake in intestine and free fatty acids in adipose tissue	(27)
Mangiferin	Iron overload in animal models	Sprague-Dawley rats	Reduction of iron accumulation in liver, spleen and heart	(53)
	Cisplatin-induced nephrotoxicity	Male Wistar albino rats	Protection of kidney cells from apoptosis through modulation of the MAP kinase pathway	(54)

the acetylation of lysine residues at the ε-amino groups of histones (92). This epigenetic modification is controlled by two different groups of enzymes known as histone acetyl transferases (HATs) and histone deacetylases (HDACs). HATs transfer the acetyl group from Acetyl-Co A to amino acid group of the targeted lysine residues found in the histone tails, while HDACs counteract the actions of HATs (92).

Based on the structural homology, HATs are classified into three different families known as Gcn5-related N-acetyltransferases (GNATs), MOZ, Ybf2, Sas2, TIP60

Table III. Compounds isolated from different *Mangifera* species and their effects on cancer signalling pathways.

Mangifera species	Identified compounds	Cell lines used	Pathway/s affected	(Refs.)
Mangifera indica	(-)-Epicatechin gallate	SCC7, Tu177 and Tu212	Inhibition of the canonical Wnt pathway	(55,56)
			Downregulation of cyclin D1 expression	(55,56)
	4,6-di (1,1-Dimethylethyl)-2-methylphenol	MCF-7 and MDA-MB-231	Apoptosis and oxidative stress	(12,45)
	Chlorogenic acid	HCT116	Generation of reactive oxygen species	(57,58)
		HT29	Cell cycle arrest at S phase	(57,58)
	Ferulic acid	HeLa and Caski	Downregulation of MMP-9 expression	(59)
	Gallic acid	SMMC-7721	Induction of apoptosis	(60)
	Isomangiferin	MCF-7	Induction of apoptosis by inhibition of VEGFR 2 kinase	(61)
	Kaempferol 3-*O*-β-D-glucoside	HL-60	Intrinsic pathway of apoptosis Generation of reactive oxygen species Induction of JNK/SAPK and ERK1/2 signalling	(56,62)
	Mangiferin	HL-60	Inhibition of ATR, Chk1, Wee1, Akt, and Erk1/2 phosphorylation	(63)
		K562	Overexpression of BCR and ABL	(64)
		OVCAR3	Induction of apoptosis through the Notch3 pathway	(65)
	Penta-1,2,3,4,6-*O*-galloyl-β-d-glucose	LNCaP	Apoptosis	(33,66)
	Protocatechuic acid	HL-60	Suppression of Bcl-2 and upregulation of Bax	(33)
	Quercetin	MGC803	Modulation of the PI3K/Akt/mTOR pathway	(67)
		Nalm6	Cell cycle arrest at S phase	(68)
		HCT116 and HT29	Suppression of HSP27	(57,68)
Mangifera zeylanica	Chloro-mangiferamide	MDA-MB-231	Apoptosis, downregulation of protein kinases, histone deacetylases and heat-shock proteins	(41)
Mangifera casturi	Lupeol	HCT116	Canonical Wnt pathway	(69,70)
Mangifera pajang	Taxifolin	HCT119 and HT29	Canonical Wnt pathway and cell cycle	(71,72)

(MYST) and orphan [p300/CREB binding protein (CBP) and nuclear receptors] (93). These enzymes neutralize positive charges of the histone proteins, resulting in weakened interactions between histones and DNA, rendering chromatin less condensed and DNA more accessible to transcription factors (94). Histone acetylation is however targeted to specific regions of DNA through sequences specific co-factors of HATs, including CBP, p300, MYST, and GNAT. The deacetylation of histones leads to condensed chromatin, resulting in the transcriptional silencing of genes (95).

Apart from the acetylation of histones, several other modifications, such as the phosphorylation, methylation and ubiquitination of histone subunits have also been identified. Research performed using normal tissues, tumours and mouse models has reported that the loss of acetylated Lys16 (K16-H4) of histone H4 is a frequent event in human cancers (95). Moreover, a reduction in histone acetylation has been shown to be associated with invasion and metastasis in gastrointestinal tumours (95). Mutations, such as missense mutations, truncations, translocations and frame shift mutations of different families of HATs have been identified in several human cancers, including colorectal, head, neck, breast and lung cancers (96).

