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Revisión | Review

Pharmacological importance of *Manilkara zapota* and its bioactive constituents

[Importancia farmacologica de *Manilkara zapota* y sus constituyentes bioactivos]

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Abstract: *Manilkara zapota* (Sapotaceae), commonly known as Sapodilla, is widely known for its delicious fruit. Various parts of this plant are also used in folk medicine to treat a number of conditions including fever, pain, diarrhoea, dysentery, haemorrhage and ulcers. Scientific studies have demonstrated analgesic, anti-inflammatory, antioxidant, cytotoxic, antimicrobial, antidiarrheal, anti-hypercholesteremic, antihyperglycemic and hepatoprotective activities in several parts of the plant. Phytochemical studies have revealed the presence of phenolic compounds including protocatechuic acid quercitrin, myricitrin, catechin, gallic acid, vanillic acid, caffeic acid, syringic acid, coumaric acid, ferulic acid, etc. as main constituents of the plant. Several fatty acids, carotenoids, triterpenes, sterols, hydrocarbons and phenylethanoid compounds have also been isolated from *M. zapota*. The present review is a comprehensive description focused on pharmacological activities and phytochemical constituents of *M. zapota*.

Keywords: *Manilkara zapota*; Ethno medicine; Pharmacological activities; Phytoconstituents

Resumen: *Manilkara zapota* (Sapotaceae), comúnmente conocida como Sapodilla, es ampliamente conocida por su delicioso fruto. Variadas partes de esta planta se usan en medicina popular para tratar una serie de afecciones, como fiebre, dolor, diarrea, disentería, hemorragia y úlceras. Estudios científicos han demostrado actividad analgésica, antiinflamatoria, antioxidante, citotóxica, antimicrobiana, antidiarreica, antihipercolesterolémica, antihiperglucémica y hepatoprotectora en diferentes partes de la planta. Los estudios fitoquímicos han revelado la presencia de compuestos fenólicos que incluyen ácido protocatechúico, quercitrina, miricitrina, catequina, ácido galico, ácido vanílico, ácido cafeico, ácido sirínico, ácido cumárico, ácido fúnico y ácido ferúlico como componentes principales de la planta. Varios ácidos grasos, carotenoides, triterpenos, esteroles, hidrocarburos y compuestos feniletanoides también han sido aislados de *M. zapota*. La presente revisión es una descripción exhaustiva centrada en las actividades farmacológicas y los constituyentes fitoquímicos de *M. zapota*.

Palabras Clave: *Manilkara zapota*; Etnomedicina; Actividad farmacologica; Fitoconstituyentes

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INTRODUCTION

Human companionship with the nature for food and shelter dates back to the origin of mankind. Healing power of the plants has been recognized by humans for thousands of years (Summer, 2000). Even today, more than 80% of the global population depends on traditional plant-based therapy for treating various diseases (Smith-Hall *et al*., 2012). Medicinal plants are defined as plants used for maintaining health and/or treating specific ailments. More than 9000 plants have been identified and recorded for their curative properties (Aktar & Foyzun, 2017). There is a worldwide increase in the utilization of natural resources especially medicinal plants due to their perceived safety and efficacy, affordability and cultural acceptability (Gilani & Atta-ur-Rahman, 2005). Medicinal effects of the plants are the result of the presence of different chemical compounds, also known as secondary metabolites, in the plants.

Manilkara is a genus of trees in the family *Sapotaceae* consisting of ~79 species. *Manilkara zapota* (L.) P. Royen, commonly known as sapodilla, chiku and chicle, grows well in tropical conditions and is widely cultivated world over in tropical countries for various benefits like edible fruits, timber, latex, etc. The fruit has an exceptionally sweet, malty flavour (Uekane *et al*., 2017). Sapodilla fruit holds tremendous nutritional value as it is rich in sucrose and fructose. The fruit is consumed fresh or used to produce jams, compotes, and beverages (Shafii *et al*., 2017). Traditionally *M. zapota* has been used for several medicinal purposes. All parts of the plants are ascribed to carry medicinal properties and are used for a range of disease including diarrhea, cold, fever and ulcers. Scientific studies on *M. zapota* have revealed the presence of a wide range of bioactive constituents in this plant.

This review is a comprehensive account of scientific reports, available in international databases (PubMed, Science Direct, and Elsevier), Google Scholar or repositories and libraries of different academic institutions, pertaining to pharmacological activities and chemical constituents of *M. zapota*, to highlight its pharmacological potential and identify this plant as a natural source for potential drug leads.

