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Nutraceutical and medicinal property of Mulberry fruits: A review on its pharmacological potential

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Abstract

Mulberry (*Morus*) cultivated worldwide in diverse agro-ecological conditions recognized as the fodder of silkworms (*Bombyx mori*). In India, ranging from high altitude Himalayan region to coastal region, the farmers generally cultivate these four species of mulberry (*Morus alba, M. indica, M. serrata,* and *M. laevigata*). Mulberry fruit is used in traditional medicine for several years in China and also consumed as food material in different countries of Asia and Africa. Mulberry fruit, along with high nutritious value, contains many bioactive phytochemicals that are of health benefits and can fight against many diseases. Many researchers attracted to this property of mulberry fruit, and they isolated bioactive polysaccharides, anthocyanins, flavonols, flavonols, phenolic acids, alkaloids, and melatonins. These compounds have antioxidant property and due to this, either in synergistically or in the pure form, these components have direct or indirect curative activity on diabetes, inflammation, tumor, hepatic diseases, immunomodulation, hyperlipidemia, neural damage, and chronic diseases. This tremendous bioactivity of mulberry fruit extract may open up a new dimension in the food and medicine industry. The present review provides recent findings of the phytochemical foundation and their bioactivities, which may encourage many researchers to explore the molecular mechanism of the biological activities which can be used for human welfare.

KEYWORDS: Mulberry fruit, phytochemicals, bioactive components, pharmacological properties

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INTRODUCTION

Sericulture is one leading agriculture-based industry that practiced worldwide due to its revenue-generating capacity(1). *Bombyx mori* produces high-quality silk yarn in the form of the cocoon, which has high demand in textile as a monophagous insect *B. mori* is solely dependent on the leaves of a single host plant known as Mulberry(2). Mulberry (*Morus*) plants belong to the family Moraceae which cultivated from tropical to temperate region with diverse topographical and meteorological conditions(3). Mulberry includes 68 species and 1 subspecies with at least 100 known varieties of which most of them cultivated in Asia(4,5). In India Mulberry cultivation practiced from high altitude to sea level includes several states as Jammu & Kashmir, West Bengal, Assam, Andhra Pradesh, Karnataka, Tamilnadu, Meghalaya, Nagaland and Maharashtra(6). In India, there are many species of *Morus*, of which *Morus alba*, *M. indica*, *M. serrata*, and *M. laevigata* are the most dominating species(5).

Recently, the demand for mulberry fruit is increasing as a healthy natural product because of its good taste, dietetic value, and biological activities(7). In conventional Chinese folk medicine, mulberry fruits have been used in to treat diabetes, hypertension, anemia, and arthritis(8). Natural products are always enriched with bioactive compounds(9–11). These bioactive ingredients of mulberry fruits have drawn the attention of many researchers due to their nutritional and therapeutic properties that reduce the risk of developing some chronic diseases(12,13). About 50% of the approved drugs present in the market are made up of natural products(10). At present, about 80% of the world population uses the plant-derived drug, and this phytomedicine industry is expected to attain approximately $35 billion market value up to 2020(14). Due to the presence of many natural bioactive compounds, mulberry fruits have an immense opportunity to be useful therapeutic products. In the present review, we mainly focused on understanding the nutritional

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and phytochemical properties of mulberry fruit along with its efficacy towards various metabolic disorders and other life-threatening diseases.

PHYTOCHEMICAL COMPOSITION

In comparison to mulberry leaves, records of traditional use of mulberry fruits are very limited due to a lack of awareness of its nutritional and medicinal value(15). At present, isolation and characterization of the phytochemicals from mulberry fruits are imperative, as these fruits are consumed in many countries for dietary enhancement(10). Mulberry fruits harbor a diverse array of biological elements that have elite nutritional value and, many of them decorated with antioxidant properties due to the presence of polyphenolic groups(16).

Nutrients

Mulberry fruits are excellent in tastes with sour flavor (pH < 3.5) and low-calorie content(17,18). This fruit contains plentiful primary metabolites (Table 1) in the form of carbohydrate, protein, lipid, vitamins, minerals, and fiber that provide a healthy dietary option to the consumers. The principal carbohydrates are found in the form of monosaccharide and polysaccharides whose amount increases during ripening(19–21). The monosaccharide of mulberry fruits is comprising of glucose, arabinose, galacturonic acid, and galactose(22). While the immense majority of the polysaccharide reported from mulberry fruits (Table 2) are acid heteropolysaccharides, which are the primary source of α, β-glycosidic linked glucans, these mulberry fruit polysaccharides (MFPs) exert remarkable medicinal effects on human health(23). Mulberry fruit (*M. alba*) contains a higher amount of proteins (1.44g/100g) in comparison to strawberries, raspberries, and blackberries (0.67g/100g, 1.20 g/100g, and 1.39g/100g

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respectively)(7). Interestingly higher protein content was revealed from the Indian subcontinent with a value of 1.73g/100g in *M. laevigata* (large black fruit) fruiti(24). Mulberry fruit contain 18 amino acids, out of which nine are belong to essential amino acids group that obligatory for humans. The ratio between the essential amino acid and total amino acid (EAA/TAA) of mulberry fruit is 42%, that is quite akin to milk and fish(25). World Health Organization recommended mulberry fruit as an excellent dietary product as its essential amino acid score is more than 100(26). The most predominant essential amino acid in mulberry fruit is linoleic acid (C18:2), which has high nutritional and therapeutic value for a human being(27).