Investigations carried out with histone deacetylase inhibitors (HDACis) have proven the role of HDACs in the regulation of p21 protein (97). p21 Protein is a cyclin-dependant kinase inhibitor which inhibits cyclin D1, A and E. The inhibition of p21 leads to cell cycle arrest at the G1 or G2/M phases (98). In prostate cancer cells, exposure to trichostatin A, an HDAC

Table IV. Comparison of anticancer activities of different parts of MI and MZ and grapes (*Vitis vinifera*).

Plant part	*Mangifera indica*	*Mangifera zeylanica*	*Vitis vinifera*	(Refs.)
Bark	Induces apoptosis of MCF-7 breast cancer cells	Induces apoptosis of MCF-7 cells	Not reported	(42,73)
Leaves	Induces apoptosis of MCF-7 breast cancer cells by upregulating *Bax* and downregulating *Bcl*	Induces apoptosis of NCI-H292 lung cancer cells by upregulating *p53, Bax* and downregulating *Survivin* (unpublished data)	Water and ethanol extracts increase the expression of *Bax* in HUVECs and HepG2 liver cancer cells	(34,74)
Fruit pulp	Mango beverage inhibits growth in CCD-18Co by modulating miR-126/PI3K/AKT/mTOR axis	Not reported	Induces autophagy in MCF-7 breast cancer cells	(39,75)
Seed	Ethanolic extract enhances cytotoxicity to MCF-7 and MDA-MB-231 breast cancer cells	Hexane extract shows cytotoxicity to NCI-H292 lung cancer cells (unpublished data)	Increases apoptosis in DU145 and LNCaP prostate cancer cells	(36,76)
Fruit peel/skin	Ethanol extract inhibits MCF-7 breast cancer cell growth by downregulating the *CYP19A1* gene. Methanol extract inhibits Ca^{2+} channels in MCF-7 cells	Chloroform extract induces oxidative stress in MCF-7 breast cancer cells	Induces apoptosis of prostate cancer cells by targeting the phosphatidylinositol 3-kinase-Akt and mitogen-activated protein kinase survival pathways	(43,49,77)

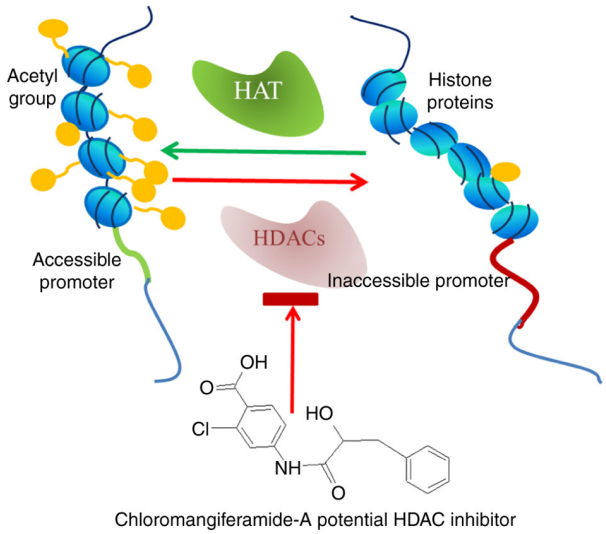

Figure 3. Schematic diagram of the potential efficacy of chloromangiferamide, isolated from the bark of *Mangifera zeylanica* bark, to target HDACs in MDA-MB-231 triple negative breast cancer cells. Chloromangiferamide isolated from the bark of MZ has been reported to reduce the expression of histone deacetylases (HDAC1-4, 6-8 and 11) in MDA-MB-231 triple-negative breast cancer cells and to exert less cytotoxic effects in normal mammary epithelial cells (40). Histone acetylation is another major epigenetic modification event, which involves acetylation of lysine residues at the ε-amino groups of histones. This epigenetic modification is controlled by two different groups of enzymes known as HATs and HDACs. HATs transfer the acetyl group from the Acetyl-Co A to amino acid group of the targeted lysine residues found in the histone tails, while HDACs counteract the actions of HATs. HDAC inhibitors can correct aberrant acetylation profiles in cancer. HDACs, histone deacetylases; HATs, histone acetyl transferases.

inhibitor, has been found to induce the activation of p-glycoprotein expression through the modulation of the histone markers, H3K4me2, H3K4me3, H3K9Ac, H4Ac and H3Ac, indicating an involvement of an epigenetic mechanism in the regulation of p-glycoprotein expression (99).

