Review Article

Morus alba (The Mulberry Fruit): Budding and unrecognised potential

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Abstract

Ayurvedic and many other traditional medical systems have long used *Morus alba* Linn, a well-known medicinal plant from the Moraceae family. The new information on its phytochemicals and pharmacological activity is described in the current paper. Depending on the cultivars and stages of maturation, mulberry fruit contains a wide range of nutritive substances, including fatty acids, amino acids, vitamins, minerals, and bioactive substances including anthocyanins, rutin, quercetin, and chlorogenic acid. The plant also contains carotene, vitamin B1, folic acid, folinic acid, isoquercetin, quercetin, tannins, flavonoids, and saponins. It is a very good source of ascorbic acid, of which over 90% is available in a reduced form. These studies are very positive and suggest that further research should be done to determine the therapeutic potential of herbs. The review highlights a wide range of significant pharmacological actions, such as anti-diabetic, anti-microbial, anti-mutagenic, antioxidant, anti-cancer, anxiolytic, anthelmintic, anti-stress, immunomodulatory, hypocholesterolemic, nephroprotective, and hepatoprotective. Adaptogenic actions, effects on hyperlipidemia, reduction of melanin production, and other effects are also utilised to treat psychiatric problems as well as disorders of the stomach and airways.

Keywords*: *Morus alba, antidiabetic, flavonoid, neutraceutical, multifunctional

Introduction

Mount *Morus alba* also known as white mulberry, is a member of the Moraceae family and is also known as Tut in India. The three to six-metre tall *Morus alba* tree is a medium-sized tree. The development of new chemical compounds that result in new drugs often begins with the study of medicinal plants (Kalia, 2009). In every region of the world where silkworms are bred, white mulberry is grown. The silkworms' primary food source is the white mulberry leaves. Sanskrit: Tutam; Hindi: Tut; English: Mullberry; Malayalam: Malbari; Tamil: Musukette arisnly a few of the many names for the plant that are used in different languages. The plant species of the genus Morus, also referred to as mulberry and a member of the family Moraceae, are among those used medicinally. The three most well-known species are *Morus alba*, Rubra, and nigra. This species is a small to medium-sized mono- or dioic plantar that is extensively found in places like India, China, Japan, North Africa, Arabia, and southern Europe (Sánchez-Salcedo et al., 2017). Given their antioxidant qualities, flavonoids and anthocyanins, which are of great biological, pharmacological, and structural importance, are abundant in the genus Morus (Sánchez-Salcedo et al., 2017). Due to their antioxidant characteristics, the species have historically been employed for the prevention of liver and renal illnesses, joint damage, and anti-aging (Fresno et al., 2011). *Morus alba* is 3.10 m high tree or shrub, bark colored, with shallow grooves, twigs with fine hair. Reddish brown, ovoid, and finely haired winter buds. Lanceolate, 2.3-5 cm long, densely coated with small hairs. Petiole 1.5-5.5 cm, pubescent; Leaf blade oblong to broadly oval, irregularly lobed, 5.30 to 5.12 cm; abaxially light green and glabrous; base rounded to cordate; margin serrate to crenate; tip pointy, pointed, or blunt; adaxially light green and glabrous. Pendulous, 2.3-5 cm long, thickly

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white-haired male catkins (Mena et al., 2016).

Due to its hypoglycemic effects, it has also been demonstrated to be helpful in the treatment of type 2 diabetes mellitus (DM2) (Asghar et al., 2017). Both obesity and DM2 are characterized by high serum free fatty acid (FFA) concentrations, reflecting increased macrophage infiltration into white adipose tissue (WAT) and lower insulin sensitivity (Petersen et al., 2006). In addition to increased FFA levels, other active metabolites are implicated in obesity, such as ceramides, diacylglycerols, and acetyl-CoA, which act by stimulating protein kinases such as N-terminal c-Jun kinase (JNK), protein C kinase (PKC), and Nuclear factor B (NFB) inhibitors responsible for impairing insulin sensitivity by increasing inhibitory phosphorylation (Mohamed, 2014; Konno et al., 2006). Insulin resistance (IR) is one of the main triggers of DM2 and is recognized as an important co-morbidity associated with obesity and metabolic syndromes. The IR process involves a decrease in glucose uptake in peripheral tissues, overproduction of glucose by the liver, functional damage to pancreatic cells, and a decrease in the mass of cells (Asano, 2009). Leaves of several cultivars of the Morus species have a high concentration of sugar-like alkaloids known to have hypoglycemic properties, such as 1,4-dideoxy-1,4-imino-D-arabinitol, 1-deoxynojirimycin, and 1,4- Dideoxy-1,4-imino-D-ribitol (Liu et al., 2016). They are able to inhibit all or some of the intestinal disaccharidases and pancreatic amylases by regulating the uptake of monosaccharides and are therefore used therapeutically in the oral treatment of type 2 diabetes mellitus (Choi et al., 2016). In addition, mulberry leaf extract is able to attenuate RI by modulating gene and protein expression involved in glucose homeostasis in liver cells. The activities of the gluconeogenic enzymes phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G-6-Pass) are suppressed, while the activities of the glycolytic enzymes (glucokinase (GK), phosphofructokinase (PFK) and pyruvate kinase (PK) are suppressed and stimulated in a dose-dependent manner. In addition, the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT) and glycogen synthase kinase-3 (GSK-3) signaling pathways are activated by increasing the translocation of the glucose transporter (GLUT-4) in skeletal muscle and in adipose tissue (Ahn et al., 2017). Medicinal hypoglycemic agents such as metformin and rosiglitazone are used to regulate protein kinases activated by adenosine monophosphate (kappa), which is responsible for energy control in cells and plays a central role in regulating glucose uptake and insulin sensitivity. However, such drugs can cause side effects such as liver or cardiovascular problems. Therefore, there is a growing search for innovative therapies derived from natural compounds with hypoglycaemic effects as an alternative or as an adjunct to conventional drug treatment (Friedman, 2016). Given the attractiveness of natural compounds as alternatives to therapeutic treatments in obesity-related metabolic disorders, particularly DM2, it is important to assess their biochemical and molecular pathways of action and to know their long-term effects. Therefore, the aim of this review is to discuss the potential of the genus Morus as a nutraceutical or drug for metabolic disorders, highlight its importance in the treatment of DM2, and assess its chemical composition, nutritional properties, toxicity, and mechanisms of action.