Mulberry fruit contains more abundant polyunsaturated fatty acids are in comparison to monounsaturated and saturated fatty acids. Many researchers have been isolated 14 different fatty acids from mulberry fruit extract (MFE), and they suggested that profile of these fatty acids are varying due to difference in environmental conditions and genetic factors(3,4,28). This fruit is an excellent source of different minerals and vitamins. Minerals include calcium, sodium, potassium, iron, zinc, and magnesium. Vitamin C (ascorbic acid), vitamin A, vitamin B, vitamin E (α-tocopherol, β –tocopherol, δ -tocopherol and γ-tocopherol), and vitamin K are the most abundant vitamins present in mulberry fruit(29,30). Ascorbic acid has a direct effect on antioxidant activity. Out of the four mulberry species predominantly cultivated in the Indian subcontinent, *M. laevigata* (large black fruit) possesses the highest level of ascorbic acid (17.03 mg/100g), followed by *M. indica*, *M. nigra* and *M. alba*(24). These reported nutrients have a decisive role in human health.

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Bioactive components

In recent days many researchers are focusing on the pharmacological property of mulberry fruit as it possesses various bioactive phytochemicals. Bioactive components of mulberry fruit are preciously categorized in polyphenol, alkaloid, and melatonin (Table 3, Fig. 1).

Polyphenols

Polyphenols of mulberry fruit represented a substantial and diversified family that includes flavonoids (anthocyanins, flavanol, and flavonols) and phenolic acids (benzoic acid and hydroxycinnamic acid)(10). Bae and Suh(31) revealed that total phenols and total flavonols in the alcoholic extract of mulberry fruit were equivalent to the range of 6-65 µg/g catechins, 137-2057µg/g malvidin-3-glucoside and 960-2570µg/g gallic acid. These phenolic contents of mulberry are quite higher than other berries and vary among different species and variety(32,33).

Anthocyanins

Anthocyanins belong to the subfamily of flavonoids and responsible for red to blue and purple color of flower and fruit. Mulberry fruit anthocyanins are the most diverse group of polyphenol with remarkable antioxidant property and multiple therapeutic values(34). 20 different anthocyanins were isolated and identified from MFE viz., Cyanidin 3-O-rutinoside, Cyanidin 3-O-glucoside, Cyanidin 3-O-β-D-galactopyranoside, Cyanidin 7-O-β-D-glucopyranoside, Cyanidin 3-O-β-D-glucopyranoside, Cyanidin galloyl hexoside, Cyanidin hexoside, Cyanidin hexosylhexoside, Cyanidin pentoside, Cyanidin 3-O-(6″-O-α-rhamnopyranosyl-β-D-galactopyranoside), Cyanidin 3-O-(6″-O-α-rhamnopyranosyl-β-D-glucopyranoside), Cyanidin rhamnosylhexoside, Delphinidin acetyl hexoside, Delphinidin hexoside, Delphinidin

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rhamnosylhexoside, Pelargonidin 3-O-glucoside, Pelargonidin 3-O-rutinoside, Pelargonidin hexoside, Petunidin rhamnosylhexoside and Pelargonidin rhamnosylhexoside(32,35,36). Out of the 20 components, the chief anthocyanin isolated from mulberry fruit is Cyanidin 3-O-glucoside (301.75 mg/ g of mulberry anthocyanin extract), which exerts antidiabetic and antitumor activity(23,37).

Flavanols and Flavonols

These compounds also belong to the flavonoid subfamily. Flavanols and flavonols and are closely related structures only differ in the presence of double bonds in C2, C3, and C4. Mulberry fruit possesses non-glycosylated flavanols in the form of catechin, procyanidin B1, procyanidin B2, epicatechin, and epigallocatechin gallate. Catechin is the most abundant (309.26−750.01 mg/100 g dry weight) flavanol extracted from mulberry fruit of variable cultivars(33). Mulberry fruit flavonol includes rutin, quercetin, myricetin, and kaempferol(32,33,38). In contrast to flavanols, Natic et al.(32) (2015) revealed the presence of glycosylated derivatives of flavonols as quercetin 3-O-galactoside, quercetin 3-O-glucoside, quercetin 3-O-rutinoside, kaempferol 3- O-rutinoside and kaempferol 3-O-glucoside in many verities of *Morus*.

Phenolic acids

Phenolic acids extracted from mulberry fruit are mainly present as benzoic acid and hydroxycinnamic acid(10). Benzoic acid derivatives reported in MFE are vanillic acid, gallic acid, hydroxybenzoic acid, and protocatechuic acid.

Hydroxycinnamic acid derivatives in MFE were identified as cinnamic acid, chlorogenic acid, o-coumaric acid, p-coumaric acid, ferulic acid, and caffeic acid. Mahmood et al.(19) revealed that mulberry fruit contain chlorogenic acid as most teeming phenolic acid derivative, while Butkhup,

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Samappito, and Samappito(33) quantified that cinnamic acid was the most abundant phenolic acid derivative extracted from the mulberry fruit. This deference observed due to differences in the genetic constituent and agro-ecological condition of the cultivars(28,32).