HDACis, also known as chromatin-modifying agents, have been identified as a promising class of anticancer agents. HDACis have the ability to re-establish dysregulated acetylation profiles of cancer cells and re-activate the expression of epigenetically silenced tumour suppressor genes, allowing cancer cells to undergo programmed cell death (apoptosis) (6). To date, several pan or isoform specific HDACis (natural and synthetic) have been developed and, these HDACis allow for the identification of the role of various HDACs in tumorigenesis (100). Vorinostat (SAHA) for the treatment of cutaneous T-cell lymphomas (CTCL), panobinostat (LBH-589) for the treatment of multiple myeloma, belinostat (PXD101) for the treatment of peripheral T-cell lymphomas (PTCL) and romidepsin for the treatment of CTCL and PTCL are the only four FDA-approved HDACis in clinical use to date (100). Natural compounds, such as curcumin, epigallocatechin gallate, sulforaphanes, kaempferol, resveratrol and butein are some examples for natural HDACis (7).

miRNAs. A group of short RNA molecules (18-22 nucleotides), known as miRNAs, also contribute to the epigenetic regulation of gene expression (101). miRNAs are transcribed by RNA polymerase II to yield primary-miRNAs (pri-miRNAs), which are then cleaved into 65-70 nucleotide-long hairpin RNA duplexes by DROSHA and PASHA (microprocessors) (101,102). These are then exported to the cytoplasm and further cleaved by a protein complex known as Dicer to generate functional miRNAs. A complex comprised of miRNAs and a protein known as RISC (RNA induced silencing complex) bind to the target mRNA and degrade it, causing gene silencing (103).

miRNAs play crucial roles in the development, apoptosis, cell differentiation and proliferation under normal conditions (104).

There is experimental evidence to indicate that a considerable number of miRNAs can play oncogenic or tumour-suppressive roles (105). The upregulation of oncogenic miRNAs, also referred as oncomirs, is frequently observed in a range of human cancers (105). It has been reported that any functional irregularity in the expression and function of tumour suppressor miRNAs can cause tumorigenesis (105). The Let-7 family miRNAs (let-7a, let-7b and let-7g), miR-205, members of the miR-200 family (miR-200a, b and c, miR141 and miR-429), miR-200c, miR-145 and miR-142-3p have been reported to function as tumour suppressor miRNAs, while oncogenic roles of miRNAs, such as miR-21, miR-10a, miR-10b, miR-155, miR-17-92, miR-17-5p, miR-27a, miR-96 and miR-182 have also been identified (98,106,107). It has been found that epigenetic modifications, such as histone deacetylation in promoter sites and DNA methylation in CpG islands cause alternations in mRNA expression. Therefore, epigenetic mechanisms provide promising drug targets since DNA-demethylating agents and HDACis can be used to re-establish mRNA expression implicated due to epigenetic alternations (99). Several miRNAs have also been identified to play a regulatory role in cancer stem cells (CSCs). For example, the Let-7 family miRNAs have been reported to play a role in CSC differentiation (99).

Mango compounds as epigenetic modifiers. Several mango compounds have been reported to function as epigenetic modulators. Epicatechin gallate has been found to upregulate HDAC5 and HDAC7, while downregulating HDAC 1 and HDAC3. Moreover, the DNMT inhibitory activities of catechin have also been reported (108).

Experiments performed using A/J mice have revealed that epicatechin gallate leads to a significant elevation in the levels of miRNAs related to lung tumours induced by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. These miRNAs include mmu-miR-2137, mmu-miR-449a, mmu-miR-144, mmu-miR-193, mmu-miR-5030 and mmu-miR-2861. Moreover, the downregulation of mmu-miR-969, mmu-miR-449c, mmu-miR-7a, mmu-miR-205 and mmu-miR-218 has also been observed due to the exposure to epicatechin gallate (109).

A previous study performed using ATDC5 cells revealed that mangiferin upregulated miR-181a expression. The upregulation of miR-181a resulted in protection from lipopolysaccharide-induced cell damage, by suppressing the levels of PTEN and the NF-κB pathway (110). Another study performed using glioma cells demonstrated that mangiferin upregulated miR-15b expression, resulting in the suppression of MMP-9 in U87 cells, indicating the ability of mangiferin to reduce metastasis (111).

