Journal of Medicine and Health Sciences (Medisci)
e-ISSN: 3046-7322
p-ISSN: 3032-7326

Narrative Review: The Potential Of Morus Alba And Morus Nigra As Anti-Inflammatory And Antioxidant

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Abstract.
Introduction: Oxidative stress causes various diseases. Inflammation is the body's response to tissue infections and injuries. Mulberry is a multifunctional plant with bioactive components that have potent antioxidant and anti-inflammatory activities. This study aims to determine the activity of antioxidants, anti-inflations, extraction processes, active compounds, and methods used for antioxidant and anti-inflammatory testing.
Methods: Narrative review using a literature search using Google Scholar and PubMed.
Results: The results of Morus alba and Morus nigra have antioxidant activity, the plant parts used by leaves, fruits, and roots. Various methods were used to determine antioxidant activity, including DPPH, *reducing power assay, β-carotene bleaching,* and *Hydroxyl radical scavenger capacity*.
Conclusion: Anti-inflammatory mechanism of mulberry bioactive compounds by inhibiting several cytokines and inflammatory mediators such as IL-1β, IL-6, IL-8, IL-9, IL-10, IL-23a, IFN-ɣ, TNF-ɑ, MMP-3, MMP-9, TLR, COX-2, NF-kB and iNOS. Testing of antioxidant activity by DPPH, ABTS, FRAP, *reducing power assay, β-carotene bleaching,* and *Hydroxyl radical scavenger capacity*

Keywords: Morus alba, Morus nigra, antioxidant, anti-inflammatory

INTRODUCTION

Previous research has shown that mulberry has secondary metabolite components and chemical compounds of flavonoids, anthocyanins, carotenoids, triterpenoids, and phenols that play an essential role in pharmacological activity. Mulberry (*Morus alba* L.) is one of the plants of the family *Moraceae*, and it is widespread in various environmental and climatic conditions, both tropical and temperate. Mulberry belongs to the family *Moraceae*, a flowering plant with more than twenty-four species with one subspecies, and more than a hundred varieties have been identified. (Jan *et al.*, 2021). Almost all varieties of mulberry plants are known in the traditional medicine system of both Unani, Ayurveda, and Chinese, with some pharmacological activity.

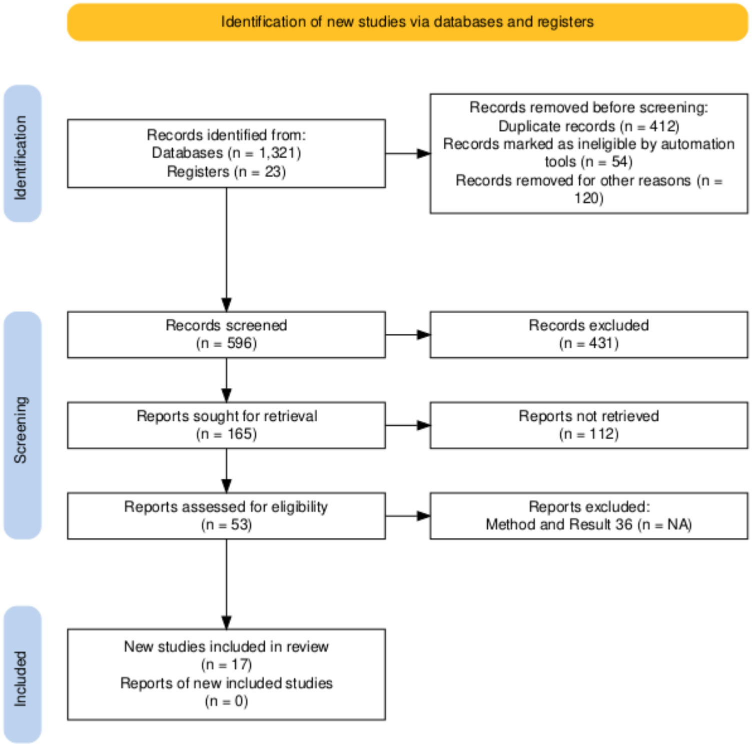
Almost all parts of the plant, including leaves, fruits, and roots, are among the most widely consumed traditional Chinese food crops. Mulberry leaves are rich in active compounds, including alkaloids, flavonoids, polysaccharides, and phenolic compounds, which have a variety of pharmacological activities such as antithrombotic, antidiabetic, antihypertensive, antibacterial, anti-inflammatory, and anti-aging (Rice) *et al.*, 2020). As for mulberry fruit, it is rich in active compounds, including alkaloids, flavonoids, polysaccharides, and phenolic compounds, which have a variety of pharmacological activities containing antithrombotic, antidiabetic, antihypertensive, antibacterial, anti-inflammatory, and anti-aging. This bioactivity is linked to its phenolic constituents, such as flavonoids, anthocyanins, and phenylpropanoids. (Kawvised, Wattanathorn and Thukham-me, 2017).