Plant profile

Synonyms

Achras sapota L., *Achras zapotilla* Nutt., *Achras zapota* L., *Achras mammosa* L., *Calocarpum mammosum* (L.) Pierre, *Lucuma mammosa* (L.) C.F. Gaertn, *Manilkara achras* (Miller) Fosberg, *Manilkara zapotilla* (Jacq.) Gilly, *Pouteria mammosa* (L.) Cronquist, *Sapota zapotilla* (Jacq.) Coville, *Sapota achras* Miller (Bano & Ahmed, 2017).

Common names

Mexico, Hawai, California, southern Florida: Chickoosapote, Chickoozapote, **Urdu**: Cheeku, **Hindi**: Chickoo, Sapota, **Bengali**: Sopeta, Sofeda, **Thai**: Lámut farang, **Brazil, Haiti**: Sapoti, **Malay**: Ciku, Sawo manila, **Colombia, Venezuela**: Nispero (Bano & Ahmed, 2017; Shafii *et al*., 2017).

Distribution

M. zapota plant usually grows in tropical parts of the world. It is native to Southern Mexico, northern Belize and north-eastern Guatemala and has been cultivated throughout Central America and the Caribbean islands, where it is a tall tree found in forests. *M. zapota* is also abundantly cultivated in Asian countries including Bangladesh, India, Pakistan, Thailand, Malaysia, Cambodia and Indonesia as popular fruit tree (Kirtikar & Basu, 1956; Bhowal *et al*., 2014).

Description

M. zapota is a large, evergreen, glabrous forest tree more than 30 m in height and with an average trunk diameter of 1.5 m. The height of a cultivated tree, however, varies between 8-15 m, depending on location, and the diameter generally does not exceed 50 cm. The tree bears rough dark grey bark and dense crown (Singh *et al*., 2011; Shafii *et al*., 2017).

The ornamental leaves are medium green and glossy. They are alternate, elliptic to ovate, 7.5-12.5 cm long, with an entire margin and numerous very fine inconspicuous secondary nerves. Tap root system is observed in this plant (Kirtikar & Basu, 1956; Shafii *et al*., 2017).

The pedicelled flowers are inconspicuous and bell-like with six white petals. The edible fruit is a large berry, round, ovoid, ellipsoid or conical in shape, 4–8 cm in diameter. The fruit contains pale yellow to an earthy brown flesh with a grainy texture and brownish epicarp. There are 5 large black shining seeds in the fruit which resemble beans with a hook at one end (Kirtikar & Basu., 1956).

a: *Manilkara zapota* Linn. tree

b: *Manilkara zapota* Linn. fruit

Traditional uses

Seeds of *M. zapota* are traditionally used as aperients, diuretic, tonic and febrifuge. The crushed seeds of *M. zapota* are used to expel bladder and kidney stones and are considered effective in rheumatism (Singh *et al*., 2011). The bark is believed to carry antibiotic, astringent and febrifuge effects and the bark decoction is used as a tonic and in the treatment of paludism, fever, pain, diarrhea, and dysentery (Ankli *et al*., 2002). *M. zapota* bark is rich in white, gummy latex called chicle, which is used in dental surgery and to make chewing gums. The leaf decoction is used to treat cough, cold, and diarrhea (Kirtikar & Basu, 1956; Bhowal *et al*., 2014). The leaf decoction is also used for fever, hemorrhage, wounds and ulcers.

Fruit and flower decoction are used as an expectorant, for the treatment of diarrhea, pulmonary problems and nervous system disorders including depression, stress, anxiety and insomnia (Singh *et al*., 2011).

PHARMACOLOGICAL STUDIES

Antinociceptive activity

The traditional application of *M. zapota* as pain relieving medicine has been verified by a number of scientific studies demonstrating the presence of analgesic activity in almost all parts of the plant. Ethanolic extract of *M. zapota* leaves was evaluated for antinociceptive activity in acetic acid-induced writhing and tail flicking method using Swiss albino mice as experimental animals (Ganguly *et al*., 2016). The leaf extract caused a dose-dependent antinociceptive effect in both the models at 200 and 400 mg/kg doses. In another study, ethanolic extract of *M. zapota* bark exhibited 38.55% and 56.42% suppression of acetic acid-induced writhing in mice at respective doses of 250 and 500 mg/kg (Hossain *et al*., 2012). In a similar study, methanolic extract of *M. Zapota* whole plant produced a dose-dependent analgesic effect at 200 and 400 mg/kg doses in both hot plate and acetic acid-induced writhing tests (Khan, 2016). Acetic acid induced nociception involves the release of endogenous pain mediators, at the site of injection, stimulating the nociceptive neurons, whereas, pain in both tail flick and hot plate methods involves stimulation of thermoreceptors which transmit pain signals to the higher areas of the CNS via C-fibres (Bars *et al.,* 2001). This suggests that the analgesic effect *M. zapota* is mediated through the central as well as peripheral actions.

