A REVIEW: THE NATURAL ANTIOXIDANT ACTIVITY OF BLACK MULBERRY AND ITS OTHERS FUNCTION

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ABSTRACT

Antioxidants are compounds that can be synthetic or natural products. These compounds have a mechanism which suppresses or delays the oxidation process of other molecules because of free radicals. Free radicals such as reactive oxygen species (ROS) are produced during cellular metabolism and environmental such as heavy metal ions, cigarette smoke. Natural antioxidants have been developed from several parts of the plants which contain flavonoids, phenolic acids, tannins, quinones and other phenolic compounds. One of the many plants examined for its antioxidant activity is black mulberry (Morus nigra L.). Black mulberry is known for their high content of phenolic compound. Thus have high antioxidant activity. This review attempt to focus on the relationship between antioxidant activity of black mulberry and composition of phytochemicals, especially phenolic compounds in black mulberry and to explore other potential functions of black mulberry in medicinal uses.

Keywords: *Antioxidants, Morus nigra, Antioxidant Activity, Phenolic Compounds*

ABSTRAK

Antioksidan merupakan senyawa yang didapat secara sintetis atau alami yang memiliki mekanisme untuk menekan atau menghambat proses oksidasi molekul lain karena adanya radikal bebas. Radikal bebas, seperti *reactive oxygen species* (ROS) diproduksi melalui metabolisme sel dan dari lingkungan, seperti dari ion logam berat, asap rokok. Antioksidan alami diteliti dari berbagai bagian tumbuhan yang mengandung flavonoid, asam fenolat, tannin, quinon dan senyawa fenol lain. Salah satu tanaman yang diteliti aktivitas antioksidannya adalah mulberi hitam (*Morus nigra* L.). Mulberi hitam dikenal dengan tingginya kadar senyawa fenol sehingga memiliki aktivitas antioksidan yang tinggi. Artikel kupasan ini berfokus terhadap hubungan antara aktivitas antioksidan dan kandungan fitokimia dalam mulberi hitam, terutama kandungan senyawa fenolnya dan memahami potensi lain dari mulberi hitam dalam pengobatan.

Kata Kunci: Antioksidan, *Morus nigra*, Aktivitas antioksidan, Senyawa Fenol.

Diserahkan: 4 Juli 2018, Diterima 4 Agustus 2018

Introduction

Antioxidants are compounds that can be synthetic or natural products. These compounds have a mechanism which suppresses or delays the oxidation process of other molecules (Velioglu, et al., 1998).

The oxidation process can occur in foods and inside the human body. In foods, the oxidation of lipids is the cause of the formation of off-flavours and detrimental to health of the person who consume the products of food because of the presence of undesirable chemical compounds in foods after oxidation process, so the used of antioxidants in the food industry is needed to delay the oxidation process (Brand-Williams, et al., 1995). In the human body, the various processes of physiological and biochemical may produce by-products, such as oxygen-centered free radicals and other reactive oxygen species (ROS). Accumulation and over production of free radicals in the human body may cause oxidative damage to biomolecules, such as lipids, protein and DNA. The damage in the human body may lead to many chronical diseases, such as diabetes, early-aging, cancer, atherosclerosis and other degenerative diseases (Halliwell, 1994; Niki, 1997; Poulsen et al., 1998).

Synthetic antioxidants for instance butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) have been used in many products as antioxidants with some limitation due to their carcinogenicity, hence natural antioxidants gain interests with their phenolic compounds (Velioglu, et al., 1998). Many of the natural antioxidants have been developed from several parts of the plants which contain flavonoids, phenolic acids, tannins, quinones and other phenolic compounds (Cai, et al., 2004). One of the plants has been studied for their antioxidant activity is black mulberry or blackberry (*Morus nigra* L.). *Morus nigra* L. is a plant belongs to genus *Morus* and family Moraceae (Datwyler and Welbien, 2004; Orban and Ercisli, 2010). The black mulberry has been known with their high content total phenolics, so their in vitro antioxidant properties were investigated (Ercisli and Emine, 2007; Kutlu, et al., 2011).

The antioxidant activity of black mulberry and their contents of phenolic acids and other phenolic compound have been reported (Kutlu, et al., 2011; Arfan, et al., 2012) The current review attempt to focus on the relationship between antioxidant activity of black mulberry and composition of phytochemicals, especially phenolic compounds in black mulberry and to explore other function of black mulberry on degenerative diseases or other diseases more or less based on their antioxidant activity. This review will summarized it and help us to fully understanding and broaden our knowledge of the potential effect of black mulberry in medicinal uses.