The stem part of mulberry contains compounds such as triterpenoids (alpha-betaamyrin, sitosterol, sitosterol-alpha-glucoside), coumarin (umbelliferone, and scopoletin), and flavonoids (morusin, cyclomorphine, and oxyhydromorusin). The bark of the mulberry tree root (*Morus alba* L.) has been utilized in herbal medicine as an anti-physlogist, liver protector, kidney protector, hypotension, diuretic, anti-cough and analgesic agent (Eo et al., 2014). Mulberry root bark has a variety of active components such as mulberosside A, oxyresveratrol, mulberrofuran G, kuwanon C, kuwanon G, kuwanon H and morusin. Among these active components, kuwanon C and kuwanon G have anti-inflammatory effects (Cheon et al., 2000; Yang et al., 2011).

Various methods are used to determine antioxidant activity in mulberry plants, including the DPPH method, *reducing power assay*, *β-carotene bleaching*and *Hydroxyl radical scavenger capacity* (YJae Sik Yu, Sung Ho Lim, 2021). However, there have not been many studies that specifically examine the anti-inflammatory and antioxidant potential of Morus alba and Morus nigra, so this article was made to be able to provide special information on the anti-inflammatory and antioxidant potential in Morus alba and Morus nigra.

METHOD

The method used is a literature search using the PRISMA (Preferred Reporting Item for Systematic Review and Meta -analysis) model. All information was obtained from secondary data cited on the official scientific publication website Google Scholar and pubmed. The population used is articles in national and international journals published in the 2014-2024 period to find out the progress of research on the antioxidant and anti-inflammatory activity of mulberry plants in the last decade. This is mapped in the data search flow diagram and summarized in Figure 1.



Picture 1 Identification from research

Some of the information you want to know is the parts of the plant used, the extraction process, chemical content, antioxidant analysis methods, and also the method of anti-inflammation activity both in vitro and in vivo. The keyword used is Mulberry combined with Boolean AND, OR, and NOT operators such as "Morus alba AND antioxidant AND anti-inflammatory. The Exclusion Criteria are antiques in the form of reviews, only containing abstracts and those that do not include an IC value of 50.

DISCUSSION

A fast-growing tree mulberry in warm and humid climates can withstand cold weather and drought. Various parts of mulberry are rich in flavonoids and have anti-inflammatory and antioxidant activity, including the bark of the roots, fruits, and leaves. From several articles that have been collected and resumed, the results of the literature study on the articles are shown in the following table: 1.