Plant constituents

The plant contains carotene, Vitamin B1, folic acid, folinic acid, isoquercetin, quercetin, tannins, flavonoids, and saponins, which are all good sources of natural antioxidants. Ascorbic acid, of which over 90% is present in the plant in a reduced form, is also present in very high concentrations. Triterpenes (lupeol), Sterols (-Sitosterol), Bioflavonoids (rutin, moracetin, quercetin-3-triglucoside, and isoquercitrin), Coumarins, Volatile Oil, Alkaloids, Amino Acids, and Organic Acids are all found in White Mulberry Leaf. Rutin, quercetin, and apigenin are bioactive components found in *Morus alba* leaves (Mohamed, 2014; Konno et al., 2006). 1-Deoxynojirimycin is one of *Morus alba*'s main ingredients (Konno et al., 2006). Nitric acid, prostaglandin E2, and cytokines have all been discovered to be produced in macrophages by *Morus alba* leaf extract. Moreover, a polysaccharide isolated from the root bark of *Morus alba* (Asana, 2009). Numerous flavones were identified as active ingredients from the root bark (Liu et al., 2016). Moranoline, Albafuran, Albanol, Morusin, Kuwanol, Calystegin, and Hydroxymoricin are just a few of the biochemical substances that have been identified from mulberry plants and are significant in the pharmaceutical industry (Choi et al., 2016). Thiamine, protein, and carbs are present, according to the review. The plant is reported to contain the phytoconstituents tannins, phytosterols, sitosterols, saponins, triterpenes, flavonoids, benzofuran derivatives, morusimic acid, anthocyanins, anthroquinones, glycosides and oleanolic acid as the main active principles (Ahn et al., 2017; Friedman, 2016).

Immuno Stimulation by *M. alba*

Alkaloids and polysaccharides, which are more common in the fruit than in any other part of the plant, are thought to be immune-stimulating elements in *M. alba*. Polysaccharides are of critical importance in a variety of physiological and pathological activities according to numerous scientific studies (Pramudya et al., 2019; Sánchez-Salcedo et al., 2017).

Alimentative composition of *Morus alba*

People consume mulberry species in different countries due to their nutritional value, deliciousness, non-toxicity and numerous active benefits. The leaves of *M. alba* species are rich in proteins, carbohydrates, fiber and vitamins, especially ascorbic acid and carotene (Bozhüyük et al., 2015). Studies have also found that the leaves contain a large amount of important minerals such as Calcium (Ca), Potassium (K), Magnesium (Mg), Zinc (Zn) and many others. Furthermore, according to (Snchez-Salcedo et al., 2017; Srivastava et al., 2006). *M. alba* leaves possessed high levels of iron (Fe) (119.3241.8 mg/kg) and low sodium (0.01 mg/100 g), making them a suitable dietary material for individuals with sodium limitations.

The leaves also contain a significant amount of organic acids including citric acid (0.263.85 mg/g FW), malic acid (7.3712.49 mg/g FW), tartaric acid (0.0850.212 mg/g FW), succinic acid (1.025.67 mg/g FW), lactic acid (0.290.83 mg/g FW), fumaric acid (0.0580.39 mg/g FW) and acetic acid (0.0290.1 mg/g FW) which contribute the potential health benefits of *M. alba* leaves (Owon et al., 2016). The same nutritive richness is present in *M. alba* fruit, with a higher protein content (10.15–13.33%) than other mulberry species (Thabti et al., 2012). A study by (Owon et al., 2016; Lonnie et al., 2018). showed a higher protein value of *M. alba* fruit (12.98%) compared to black mulberry (10.85%), golden berry (9.16%) and strawberry (7.65%). Their large amount of protein has proven their ability to contribute to the Recommended Daily Allowance (RDA) of protein, which is 0.8 g/kg body weight.