Alkaloids

Different authors' advocated mulberry fruit as a good source of alkaloids, which is a bioactive compound and acts as antifeedant(15,39,40). Alkaloid concentration increases with the ripening of the fruit as it belongs to secondary metabolites. Kim et al.(39) and Kusano et al.(15) revealed the presence of 5 nortropane and 21 pyrrole alkaloids. 2β,3β-dihydroxynortropane, 2α,3β-dihydroxynortropane, 3β,6exo-dihydroxynortropane, 2α,3β,4α-trihydroxynortropaneand, 2α,3β-6-exo-trihydroxynortropane were the north pane alkaloid that was isolated from the extract of the fully ripened *Morus* fruits cultivated in Turkey. Pyrrole alkaloids were reported after magnetic resonance analyses of fruit from different mulberry cultivars of Korea which includes morrole A, morrole B, morrole C, morrole D, morrole E, morrole F, 2-(5-hydroxymethyl-2',5'-dioxo-2',3',4',5'-tetrahydro-1'H-1',3'-bipyrrole)carbaldehyde, 5-(hydroxymethyl)-1H-pyrrole-2-carboxaldehyde, 4-[formyl-5-(hydroxymethyl)-1H-pyrrol-1-yl]butanoate, 4-[formyl-5-(hydroxymethyl)-1H-pyrrol-1-yl]butanoate, 2-formyl-1H-pyrrole-1-butanoic acid, 2-formyl-5-(methoxymethyl)-1H-pyrrole-1-butanoic acid, 2-formyl-5-(hydroxymethyl)-1H-pyrrole-1-butanoic acid, 4-[formyl-5-(methoxymethyl)-1H-pyrrol-1-yl]butanoic acid, methyl 2-[2-formyl-5-(methoxymethyl)-1H-pyrrole-1-yl]propanoate, 2-(5'- hydroxymethyl-2'-formylpyrrol-1'-yl)-3-(4-hydroxyphenyl)-propionic acid lactone, methyl 2-[2-formyl-5-(methoxymethyl)-1H-pyrrol-1-yl]-3-(4-hydroxyphenyl)propanoate, 2-(5'-hydroxymethyl-2'-formylpyrrol-1'-yl)-3-phenyl-propionic acid lactone, 2-(5-hydroxymethyl- 2-formylpyrrole-1-yl)propionic acid lactone, 2-(5-hydroxymethyl-2-formylpyrrol-1-yl)isovaleric acid lactone, 2-(5-hydroxymethyl-2-

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formylpyrrole-1-yl)isocaproic acid lactone and 2-[2-formyl-5-(hydroxymethyl)-1-pyrrolyl-]3-methylpentanoicacid lactone(41).

Melatonin

Melatonin is a neurohormone which regulates circadian rhythms and sleeping disorder in human (42,43). However, melatonin synthesis decreases with aging and metabolic disorder in humans(44,45). Therefore, melatonin deficiencies can be conquering by melatonin through food supplementation to boost human health(44,46). Melatonin in the form of N-acetyl-5-methoxytryptamine reported from mulberry fruit and widely assorted with antioxidant and anti-inflammatory effects(42,47,48). A higher concentration of melatonin (5.76 ng/g frozen weight) has been reported in MFE of setting the stage, but melatonin content then decreased in the ripening stage. The optimal level of melatonin (31.59 ng/ml) recorded during ethanol fermentation of mulberry fruit extract at 250 °C(49).

MEDICINAL PROPERTIES

As discussed earlier, mulberry fruit is enriched with the different bioactive components, which has a therapeutic effect on human health(50,51). Out of these bioactive components, anthocyanins of mulberry fruits can restrain low density lipoprotein (LDL) oxidation and scavenge the free radicals(52,53). Experiments conducted with MFE in animal models as dietary supplements improve health and a wide array of pharmacological benefits.

Antioxidant Activity

Antioxidant activity of MFE has shown a significant difference between mulberry cultivars with the definite correlation between the polyphenolic content and antioxidant activity(31,54).

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Ripen fruits are affluent with anthocyanins (polyphenol), which are tremendous antioxidant agents with stronger scavenging activity against free radicals, viz., 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS), hydroxyls and superoxide anion radicals(36,55). Jiang et al.(56) also revealed that MFE polyphenols (anthocyanin, flavonoid, and phenolic acid) showed significant ($P < 0.01$) scavenging activity against free radicals.

There is collective evidence exhibited antioxidant activity of MFP fraction (MFP1, MFP2, MFP3, and MFP4)(57–61). MFPs show antioxidant activity because the carboxyl/ carbonyl group assists the binding of peroxy radicals to hydrogen atoms and ceases radical chain reaction. Slenyl or seleno-acid ester group activates anomeric carbon of the MFPs, which exhibits accelerated antioxidant capacity(38). Out of the four MFPs, MFP-4, possesses a massive part of low molecular weight fractions and more galacturonic acid that facilitates with highest DPPH scavenging activity(37).

The in-vitro experiment showed that ethanolic MFE increases the viability of MIN6N β-cells of the pancreas (53.8%-71.6%) by restricting the accumulation of ROS and lipid peroxidase activity in a dose-dependent manner(62). Yan et al.(63) reported an ameliorative effect MFE on Oxidative stress in HepG2 cells and also inhibited H_2O_2-activated cell death through apoptosis(63). Wang et al.(17) also reported that ethyl acetate-soluble MFE increased superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) activities and consequently increased the antioxidant activities of organs and serum in hyperglycemic mice resulted into beneficial effect on the experimental model.

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Anti-diabetic activity

Experimental evidence suggests that MFPs are significantly diminishing glycosylated serum protein (GSP) and fasting blood glucose (FBG) levels in hyperglycemic rats(61,64). It was revealed that MFPs could amplify the level of insulin, which improves the insulin sensitivity of the cells(57,61). MFP3P-Se showed strong anti-hyperglycemic effects than MFP3P by enhancing the proliferation of the pancreatic cell, insulin secretion, and glucose uptake(37). More importantly, MFPs can reduce β-cell dysfunction with antioxidant and anti-inflammatory property, increase β-cell viability by inhibiting β-cell apoptosis and, slow down α-glycosidase and α-amylase activity, restore glucose uptake through insulin-dependent and insulin-independent pathways(23).