Table 1 Results of the Literature Study on Antioxidant and Anti-Inflammatory Mulberry

It	Pharmacological Activity	Plant parts	Test methods	Result	Reference
1	Antioxidant	Fruit	DPPH ABTS FRAP	IC 50 133.6 ± 4.7 IC 50 216.6 ± 28.8 EA 3.727 ± 0.055	(YJae Sik Yu, Sung Ho Lim, 2021)
			In vivo	The ethyl acetate fraction increases SOD, Gpx, and Cat levels to the top.	
	Anti-inflammatory		In vivo Macrophage cells stimulated by LPsS.	The fraction of EA, HX, and MC increases cell viability better than the butanol fraction.	
2	Antioxidant	Leaf	DPPH FRAP LPS	DPPH Method: MLF 50% IC 50 12.35 ± 0.55 FRAP Method: MLF 30% 41.69 ± 2.41 b	(Lin *et al.*, 2022)
	Anti-inflammatory				
3	Anti-Inflammatory	Fruit	Extraction Fractionation Separation with column chromatography	There are 22 compounds, and five compounds can induce NO. This inhibitory effect is mediated through inhibition of the NF-κB/I-κBα pathway	(Lee et al., 2021)
4	Anti-Inflammatory	Root bark	Maceration Fractionation	Provides anti-inflammatory activity with an inhibition mechanism of NF-κB and ERK1/2 Activation.	(Waist *et al.*, 2014)
5	Anti-Inflammatory	Bark	Maceration	Inflammation reduction effect by 42%	(Lallo *et al.*, 2020)
6	Antioxidant	Leaf	Isolation	Neochlorogenic acid (98% purity nCGA) inhibits cytokines stimulated by LPS	(Rice) *et al.*, 2020)
	Anti-Inflammatory				
7	Antioxidant	Fruit	Extraction Fractionation Purification	There are 50 compounds, and 3 of them are new and have anti-inflammatory and antioxidant activity.	(Cent *et al.*, 2020)
	Anti-Inflammatory				
8	Antioxidant	Leaf	Maceration Microwave Assisted Extraction	Highest antioxidant anti-activity in 70% ethanol extract	(Indawati *et al.*, 2023)

			DPPH CAA	The antioxidant activity of moracin is more vigorous than resveratrol and quercetin.	(From *et al.*, 2019)
			Maceration	The IC50 values were 1.7831 ppm, 0.8215 ppm, and 0.7668 ppm, respectively.	(Pogaga, Yamlean and Lebang, 2020)
			DPPH FRAP	There is a relationship between the content of g total phenolics (TPC), flavonoids (TFC), and phenolic acids (TPAC) content.	(Polumackanycz, Wesolowski and Viapiana, 2021)
		Fruit	Freeze-dried	It was identified to contain 16 types of anthocyanins that have antioxidant activity.	(Kim and Lee, 2020)
			Ultrasonic-assisted extraction	The antioxidant activity of mulberry fruit from Dechang is the highest.	(Chen *et al.*, 2022)
			Polysacharide Extraction	The total content of mulberry polysaccharides (TMP) as potential antioxidants reduces ROS	(Li *et al.*, 2023)
			Maceration Phenol extraction	White mulberry fruit (MA) 's antioxidant capacity is lower than black mulberry fruit (MN).	(Money *et al.*, 2022)
9	Antioxidant	Leaf	DPPH	Philippine genotype: IC50 is about 30 µg/mL. Italian genotype: IC50 is about 25 µg/mL.	(Leyva-Jiménez *et al.*, 2020)
	Anti-inflammatory		Gene expression (RT-qPCR) Animal models	Reduces the expression of pro-inflammatory mediators (Tnf-α, Il-1β, Il-6) and increases adinopectin and AMPK levels	
10	Antioxidant	Root bark	DPPH ABTS FRAP Super Oxide	The SC50 of Morus alba root bark was 242.33 µg/mL in the DPPH test and 129.28 µg/mL in the ABTS test	(Hsu, Yang and Chen, 2022)
	Anti-inflammatory		Measurement of anti-nitric oxide (NO) activity	IC50 of 10.81 µg/mL and 12.00 µg/mL, respectively. This suggests that both extracts are effective in reducing inflammation.	

