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Research Article

CHEMICAL COMPOUNDS AND PHARMACOLOGICAL ACTIVITY OF *Morus nigra* AS A POTENTIAL PRODUCT OF DRUG: A REVIEW

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ABSTRACT

Black mulberry fruit (*Morus nigra* L.) is spread over the subtropical regions of the earth and can grow in various topography and climatic conditions. Its fruit mostly proceeds to become juice, jam, coloring agent and a flavoring for ice cream. Traditionally, the leaves and fruit of *Morus nigra* L. are used to treat dysentery, diabetes mellitus, hypertension, arthritis, and anemia and can also act as a laxative, odontalgia, anthelmintic, expectorant, hypoglycemic and emetic agent. These pharmacological activities might be caused by a high amount of active compounds in black mulberry. Based on the literature studies, there are 56 compounds isolated from various parts of black mulberry, including the root bark, roots, bark, wood, leaves and fruit. The chemical constituents found in black mulberry contribute to its pharmacological properties, such as antihyperglycemic, cytotoxic against leukemia cells, antioxidative, antibacterial, anti-inflammatory and inhibition of tyrosinase.

Key word: black mulberry, Chemical Compounds**,** bioactivity

INTRODUCTION

Black mulberry can be found growing in several regions such as West Asia, Central and South Europe, North Africa, Central Asia and the United States. Generally, it can grow best on clay media. Mulberry fruit plants are easy to cultivate in tropical climates, such as Indonesia, and can produce fruit throughout the year[1].

The black mulberry tree (*Morus nigra* L.) can reach a height of 9 meters. The optimum growth temperature is 24-29^{o}C and humidity of about 65-80%. The fruit is oval, watery, purple to black and can be consumed[2].

Some compounds contained in black mulberry, such as anthocyanins, flavonoids, and carotenoids, are phenol compounds that are sourced in colored fruits. Mulberry fruit is rich from phenolic compounds and has a refreshing acidic taste. Empirically, the fruit is used for curing dental diseases, hypertension, diabetes, anemia, and arthritis[3].

Based on the nutritional value contained in the mulberry fruit, it can be consumed either directly or after processing. The mulberry fruit can be processed to become high grade syrup, jam, ice cream, vinegar, and alcoholic drinks[4].

The traditional usage of black mulberry fruit has been studied in vitro, in vivo, and in clinical trials. These research efforts support use of the constituents of the black mulberry plant as an alternative treatment of various diseases.

ETHNOMEDICINAL *Morus nigra* L.

The *Morus* genus has 24 species with 1 subspecies and 100 known varieties [5,6]. Geographically, this genus can be found in the subtropics and has the ability to grow under variations in soils, topography, and climatic conditions[5]. The most commonly known and well-growing mulberry species are the white mulberry (*Morus alba* L.), the red mulberry (*Morus rubra* L.) and the black mulberry (*Morus nigra* L.). The species is distributed in west, east, and Southeast Asia, Southern Europe, some parts of Africa, northwest South America, and southern North America[6].

Morus nigra leaves are used as a food source for silkworms and forage. An infusion of the leaves can be used to control blood pressure and blood sugar levels. The fruit can be used as a laxative, while the wood can be used as a fuel and as construction material[1].

Traditionally, the leaves and fruits of *Morus nigra* L. are used to treat various diseases. In Turkey, it is used for treating wounds, especially of the mouth. A fruit infusion is used for curing mouth and throat diseases and dysentery and as a laxative, anthelmintic, expectorant, hypoglycemic and emetic agent. The root part or bark is used as a laxative and anthelmintic. An infusion of the leaves is used as a diuretic and antipyretic. A leaf extract is used for treating diabetes mellitus. Meanwhile, its root juice is able to lower blood sugar levels in diabetic patients[7].

The black mulberry fruit (*Morus nigra* L.) is mostly used to produce foods, such as juice, jam, alcoholic drinks, natural dyes and ice cream[6]. In addition, it can also be used to treat dysentery and may act as a laxative, odontalgia, antiacne, anthelmintic, expectorant, hypoglycemic and emetic agent[5,8,9].

Chemical Constituents and Pharmacological Activity

The black mulberry root bark contains deoxyjirimycin (DNJ) which is effective against HIV. It also contains calcium maleate, tannin, sugar, phytosterol, fatty acid, and phosphoric acid[10].