An anti-diabetic effect (Fig. 2) of MFE enriched with anthocyanin was examined in diabetic db/db-C57BL/KsJ mice(65). Anthocyanins improve the hyperglycemic condition in mice through phosphorylated protein kinase B in insulin susceptible tissues. Yan, Zhang, Zhang, Zheng(2016), and Yan, Dai, Zheng (2016) studied the hypoglycemic activity of MFE in HepG2 cells (*in vitro*) of human and proposed its probable mechanism(63,66) (Fig. 2). They advocated MFE act as a robust anti-diabetic agent by accelerating the synthesis of glycogen, promoting gluconeogenesis, and remodeling of insulin resistance via AKT/PI3K pathway. These experimental studies showed that MFE could improve insulin sensitivity, decrease gluconeogenesis, amplify skeletal muscle glucose transporter-4 (GLUT4). It shows that mulberry fruits decrease phosphoenolpyruvate carboxykinase and glucose 6-phosphatase levels in the liver to exert an anti-diabetic effect.

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Immunomodulatory Activity

Much evidence suggests that MFP decorated with immunomodulating action that has been examined on T-cells, B-cells, dendritic cells, and macrophages. Mulberry fruit glycoprotein named MP can significantly increase T and/or B cell proliferation at a dose of 125–2000μg/ml(67,68). MP inhibits apoptosis by increasing Bcl-2/Bak protein expression ratio. MFPs also induce maturation, migration, and survival of dendritic cells through activating MAP kinase and NF-κB signaling pathways, p38, and extracellular protein kinase (EPK)(69). Further study revealed that MFP (JS-MP-1) and pyrrole alkaloids have an immunomodulatory effect on macrophage(70,71). They reported JS-MP-1 enhances the secretion of inflammatory chemokines (MIP-1α and RANTES) and cytokines (IL-6 and TNF-α) from macrophage cells (murine RAW264.7), while pyrrole alkaloids stimulate IL-12, TNF-α, and nitric oxide production.

Anti-atherosclerosis Activity

Atherosclerosis is a cardiovascular disease associated with the buildup of lipids (mainly oxidative low-density lipid) in the innermost layer of the artery(72). Consumption of natural antioxidant reduces the risk of atherosclerosis development(73,74). Anthocyanins, rutin, protocatechuic acid, caffeic acid, and naringenin are the main polyphenolic compounds that could reduce atherogenesis (Fig. 1 and 3). Liu et al.(75) and Chan et al.(76) examined the anti-atherosclerosis effect of MFE. They proposed, MFE with great antioxidant property inhibited electrophoretic mobility, thiobarbituric acid formation, and ApoB fragmentation in oxidative LDL. They also advocated that anthocyanin extract of mulberry fruit was tenfold higher effective than mulberry water extract. Chan et al.(76) proposed that polyphenolic extract could arrest cells of

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smooth muscle in thoracic aorta of A7r5 rat through induction of NO production and p53/AMPK activation at the G0/G1 phase to diminish atherosclerosis.

Anti-Obesity activity

Hypolipidemic activity of MFE was investigated high lipid diet-induced obese rat. MFE significantly reduces fasting blood sugar and body weight gain in a dose-dependent mode(77). Also, MFE showed a synergistic effect with MLE, decreased total cholesterol (TC), serum triglyceride (TG), serum LDL cholesterol, LDL/HDL ratio, liver TG and liver TC(29) . Peng et al. (2011) reported that MFE in hyperlipidemic male hamsters significantly decreases 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and fatty acid synthase, and elevated carnitine palmitoyltransferase-1 and hepatic peroxisome proliferator-activated receptor(78). They suggested that MFE could reduce body weight by regulating lipolysis and lipogenesis. Sirikanchanarod et al.(79) revealed that consumption of MFE by hypercholesterolemic patients (aged 30−60 years) markedly reduces TC and LDL profiles in comparison to controls. All results establish the anti-obesity activity of mulberry fruit.

Anti-tumor activity

In order to understand the anti-tumor property, a series of experiments were conducted with crude extract and pure compounds of fruits(80,81). After research over the years, crude MFE and pure Phyto-components established as anti-tumor agents that acted in different pathways to cure cancer(82,83). Mulberry fruit anthocyanin inhibited tumor xenograft growth of atypical glandular cells (AGS) of the gastrointestinal tract in mice(84). Later Chen et al.(85) (2016) revealed that

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anthocyanin of MFE effectively inhibits human carcinoma cell (A549) migration and in a synergistic effect as anthocyanin/ paclitaxel can arrest cancer cells (TSGH 8301) of human bladder. Cell cycle arrest of TSGH8301 cells achieved at G2/M phase, which induces mitotic catastrophe and inhibits early endosomes generation that may be associated with Caspase 3 and PTEN expression. The synergistic effect of the drug had a more significant effect on the cancer cells than the use of either drug alone. Chen et al.(85) suggested that combinations of anthocyanin/paclitaxel can provide a novel and effective treatment of the cancer cells for human bladder. Chang et al.(86) also reported the synergistic property of MFE/ drug 5-fluorouracil in mice that transplanted with the CT26 cells, where after treatment spleen mass, leukocyte counts, Natural Killer cells, and Cytotoxic T-Lymphocyte activity in tumor xenograft of mice was considerably improved. This anti-tumor action was believed to be the consequence of the immune-stimulatory effect. Lee et al.(87) isolated a new derivative of oxolane known as *odisolane* (Fig. 3) from MFE, might radically suppress tube formation in human umbilical vein vascular endothelial cells (HUVECs). The molecular mechanism of suppressing angiogenesis is allied to the inhibition of the phrase of the vascular endothelial growth factor, p- p-ERK protein and Akt in HUVECs. These findings revealed that phytochemicals of mulberry fruit may be advantageous in anti-angiogenesis therapy for the treatment of cancer. In future, the molecular mechanisms of the anti-tumor activity exerted by MFE need to be further illuminated.