Description: BuOH (butanol); EA (ethyl acetate); HX (hexane); MC (methylene chloride); PE (Petroleum ether); DPPH (2,2-diphenyl-1-picrylhydrazyl); ABTS (2,20-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); FRAP (ferric reducing antioxidant power); GAE, gallic acid equivalent; CAE (catechin equivalent); IC50, half-maximal inhibitory concentration; LPS (lipopolysaccharide; SOD (superoxide dismutase); GPx (glutathione peroxidase); CAT (catalase) . Reactive oxygen and nitrogen species (ROS and RNS)

Extraction and Bioactive Components

Extraction is withdrawing soluble chemical content to separate it from insoluble materials with liquid solvents (Saputra et al., 2020). Extraction aims to attract the chemical components found in natural materials. This extraction is based on the principle of mass transfer of substance components into the solvent. The transfer begins to occur in the interface layer and then diffuses into the solvent (Meigaria, K. M, Mudianta I. W. and Martiningsih, 2016). To obtain the active content of mulberry, maceration and fractionation are carried out by (YJae et al. L *et al.* (Waist *et al.*, 2014). Phytochemical analysis of M. alba fruit ethanol extract can isolate as many as 22 compounds tested for anti-inflammatory activity using the NO method on RAW macrophages 264.7 lipopolysaccharide-stimulated rats (LPS) (Lee *et al.*, 2021).

Various extraction methods are used to obtain active substances from Morus alba and Morus nigra. Research conducted by (Lallo *et al.*, 2020) The bark of the mulberry stem root is extracted using fractionated 70% youthful ethanol. The yield of ethanol extract was 6.5%, while the fractionation results were obtained from the ethyl acetate fraction of 16.2%, the hexane fraction of 8%, and the ethanol fraction of 32.8%. The ethyl acetate fraction had the highest inflammatory power (42.7%)—optimization study of Morus alba leaf extraction with ethanol of various concentrations and NADES with several comparisons. The result is that 70% ethanol extract has the highest flavonoid value and phenolic and antioxidant activity. (Indawati *et al.*, 2023).

Another method is maceration with an ultrasonic bath followed by fractionation with solvents ethyl acetate and hexane (Polumackanycz, Wesolowski and Viapiana, 2021). Ultrasonic extraction with a solvent of a mixture of ethanol and hydrochloric acid (Chen *et al.*, 2022). The extraction of phenolic compounds from Morus alba leaves was used ultrasonic bath (Ban delin, Sonorex, RK52, Berlin, Germany) at a frequency of 35 kHz. The solvent ratio of the sample (v/w) of 40% identification with HPLC-ESI-TOF-MS was obtained 21, and the most abundant glucoside compounds were protocatechuic acid, cryptochlorogenic acid, quercetin-3-O-(6-acetylglucoside) and rutin, which represented more than 55% of the total phenolic content. (Martín-García *et al.*, 2022)Another method for phenol extraction in black mulberry fruits is freezing the raw material at −40 $^{\circ C\ and}$ then freeze-drying it at −50 ◦C, 7.23 Pa, with a vacuum freeze dryer. After being mashed, the fruit is extracted with 80% methanol and acidified with 0.5% HCl. Antioxidant capacity measurement was carried out by DPPH, ABTS, and FRAP methods. (Money *et al.*, 2022).

DOI 10.62885/medisci.v2i1.400

Extraction of mulberry root bark with 80% methanol maceration with stirring for 24 hours is carried out by thickening with a rotary evaporator, then fractionated with petroleum ether and ethyl acetate, then re-concentrated with a vacuum evaporator. (Waist *et al.*, 2014). Extraction of polysaccharides from black mulberry fruit (Morus nigra). The solvent used in ultrapure water uses 220w ultrasonics and a temperature of 70°C followed by centrifugation at 5000 rpm, supernatant plus 80% ethanol (v/v). Furthermore, deproteinization is carried out and several subsequent stages until polysaccharides are obtained, which are calculated as total Mulberry Polysaccharides (TMP). TMP is an antioxidant that reduces the amount of ROS (Reactive Oxygen Subtance) induced by H2O2 on HepG2, which can cause liver damage. (Li *et al.*, 2023).