Phytoconstituents of *Morus alba* leaves

M. alba leaves contain flavonoids, which are vital bioactive substances with significant antioxidant properties (Thabti et al., 2012; Memon et al., 2010). reported the presence of 10 other known compounds (1-caffeoylquinic acid, 5-caffeoylquinic acid, 4-caffeoylquinic acid, caffeic acid, rutin, quercetin-3,7-d-O-d-glucopyranoside, quercetin-3-O-glucoside, quercetin-3-O-(6- malonyl)-d-glucopy Both (Sánchez-Salcedo et al., 2017; Fresno et al., 2011) and (Memon et al., 2010; Zhang et al., 2019). corroborated these conclusions. They identified the primary phenolic acids in the leaves as chlorogenic, gallic, vanillic, p-hydroxybenzoic, syringic, p-coumaric, protocatechuic, ferulic, and m-coumaric acids. Moracinflavan A through G and moracinfurol A and B, two novel chemicals derived from 2-arylbenzofurans, were discovered in *M. alba* leaves (Wulandari et al., 2019). Alkaloids, phenolic, flavonoids, tannin, and terpenes—the same important phytochemical groups—were extracted from leaves of two different maturities, with mature leaves containing greater levels of 1-deoxynojirimycin (DNJ) and secondary metabolite values (Jia et al., 2018). Only simple terpenes, as opposed to alkaloids and phenolics, were identified using pyrolysis gas chromatography-mass spectroscopy (Py/GC/MS), presumably because they lack a polar group, which makes them more volatile. More chemicals from the leaves of *M. alba* may be isolated through additional testing at various pyrolysis temperatures (Pohlumackanycz, et al., 2019). Finally, among the primary phytochemical classes of *M. alba* leaves, rutin, apigenin, and quercetin were the three most bioactive ingredients (Ali et al., 2020). Additionally, *M. alba* leaves were shown to include alkaloids, carbohydrates, fatty acids, phytosterols, glycosides, proteins, tannins, gums, and amino acids in five different solvents (Cui et al., 2019).

Antioxidative Activity

M. alba is rich in bioactive compounds and its flavonoids possess high antioxidant abilities based on the analysis of various assays: 1,1-diphenyl-2-picrylhydrazyl (DPPH), 2,2-azinobis-(3-ethylbenzothiazoline-6 -sulfonate) (ABTS) and iron-reducing antioxidant power (FRAP) (Swapana et al., 2012). Antioxidant property of flavonoids demonstrated oxidative modification of human lipoproteins (Jha et al., 2018) isolated 0.53 kDa oligopeptides from *M. alba* leaves that exhibit high scavenging activity in DPPH (322.67–876.92 g/mL), ABTS (141.29256.59 g/mL), nitric oxide (5 .11176.38 g/ml) and FRAP (24.32258.99 AAE/g). The isolated peptides showed levels of 169.55328.57 g/mL for ferrous ion chelation and 202.3315.5 g/mL for malondialdehyde (MDA) inhibition, which is important for the production of highly reactive prevent hydroxyl radicals. The *M. alba* fruit also has powerful antioxidant activities. According to (D'urso et al., 2020). phenylpropanoids and flavonols were the two main compounds responsible for the antioxidant activity of the fruit. The flavonoids showed hemolytic and antihemolytic abilities in the hemolysis of H2O2 in red blood cells induced in mice. In addition, inhibition of lipid peroxidation in the liver, microsomes and mitochondria was demonstrated by 45.5%, 42.8% and 39.4%, respectively. Meanwhile, in *M. alba* seeds, stronger DPPH radical activity than L-ascorbic acid (IC50 = 31.5 M) and -tocopherol (IC50 = 52.3 M) was induced by rutin (IC50 = 20.2 M), isoquercitrin (IC50 = 22.5 M) uncovered. , quercitrin (IC50 = 24.6 M), quercetin (IC50 = 27.8 M), (+)-dihydroquercetin (IC50 = 28.9 M) and chlorogenic acid (IC50 = 30.6 M). These results indicate that *M. alba* contains antioxidant phenolic compounds that may be useful as nutraceuticals in functional foods (Figure 1).