Hepatoprotective activity

Hepatoprotective protective activity of MFPs was studied in acute and sub-acute alcoholic-induced liver injured mice(60). Hepatic indicators (glutathione reductase, superoxide dismutase, glutathione peroxidase, and malondialdehyde) and serological indexes (aspartate aminotransferase

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and alanine aminotransferase) improved following oral administration of MFPs. The histopathological investigation also revealed definite lipid degeneration, loss of necrotic cells, and regeneration of the hepatocytes upon MFP exposure. The results of these studies indicate that the hepato-protecting action of MFPs may be associated with the elimination of free radicals, activation of ethanol dehydrogenase, and the inhibition of lipid peroxidase(88).

Neuroprotective Activity

Kang et al.(89) studied the neuroprotective activity of MFE and cyanidin-3-O-glucoside (C3G) in oxygen-glucose-deprived PC12 cells. They reported that the pure extract of C3G actively prevent ROS generation and reduces neural damage to improve cell viability. C3G established as a more neuroprotective component than crude MFE to cure cerebral ischemia. Another study on Parkinsons's disease (PD) models conducted by Kim et al.(90) revealed that ethanolic MFE significantly protects neural cell damage from neurotoxins in both *in vivo* and *in vitro* experiments. This neuroprotective effect is executed through the antioxidant and antiapoptotic activity of C3G component. MFE was also sufficient to improve the function of ameliorating motor, olfactory neurons, and dopaminergic neurons, restrain the up-regulation of ubiquitin and α-synuclein and reduces acetylcholinesterase activity in case of middle cerebral artery occlusion(91,92). Qiao et al.(93) isolated Artoindonesianin O (AIO) (Fig. 3) and reported its healing activity on neural damage. They suggested AIO treatment lowered okadamic acid-induced tau hyperphosphorylation and reduced N-methyl-D-aspartate or Aβ42-activated neurotoxicity in neuron cells. The molecular mechanism of AIO is allied with the inhibition of

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expression of the kinase p-ERK1/2. Dendritic spine count also amplified following treatment with AIO *in vivo* experiments. These findings strongly advocated that C3G and AIO are the chief components of MFE that exerts significant neuroprotective property on neurons.

CONCLUSIONS AND FUTURE RESEARCH

The present study has highlighted the nutrients content and bioactive phytochemicals of mulberry fruits that exert health benefits to the human being. The bioactive compounds such as polysaccharides, polyphenols, and alkaloids present in mulberry fruits are dependent on the variable cultivars and agro-ecological conditions. Although these bioactive phytochemicals may work synergistically with each other and with chemical drugs to promote health benefits and to cure many diseases, there are insightful gaps in our understanding regarding the molecular mechanism of such biological activities. Extensive studies were done to isolate and characterize MFE, but still, there is a bottleneck to relate the bioactive components of MFE with biological activities.

Moreover, there are very few reports on the molecular mechanism and metabolic pathway of such bioactive components. Thus, it is crucial to understand the mechanism of how these bioactive phytochemicals combat against various diseases. Broad understanding of such property of MFE may broaden opportunities for a researcher working on the food and pharmaceutical industry.

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TABLE 1. Phyto-nutrient composition of mulberry fruit (Imran et al., 2010, Liang et al., 2012, Yuan & Zhao, 2017)

Component	**Quantity (per 100 g)**	**Component**	**Quantity (per 100 g)**	**Component**	**Quantity (per 100 g)**
Moisture	78.03 g^{FW}	Polyunsaturated fatty acid	0.207g^{FW}	Phosphorus(P)	38 mg^{FW}
Total dry weight	21.97 g^{DW}	Fiber	0.81 g^{DW}	Vitamin A	1 μg^{FW}
Total sugar	10.89 g^{FW}	Energy	84.22 $Kcal^{DW}$	Riboflavin	0.101 mg^{FW}
Reducing sugar	8.11 g^{FW}	Potassium (K)	1644mg^{FW}	Thiamin	0.029 mg^{FW}
Non-reducing sugar	1.78 g^{FW}	Calcium (Ca)	576mg^{FW}	Niacin	0.620 mg^{FW}
Pectin	0.76 g^{FW}	Sodium (Na)	264mg^{FW}	Vitamin B6	0.050 mg^{FW}
Total protein	1.73 g^{DW}	Magnesium (Mg)	243mg^{FW}	Folate	6 μg^{FW}

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Total Lipid	0.71 g^{DW}	Iron (Fe)	63.6mg^{FW}	Vitamin C	36.4 mg^{FW}
Saturated fatty acid	0.027g^{FW}	Zinc (Zn)	50.8mg^{FW}	Vitamin E	0.870 mg^{FW}
Monounsaturated fatty acid	0.041g^{FW}	Nickel (Ni)	1.8mg^{FW}	Vitamin K	7.8 μg^{FW}