The results of the study by identifying the active components of Morus alba fruit, L found the following components: tannins—0.16%, quercetin—0.009%, alkaloids—3.37%, polysaccharides—7.52%. This component provides significant pharmacological effects flavonoids as antioxidants and antidiabetics, Alkaloids as strong anti-inflammatory through the regulation of MAPK signals in macrophages and polysacharides, in addition to anti-inflammatory also have immunostimulant properties due to the activation of the body's immune system (Zhumabayev *et al.*, 2024).

Mulberry fruits were extracted and fractionated, the chemical content of each fraction was analyzed by ultra-high-performance liquid chromatography-quadrupole-time-of-flight-high-resolution mass spectrometry UHPLC-QTOF_HRMS). The results of the analysis of the active substances identified in the hexane fraction Ar-Turmerone ;(2S,4aR,4bR,6aR,8S,10aR, 10bR,12aS)-8-(Acetyloxy) hexadecahydro-2,4a,4b,7,7,10a-hexamethyl-2-(3-oxobutyl)-1(2H)- chrysenone and Stigmasterol. In the Methylene chloride fraction identified: odisolane; 3-Benzofurancarbox yaldehyde; loliode; (R)-5-Hydroxypyrrolidin-2-one; Methyl R-pyroglutamate and Indole. The ethyl acetate fraction contains quercetin; kaempferol; luteolin; astragalin; taxifolin; morrole A and methyl chlorogenate. The n-butanol fraction contains quercetin 3-O-β-glucoside; kaempferol; 3-O-β-rutinoside; routine and Butyl L-pyroglutamate (YJae Sik Yu, Sung Ho Lim, 2021). Morus nigra or black mulberry has activity as an anti-inflammatory and antioxidant. The active content in black mulberry that has been identified is 29, among which in silico tests have been carried out, the results of which have potential as anti-breast cancer include Cudraflavone C, Cudraflavone B, 3 Oxyresveratrol-2O-β-D-glucopyranoside, Steppogenin-7-O-β-D-glucoside; 2,4,2',4'- tetrahydroxychalcone; Morachalcone A;

Morin-7-O-β-D-glucosidase, Moracin M, Norartocarpetin; Oxyresveratrol-3'-O-β-glucopyranoside (Prasetiawati *et al.*, 2023). One of the compounds in Morus alba that has been isolated is moracin with an extraction isolation process with 95% ethanol, ethanol extract fractionated with ethyl acetate, petroleum ether, separated by a silica gel column with a chloroform-MeOH motion phase (99:1–80:20) resulting in 12 subfractions (1–12). Subfraction 8 is separated by a column of C18 which is diluted with methanol-water (35%–80%) to produce 14 further fractions separated by HPLC (From *et al.*, 2019).

Antioxidant

The most commonly used antioxidant activity testing is DPPH, ABTS and FRAP methods. This method is used to test samples containing phenolic derivatives due to the transfer of electrons from phenolic compounds to stable free radicals (DPPH and FRAP). The antioxidant activity of mulberry fruit extract was obtained by ABTS method of 3.69±0.05 (mgVCE/gFW); DPPH method 2.45±0.15 (mgVCE/gFW) and FRAP method 2.54±0.08. Total phenol and total flavonoid levels obtained 502.43 ± 5.10 and 219.12 ± 4.45 mg QE/100 g (QE) (Chen *et al.*, 2017).