Anti-inflammatory and antipyretic activity

Various parts of the plant have also been demonstrated to possess anti-inflammatory and antipyretic effects. Hossain *et al*. (2012) studied anti-inflammatory activity in *M. zapota* bark extract prepared in 80% methanol. The activity was tested against carrageenan and histamine-induced edema in rats. Oral administration of the bark extract, at 400 mg/kg dose, caused significant suppression of the inflammation which was comparable in both the models. In another study, ethanolic extract of the leaves produced anti-inflammatory effect against carrageenan-induced paw edema at 300 mg/kg dose. The leaf extract was also investigated on yeast-induced pyrexia in the Wistar rats. It was found that oral administration of the leaf extract significantly reduces the rectal temperature of the rats at 300 mg/kg and the effect was maximally expressed 4 hours after the dose administration. On activity guided fractionation, the antipyretic effect of the leaf extract was found to be concentrated in its petroleum ether fraction (Ganguly *et al*., 2013). *M. zapota* whole plant extract has also shown to possess anti-inflammatory effect (Khan, 2016). In this study, the whole plant methanolic extract caused dose and time-dependent inhibition of carrageenan and histamine-induced edema in the animals at 200 and 400 mg/kg oral doses.

Metabolic effects of M. zapota

M. zapota extracts have been evaluated for certain metabolic effects including anti-hyperglycemic and anti-hypercholesteremic. Anti-hyperglycemic effect of ethanolic and aqueous leaf extracts of *M. zapota* was investigated on alloxan-induce hyperglycemia in male Wistar rats. Both the extracts significantly lowered blood glucose levels in hyperglycemic rats when administered at 53.6 mg/kg doses daily for six weeks. However, the extracts did not cause any significant effect on blood glucose levels of the normal rats. Anti-hyperglycemic effect of the extracts was found comparable to metformin.

Both ethanolic and aqueous leaf extracts also caused a significant cholesterol-lowering effect in hypercholesteremic male Wistar rats. In this investigation, the leaf extracts were administered at 53.6 mg/kg doses to the rats fed with a hypercholesteremic diet containing 1% cholesterol and 0.25% bile salts powder. The hypercholesteremic effect of both the extracts was quantitatively closed to the standard drug, atorvastatin. The aqueous extract also lowered blood cholesterol levels in normal rats but ethanolic extract had no effect on normal blood cholesterol levels (Fayek *et al*., 2012).

Antidiarrheal activity

Scientific investigations on *M. zapota* have reclaimed its traditionally recognized efficacy in diarrhea. In a study, the antidiarrheal activity of *M. zapota* bark ethanolic extract was demonstrated against castor oil-induced diarrhoea in mice. Treatment with the bark extract reduced fecal output by 29.31% and 41.37%, at 250 mg/kg and 500 mg/kg doses, respectively (Hossain *et al*., 2012).

In another study, the ethanol extract of *M. zapota* leaves exhibited an antidiarrheal effect, at 200 and 400 mg/kg doses, against castor oil induced diarrhoea in mice. The respective doses of the ethanol extract reduced diarrheal faeces by 53.57 and 60.71%, compared with 71.42% reduction obtained

by the standard, loperamide (Ganguly *et al*., 2016).

Antibacterial activity

M. zapota has shown antibacterial activity against a range of clinically important Gram-positive and Gram-negative bacteria. Methanolic leaf extract of *M. zapota* exhibited moderate inhibitory effect against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Mucilaginibacter flavus*, *Pseudomonas pseudoalcaligenes*, *Enterobacter aerogenes*, *Morganella morganii*, *Alcaligenes fecalis* and *Klebsiella pneumonia*, as determined by agar well diffusion assay (Nair & Chanda, 2008).

In a similar study, the methanolic extract of *M. Zapota* leaves caused antibacterial activity against *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Salmonella typhimurium* and *Enterobacter aerogenes* (Kaneria *et al*., 2009). Kaneria & Chanda (2012) have also reported antibacterial activity in leaf extract of *M. zapota* against some additional bacteria including *Corynebacterium rubrum*, *Bacillus megaterium* and *Proteus mirabilis*. The activity was tested by agar well diffusion method.