The black mulberry fruit (*Morus nigra* L) contains high concentrations of phenol, flavonoid and ascorbic acid[11,12]. Here is the content analysis of black mulberry fruit: 0.7% protein, 0.4% fat, 12.2% carbohydrate, 0.8% fiber, 0.4% minerals and 85.5% water. The nutritional value of black mulberry fruit states that it contains 60 mg calcium, 20 mg phosphate, 2.6 mg/100 g iron, 58 mg thiamine, 0.2 mg nicotinic acid, 92 mg riboflavin, and 10 mg/100g ascorbic acid[10].

The phenol content of black mulberry fruit can provide pharmacological activities such as antioxidant[13], antibacterial[14], hypolipidemic effect[15] and macrophage activation effect[16]. The highest concentration of phenol can be found in black mulberry fruit (*Morus nigra* L)[17], and with this high phenolic content black mulberry has potential for antioxidant activity[1,18].

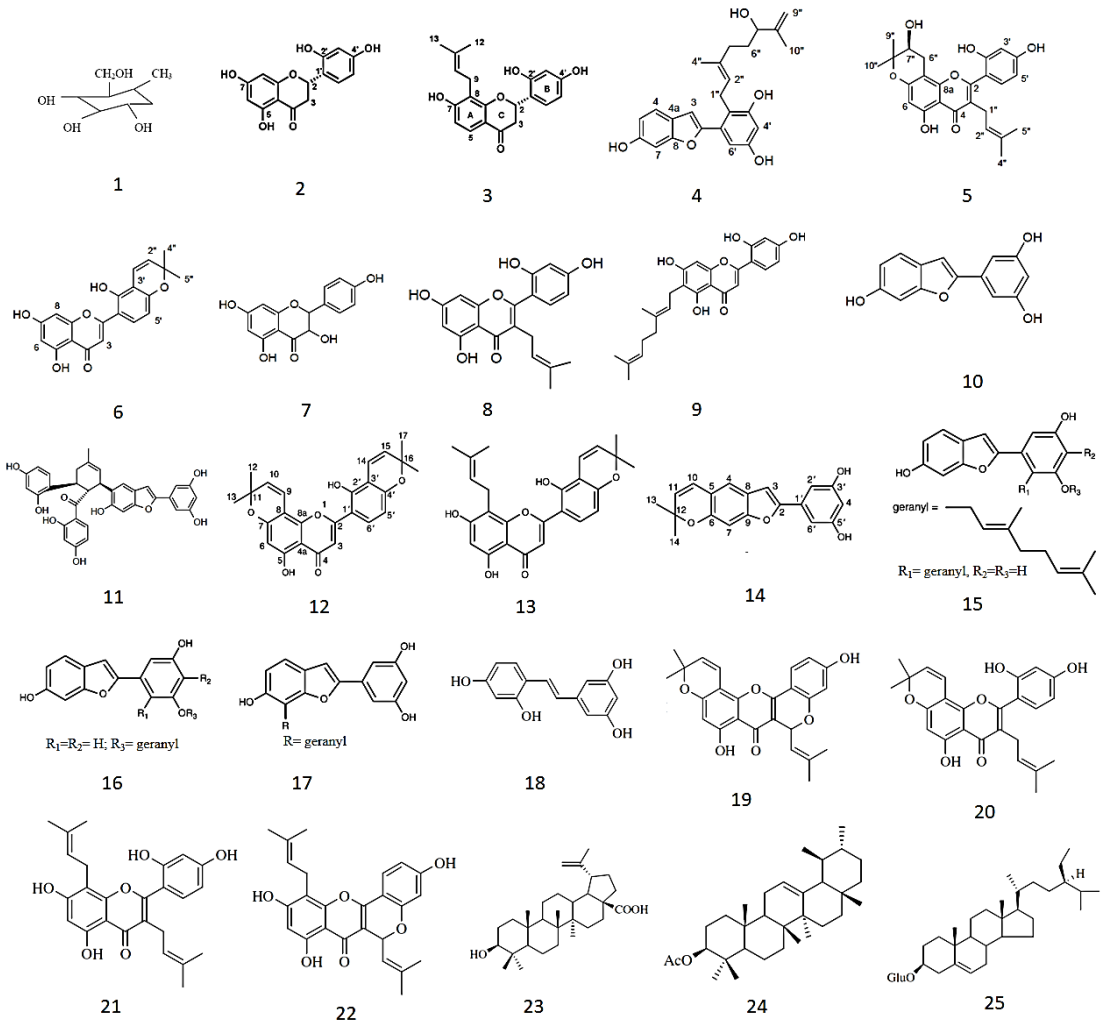
The active compounds present in black mulberry fruit promote pharmacological activity. This suggests that black mulberry has potential in the medical world as an alternative medicine for various diseases. The active compounds and bioactivity of black mulberry fruit are listed in the following table 1.