DPPH is a stable free radical that is purple in color with the presence of antioxidants, the purple color will be reduced or lost, turning into *2.2-diphenyl-1-picrylhydrazine* which is not a free radical (Molyneux, 2004). The ABTS test measures the antioxidant capacity by capturing ABTS+ free radicals resulting from the reaction of the parent compound with a strong oxidizing agent such as potassium persulfate. This method can be used in a wide pH range in both aqueous and organic solvents (Awika, J.M.; Rooney, L.W.; Wu, X.; Prior, R.L.; Cisneros-Zevallos, 2003). The FRAP method directly evaluated the total antioxidant power, in which the iron-tryptylyltriazine complex (Fe3+-TPTZ) was reduced to an iron form (Fe2+) at low pH, which was deep blue in color (Wang, Y.; Xiang, L.; Wang, C.; Tang, C.; He, 2013).

The antioxidant activity of MA root extract and bark fraction was tested in vitro by DPPH, ABTS and FRAP methods, the highest activity was in the ethyl acetate fraction with an IC value of 50 133.6 ± 4.7 (DPPH); 216.6 ± 28.8 (ABTS) and 3,727 ± 0.055 (FRAP). The antioxidant activity based on enzyme capacity obtained the highest results, namely: methyl acetate fraction MA with SOD capacity of 91.1%, crude ethanol extract GPx (Glutathion peroxidase) 2,776 ± 0.025 (nmol/min), hexane fraction in catalase 2,776 ± 0.025 9units/mL0 (YJae Sik Yu, Sung Ho Lim, 2021)

DOI 10.62885/medisci.v2i1.400

Research conducted by (Chen *et al.*, 2022) Morus alba with different varieties has different antioxidant activity. The samples from Dechang had the best total antioxidant capacity followed by those samples from Jurong, Fengcheng, Anji, Liyang, Chongqing, Zhenjiang, and Shuangchen. Testing with the FRAP method measures the amount of (mmol $Fe2+/g$) that changes to (mmol $Fe2+/g$). Morus alba extak has strong antioxidant activity because of its high total phenolic content reaching 502.43 ± 5.10 mg equivalent (QE)/100 g of fresh weight (FW), higher than blackberries, blueberries, raspberries, and strawberries. (Chang, Koo and Kim, 2021)

Moracin is identified as a bioactive chemical from mulberry leaves, this compound has a structure similar to resveratrol. Testing of moracin antioxidant activity with DPPH and Cellular antioxidant activity (CAA) methods showed better results compared to resveratrol and quercetin. Testing with the cellular antioxidant activity (CAA) assay method using HepG2 cells, fluorescence was observed at an emission wavelength of 538 nm and an excitation wavelength of 485 nm. Cellular antioxidant activity calculated by the formula (From *et al.*, 2019) :

$$Cellular\ antioxidant\ activity = 1 - \frac{\int SA}{\int CA}$$

The main anthocyanin derivatives in mulberry fruit are cyanidin-3-O-glucoside and cyanidin-3-O-rutinoside are owned by Iksu cultivars and have the highest antioxidant activity. This type of anthocyanin is obtained from mulberry fruits that undergo a freeze-dried process that is crushed into powder. Freeze-dried mulberry extract and/or syrup can be applied to foodstuffs such as beverages, jellies, bakery products, and cosmetics etc. (Kim and Lee, 2020).

Anti-inflammatory

Inflammation is a condition in which the body reacts to infection, irritation or injury which is characterized by redness, heat, swelling, and also pain. Inflammatory reactions are known as non-specific immune responses. Inflammation/inflammation is also defined by the presence of five microscopic pathological phenomena, namely tumor (swelling of the tissue), heat (increase in tissue temperature), rubor (redness like the color of blood from vascular tissue in the area where inflammation occurs), dolor (organ function disorder)(V. Stankov, 2012). The enzymes that play a role in the synthesis of thromboxane, prostaglandins, and prostacyclines are the enzyme Cyclooxygenase (COX) which causes inflammation, platelet aggregation and pain