Antibacterial activity has also been demonstrated in *M. zapota* seeds extracts. The methanolic extract of *M. zapota* seeds showed bacteriostatic effect against *Salmonella paratyphi*, *Shigella flexneri* and *Vibrio cholera* with minimum inhibitory concentrations (MIC) of 945-950 µg/ml, whereas, the acetone extract exhibited bactericidal activity against *Vibrio cholerae* and *Pseudomonas oleovorans* with minimum bactericidal concentrations in the range of 216.5-323 µg/ml (Kothari & Seshadri, 2010). In another study, *M. zapota* seed extracts prepared by using four different solvents including ethanol, acetone, ethyl acetate and water in succession were tested against six bacterial strains including *Enterobacter fecalis*, *Haemophilus* sp., *Yersinia* sp., *Escherichia coli*, *Bacillus subtilis* and *Staphylococcus aureus* by agar well diffusion method, while MIC was determined by disc diffusion method. All tested species were found sensitive to ethyl acetate, ethanol and acetone extracts of *M. zapota* seeds and the effect was comparable to the standard drugs, gentamycin and cephalosporin, whereas the aqueous extract was active against *Haemophilus* sp. only. The extracts produced their antibacterial activity with the MIC in the range of 5-20 µg/ml. (Shanmugapriya *et al*., 2011). Ethyl acetate extract of *M. zapota* stem bark showed moderate activity, with inhibition zones in the range of 08 to 15 mm, against Gram positive (*Bacillus subtilis*, *Bacillus megaterium*, *Bacillus cereus* and *Sarcina lutea*) and Gram negative (*Escherichia coli*, *Shigella sonnei*, *Shigella shiga*, *Shigella dysenteriae* and *Salmonella typhi*) pathogenic bacterial strains (Osman *et al*., 2011a).

Methanolic and aqueous extracts of *M. zapota* flowers were tested against four bacterial strains namely *S. aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Salmonella typhi* (Priya *et al*., 2014). Both the extracts were effective against all the tested bacteria. The zone of inhibition of methanol extract was highest for *B. subtilis* (29 mm), followed by *S. aureus*, *P. aeruginosa* and *S. typhi* (27.5 mm). With the aqueous extract, *S. typhi* (28.5 mm) showed a maximum zone of inhibition followed by *S. aureus*, *B. subtilis* and *P. aeruginosa* (26 mm).

M. zapota root extract has been demonstrated to possess growth inhibitory effect against *E. coli* and *Staphylococcus aureus* (Bhargavi *et al*., 2013).

Antifungal activity

Studies have demonstrated antifungal activity in various parts of *M. zapota* plant. Kaneria & Chanda (2012) found the presence of antifungal activity in *M. zapota* leaf extracts against three fungal species including *Candida glabrate* and *Candida neoformans* and *Cryptococcus leuteolus*, as determined by agar well diffusion method.

In another study, *M. zapota* seed extracts prepared by using four different solvents including ethanol, acetone, ethyl acetate and water in succession were tested against *Cephalosporium* sp., *Aspergillus niger*, *Penicillium notatum* and *Candida albicans* using potato dextrose agar well diffusion method. Among various solvent extracts, aqueous and acetone extracts showed antifungal activity against *Cephalosporium* sp. and *A. niger*, whereas, ethyl acetate extract was active against *C. albicans* only. Ethanol fraction did not exhibit significant antifungal activity against any of the species tested (Shanmugapriya *et al*., 2011).

Week antifungal activity has also been demonstrated in *M. zapota* stem bark. In a study, ethyl acetate extract of the stem bark inhibited the growth of *Aspergillus flavus*, *Fusarium* sp. and *Vasianfactum* sp. at high disc doses of 300-900 µg/disc (Osman *et al*., 2011b).

Anthelmintic activity

Anthelmintic effect of chloroform and ethanolic extracts of *M. zapota* seed embryo was studied for intestinal roundworm parasites of human beings by using Indian adult earthworms (*Pheretima posthuma*) as the model organism (Kumar *et al*., 2012). Both extracts paralyzed and then killed earthworms in a concentration-dependent manner (50 to 250 mg/20 ml saline).

Cytotoxic and antitumor effects

Presence of cytotoxic and antitumor activities have been demonstrated in *M. zapota*. In a study, ethyl acetate extracts of *M. zapota* stem bark and leaves showed cytotoxicity against brine shrimp nauplii (*Artemia salina*). The leaves extract exhibited the highest toxicity with the median lethal concentration (LC_{50}) of 16.17 µg/ml, whereas the stem bark extract caused mild effect with the LC_{50} value of 50.26 µg/ml, in comparison with ampicillin trihydrate (LC_{50}: 12.38 µg/ml) (Osman *et al*., 2011b). Ethanolic extract of *M. zapota* stem bark has been studied against five cancerous cell lines including HL-60 (Human leukemia cell lines), HT-29 (Human colon cancer cell lines), MCF-7 (Human breast cancer cell lines), A 431(Human skin cancer cell lines) and A 549 (Human lung cancer cell lines), using trypan blue dye exclusion technique and MTT based cytotoxicity assay. The ethanolic extract demonstrated concentration-dependent (10-80 µg/ml) reduction in the viability of all the cell lines. Inhibitory effect against HL-60 and HT-29 was noticed at lower EC_{50} values of 24 µg/ml and 64 µg/ml, respectively, however, moderate cytotoxic activity was observed against A 549, A 431 and MCF-7 with EC_{50} values greater than 80µg/ml (Awasare *et al*., 2012).