However, the temperature influences the content of

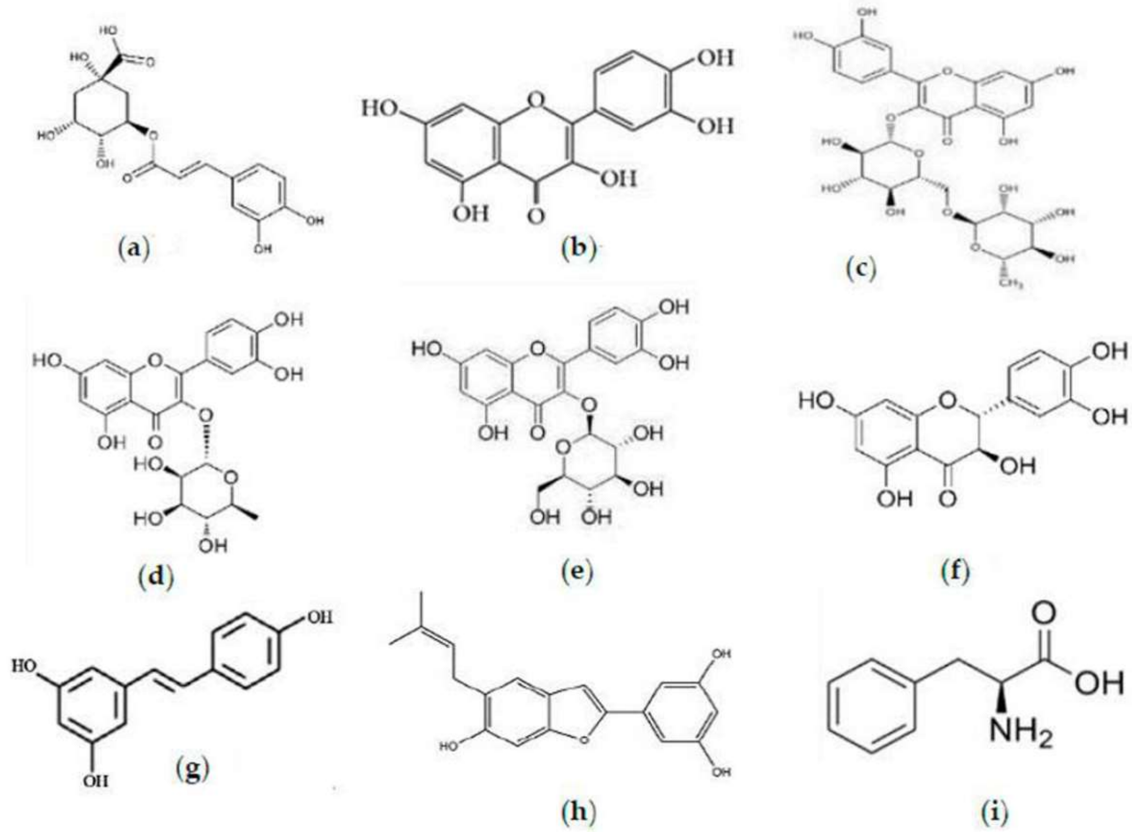

Figure 1. Natural compounds in *M. alba* with antioxidative abilities. (**a**) Chlorogenic acid; (**b**) quercetin; (**c**) rutin; (**d**)quercitrin; (**e**) isoquercitrin; (**f**) dihydroquercetin; (**g**) resveratrol; (**h**) moracin; (**i**) phenylpropanoids. 1 Refers to Compounds in *M. alba* leaves; 2 refers to compounds in *M. alba* fruit; 3 refers to compounds in *M. alba* seeds

phenolic acids and flavonoids during the drying processes (Przeor et al., 2019). Therefore, studies should be conducted with different drying methods, types of solvents, and extraction conditions that are more efficient and can effectively maintain yields, bioactive components, and biological activities. Overall, the existing literature has evidently demonstrated the efficient antioxidant capacity of *M. alba* both in vivo and in vitro, making *M. alba* a promising ingredient for nutraceutical development.

Hypoglcaemic Property

Natural plant extracts are a key component in the treatment of diabetes because they can increase the generation of insulin and reduce intestinal glucose absorption (Malviya et al., 2010) (Ahnet al., 2017). observed a substantial decrease in plasma total cholesterol, hepatic T-C, and triglyceride contents in diabetic mice fed with *M. alba* over 14 days. But the group receiving *M. alba* leaf as a supplement displayed the most notable effects, including reduced levels of plasma glucose and insulin and elevated levels of protein S6 kinase (pS6K), phosphorylated Akt (pAKT), and phosphorylated (p)-AMP-activated protein kinase (pAMPK).

These demonstrated that, in comparison to the fruit, *M. alba* leaves have superior antidyslipidemic and anti-diabetic activities. Additionally, it was discovered that the - glucosidase and -amylase enzymes were both potently inhibited by *M. alba* leaf extract and oligopeptides (0.53 kDa) (D'urso et al., 2020; Eruygur et al., 2019). This enables a delay in the breakdown of sugar, slowing down the absorption of glucose and lowering post-meal hyperglycemia. This led to the discovery that *M. alba* leaves contain 30170 mg/100 g DW DNJ, a powerful β-glucosidase inhibitor, which, when administered in doses as low as 6.5 mg, efficiently suppresses the rise in postprandial blood sugar (Vichasilp et al., 2012). Furthermore, (Jeon et al., 2019) identified eight substances that have β-glucosidase inhibitory activity, with chalcomoracin (IC50 = 6.00 M) and 40-prenyloxyresveratrol (IC50 = 28.04 M) having the strongest inhibitory effects. Additionally, mice with type 2 diabetes supplemented with *M. alba* fruit extract for two weeks displayed enhanced insulin sensitivity and reduced hepatic glucose production (Choi et al., 2016). The fruit-supplemented mice exhibited significantly lower blood glucose levels and haemoglobin (9.083 percent) that had been glycosylated (HbA1c) than the diabetic control and rosiglitazone mouse groups (12.921 percent and 7.454 percent, respectively). The fruit extract also significantly