Oxidants

Free radicals in the human body derived from oxygen, sulphur and nitrogen molecules that are highly active to interact with other molecules in chemical reaction due to this atoms, ions or molecules have unpaired electrons. Free radicals derived from oxygen are named reactive oxygen species (ROS) which include superoxide anion ($O_2^{-\bullet}$), hydroxyl radical (•OH), hydrogen peroxide (H_2O_2), perhydroxyl radical ($HO_2^{\bullet}$), singlet oxygen ($^1O_2$) and others. Free radicals derived from nitric oxide are named reactive nitrogen species, nitric oxide will form peroxynitrite ($ONOO^-$) through reaction with $O_2^{-\bullet}$ (Lü, et al., 2010). Free radicals termed as reactive sulphur species are formed through reaction between thiols and ROS (Giles and Jacob, 2002).

The human body will produce ROS during cellular metabolism called endogenous sources and exogenous sources from environmental such as ozone exposure, heavy metal ions, cigarette smoke, and ionizing radiation. ROS in normal concentration that is low or moderate will operate and have important roles in physiological cell processes such as cell signalling, gene expression, apoptosis and ion transportation. However, in excessive or high concentration, ROS will attack or induce adverse modification to cell component for instance lipid, protein, DNA. ROS, in which hydroxyl radical is the strongest oxidant will attack double bonds in unsaturated fatty, amino acid side chain in proteins and bases in nucleic acids, these called as oxidative stress, in which there is an unbalance in concentration between oxidant and antioxidant in favour of oxidant (Vajragupta, et al., 2004; Birben, et al., 2012). Oxidative stress will cause the pathological conditions in body, such as inflammatory disease, diabetes, neurological disorder, cancer, cardiovascular disease (e.g. atherosclerosis, hypertension, ischemia), aging and many more (Ames, et al., 1993; Jenner, 2003; Geier, et al., 2009; Lyras, et al., 1997; Sayre, et al., 2001; Dhalla, et al., 2000; Kerr, et al., 1999).

Antioxidants

Antioxidants are molecules in which they will neutralize free radicals so that the oxidation process is suppressed or delayed through accepting electron of free radicals or donating electrons to free radicals to stabilize the radical because of the loss of the unpaired electron (Velioglu, et al., 1998; Lü, et al., 2010). Antioxidants work in the body to prevent the formation of reactive species which act as chelator/deactive metals, remover ROS, and scavenger singlet oxygen, to break chain reaction of free radical or reactive species using catalytic and non-catalytic molecules and to repair damaged cells (Zhivotovsky and Orrenius, 2011; Vertuani, et al., 2004). Antioxidants present at low concentrations but have significant activity and react directly to scavenge or stabilize free radical, thus prevent adverse effect and stop the damage that will happen from oxidation of the oxidizable substrate (Kohen and Nyska, 2002; Kunwar and Priyadarsini, 2011; DeFeudis, et al., 2003). Antioxidants may act as enhancer to the immune system because they prevent oxidative stress which is a major role in the development of degenerative diseases or chronic, thus antioxidants may lower the risk of cancer and degenerative diseases (Sevanian and Ursini, 2000; Lian, et al., 2008).

Antioxidants produced naturally in the body as a defence mechanism to counteract oxidative stress, these antioxidants are called endogenous antioxidants which can be divided into enzymatic and nonenzymatic (Birben, et al., 2012; Kohen and Nyska, 2002). Enzymatic antioxidants are superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT) and glutathione reductase (GRx) (Mates, 2000). The nonenzymatic antioxidants are L-arginine, uric acid, lipoic acid, glutathione, bilirubin and nutrient antioxidants that obtained outside the body and cannot be produced, so they are obtained from foods (Kohen and Nyska, 2002; Radimer, et al., 2004). Other sources of antioxidants are from foods, herbs, vegetables and/or supplement that called exogenous antioxidants for instance vitamin C, carotenoids, vitamin E, phytochemicals like flavonoids, flavones, isoflavones, polyphenolics, coumarins, catechins, terpenoid, alkaloids and others which obtained from plants and can be made into drugs after being used in preclinical and clinical trials (Radimer, et al., 2004; Noori, 2012).

Antioxidant Activity of Black Mulberry

Black mulberry (*Morus nigra* L.) is a species of genus *Morus* and include in Moraceae family. Other common species from this genus are *M. alba* L. or white mulberry, and *M. rubra* L. or red or American mulberry (Kostić, et al., 2013). The black mulberry is a flowering plants so it has fruits with unique delicious fruity, refreshing and sour in taste that has been grown in Europe for its fruits though it is native to western Asia (Kutlu, et al., 2011; Ozgen, et al., 2009). The black mulberry has least cold tolerance than white mulberry and red mulberry so it is a concern to grow it in cold climates or in humid summers, it is best to plant in warm and well-drained soil with 4,57 m distance between each trees, thus it will bear fruits for years with small leaves with broadly ovate blade, sturdy twigs, bark dark brown, fat buds, flower that pollinated by wind and become large fruits with succulent and full of juice so it becomes the best-flavoured species of mulberry (Gerasopoulos and Stavroulakis, 1997; Everett, 1960; Facciola, 1990; Kostić, et al., 2013; Zeng, et al., 2015).

