



Morinda Citrifolia: Bioactivity and Utilization as Traditional Medicine and Food for the Community

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Abstract

Morinda citrifolia is a medicinal plant has been long used as traditional medicine and food ingredients. The plant bioactivity as a drug is related to its secondary metabolites. The writing of the article is based on a review to scientific published online or offline of the journals and books. In the Indonesian home garden, the MC most found and cultivated as traditional medicinal. The fruit of MC has been commercialized as a health drink, but the anthraquinone content used as an indicator its security. The bioactivity of MC is antioxidant, anti-cancer, anti-microbial, anti-cancer, immunomodulatory, increasing central nervous system activity, anti-psychotic, antihepatitic and hepatoprotective. The 6-O- (b-D-glucopyranosyl) -1-O-octanoyl-b-D-glucopyranose and asperulosidic acid have anti-cancer activity, while pheophorbide a and pyropheophorbide a have anti-hepatitis activity.

Keywords: anticancer, anthraquinone, *Morinda citrifolia*

1. Introduction

Morinda citrifolia (MC) is a multi-function plant, which is used as food and medicine. In Indonesia, MC is easy to find in various landscapes such as yards, gardens, succession land and roadside. MC fruit has many seeds so naturally these plants are easy to breed. MC fruit is widely consumed in tropical regions of Indonesia to the Hawaiian Islands (Pandy et al 2012) and has long been developed into commercial juices in Thailand (Nandhasri 2005). Nandhasri (2005) states that MC fruit juice contains high vitamin C, high vitamin B complex content, anthraquinone, flavonoids, saponins and scopoletin, sodium, potassium, calcium, iron, and selenium.

Utilization of MC as a medicinal material has long been studied both ethnobotany, and bioactivity. Traditional Polynesia treatment has used MC for more than 2,000 years to overcome headaches, fever, arthritis, gum inflammation, respiratory disorders, infections, tuberculosis, diabetes (Sefarini et al 2011),

central nervous system disorders (Pandy et al 2012). MC fruit juice in the islands of Hawaii and Tahiti is used to treat cancer (Liu et al 2001) and is believed to have analgesic, anti-inflammatory, antioxidant, detoxification, and cell rejuvenation properties (Khannan et al 2014). MC roots are used for cancer and heart disease (Lishuang et al 2011), antibacterial, antiviral, antifungal, antitumor, anthelmintic, analgesic, hypotensive, anti-inflammatory, and immune enhancing (Singh 2012; Assi et al 2017). Since 1996, MC has been widely sold in the United States as a remedy for various health problems such as cancer, diabetes, HIV / AIDS, peptic ulcers, hypertension, infections, depression, and chronic fatigue (Yu et al 2011).

Utilization of plants as food is related to the nutritional content, while utilization as a medicinal ingredient is related to the content of secondary metabolites. It is generally believed that the use of natural ingredients as medicines is considered safe, although various scientific reports show that the use of doses or improper processing methods can be toxic. For example, the use of raw juice from young shoots of *Sauropus androgynus* as an anti-obesity agent can cause lung problems, which in turn leads to death (Wei 1997). Products that contain seeds or leaf ingredients all contain large amounts of anthraquinone (Bussmann et al 2013), therefore knowledge and information about bioactive compounds and bioactivity of medicinal plants is needed to minimize their negative effects. MC fruit juice is high in potassium and needs to be monitored by patients with kidney, liver, or heart problems (Brown 2012). This article aims to explain the relationship between the benefits and bioactivity of MC so that they can support their use as standardized traditional medicines and herbs.

2. Materials and Methods

2.1. Methods

The writing of this article is based on a literature review to explain the botany, benefits, and bioactivity of *Morinda citrifolia*. Literature is obtained online and offline in the form of research results published in journals, theses, theses and dissertations. Some keywords used to search literature include: *Morinda citrifolia*, bioactivity of *Morinda citrifolia* and noni. Information obtained from the literature was synthesized to explain the benefits and bioactivity of MC.