In another study, ethyl acetate extract of *M. zapota* stem bark was assessed at the doses 50, 100 and 200 mg/kg body wt. for its antitumor activity against Ehrlich ascites carcinoma (EAC). Intraperitoneal administration of the stem bark extract to albino mice, at 100 and 200 mg/kg doses, significantly reduced viable EAC cells count 14 days after intraperitoneal tumor inoculation, the increased survival time of the mice and restored altered hematological parameters (Osman *et al*., 2011b).

In a similar model, ethyl acetate extract of *M. zapota* leaves also demonstrated antitumor effect against EAC. The antitumor effect of the leaves extract was exhibited as significant ($p<0.05$) reduction in viable cell count, increase in median survival time and reduction in weight gain at the doses of 100 and 200 mg/kg. The crude extract also restored the altered hemoglobin levels and RBC and total WBC count near to normal but could not normalize the altered differential leucocyte count (Rashid *et al*., 2014).

Ethyl acetate extract of *M. zapota* fruit was tested by brine shrimp lethality assay and antitumor activity against EAC in mice. In the brine shrimp lethality bioassay, the fruit extract showed potent cytotoxicity against brine shrimp nauplii with LC_{50} of 3.06 µg/mL, whereas ampicillin trihydrate showed LC_{50} of 7.21 µg/mL. The fruit extract also significantly ($p<0.05$) reduced the viable cells EAC cell count and mean survival time of the mice at 100 mg/kg b. wt dose. The extract treatment also reduced gain in body weight seen with untreated mice and restored altered haemoglobin levels and RBC and WBC count and significantly reduced serum alkaline phosphatase and serum glutamate oxaloacetate transaminase (SGOT) levels compared to the untreated group but had no effect on raised serum glutamate pyruvate transaminase (SGPT) (Khalek *et al*., 2015).

Among polyphenols isolated from the fruit, methyl 4-O-galloylchlorogenate showed cytotoxicity in the HCT-116 and SW-480 human colon cancer cell lines with the IC_{50} values of 190 and 160 µM, respectively, while 4-O-galloylchlorogenic acid displayed cytotoxicity in the respective cells lines with the IC_{50} values of 154 and 134 µM (Ma *et al*., 2003).

Antioxidant activity

The plant has extensively been studied for its antioxidant activity. Antioxidant potential of *M. zapota* leaves extracts, prepared by using solvents of increasing polarity in succession, was assessed by total phenolic and flavonoid contents and the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging effect. The highest phenolic content, 194 mg gallic acid equivalent (GAE)/g, was noticed in the methanolic extract, whereas, flavonoid content, measured as quercetin equivalent (QE)/g was found highest in the petroleum ether fraction (39 mg) followed by the methanol extract (35 mg). The antioxidant activity was concentrated in the methanol extract, which caused DPPH scavenging effect with the median inhibitory concentration (IC_{50} value) of

24.5 µg/ml (Kaneria *et al*., 2009).

Antioxidant effect of *M. zapota* fresh fruit was measured through oxygen radical absorption capacity (ORAC), total phenolic content and ascorbic acid concentration. Hydrophilic ORAC of the fruit was 48.47 µmol Trolox equivalent/g fresh weight (FW) and was highest among all 38 fruits tested notably strawberry, starfruit guava, apple, grapes, grapefruit, kiwifruit and orange. The total phenolic content was also highest in *M. zapota* and was measured as 15.94 (mg GAE/g FW). The ascorbic acid (AA) content of the fruit was 101.4 µg AA/g FW (Isabelle *et al*., 2010). In another study, comparing the antioxidant potential of fruit pulp and peel, higher total antioxidant activity was found in the peel than the fruit pulp (Gomathy *et al*., 2013).

To evaluate the antioxidant activity of *M. zapota* seed, ethanol, acetone, ethyl acetate and water extracts of the seed were studied for antioxidant activity. The phenolic constituents were maximally extracted by ethanol as phenolic content of ethanolic seed extract was 4.00 mg GAE/g, whereas, respective phenolic contents were evaluated as 2.26 mg/g, 2.54 mg/g and 1.21 mg GAE/g of the acetone, ethyl acetate and aqueous extracts. Respective total flavonoid content was estimated at 3.98, 2.19, 1.01 and 0.74 mg/g of QE/100 mg of ethanol, acetone, ethyl acetate and aqueous extracts. The reducing power was found as 13.96 µg/ml, 10.43 µg/ml, 10.48 µg/ml and 09.41 µg/ml, while DPPH radical scavenging activity, measured as the IC_{50} values, was 300 µg/ml, 400 µg/ml, 500 µg/ml and 500 µg/ml respectively in ethanol, acetone, ethyl acetate and aqueous extracts. In ABTS radical scavenging assay, the IC_{50} value was found to be 200 µg/ml for ethanol, 300 µg/ml for acetone, 400 µg/ml for ethyl acetate and 500 µg/ml for aqueous extracts of *M. zapota* seeds (Shanmugapriya *et al*., 2011).