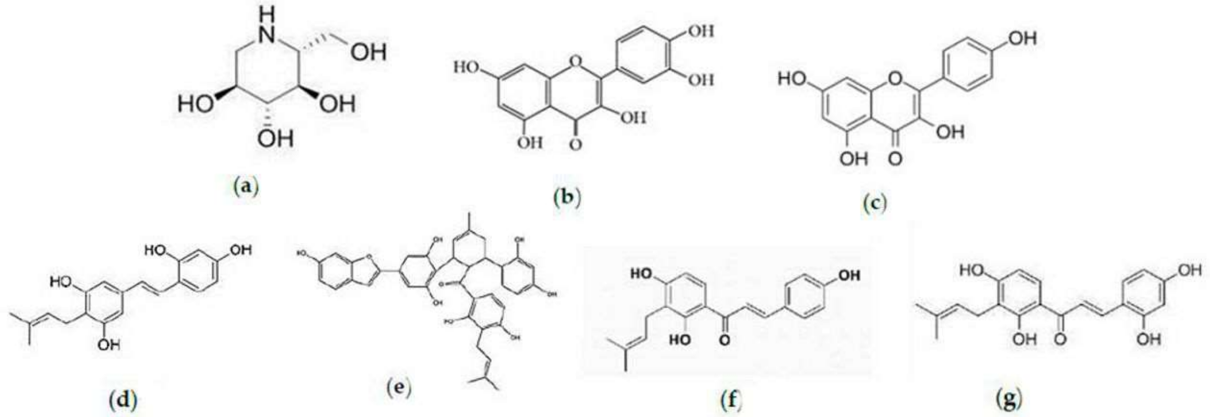

Figure 2. Natural compounds with antidiabetic activities. (**a**) 1-Deoxynojirimycin (DNJ); (**b**) quercetin; (**c**) kaempferol; (**d**) 4′-prenyloxyresveratrol; (**e**) chalcomoracin; (**f**) isobavachalcone; (**g**) morachalcone. 1 Refers to compounds in *M. alba* leaves; 2 refers to compounds in *M. alba* fruit.

increased the activation of pAMPK and p-Akt 160 kDa substrate (pAS160). By significantly lowering the levels of hepatic glucose-6-phosphatase and phosphoenolpyruvate carboxykinase and raising skeletal muscle GLUT4 levels, it was able to stop the production of gluconeogenesis in the liver (Choi et al., 2016). According to a recent study, 16 flavonoids from *M. alba* fruit have the ability to block the enzyme β-glucosidase. The majority of them had IC50 values greater than acarbose, including quercetin (IC50 = 16.00 M), kaempferol (27.61 M), morachalcone (49.07 M), and isobavachalcone (51.84 M) (122 .22M). Figure 2 depicts the structures of these compounds. Based on minor structural changes caused by the hydroxylation of the C-3 position of dihydroflavones, which significantly increased the β-glucosidase inhibitory ability of (2R)- Eriodictyol (IC50 = 168.72 M) compared to (2R,3R)-dihydroquercetin (m), flavonoid inhibitory ability is interchangeable. Overall, *M. alba*'s leaves and fruits have a lot of β-glucosidase inhibition.

Hypolipidaemia and Antiobesity Activity

According to research, *M. alba* leaves can post a mitochondrial fraction of cholesterol-induced mice and significantly lower blood plasma cholesterol, triglyceride, and lipid peroxidation levels. These effects are followed by a reduction in body weight gain, other genic index, coronary artery indices (CRIs), Lees index, and waist circumference (Khyade et al., 2019; Metwally et al., 2019).

Adiponectin was upregulated (1.53-times) whereas leptin and resistin were downregulated (0.39 and 0.71 fold, respectively), allowing *M. alba* leaves to directly affect visceral fat mass and its adiposity while attenuating interference. The polyphenols in *M. alba* leaves, notably chlorogenic acid, quercetin, caffeic acid, rutin, and kaempferol, have been shown to regulate obesity, reduce visceral adiposity, and cause cardiometabolic alterations (Metwally et al., 2019). Ten substances, including three benzofuran derivatives, two phenol derivatives, two flavonoids, one alkaloid, one lignin, and one coumarin, were discovered to have anti-adipogenic activity. On 3T3-L1 adipocytes, these substances exhibited 2,136.6 percent anti-adipogenic action (Li et al., 2018).

Proprotein convertase subtilisin/kexin type 9 (PCSK9), a crucial regulator of the LDL receptor, is expressed in much lower amounts when *M. alba* leaves are used, as shown by (Lupo et al., 2019). Following the publication of this study, fatty acid synthase (FAS) and 3-hydroxy-3-methyl-3-glutaryl-coenzyme A reductase (HMGCR) levels in HepG2 cell mRNA decreased significantly by 51.1 percent and 37 percent, respectively. However, the LDL receptor's expression was enhanced 1.8-fold at the protein level. Despite its inhibition of expression at both the mRNA and protein levels, the PCSK9 promoter's activity was not significantly impacted in liver cells. Thiobarbituric acid-related substances (TBARS) in mice's serum and liver were significantly reduced by dietary supplements of *M. alba* fruit at both 5 and 10 percent (Ang et al., 2010). Only 10% of the mice who received fruit supplements, in contrast, saw levels of red blood cells, liver superoxide dismutase, and blood glutathione peroxidase significantly rise. It has been asserted that the fruit's total anthocyanin and flavonoid content (0.0087 percent and 0.39 percent, respectively) is what produced the variations in HDL-C and LDL-C in high-fat animals. These findings proved that *M. alba* fruit can control hyperlipidemia. In a different study, *M. alba* fruit increased lipolysis and decreased lipogenesis and fibrosis in obesity-induced high-fat meals, which reduced the effects of obesity-induced heart dysfunction (El-Baz et al., 2014). In obese mice, fruit extract also reduced collagen while attenuating reactive oxygen species (ROS), vascular function,