The inflammatory process is regulated by the activation of the nucleus of the activated light-chain b-cell augmentation factor (NF-κB) present in the cytoplasm through binding to IκBα in normal cases, whereas in hyperglycemia, IκBα is phosphorylated by IκB kinase (IKK) (Putra, Herbani and Wahyuningsih, 2019). Then NF-κB breaks away and emigrates to the nucleus and binds to NF-κB response element and leads to the development of inflammatory processes and induces cardiomyocyte injury. In particular, the NF-κB cascade is inhibited by AMP-activated protein kinase (AMPK) through IKK suppression, and maintains IκBα. However, mitogen-activated proteinkinase phosphorylation (MAPK) triggers the NF-κB cascade (Al-Rasheed et al., 2017; Li et al., 2017). A high-fat diet spurs the production of TNF-α. Likewise, endothelial dysfunction causes the release of acidase and TNF-α molecules, which can stimulate proinflammatory cytokines (Putra, Herbani and Wahyuningsih, 2019). Mulberry has the active compound quercetin 3-(6-malonylglucoside) and rutin which is able to inhibit LDL1 oxidation (Sujono, Kartikasari and Quntari, 2015).

Highest activity of ethyl acetate fraction:

IC 50 133.6 ± 4.7
IC 50 216.6 ± 28.8
EA 3.727 ± 0.055
Highest Total Phenols
BuOH fraction 204.3 ± 4.7 mg GAE/g
Highest Total Flavonoids

Cell viability

In the research conducted by (YJae Sik Yu, Sung Ho Lim, 2021) It is known that the ethyl acetate, hexane, and methyl chloride fractions can increase cell viability better compared to the butanol fraction. There was no significant material compared to the positive control of quercetin, which recovered up to 100%. Ethanol extracts, ethyl acetate fractions and methyl chloride fractions can also inhibit ROS by increasing the % of superoxide dismutase (SOD) and glutathione peroxidase (Gpx).

Mulberry leaf flavonoids (MLFs) were extracted with 30%, 505 and 75% of ethanol. 0%MLF, 50%MLF, and 75%MLF all significantly inhibit the production of nitric oxide (NO), prostaglandin E2 (PGE2), inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2) in LPS-induced RAW 264.7 cells.

Anti-inflammatory

EtOH extract and MC and HX fractions can significantly inhibit NO production. showed a strong inhibitory effect on NO production at the maximum concentrations tested (20.2%, 29.9%, and 32.8%, respectively compared to NO levels treated with control LPS), a study conducted by(Waist *et al.*, 2014) Morus alba root bark extract has the potential to be anti-inflammatory and anticancerous. Antiinfiltration test with mouse macrophage cells, RAW264.7, and anticancer test using SW480 colorectal cancer cells in 10% bovine fetal serum (FBS), 100 U/ml penicillin, and 100 µg/ml streptomycin. These cells are maintained at 37°C with a humidity of 5% CO2. Mulberry root bark extract (MRBE) is dissolved in dimethyl sulfoxide (DMSO).

M. alba leaf ethanol extract effectively reduces pro-inflammatory mediators and cytokine production by modulating LPS-induced macrophage cell activation by suppressing nuclear factor-jB (NF-jB) activation (Park *et al*., 2013). M. alba stem extract ethanol at concentrations of 20 and 40 mg/ml showed anti-inflammatory activity in RAW264.7 stimulated by LPS macrophage cell line by inhibiting NO production through protein suppression and mRNA iNOS.

The anthocyanins in M. nigra fruit are reported to have anti-inflammatory activity. C3G and C3R exert anti-inflammatory effects through the inhibition of pro-inflammatory cytokines in xylene-induced ear edema and carrageenan-induced foot edema in mice (Chen *et al*., 2016). M. alba root water extract has strong antihistamine and antiallergic activity by inhibiting compound 48/80-induced systemic allergic reactions and histamine release in vitro and in vivo. Mast cell-mediated type allergic reactions are also inhibited by M. alba root extract (Bottle *et al.*, 2005).

CONCLUSION

Based on the literature studies that Murbei has conducted, both Morus Alba and Morus nigra have antioxidant and anti-inflammatory activities. Bioactive compounds that have this potential have been identified, including oxyresveratrol and moracin.

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