Table 1. List of Pharmacological Compounds and Activities from *Morus nigra* L.

No.	Active compound	Part of plants	Bioactivity
1.	1-Deoxynojirimycin (DNJ)	root, leaves, fruit	Alfa glucosidase inhibitor helps to balance the high glycemic in patients with type 2 diabetes. DNJ powder from the mulberry leaves can push the improvement of glucose post-prandial significantly. Now, powders enriched with DNJ are available and can be used as a supplement for diabetes mellitus prevention[19].
2.	Flavanonee compound: norartocarpanone	wood	It has cytotoxic properties to the cell line of leukemia P-388; IC_{50} is 7.8 µg/mL. It also has anti-inflammation activity by inhibiting formation of β-glucoronidase (67.7%)[20].
3.	Flavanone compound: eucrenon	wood	The cytotoxic properties to the cell line of leukemia P-388; IC_{50} is 12.7 µg/mL[20].
4.	2-arylbenzofuran derivative: mornigrol D	bark	It has in vitro anti-oxidative activity (98% and 99%, on 10^{-4} mol/L). Besides that, there is anti-inflammation activity by inhibiting formation of β-glucoronidase (65.9%)[21].
5.	Flavanone compound: mornigrol G	bark	Activity test has not been done yet[21].
6.	Flavanone compound: mornigrol H	bark	Activity test has not been done yet[21].
7.	Dihydrokaempferols	bark	Activity test has not been done yet[21].
8.	Albanin A	bark	Activity test has not been done yet[21].
9.	Albanin E	bark	Activity test has not been done yet[21].
10.	2-arylbenzofuran compound: Moracin M	bark, wood, root, leaf	It has antibacterial activity to methycilline-sensitive *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus*, *Streptococcus faecalis*, and *Pseudomonas aeruginosa*[21,22,23].
11.	Albafuran C	bark	It has in vitro anti-oxidative activity (98% and 99%, on 10^{-4} mol/L)[21].
12.	Flavonoid compound: Morunigrol A	bark	Activity test has not been done yet [21].
13.	Flavonoid compound: Morunigrol B	bark	Activity test has not been done yet[21].
14.	*2-phenylbenzofuran* compound: Morunigrol C	bark	Activity test has not been done yet[21].
15.	Albafuran A	bark	It has anti-hyperglycemic activity and protein tyrosine phosphatase 1B (PTP1B) inhibitor.
16.	Albafuran B	bark	It has anti-hyperglycemic activity and protein tyrosine phosphatase 1B (PTP1B) inhibitor [21,24,25,26].
17.	Mulberrofuran L	bark	Activity test has not been done yet[21].
18.	Stilbenoid oxyresveratrol	bark, wood	Antibacterial effect against *Staphylococcus aureus* [23].
19.	Isoprenylated flavonoids: cyclomorusin	bark. wood	Anti-hyperglycemic, cytotoxic to many cancer cells, anti-platelet, and inhibits cholinesterase [23,27,28,29]
20.	Isoprenylated flavonoids: morusin	bark, wood, roots, leaves	It has antioxidant and antibacterial activity against *E. coli* and *S. typhimurium.* Also specific activity against *S. epidermis* and *S. aureus* [23, 30].
21.	Isoprenylated flavonoids: kuwanons C	bark, wood	It has antioxidant, inhibitory effect of 5-LOX, 12-LOX suppressor of iNOS, and antibacterial effect against *E. coli* and *S. typhimurium* [23,30].
22.	isoprenylated flavonoids: kuwanons C derivative	bark, wood	Antibacterial effect against *E. coli* [23].
23.	Triterpene: betulinic acid	bark, wood	Anti-hyperglycemic, anti-hyperlipidaemia, and inhibitory activity against tyrosinase [23,27,32,33].
24.	Triterpene: α-amyrin acetate	bark, wood	Inhibitory activity against tyrosinase [23,32].
25.	Steroidal saponin*:* β-sitosterol-3-O-β-D-glucoside	bark, wood	Activity test has not been done yet [23].
26	Flavonol glycoside: quercetin-3-o-rutinoside	fruit	Anti-inflammatory effect, antioxidant, and inhibitor of enzyme hyaluronidase and collagenase[7].
27	Flavonol glycoside: kaempferol-3-o-rutinoside	fruit	Anti-inflammatory effect, antioxidant, and inhibitor of enzyme hyaluronidase and collagenase[7].
28	Cyanin	fruit	Antioxidant[34]
29	Germanicol	leaves	Anti-inflammatory [35]
30	Diels Alder type adduct: Soroceal	root bark	Anti-inflammatory effect and decrease TNF α levels[36]
31	Diels Alder type adduct: Sanggenon E	root bark	Anti-inflammatory effect and decrease TNF α levels[36]
32	5'-geranyl-5,7,2',4'-tetrahydroxyflavone	roots	Inhibitory activity against tyrosinase (IC_{50}): 37.09 ± 1.74 µM[37]
33	steppogenin-7,40-di-O-β-D-glucoside	roots	Inhibitory activity against tyrosinase (IC_{50}): >300 µM[37]