5. Phytochemicals common to both MI and MZ

Mangiferin is one of the well-known phytochemicals found in MI. Mangiferin has also been isolated from the bark of MZ (112). The therapeutic potential of mangiferin has also been investigated. Mangiferin has been found to exert preventive roles against mitochondrial depolarization, oxidative stress and neuronal death (112). Lemus-Molina *et al* (113) demonstrated that the consumption of MI extracts rich in mangiferin attenuated neuronal death during normal aging and in neurodegenerative disorders. Another study reported that mangiferin exerted potent antioxidant effects (114). Mangiferin has also been reported to exert cytotoxic effects in cancer cells (63,64). Another study states that mangiferin can protect rats from cardiac and renal damage (115). Rajendran *et al* (116) demonstrated cytoprotective and antioxidant effects of mangiferin. Apart from these effects, mangiferin is capable of antagonizing the cytopathic effect of HIV *in vitro* (117). Furthermore, a previous study demonstrated that mangiferin induced apoptosis through the PKC/NF-κB pathway and the cell cycle arrest of multiple myeloma cells (118). Biersack (119) reported that mangiferin can mediate the regulation of tumor suppressor miRNAs including miR-15b and miR-182.

Apart from mangiferin, gallic acid and quercetin are commonly found in the genus *Mangifera*. In a previous study, Ediriweera *et al* (41) isolated quercetin from the bark of MZ. The anti-proliferative effects of gallic acid mediated by the epigenetic regulation of miRNAs have been reported in glioma T98G cells (120). Sundaram *et al* (121) demonstrated that quercetin exerted anti-proliferative effects in human cervical cancer cells. Quercetin treatment has been shown to decrease the activity of DNMTs, increasing the global acetylation of H3 and H4, and induce the enrichment of acetylated histone H3 and H4 to the promoters of genes related to apoptosis (121). Previously, PLGA [poly(lactic-co-glycolic acid)]-loaded gold nanoparticles prepared with quercetin were found to exert anti-proliferative effects in hepatocellular carcinoma cells through down-regulation of HDAC-Akt activities (122). On the whole, these studies indicate that phytochemicals from MI and MZ are useful epigenetic regulators.

6. Conclusion

MI is a pharmacologically and phytochemically diverse plant. Extracts prepared from different parts (skin and pulp of the fruit, leaves, bark, roots and seeds) of MI are used in traditional medicine for the treatment of numerous diseases and ailments. The fruits of MI are rich in vitamins, essential amino acids and a range of polyphenols. *In vitro* and *in vivo* experimental evidence indicates that different extracts and major phytochemicals of MI can lead to beneficial pre-clinical outcomes against several health conditions, including cancer (1). Mango phytochemicals and mango extracts have been reported to target aberrantly expressed cancer signalling pathways (e.g., the PI3K/AKT/mTOR signalling pathway) (1,39). Some major mango polyphenols have the ability to re-store dysregulated epigenetic profiles in human cancers. Of note, *in vivo* experimental evidence demonstrates that MI extracts and some major compounds exert less toxic effects, justifying their use in human systems without causing adverse side-effects (14-19,21,22,25,26,29).

MZ is an endemic mango species found in Sri Lanka. The bark of MZ has been used in Sri Lankan traditional medicine for the treatment of a number of diseases, including cancer. Efforts have been made to validate its traditional use scientifically. For example, hexane and chloroform extracts of its bark and certain novel compounds isolated from the bark of

MZ have been reported to exert anticancer effects in breast and ovarian cancer cells (41,42). Moreover, peel chloroform extract prepared from MZ fruits also exerts anticancer effects, indicating that the anticancer potential of MZ is not limited to its bark. However, to obtain a clear anticancer profile for MZ, *in vivo* studies with distinct mouse models for cancer and the evaluation of the toxic effects of MZ extracts are necessary. Dysregulated epigenetic events have been reported to drive tumorigenesis. A number of phytochemicals have exhibited the ability to re-establish aberrant epigenetic profiles in a range of human cancers. The present review article highlighted the ability of certain mango compounds to function as epigenetic modifiers.

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Availability of data and materials

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Authors' contributions

All authors (IS, AV, NP, MKE, DN, SRS, KHT and VV) contributed to the conceptualization, writing, drafting, revising, editing and reviewing of the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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