3. Results and Discussion

3.1. Botany of *Morinda citrifolia*

Morinda citrifolia is one of the species in the family Rubiaceae and is the only widely distributed member of the pantropical genus *Morinda* sensu stricto (Rubiaceae) (Razafimandimbison et al 2010). MC is widely distributed in the tropics including Indonesia, the United States, Brazil, Tahiti, Malaysia, and Australia. Seeds, bark, leaves, roots and flowers are used in the treatment of fruits but are considered to contain the most valuable chemical compounds (Assi et al 2017). MC is exclusively in the tropical climate of India from India through Southeast Asia and Australia to East Polynesia and Hawaii (Gilani et al 2010).

Morinda citrifolia has characteristics: in the form of shrubs to small trees with a height of up to 8 m or more. The young stems are rectangular and have stipules at the base of the petiole. Stipules are oval or triangular in shape with a length of 4-16 cm. The leaf is a leaf which is arranged in front of each other and alternately. Petiole has a length between 5–20 mm (Figure 1a). Leaf shape is oval, oval, oval or round egg, 10–25 × 5–13 cm and the surface of the leaf is shiny. Flowers are compound that are composed of tubers. Flower stalk length 1–1.5 cm and diameter 5–10 mm. The petals are small, while the mouthpieces are funnel-shaped and tubular with a size of about 1.5 cm (Figure 1b). The fruit is ovate or nearly round with a size of 2.5–5 cm green when young, while the ripe fruit is creamy white (Figure 1c) (Silalahi et al 2019).



Figure 1. *Morinda citrifolia*, A. Position of opposite leaf; B. Inflorescence; C. Young fruit is green while old fruit is cream.

3.2. Bioactivity

Morinda citrifolia has long been used by various ethnic groups in Indonesia and other countries as food or as a medicinal ingredient. MC can be used as a food supplement, functional food ingredient, or as a natural health enhancer all over the world (Assi et al 2017). MC has activity as an antibacterial, antiviral, antifungal, antitumor, anthelmintic, analgesic, hypotensive, antiinflammatory and immune enhancing effect (Singh 2012; Assi et al 2017). The following will discuss some of the bioactivity of MC.

3.2.1. Antioxidant

Antioxidant compounds are compounds that can inhibit free radicals. The ability of MC as an antioxidant has been reported by Krishnaiah et al (2015a; 2015b), Piaru et al (2011), and Zin et al. (2001). Krishnaiah et al (2015a) reported that MC has antioxidant activity so that it can be used as a food additive. The antioxidant activity of many plants is associated with its phenolic content, therefore plants that contain phenolic compounds have antioxidant activity. Commercial MC juice shows the value of total phenolic content (91.90 mg gallic acid / 100 mL juice) and antioxidant activity (5.85 mmol / L) (Bramorski et al 2010).

In laboratory experiments, 2,2-diphenyl-1-pikrillhidrazil (DPPH) scavenging compounds can be used to determine antioxidant activity (Krishnaiah et al 2015b), iron thiocyanate (FTC) method, and thyobarbituric acid (TBA) test (Zin et al. 2001). Coarse root extracts, leaves and MC fruits were fractionated in the Sephadex LH-20 column with ethanol as showing very high antioxidant activity in iron thiocyanate test and thyobarbituric acid test and the activity of several fractions as well as tocopherol or BHT (Zin et al 2009).

The ability of plant extracts as an antioxidant is influenced by the compounds used in the extraction and its organs. MC root methanol extract showed high antioxidant activity and did not differ significantly ($P < 0.05$) different from α -tocopherol or butylated hydroxyl toluene (BHT), whereas fruit and leaf methanol extract showed negligible activity. Ethyl acetate extracts from all parts of MC showed significant antioxidant activity, which was comparable to α -tocopherol and BHT. Activity at the root may be caused by polar and non-polar compounds but, in leaves and fruit, only because of non-polar compounds (Zin et al. 2001). For maintenance of the antioxidant properties of MC products, it is recommended to process fresh or frozen MC powder or juice rather than fermented ones (Yang et al 2006).