34	5,7-dihydroxycoumarin-7-(6-O-β-D-apiofuranosyl-β-Dglucopyranoside)	roots	Inhibitory activity against tyrosinase (IC_{50}): >400 μM[37]
35	Mulberroside A	roots	Inhibitory activity against tyrosinase (IC_{50}): >200 μM[37]
36	Mulberroside B	roots	Inhibitory activity against tyrosinase (IC_{50}): >500 μM[37]
37	7-[[6-O-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-2H-1-benzopyran-2-one	roots	Inhibitory activity against tyrosinase (IC_{50}): >400 μM[37]
38	Xeroboside	roots	Inhibitory activity against tyrosinase (IC_{50}): >400 μM[37]
39	5,7-dihydroxycoumarin-7-O-β-D-glucopyranoside	roots	Inhibitory activity against tyrosinase (IC_{50}): >400 μM[37]
40	Steppogenin-7-O-β-D-glucoside	roots	Inhibitory activity against tyrosinase (IC_{50}): 5.99 ± 0.03 μM[37]
41	Moracinoside M	roots	Inhibitory activity against tyrosinase (IC_{50}): >200 μM[37]
42	2,4,2',4'-tetrahydroxychalcone	roots	Inhibitory activity against tyrosinase (IC_{50}): 0.062 ± 0.002 μM[37]
43	Moracin O	roots	Inhibitory activity against tyrosinase (IC_{50}): 93.58 ± 0.65 μM[37]
44	Kuwanon G	roots	Inhibitory activity against tyrosinase (IC_{50}): >200 μM[37]
45	Moracin C	roots	Inhibitory activity against tyrosinase (IC_{50}): 111.47 ± 6.96 μM[37]
46	Cudraflavone C	roots	Inhibitory activity against tyrosinase (IC_{50}): >200 μM[37]
47	Moracin N	roots	Inhibitory activity against tyrosinase (IC_{50}): 30.52 ± 1.46 μM[37]
48	Kuwanon H	roots	Inhibitory activity against tyrosinase (IC_{50}): 10.34 ± 0.19 μM[37]
49	Mulberrofuran G	roots	Inhibitory activity against tyrosinase (IC_{50}): 17.53 ± 0.26 μM[37]
50	Morachalcone A	roots	Inhibitory activity against tyrosinase (IC_{50}): 0.14 ± 0.01 μM[37]
51	Mulberrofuran J	roots	Inhibitory activity against tyrosinase (IC_{50}): 191.28 ± 4.48 μM[37]
52	Kuwanon U	roots	Inhibitory activity against tyrosinase (IC_{50}): >200 μM[37]
53	Kuwanon E	roots	Inhibitory activity against tyrosinase (IC_{50}): 77.99 ± 2.35 μM[37]
54	Oxyresveratrol-2-O-β-D-glucopyranoside	roots	Inhibitory activity against tyrosinase (IC_{50}): 29.75 ± 2.07 μM
55	Oxyresveratrol-3'-O-β-D-glucopyranoside	roots	Inhibitory activity against tyrosinase (IC_{50}): 1.64 ± 0.10 μM[37]
56	Mulberrofuran B	roots	Inhibitory activity against tyrosinase (IC_{50}): >200 μM[37]

It has been reported that phenol derivatives such as stilbene, 2-arilbenzophuran, flavonoid and Diels Alder are the main content of genus *Morus*[20]. The following figure (Figure 1) shows the structure of active compounds that have been isolated from black mulberry fruit (*Morus nigra* L.).