The antioxidant property of the methanol and aqueous extract of *M. zapota* flowers was also studied. The extracts showed high antioxidant activity in DPPH assay with the IC_{50} values 1.97 µg/ml and 4.22 µg/ml for methanol and aqueous extract, respectively (Priya *et al*., 2014).

In another study, the stem bark extract, prepared in ethanol, produced DPPH radical scavenging activity with the IC_{50} value of 16.83 µg/ml, compared with 4.87 µg/ml of the standard, ascorbic acid. The total antioxidant capacity of the stem bark was 462.44 mg AAE/gm of the extract. The extract also showed significant reducing power, similar to ascorbic acid. The phenolic content of the extract was 230.43 mg GAE/g and the total flavonoid content was 629.29 mg QE/g of the extract (Islam *et al*., 2010).

Hepatoprotective effect

Ethanolic extract of *M. zapota* stem bark protected against CCl_4 induced liver damage in rats at 300 mg/kg dose/day administered for 8 days. The effect was manifested as restoration of SGOT, SGPT, ALP, bilirubin and total serum protein levels and liver weights (Islam *et al*., 2010).

Toxicity studies

Toxicity studies on *M. zapota* are mainly focused to demonstrate Median lethal dose (LD_{50} value) by monitoring the acute toxic effect of the plant. In a study conducted on Swiss albino mice, the ethyl acetate extract of *M. zapota* stem bark was found to have LD_{50} value of 3025 mg/kg body wt. (Osman *et al*., 2011). In another acute toxicity study, methanolic extract of the stem bark was found safe up to the dose of 3200 mg/kg body wt. for 48 hours (Hossain *et al*., 2012).

The LD_{50} value of ethyl acetate extract of *M. zapota* leaves in Swiss albino mice on intraperitoneal administration has been measured as 2853.1 mg/kg/day. In the same study, ethyl acetate extract of *M. zapota* fruit did not show any toxic effect up to the dose of 2 g/kg/day (Khalek *et al*., 2015).

Bioactive Constituents

M. zapota has been reported to contain various classes of secondary metabolites including steroids, alkaloids, phenols, flavonoids, tannins, glycosides, saponins and terpenoids (Mahajan & Badgujar, 2008; Mohanapriya *et al.,* 2014).

Phenolic Compounds

Phenolic compounds including phenolic acids and flavonoids have been isolated as main constituents of *M. zapota*, most of them are present in the fruit. Ma *et al*. (2003) reported the presence of 4-O-galloylchlorogenate, 4-O-galloylchlorogenic acid, methyl chlorogenate, dihydromyricetin, quercitrin, myricitrin, catechin, epicatechin, gallocatechin, and gallic acid in *M. zapota* fruit, while Shafii *et al*. (2017) detected protocatechuic acid, resorcinol, 4-hydroxybenzoic acid, vanillic acid, caffeic acid,

syringic acid, coumaric acid and ferulic acid in the fruit pulp. Protocatechuic acid has been found as the most abundant phenolic compound in *M. zapota* fruit followed by gallic acid and quercetin.