Neolignan, americanin A, is found as a powerful antioxidant in MC extracts (Su et al 2005). MC fruit juice contains various polyphenols which are included in the group of coumarin, flavonoids and phenolic acids, and iridoids (Brat et al 2011). The biological activity of MC as an antioxidant might be related to phenolic compounds, iridoids and ascorbic acid (Brat et al 2011). In vitro tests showed that ursolic acid as an active constituent of elastase inhibitory activity. 3,30-Bisdemethylpinoresinol, americanin A, and

quercetin isolated as active constituents have tyrosinase inhibition and radical scavenging activities. Americanin A and quercetin also show activities such as superoxide dismutase (SOD) (Masuda et al 2009).

3.2.2. Anticancer

Cancer is a disease caused by excessive cell division, because cancer cells have a smaller growth factor than normal cells. Therefore, in general, anti-cancer compounds are compounds that can inhibit growth or damage cancer cells but do not damage normal cells. MC fruit juice in the islands of Hawaii and Tahiti, has long been used by residents to treat cancer (Liu et al 2001).

MC fruit juice stimulates the immune system to 'help' the body against cancer, and kills a small portion (0-36%) of cancer cells depending on the type. Components in MC juice can stimulate the immune system (Brown 2012). The ability of MC as an anti-cancer is often associated with endophytic fungi. Wu et al (2015) found as many as twelve different species of endophytic fungi obtained from leaves and three from MC. All (3) of MC leaf endophytic fungi inhibited the growth of human LU-1 (lung), PC-3 (prostate), and MCF-7 (breast) cell line carcinomas with IC50 values $\leq 10 \mu\text{g} / \text{mL}$ (Wu et al 2015).

The ability of MC as an anti-cancer is also related to the content of essential oil (Piaru et al 2011) anthraquinone (Lishuang et al 2011; Chan-Blanco et al 2006). MC fruit essential oil showed an IC50 value of 91.46 and 78.15 $\mu\text{g} / \text{L}$ for human colorectal carcinoma line cells (HCT-116) and human breast carcinoma cells (MCF-7) respectively (Piaru et al 2011). The anthraquinone compounds extracted from MC roots show a significant inhibitory effect on the proliferation of human lung and colon cancer cells (Lishuang et al 2011; Chan-Blanco et al 2006).

3.2.3. Antimicrobial

Various infectious diseases caused by microorganisms. Compounds that are able to inhibit growth and cause death of microbial cells are known as anti-microbial compounds. Extracts from MC leaves have an antibacterial effect on *Bacillus subtilis*, *Escherichia coli*, *Proteus vulgaris*, and *Staphylococcus aureus* (Zhang et al 2016), *Enterococcus faecalis* (Kandaswamy et al 2010; Murray et al 2008), *Leishmania infantum* (Almeida-Souza et al 2016), and *Candida albicans* (Jainkittivong et al 2009).

Enterococcus faecalis is a microbe that causes tooth decay and MC juice can inhibit its growth by 69% (Kandaswamy et al 2010). Dental care with MC juice and sodium hypochlorite is as effective as a 17% EDTA rinse to completely remove up to 80% of the stain coating from several aspects of the root canal. MC fruit juice is the first fruit juice identified as a possible alternative for the use of NaOCl as an intracanal irritant (Murray et al 2008). Ethanol MC contains phenolic compounds such as 5, 15-dimethylmorindol, ferulic acid, p-hydroxycinnamic acid, methyl 4-hydroxybenzoate, methyl ferulate, and methyl 4-hydroxycinnamate. Phenolic compounds may significantly contribute to the antibacterial activity of MC leaves (Zhang et al 2016).