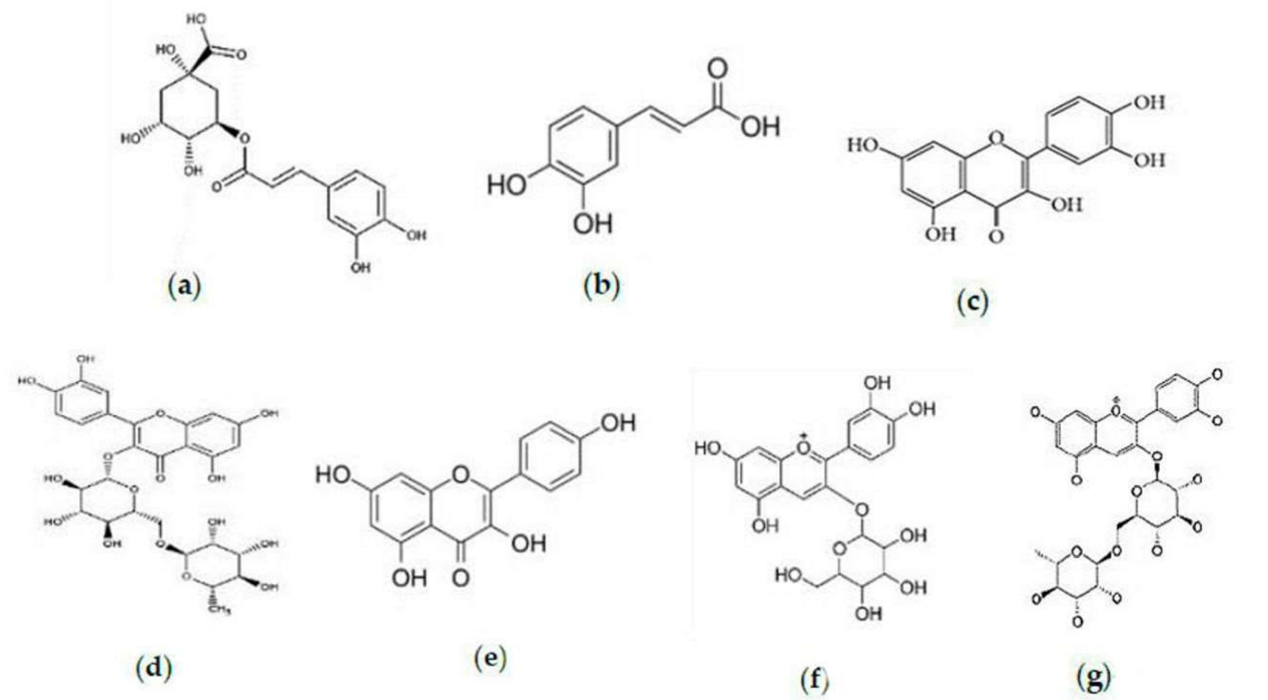

Figure 3. Natural compounds with anti-hyperlipidaemic activities: (**a**) Chlorogenic acid; (**b**) caffeic acid; (**c**) quercetin; (**d**) rutin; (**e**) kaempferol; (**f**) cyanidin-3-O-glucoside; (**g**) cyanidin-3-O-rutinoside. 1 Refers to compounds in *M. alba* leaves; 2 refers to compounds in *M. alba* fruit

inflammatory markers, and lipid accumulation. These effects are anticipated to be important in the prevention and treatment of obesity-related cardiac dysfunction and cardiac fibrosis. In figure 3 displays the chemical compositions of substances with anti-hyperlipidemia properties. In conclusion, *M. alba* leaf and fruit extracts show strong cholesterol-lowering and obesity-suppressing effects, making them a great preventative against obesity, atherosclerosis, and a condition associated with atherosclerotic hyperlipidemia. However, it is yet unclear how the active ingredients trigger the absorption of LDLR and LDL. Therefore, further studies need to explore a deeper understanding of the anti-hyperlipidemia mechanism of *M. alba*s.