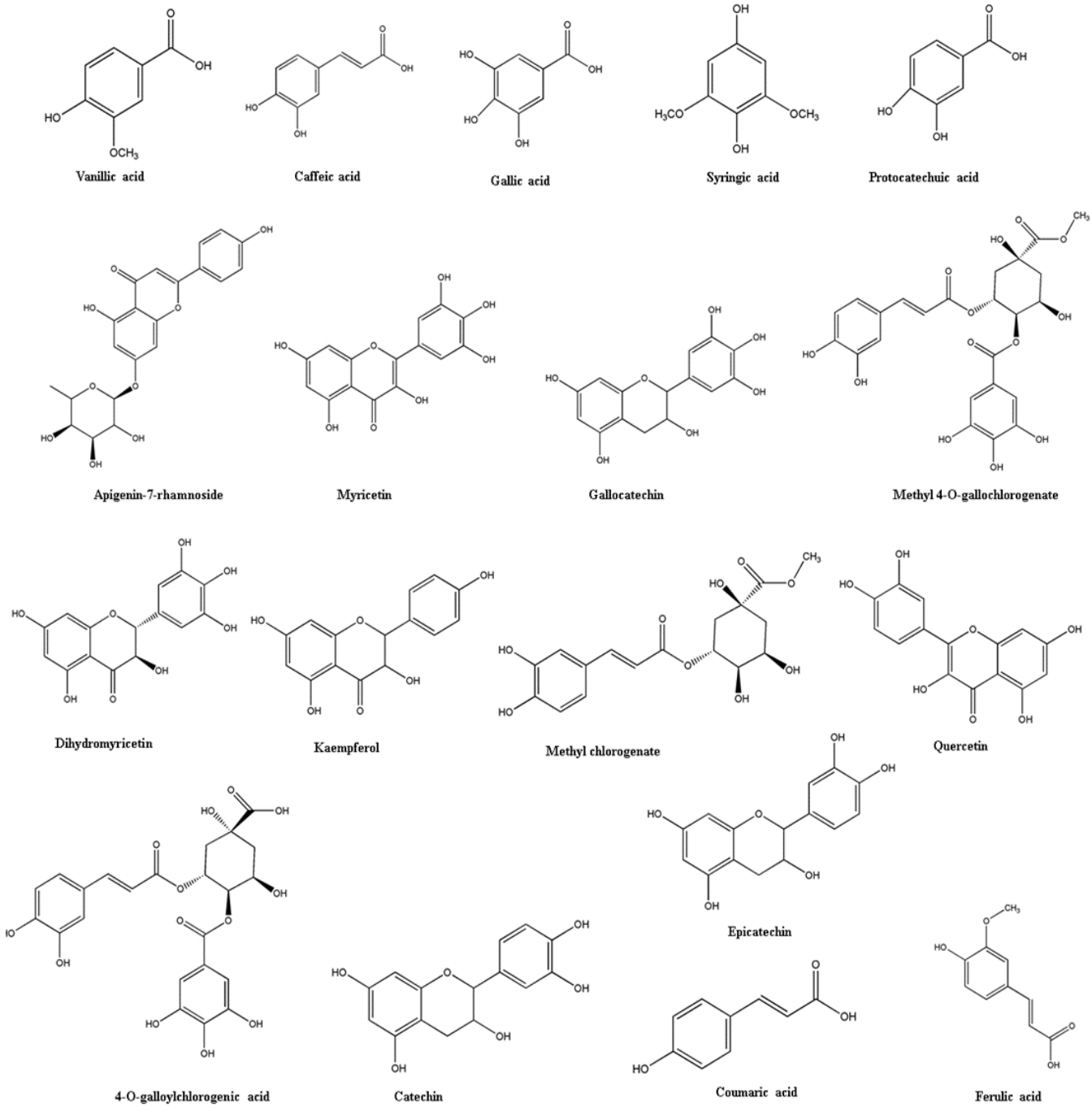

Figure No. 2
Chemical structures of important phenolic compounds isolated from *M. zapota*.

M. zapota leaves have been found to contain apigenin-7-O-α-L-rhamnoside, myricetin-3-O-α-L-rhamnoside and caffeic acid (Fayek *et al.,* 2012), while, kaempferol has been isolated from the seed extract (Shafii *et al.,* 2017). Chemical structures of various phenolic compounds isolated from M. zapota are shown in Figure No. 2. Phenolic compounds have been identified as the most important group of secondary metabolites and bioactive compounds in the plants. These compounds are reported to contain diverse pharmacological activities including anti-oxidant, anti-aging, anti-inflammatory, antidiabetic, antihyperlipidemic, antiulcer, cytotoxic and antitumor and antimicrobial activities (Ghasemzadeh & Ghasemzadeh, 2011). Ma *et al*. (2003) demonstrated the presence of antioxidant effect in all 10 polyphenols isolated from *M. zapota* fruit, of which methyl 4-O-galloylchlorogenate showed the highest antioxidant activity (IC_{50}=12.9 µM) in DPPH free-radical assay, followed by 4-O-galloylchlorogenic acid (IC_{50}=23.5 µM) (Ma *et al*., 2003).

As a major class of phytoconstituents present in *M. zapota*, phenolic compounds can be attributed for the diverse pharmacological profile of this plant, however, the involvement of other constituents in the overall medicinal potential of *M. zapota* cannot be ruled out.

Phenylethanoids

Phenylethanoid compounds, characterized by the presence of a phenethyl alcohol moiety, have been isolated from *M. zapota*. Fomani *et al*. (2015) demonstrated the presence of phenylethanoid 2-(4-hydroxyphenethyl) tetracosanoate, 2-(4-hydroxy-phenethyl) tetra triacontanoate, 2-(4-hydroxyphene-thyl) docosanoate, 2-(4-hydroxyphenethyl) eicosa-noate, 2-(4-hydroxyphenethyl) octadecanoate and 2-(4-hydroxyphenethyl) hexadecanoate in *M. zapota* seeds. Phenylethanoids isolated in this study exhibited moderate antioxidant activity in the DPPH assay.