The content mineral in black 15 mulberry plants from different countries such as Turkey, Pakistan, Korea, Serbia and Brazil has been investigated and it showed that black mulberry fruits has sufficient quantities of essential macro-element, such as potassium (K), calcium (Ca), magnesium (Mg) and sodium (Na), with K was the predominant with concentration 922-1270 mg/100 g of fruits and the least element was Na with concentration 58-272/100 g of fruits, besides essential macro-element, black mulberry fruits contain micro-elements such as iron (Fe), zinc (Zn), manganese (Mn), copper (Cu), with Fe was the most dominant with concentration ranging from 4,2 to 77,6 and the least is Cu (Imran, et al., 2011).

The polyphenolic compounds in plants are constituent of one of the most effective for antioxidative activity, so it is important to do the quantitative assay of their polyphenolic contents and link it to the contribution of their antioxidant activity (Arfan, et al., 2012). The total phenols of black mulberry (*Morus nigra* L.) is the highest compared to red mulberry (*Morus rubra* L.) and white mulberry (*Morus alba* L.) (Kostić, et al., 2013). The phenolic compounds were identified as chlorogenic acid and rutin using HPLC compared against the original standard (Arfan, et al., 2012). Other reported the presence of quercetin, apegenin, kaempferol, luteolin and morin in mulberry fruits (Chu, et al., 2006). The phenolic compounds can be found in all parts of black mulberry such as fruit, leaf and root. These parts were extracted by methanol, ethanol, water or acetone then the phenolic total was determined using a spectrophotometric method. The highest content of total phenols showed in black mulberry fruits from Turkey extracted by methanol (1943–2237 mg gallic acid Eq. 100 g of fresh fruit) and black mulberry leaves from Pakistan extracted by methanol (2004 mg gallic acid Eq. 100 g of fresh fruit) with antioxidant activities tested by DPPH scavenging ability was 65,99 quercetinn Eq. µmol/100 g (Kostić, et al., 2013; Ercisli and Orhan, 2008; Memon, et al., 2010). The total polyphenolic contents (TPC) were determined using spectrophotometry at absorption wavelengths of 320-350 nm from sugar-free extracts (SEFs) that obtain from crude extracts of mulberry fruits which separated from its sugars using columns chromatography, the highest TPC came from acetonic SFE of *Morus nigra* (173 mg catechin Eq./g) with the total antioxidant activity was 1.19 mmol Trolox/g, antiradical activity against DPPH radical measured at absorption wavelengths of 517 nm (EC_{50} 58 µg/mL) and the methanolic SFE of *Morus nigra* fruits (164 mg catechin Eq./g) with the total antioxidants activity was 1.25 mmol Trolox/g and antiradical activity against DPPH radical (EC_{50} 48 µg/mL) (Arfan, et al., 2012; Srivastava, et al., 2010). The total phenolics content of *Morus nigra* fruits was determined (1422 mg gallic acid equivalents (GAE)/100 g fresh mass), in fresh black mulberry fruits exhibited 6.64 mg/100 g fresh mass of *Morus nigra* fruits and in methanolic extracts of mulberry leaves obtained 93 mg total phenolics/g, acetonic extracts of mulberry leaves obtained 85 mg total phenolics/g and aqueous extracts of mulberry leaves exhibited 71 mg total phenolics/g (Ercisli, 2004; Imran, et al., 2010; Arabshahi-Delouee and Urooj, 2007).

The antioxidant properties of extracts of mulberry leaves were studied by various experimental methods for instance the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging activity, the iron (III) reducing capacity (FRAP), an in vitro inhibition of ferrous sulphate-induced oxidation of lipids, the total antioxidant capacity, ABTS [2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid)] assay (Arabshahi-Delouee and Urooj, 2007; Arfan, et al., 2012). The ethanolic extracts of five mulberry from Korea were found have strong inhibition of superoxide anions and hydroxyl radicals, the antioxidant activity was determined using the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging activity, reducing power and haemoglobin-induced linoleic acid system (Bae and Suh, 2007). The antioxidant potential of mulberry pulp was characterized as one of the highest value in ferric reducing antioxidant power method among 28 fruits commonly consumed in China, its value is at 4.11 mmol/100 g wet weight (Guo,et al., 2003). Extracts of mulberry leaves and mulberry tender at a concentration of 5 µg/mL have the ability of 46.5% and 55%, respectively, in superoxide ion scavenged, and in extracts of mulberry branches and mulberry bark the percentage were 67.5% and 85.5%, respectively, with the same concentration (Zhishen, et al., 1999). The antiradical activity of crude extracts of mulberry during high temperature heating was reported against the ABTS radical cation and this mulberry extracts have the ability to reduce Fe^{3+} to Fe^{2+} using the FRAP assay. (Tsai, et al., 2005; Iqbal, et al., 2010; Koca, et al., 2008).