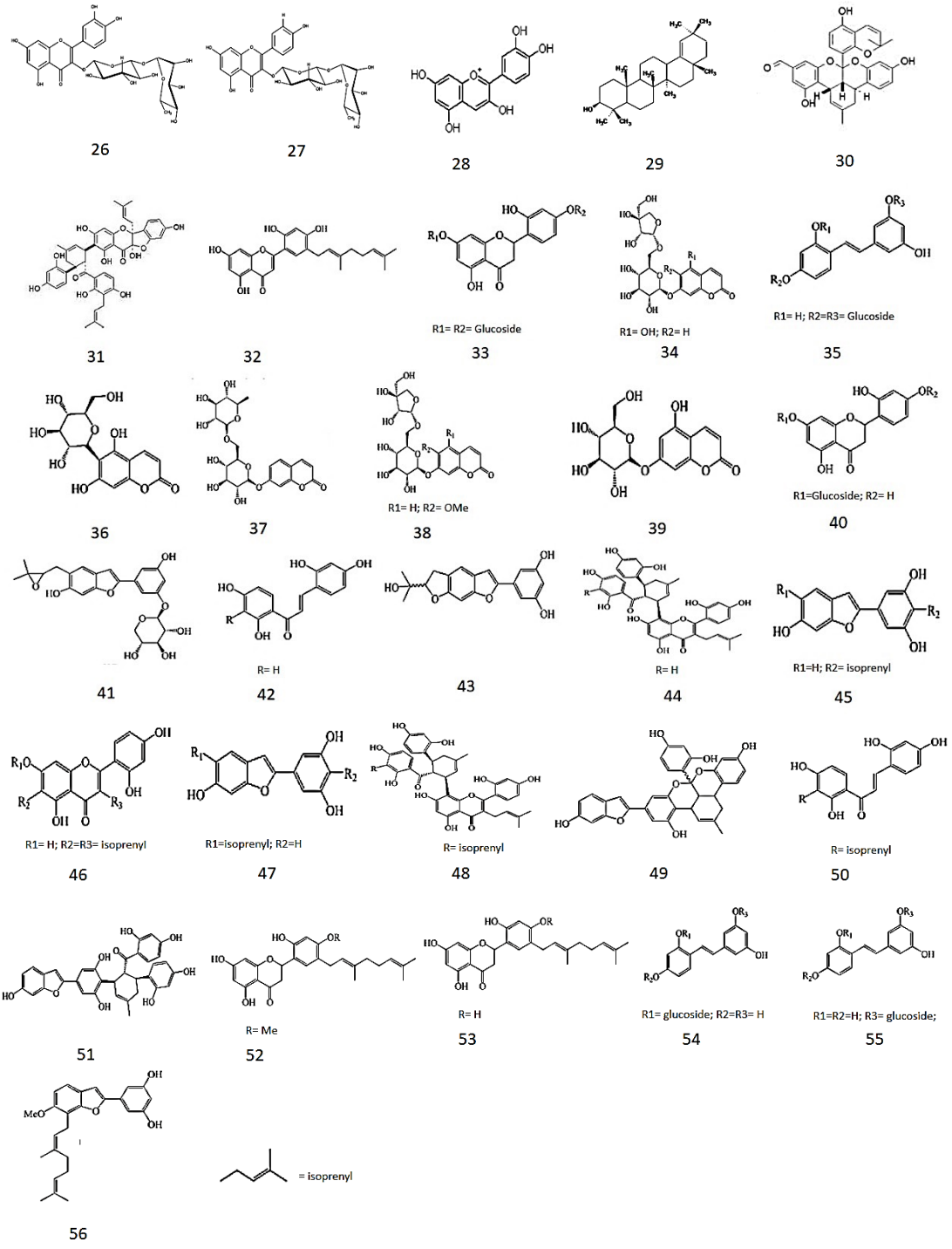


Figure 1. The structure of the isolated compounds from *Morus nigra* L.

Most of the compounds isolated from *Morus nigra* L are phenolic derivatives. The phenol content in this fruit may well lead into several bioactivities as mentioned in Table 1. Research development related to the activity test of the compounds in black mulberry fruit is proof of its empirical efficacy and its use as an alternative medicine in treating various diseases.

CONCLUSION

Morus nigra L. is distributed almost all over the world, including Asia, Europe, Africa, and North and South America. These plants are easy to cultivate in tropical climates and produce fruit throughout the year. Based on the results of literature studies, there are 56 compounds that have been isolated from various parts of black mulberry plants, including the root bark, root, bark, wood, leaves and fruit with phenol derivatives content dominating in the plant. The compounds contribute to the pharmacological activity of black mulberry, such as anti-hyperglycemic, cytotoxic properties against leukemia, antioxidant, antibacterial, anti-inflammatory and inhibition of tyrosinase.

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