Carotenoids, tocopherol and tocotrienol

M. zapota fruit has also been found to contain carotenoids including lutein, zeaxanthin, β-crypto xanthine, lycopene, α-carotene and β-carotene (Charoensiri *et al*., 2009; Isabelle *et al*., 2010; da Silva *et al*., 2014), tocopherol and tocotrienol (Isabelle *et al*., 2010).

Carotenoids, tocopherol and tocotrienol are well known for their antioxidant activity. Several studies have demonstrated other biological effects of carotenoids including inhibition of malignant tumor growth, induction of apoptosis, enhancement of immunity and prevention of breast, cervical, ovarian, colorectal cancers, and cardiovascular and eye diseases (Milani *et al*., 2016). Tocotrienols and tocopherols exhibit biological activities such as neuroprotective, anti-cancer, anti-inflammatory and cholesterol-lowering properties (Ahsan *et al*., 2014). Many biological effects of carotenoids, tocopherol and tocotrienol are attributed to their antioxidant activity. Presence of these antioxidant compounds with relevant biological activities well correlates with the pharmacological effects of *M. zapota*.

Triterpenoids

Triterpenoids including lupeol-3-acetate and oleanolic acid have been identified in *M. zapota* leaves (Fayek *et al*., 2012), whereas, the seeds are found to contain β-amyrin, oleanolic acid, lupeol and betulinic acid **(**Fomani *et al*., 2015).

Although triterpenoids from *M. zapota* source have not been studied for their pharmacological effects, those isolated from other natural sources have shown several promising pharmacological activities. Oleanolic acid has been demonstrated as hepatoprotective, anti-inflammatory, antioxidant and anticancer (Pollier & Goossens, 2012), Lupeol as anti-inflammatory, cardioprotective, cytotoxic and antiangiogenic (Wal *et al*., 2011), β-amyrin as antioxidant, anti-inflammatory, antidiabetic and hypolipidemic (Santos *et al*., 2012), while betulinic acid has shown anticancer, antibacterial, antimalarial, anti HIV, anthelmintic, anti-nociceptive, anti-inflammatory and antiprotozoal activities (Moghaddam *et al*, 2012).

Saponins

A couple of saponins including Manilkoraside, a pentacyclic triterpenoid saponin, stigmasterol-3-O-β-D-glucopyranoside have been isolated from stem bark and seeds of *M. zapota*, respectively (Awasare *et al*., 2012; Fomani *et al*., 2015). Cytotoxic effect of Manilkaroside, isolated *M. zapota*, has been demonstrated against some cancerous cell lines including HL-60, HT-29, MCF-7, A 431 and A 549. In this study, manilkaroside was found highly active against HL-60 and HT-29 cell lines but exhibited a moderate cytotoxic effect against A 549, A 431 and

MCF-7 (Awasare *et al*., 2012).

Sterols

M. zapota leaves have been reported to contain sterols including erythrodiol or 12-oleanene-3,28-diol (Rashid *et al*., 2014), stigmasterol, β-sitosterol (Fayek *et al*. (2012) and 21α-hydroxy-taraxasterol (Hossain *et al*., 2016).

Both erythrodiol and 21α-hydroxy-taraxasterol, isolated from *M. zapota*, have been demonstrated to possess antitumor effect against EAC. In a study, Erythrodiol significantly ($p<0.05$) reduced the viable cell count in experimentally induced EAC in mice at the dose of 5 mg/kg body wt. (Rashid *et al*., 2014). In a similar study, 21α-hydroxy-taraxasterol significantly decreased viable cell count, increased weight gain and elevated the lifespan of EAC cells bearing mice, as well as, significantly restored altered hematological profile such as RBCs, haemoglobin, WBC and differential count of the experimental animals, at 5mg/kg dose (Hossain *et al*., 2016).

Stigmasterol and sitosterol widely prevail in nature as constituents of plants, animals and fungi and are widely studied for their pharmacological activities. As, both Stigmasterol and sitosterol are reported to possess antioxidant, cytotoxic, antitumor, anti-inflammatory, antihypercholesterolemic, antimutagenic, antibacterial and hypoglycemic activities (Kaur *et al*., 2011), these phytosterols are possibly contributing towards medicinal effects of the crude *M. zapota* extracts by developing synergistic combinations of activities.

CONCLUSION

Plants have been proven as a promising source of lead compounds for the development of new drugs. Up to 25% of the modern medicines available today are constituting plant-derived compounds as active ingredients. There is also a worldwide increase in the use of herbal medicines as a complementary and alternative medicine to synthetic drugs once they are scientifically validated. *M. zapota* is a medicinal plant constituting versatile pharmacological profile and a wide range of compounds with diverse medicinal properties. This review, by providing a comprehensive understanding of pharmacological and chemical properties of *M. zapota*, put forth this plant as a candidate source with the potential to be explored for the discovery of new compounds with biological activities or as a validated complementary and alternative therapy through further laboratory and clinical investigations.

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