Candida albicans is a type of parasitic yeast that can cause vaginal discharge in women. Growth of *C. albicans* was not detected by administration of 50 mg / mL of MC extract at 30 minutes contact time or with 60 mg / mL of extract at 15 minutes of contact time. With the broth dilution test, the minimum fungicide concentration of the extract against *C. albicans* is 40 mg / mL at 90 minutes contact time or with 50 mg / mL at 15 minutes contact time (Jainkittivong et al 2009).

Leishmania is a type of protozoa that causes leishmaniasis which is transmitted through mosquito bites and is found in many tropical regions. MC extract in *Leishmania infantum* has an IC50 value of 260.5 $\mu\text{g} / \text{mL}$ for promastigote and 201.3 $\mu\text{g} / \text{mL}$ for intracellular amastigotes (Almeida-Souza et al 2016). Transmission electron microscopy shows cytoplasmic vacolization, lipid inclusion, increased exocytotic activity, and autophagosome-like vesicles in *L. infantum* promastigotes given with MC fruit juice (Almeida-Souza et al 2016).

3.2.4. Antihepatic

Hepatitis is one of the disorders in the liver caused by a viral infection. Research into the use of natural ingredients as hepatitis drugs, including MC fruit. The methanol, n-hexane, and ethyl acetate extracts of the MC leaf fraction had anti-hepatitis C (HCV) anti-virus activity with 50% inhibition concentration (IC₅₀) of 20.6; 6.1; and 6.6 mg / mL (Ratnoglik et al 2014). Several compounds that were successfully isolated and identified from MC leaf extracts included pheophorbide a, the main catabolite chlorophyll a, as an anti-HCV compound (IC₅₀ = 0.3 mg / mL). Piropheophorbide a has anti-HCV activity (IC₅₀ = 0.2 mg / mL). Cytotoxic concentrations of 50% (CC₅₀) of pheophorbide a and pyropheophorbide a have 10.0 and 7.2 mg / mL, respectively, selectivity indexes of 33 and 36, respectively. HCV only slightly (Ratnoglik et al 2014).

3.2.5. Antipsychotic

MC has long been used as a treatment for various diseases including central nervous system disorders (Pandy et al 2012). The antipsychotic effects of MC fruit can be tested using mouse models with climbing behavior (induced apomorphine and stereotypes) and induced methamphetamine (licking, biting, chewing, and sniffing). Mice given MC methanol extract at different doses 1, 3, 5, 10 g / kg were given orally one hour before apomorphine injection (5 mg / kg intraperitoneal) and methamphetamine (5 mg / kg) reduced the induced rat climbing behavior. and the time of climbing the rat is dose dependent. Methanol extract MC significantly inhibited the methamphetamine-induced stereotypical behavior and climbing time in dose-dependent mice. The antidopaminergic effect of MC in mice shows anti-psychotic activity so that it can be used in the treatment of psychiatric disorders (Pandy et al 2012).

3.2.6. Antidyslipidemic

Aqueous extracts of fruit, leaves, and MC roots showed antidyslipidemic effects in rats fed a high-fat diet. All three extracts caused a decrease in total cholesterol and triglyceride levels in triton induced dyslipidemia. In dyslipidemia induced high-fat diets, all of these extracts are due to significant reductions in total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), atherogenic index and TC / HDL ratio. MC root water extract also causes an increase in high density lipoprotein cholesterol (HDL-C). Anti-dyslipidemic effect of MC extract through inhibition of biosynthesis, absorption and secretion of lipids (Mandukhail et al 2010).

3.2.7. Antidiabetic

The fermented MC fruit has an antidiabetic effect in rats with murine T2DM model (type 2 diabetes mellitus). During the 90-day testing period, food and water intake decreased significantly in the group that was given a fermented MC and positive control mice compared to the diabetic group. Blood glucose levels in the FMC group were 211.60-252.20 mg / dL after 90 days while the control group was more than 400 mg / dL after 20 days. FMC supplementation also reduces glycosylation levels of hemoglobin (HbA1c), increased insulin sensitivity, and significantly decreases serum triglycerides and low density lipoprotein cholesterol (LDL). Peroxisome activated 70% MC ethanol extract (FMCE) proliferator-activated receptor- (PPAR-) and stimulated glucose uptake through stimulation of AMP-activated protein kinase (AMPK) (Lee et al 2012).