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TABLE 2. Polysaccharides of mulberry fruit and its effects on human health (Yuan& Zhao, 2017; He et al., 2018)

Component	**Main structure**	**Molecular weight**	**Bioactivity**
FMAP	Backbone composed of (1→3)-linked mannan with branches of galactosyl and glucosyl residues	$130x10^3$	ND
FMAP-2	ND	$300x10^3$	Antidiabetic
MFP-1	ND	$7.9x10^3$	Antioxidant, antidiabetic
MFP-2	ND	ND	Antioxidant, antidiabetic
MFP-3	β-glycosidic linkages	$166.7x10^3$	Antioxidant, antidiabetic
MFP-3P	(1→6)-linked Glc, (1→2,1→3)-linked Rha, (1→3)-linked Gal	$140x10^3$	Antioxidant, antidiabetic

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MFP-4	β-glycosidic linkages	1.5 x10^3	Antioxidant, antidiabetic
JS-MP-1	Backbone composed of rhamnogalacturonan with (1→4)-α-D-GalAp and (1→2)-α-L-Rhap	1600x10^3	Antioxidant, antidiabetic, antiobesity, immunomodulatory
MFPs	α-glycosidic linkages	180x10^3	Antioxidant
PMF-1	(1→2), (1→3), or (1→6)-linked hexapyranose residues	72x10^3	ND

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PMF-2	(1→2), (1→3), or (1→6)-linked hexapyranose residues, α, β-glycosidic linkages	$84x10^3$	ND
PMF-3	(1→2), (1→3), or (1→6)-linked hexapyranoseresidues,α,β -glycosidic linkages	$100x10^3$	ND

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TABLE 3. Bioactive phyto-chemicals isolated from mulberry fruits extract (Yuan & Zhao; 2017, He et al., 2018)

Type	**Class**	**Subclass**	**Component**	**Bioactivity**
Polyphenols	flavonoides	Anthocyanins	Cyanidin 3-O-glucoside	Antioxidant, Antidiabetic, antiatherosclerosis, anti-tumor, hepatoprtective, neuroprotective
			Cyanidin 3-O-rutinoside	
			Cyanidin 3-O-β-D-galactopyranoside	
			Cyanidin 3-O-β-D-glucopyranoside	
			Cyanidin 7-O-β-D-glucopyranoside	
			Cyanidin galloylhexoside	
			Cyanidin hexoside	
			Cyanidin hexosylhexoside	
			Cyanidin pentoside	

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			Cyanidin 3-O-(6″-O-α-rhamnopyranosyl-β-D-galactopyranoside)	
			Cyanidin 3-O-(6″-O-α-rhamnopyranosyl-β-D-glucopyranoside)	
			Cyanidin rhamnosylhexoside	
			Delphinidin acetylhexoside	
			Delphinidin hexoside	
			Delphinidin rhamnosylhexoside	
			Pelargonidin 3-O-glucoside	
			Pelargonidin 3-O-rutinoside	
			Pelargonidin hexoside	
			Pelargonidin rhamnosylhexoside	
			Petunidin rhamnosylhexoside	

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		Non-glycosilated flavanols	catechin, procyanidin B1	Antioxidant, Antiatherosclerosis
			procyanidin B2	
			epicatechin	
			epigallocatechin gallate	
		Non-glycosilatedflavonol	Rutin	Antioxidant, Antiatherosclerosis
			Quercetin	
			myricetin	
			kaempferol	
		Glycosilatedflavonol	quercetin 3-O-galactoside	
			quercetin 3-O-rutinoside	

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			quercetin 3-O-glucoside	Antioxidant, Antiatherosclerosis, Anti-obesity
			kaempferol 3-O-glucoside	
			kaempferol 3- O-rutinoside	
	phenolic acids	Benzoic acid	gallic acid	Antioxidant, Antiatherosclerosis, hepatoprtective
			vanillic acid	
			hydroxybenzoic acid	
			protocatechuic acid	
		Hydroxycinnamic acid	cinnamic acid	
			chlorogenic acid	

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			p-coumaric acid	Antioxidant, Antiatherosclerosis
			o-coumaric acid	
			ferulic acid	
			caffeic acid	
Alkaloids	Nortropane alkaloids		2α,3β-dihydroxynortropane	Antioxidant, anti-obesity, hepatoprtective
			2β,3β-dihydroxynortropane	
			3β,6exo-dihydroxynortropane	
			2α,3β,4α-trihydroxynortropane	
			2α,3β-6exo-trihydroxynortropane	

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	Pyrrole alkaloids		morrole A-F	Antioxidant, anti-obesity, hepatoprtective
			2-(5-hydroxymethyl-2',5'-dioxo-2',3',4',5'-tetrahydro-1'H-1',3'-bipyrrole)carbaldehyde	
			5-(hydroxymethyl)-1H-pyrrole-2-carboxaldehyde	
			4-[formyl-5-(hydroxymethyl)-1H-pyrrol-1-yl]butanoate	
			4-[formyl-5-(hydroxymethyl)-1H-pyrrol-1-yl]butanoate	
			2-formyl-1H-pyrrole-1-butanoic acid	
			2-formyl-5-(methoxymethyl)-1H-pyrrole-1-butanoic acid	
			2-formyl-5-(hydroxymethyl)-1H-pyrrole-1-butanoic acid	
			4-[formyl-5-(methoxymethyl)-1H-pyrrol-1-yl]butanoic acid	
			methyl 2-[2-formyl-5-(methoxymethyl)-1H-pyrrole-1-yl]propanoate	