Neuroactive Ability

According to (Gupta et al., 2018) and (Rayam et al., 2019), *M. alba* leaves could facilitate the transfer of gamma-aminobutyric acid (GABA) and thus show an antispasmodic effect in rats (Diniz et al., 2015). A 25 mg/kg methanolic leaf extract actually delayed the onset of pentylenetetrazole (PTZ)-induced chronic seizures. In contrast, 50 and 100 mg/kg extracts reduced seizure duration (Gupta et al., 2018). These concentrations also significantly reduced maximal electroshock-induced tonic hindlimb extension (Gupta et al., 2018). Meanwhile, *M. alba* leaves significant antiepileptic activity at 200 and 400 mg/kg at 6.8 and 3.16 s, respectively, as reported by (Rayam et al., 2019) was observed. In the context of Alzheimer's disease, 28-day administration of 100 mg/kg ethanolic *M. alba* leaves improved both learning and memory function in spatially-impaired rats, while the 200 mg/kg and 400-mg/kg mg/kg extracts inhibited the effect on memory disorders (Tamtaji et al., 2016). High-dose (160 mg/kg daily) administration of DNJ could improve cognitive impairment, alleviate hippocampal Aβ deposition through β-Secretase 1 (BACE1) inhibition, and reduce expression of brain inflammatory factors such as TNF-, IL1β, and IL- 6 in mice (Chen et al., 2018). DNJ minimizes the decline in brain-derived neurotrophic factor/tyrosine kinase receptor (BDNF/TrkB) signaling in the mouse hippocampus. This, therefore, implies its ability to enhance the hippocampal neuron microenvironment (Chen et al., 2018). Similar results for *M. alba* fruit extract, including improved spatial memory and learning ability and reduced neuron apoptosis and Aβ plaques in hippocampal and cortical tissues of mice have been reported (Liu et al., 2020). *M. alba* fruit also increased anti-inflammatory cytokines (IL-4) and reduced astrocytes and pro-inflammatory cytokines (TNF-, IL,-1β, and IL-6) in both the hippocampus and cortex. Thus, it alleviated neuroinflammation (Liu et al., 2020). Apart from that, *M. alba* fruit extract significantly reversed the AlCl3 neurotoxin-induced alteration in striatal neurotransmitters and reduced brain acetylcholinesterase (AChE) activity by 50%. A significant increase in norepinephrine, epinephrine, 5-hydroxytryptamine serotonin, and dopamine

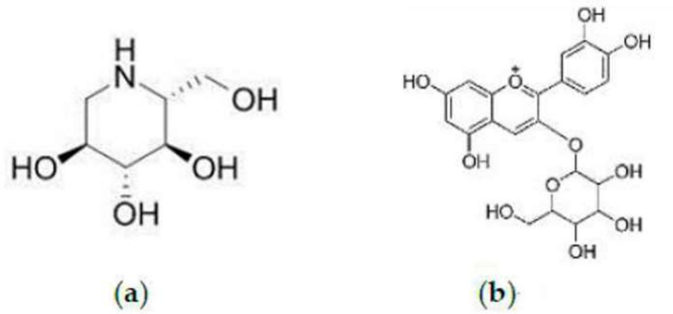

Figure 4. Structures of (**a**) 1-deoxynojirimycin (DNJ) and (**b**) cyanidin-3-O-glucoside. 1 Refers to compounds in *M. alba* leaves; 2 refers to compounds in *M. alba* fruit

neurotransmitters was observed in the treated mice (El-Baz et al., 2018). Based on these data, *M. alba* may attenuate Alzheimer's disease via reduction of A deposition, reduction of inflammatory factor, and reduction of BDNF/TrkB signaling pathway, thereby enhancing its protective effect on memory and learning abilities. Parkinson's disease is a dysfunctional motor disorder caused by progressive degeneration of dopaminergic neurons and glyphosate associated with oxidative stress (Rebai et al., 2017). According to (Rebai et al., 2017), the protective ability of the *M. alba* leaf extracts could combat the neurotoxicity and harmful effects of glyphosate. At the same time, it decreased levels of lactate dehydrogenase, malondialdehyde and protein carbonyls. Leaf extract also chelated free ions to scavenge H2O 2 and increased calcium and superoxide dismutase activity in the brain. These neuroprotective effects of *M. alba* leaves are due to synergism or antagonism between the bioactive phenolic components in the leaf extract. In addition, *M. alba* fruit extract also significantly improved and delayed the progression of Parkinson's disease-like motor and non-motor impairment symptoms in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) /Probenecid rat group (Gu et al., 2017). *M. alba* fruit inhibited olfactory dysfunction in rats due to shortened pellet recovery time; Improvement of hypokinesia and bradykinesia and inhibition of gait dysfunction. Fruit extract also inhibited dopaminergic neuron degeneration and Lewy body formation through synuclein suppression, while correcting the adverse effects of MPTP/Probenecid on ubiquitin expression in both the substantia nigra and striatum (Gu et al., 2017). The cyanidin-3-glucoside (C3G) (Figure 4) from *M. alba* fruit dose-dependently prevented membrane damage and preserved mitochondrial function and mitochondrial membrane potential (MMP) of primary cortical neurons in rats when subjected to oxygen-glucose starvation 3, 5 h (Bhuiyan et al., 2011), indicating the neuroprotective effect of C3G. In summary, the results of various studies served as proof of the worthy neuroprotective effects of the leaves and fruits of *M. alba*. This makes it a promising nutraceutical ingredient to combat neurodegenerative diseases, particularly Alzheimer's and Parkinson's disease.