Other Functions of Mulberry

1. Lipid Peroxidation

Mulberry leaves contained rutin, quercetin 3-(-malonylglucoside), and isoquercitin, it has been investigated that mulberry leaves could inhibit copper induced human LDL oxidation (Katsube, et al., 2006). Extract of root barks of

Morus had a strong inhibitory effect of xanthine oxidase and lipid peroxidation (Choi, et al., 2002)

2. **Atherosclerosis**

Mulberry leaves have been studied have another function in preventing atherosclerosis, apolipoprotein E-deficient mice have atherosclerotic lesion in their aortae and in group fed by powder mulberry leaf 1% showed a reduction as much as 40% in atherosclerotic lesion size compared with control group (Harauma, et al., 2007).

3. **Anti Tumour**

Mulberry leaves have been studied have anti-tumour activity. This study showed that the methanolic extract of mulberry leaves from India can inhibit the Epstein-Barr virus anti-tumour-promoting activity using inhibition test (Arfan, et al., 2012).

4. **Anti-Inflammatory**

Extract of root barks of *Morus* had inhibitory effects on inflammatory constituents that is cyclooxygenase (COX) enzymes because of the contents of morusin, kuwanon C, sanggenons B, C, D, E and O (Rollinger et al., 2005). Those contents in other studies showed inhibitory effect on nitric oxide (NO) production (Qin, et al., 2015). Mulberry has effect on inhibiting the secretion of TNF-α in LPS-stimulated macrophages (Zelová, et al., 2014).

5. **Antimicrobial**

The methanolic extract of root barks of *Morus* has potent antimicrobiotic activities and inhibit the growth of *Streptococcus mutans, Streptococcus sobrinus*, *Streptococcus sanguis, and Porphyromonas gingivalis* that found as oral pathogen (Rollinger, et al., 2006; Park, et al., 2003).

6. **Antidiabetic**

Aqueous extracts of root barks of *Morus* can lower the elevated blood glucose level and improve serum lipid profile in induced diabetic rats by streptozotocin (STZ) (Ali, et al., 2011).

Conclusion

Antioxidants are needed in the human body to suppress free radical that can cause oxidative stress. Antioxidants work in the human body by neutralizing free radicals so that the oxidation process is suppressed or delayed through accepting electron of free radicals or donating electrons to free radicals to stabilize the radical because of the loss of the unpaired electron. Free radicals in the human body derived from oxygen, sulphur and nitrogen molecules that are highly active to interact with other molecules in chemical reaction due to this atoms, ions or molecules have unpaired electrons. Human body can produce antioxidants naturally as a defence mechanism to counteract oxidative stress, but our body still needs exogenous antioxidants from foods, herbs, vegetables and/or supplement. Antioxidants from plants were developed to be made into drugs after being used in preclinical and clinical trials because of phytochemicals content like flavonoids, flavones, isoflavones, polyphenolics, coumarins, catechins, terpenoid, alkaloids.

Black mulberry (*Morus nigra* L.) is a species from genus *Morus* and include in Moraceae family. Black mulberry contain essential macro-element, such as potassium (K), calcium (Ca), magnesium (Mg) and sodium (Na) and micro-elements such as iron (Fe), zinc (Zn), manganese (Mn), copper (Cu). Black mulberry contain polyphenolic compound and flavonoid, but polyphenolic compound in black mulberry is dominant especially for its antioxidant activity, polyphenolic compound determined as the total phenols. The total phenols of black mulberry (*Morus nigra* L.) is the highest compared to other mulberries such as red mulberry (*Morus rubra* L.) and white mulberry (*Morus alba* L.). The phenolic compounds can be found in all parts of black mulberry such as fruit, leaf and root. These parts were extracted by various solvent such as methanol, ethanol, water or acetone then the phenolic total were determined using spectrophotometric method. The high content of total phenolic in black mulberry resemble to its high antioxidant activity. The antioxidant properties of mulberry were studied by various experimental methods for instance the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging activity, the iron (III) reducing capacity (FRAP), an in vitro inhibition of ferrous sulphate-induced oxidation of lipids, the total antioxidant capacity, ABTS [2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid)] assay and other methods.

Oxidative stress will cause the pathological conditions in the body, such as inflammatory disease, diabetes, neurological disorder, cancer, cardiovascular disease (e.g. atherosclerosis, hypertension, ischemia), aging and many more. Mulberry has potential functions such as inhibit lipid peroxidation, microba and atherosclerosis, anti-tumour activity, anti-inflammatory effect.

Acknowledgement

We thank Mr. Rizky Abdullah as a lecturer and his guidance and help in this work.

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