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			methyl 2-[2-formyl-5-(methoxymethyl)-1H-pyrrol-1-yl]-3-(4-hydroxyphenyl)propanoate	
			2-(5'- hydroxymethyl-2'-formylpyrrol-1'-yl)-3-(4-hydroxyphenyl)-propionic acid lactone	
			2-(5'-hydroxymethyl-2'-formylpyrrol-1'-yl)-3-phenyl-propionic acid lactone	
			2-(5-hydroxymethyl- 2-formylpyrrole-1-yl)propionic acid lactone	
			2-(5-hydroxymethyl-2-formylpyrrol-1-yl)isovaleric acid lactone	
			2-(5-hydroxymethyl-2-formylpyrrole-1-yl)isocaproic acid lactone	
			2-[2-formyl-5-(hydroxymethyl)-1-pyrrolyl-]3-methylpentanoicacid lactone	

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Melatonin			N-acetyl-5-methoxytryptamine	Antioxidant, anti-inflammatory

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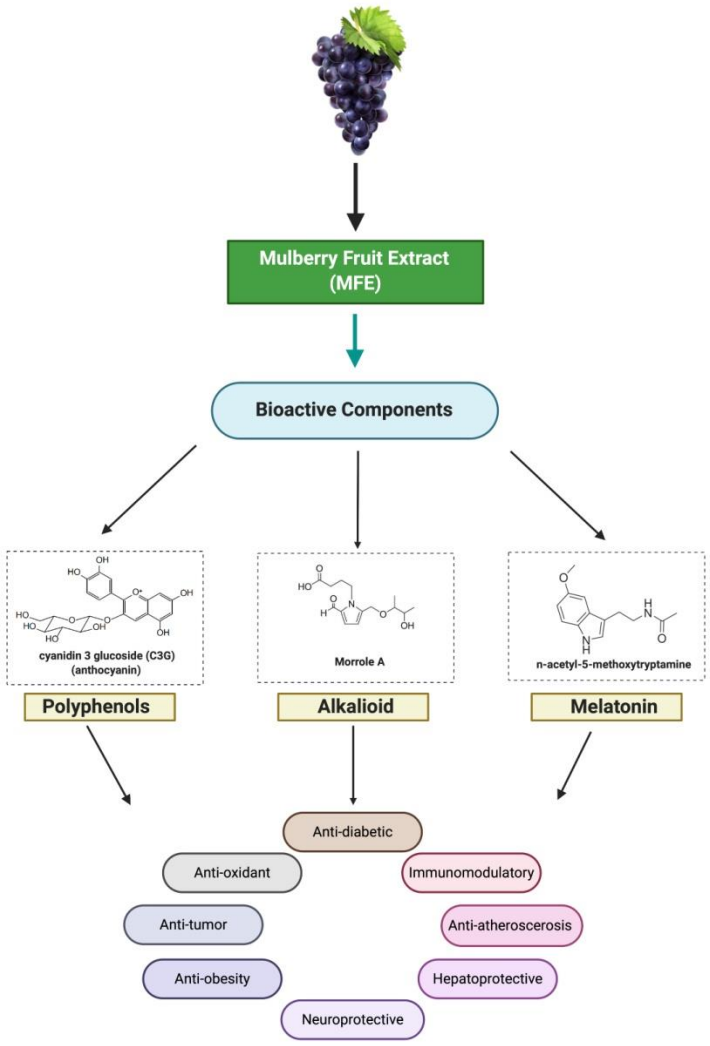

Figure for graphical abstract.

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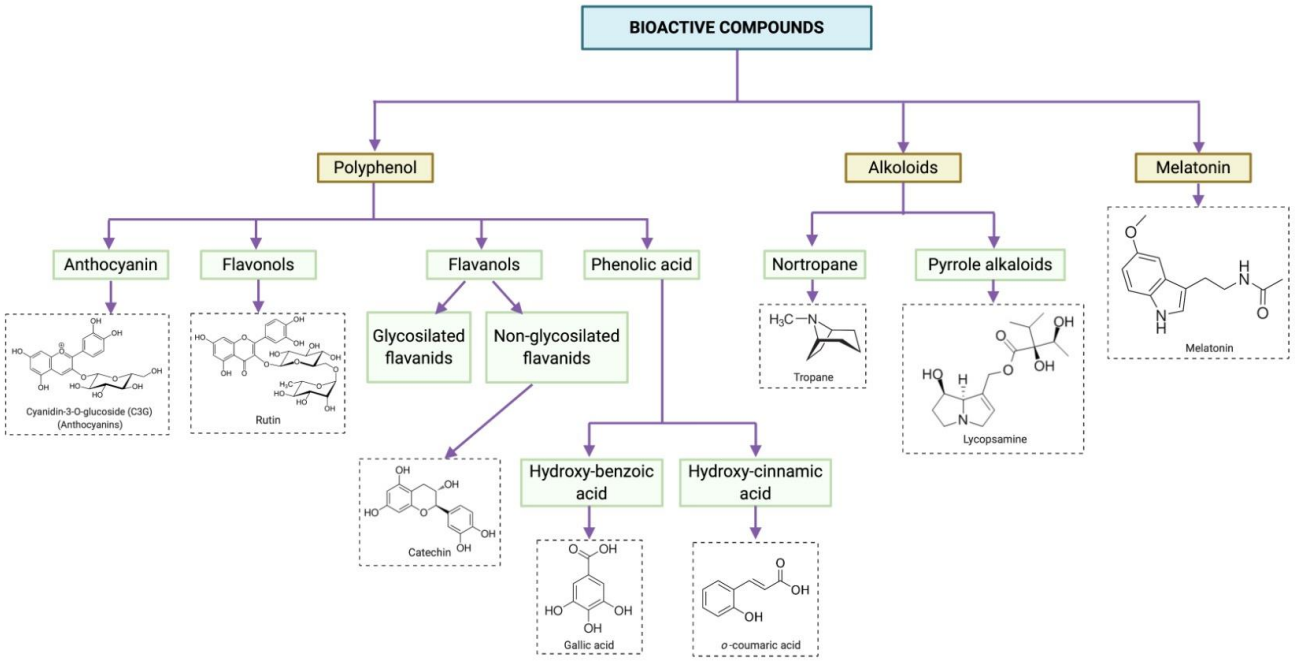