3.2.8. Immunomodulator

Immunomodulator compounds are compounds that can stimulate or increase the production of the immune system in the body. Utilization of MC fruits as immunomodulators has been reported by Schafer et al (2008) and Palu et al (2007) both in vivo and in vitro. MC fruit is a natural product that has various immunomodulatory effects (Schafer et al 2008). Neonatal calves fed pure MC showed phagocytic capacity of complete blood in Gram-negative and Gram-positive tests in vitro. Blood samples from calves fed pure MC showed significantly more killing of E. coli bacteria than controls. Bacterial deaths are increasing over time (Schafer et al 2008).

Palu et al (2007) states that MC fruit juice (1.5 mg / mL) has the potential to activate cannabinoid 2 (CB₂), but inhibits cannabinoid 1 (CB₁) receptors and their activity is concentration dependent. In vivo,

oral administration of MC juice for 16 days decreased IL-4 production, but increased IFN production. MC modulates the immune system by activating CB2 receptors, and suppresses IL-4, but increases IFN cytokine production (Palu et al 2007).

3.2.9. Pressing the Central Nervous System

MC fruit has long been used as a traditional medicine for and is believed to have analgesic properties (Khannan et al 2014). MC fruit juice extracts have anxiolytic activity, sedative effects, and hypnotic effects in rats compared to diazepam (Khannan et al 2014). MC fruit juice can overcome cognitive impairment due to stress (Muto et al 2010). Male rats were divided into four groups: control (C), stress (RS), restraint + MC (noni), and sestraint + vitamin E (VE) who were given chronic stressors (CRS) 6 days a week in 6 weeks. The levels of Malondialdehyde (MDA) MC mice were significantly higher than that of C mice, but no differences were found in MDA levels between VE and C. mice. MC fruit juice protects the brain from the stress of cognitive impairment and that this protective effect might be associated with an increase stress caused by decreased density of blood vessels in the hippocampal dentate gyrus (Muto et al 2010).

3.2.10. Treat Central Nervous System disorder

MC fruit is widely used for various diseases including central nervous system disorders. MC fruit has been reported to prevent β -amyloid-induced memory damage in mice. MC extracts affect memory, cerebral blood flow (CBF), oxidative stress and acetylcholinesterase (AChE) activity in scopolamine-induced amnesia models. Scopolamine causes memory disorders along with reduced CBF, increased AChE activity and oxidative stress in the rat brain. The ethanol extract of MC fruit and its chloroform and ethyl acetate fractions significantly improved memory and CBF. Increased oxidative stress and AChE activity after administration of scopolamine are significantly weakened by ethanol extract of MC and its fractions. MC can be useful in memory disorders because of its effects on CBF, AChE and oxidative stress (Pachauri et al 2012).

3.2.11. Hepatoprotective

Hepatoprotective is a compound that can protect the liver from various toxic compounds. MC fruit juice can protect acute liver injury caused by carbon tetrachloride (CCl₄) in mice. In rats pretreated by drinking 20% MC + CCl₄ juice caused a significant decrease in hepatotoxic lesions. Serum alanine aminotransferase levels and aspartate aminotransferase levels were significantly lower in the MC treated group than in the placebo group (West dan Zhou 2008).

4. Conclusion

Morinda citrifolia has bioactivity as an antioxidant, anti-cancer, anti-microbial, immunomodulator, increase the activity of the central nervous system, anti-psychotic, hepatitis and hepatoprotective. Compounds 6-O-(β -D-glucopyranosyl)-1-O-octanoyl- β -D-glucopyranose and asperulosidic acid have anti-cancer activity, whereas pheophorbide a and pyropheophorbide a have activity as anti-hepatitis.

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