Fig. 1. Bioactive components of mulberry fruit

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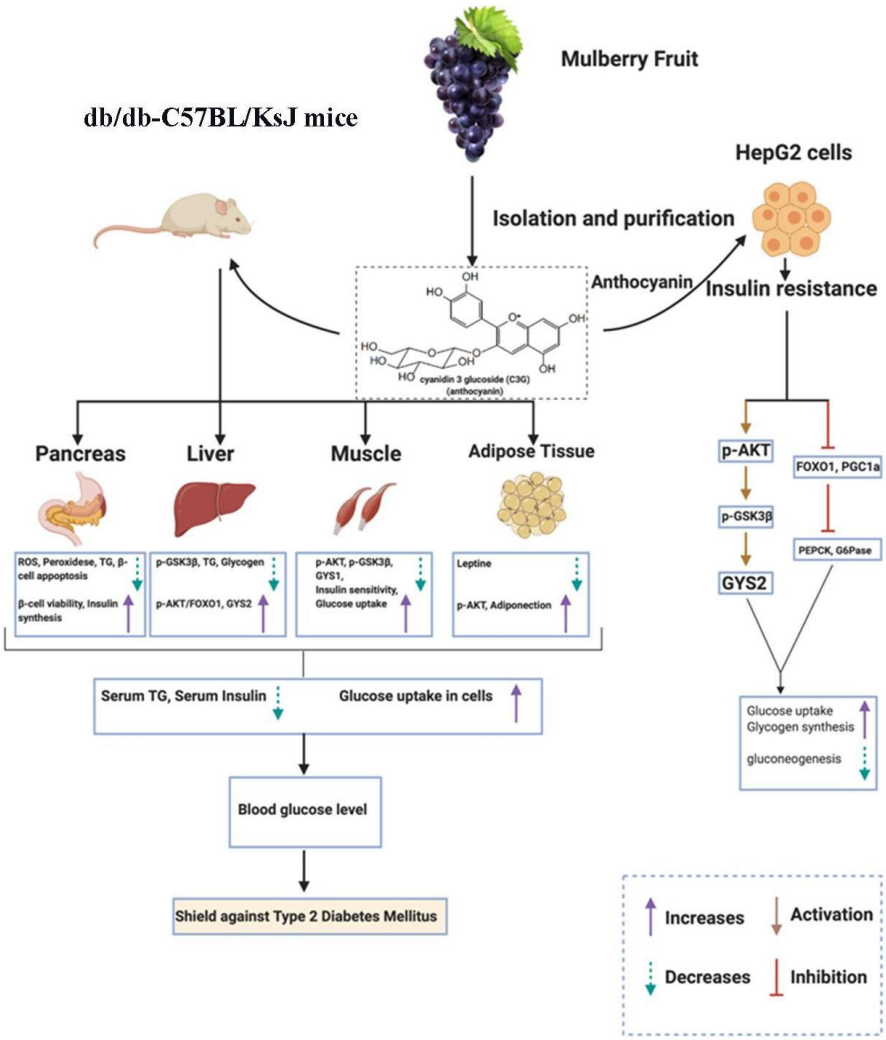

Fig.2. Anti-diabetic property of MFE enriched with anthocyanin db/db-C57BL/KsJ mice

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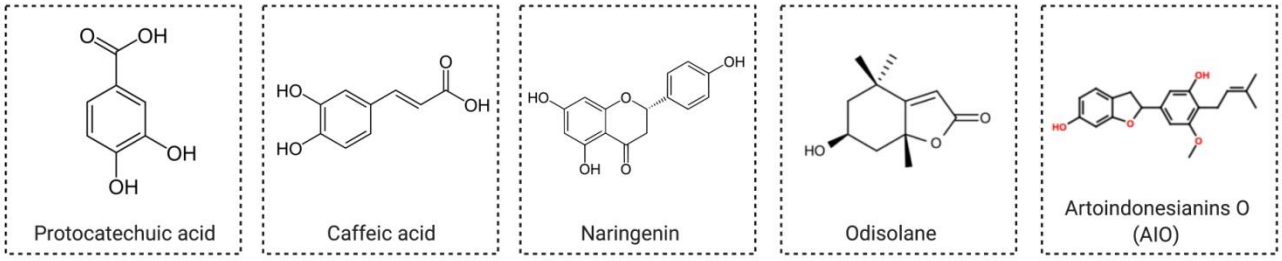

Fig. 3. Polyphenolic compounds that could reduce atherogenesis