Antiinfective and Antiviral Activity

As a result, *M. alba* leaves have been observed to impede the fluorescence growth of Staphylococcus aureus, Bacillus cereus, and Pseudomonas (Suwansri et al., 2008). However, only two of the 13 selected cultivars showed low to moderate Escherichia coli inhibition. There is a correlation between total phenolic content and antibacterial activity, as shown by the extracts with the highest total phenolic content's ability to inhibit the growth of the three bacterial strains (Suwansri et al., 2008) (Thabti et al., 2014). found that the aqueous and methanolic *M. alba* leaf extract had antibacterial activities against Salmonella ser. Typhimurium, Staphylococcus epidermis, and Staphylococcus aureus. In view of the rise in bacterial strains that are resistant to antibiotics, (De Oliveira et al., 2015) investigated the effect of ethanolic *M. alba* leaves on medically significant bacteria and fungi. In their study, the Candida albicans strains LM-106, ATCC-76645, and LM-656 developed resistance to the positive controls. However, *M. alba* leaves exhibited a minimum inhibitory concentration of 256 g/ml and significantly inhibited *Candida albicans* LM-106 growth. *Candida albicans* (ATCC-76645 and LM-106), *Candida tropicalis* (ATCC-13803 and LM-6), *Candida krusei* (LM-656 and LM-978), *Staphylococcus aureus* (ATCC-13150 and M-177), *Pseudomonas aeruginosa* (ATCC-9027 and P-03), and *Aspergillus flavus* all showed moderate activity (LM-714). Although several species of Streptococcus are weakly inhibited by morin, a chemical produced from *M. alba* fruits (Yang et al., 2012). According to studies on the antimicrobial properties of pectin isolated from *M. alba* fruit (Figure 5), at concentrations between 500 and 1000 g/m, it has antibacterial activity against a number of gram-positive and gram-negative bacteria, including *Bacillus cereus*, *Staphylococcus aureus, Streptococcus mutans*, *E. coli, Pseudomonas aeruginosa,* and *S. typhimurium*. Additionally, methanolic and aqueous extracts of *M. alba* leaves have been demonstrated to be toxic to *Staphylococcus aureus* and *S. typhimurium* (Kostíc et al., 2014). But when it came to inhibiting gram-positive bacteria, acetone extract performed better than ethanolic and methanolic extracts.In contrast, none of the extracts showed any suppression of gram-negative bacteria (Genovese et al., 2020). An attempt to biotransform *M. alba* fruit extract with Lactobacillus brevis DF01 and *Pediococcus acidilactici* K10 resulted in considerable

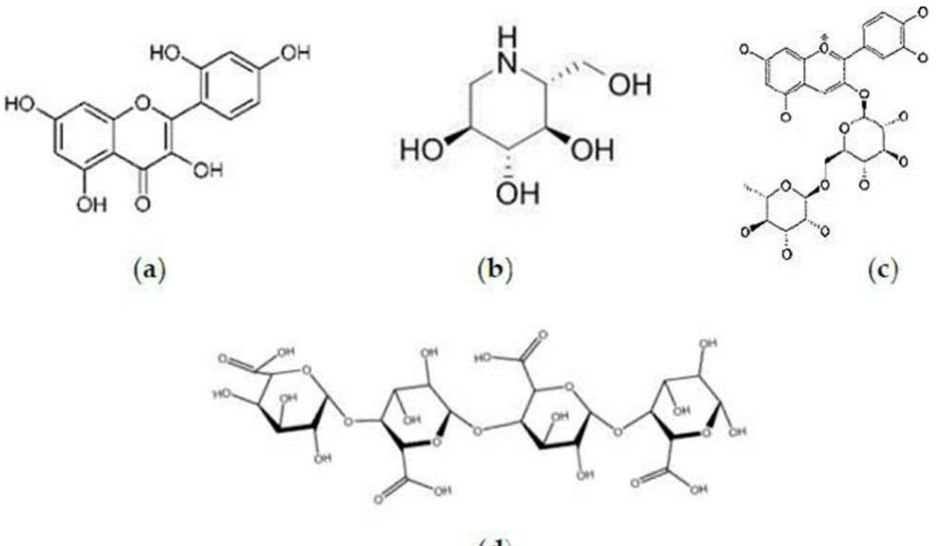

Figure 5. Natural compounds in *M. alba* possessing antimicrobial and antiviral activities. (**a**) Morin; (**b**) 1-deoxynojirimycin (DNJ); (**c**) cyanidin-3-O-rutinoside; (**d**) pectin. [1]Refers to compounds in *M. alba* fruit; [2]refers to compounds in *M. alba* seeds.

antibacterial action against *S. typhimurium* by preventing proliferation and bacterially produced biofilm in a different experiment (Kim et al., 2019). Furthermore, DNJ produced from *M. alba* fruit is efficient against the hepatitis B virus, woodchuck hepatitis virus, bovine viral diarrhoea virus, and GB virus B, according to (Jacob et al., 2007). (HBV).

Cytotoxicity and Anticancer Activities

It is well known that mulberry species are a source of substances that prevent the onset and spread of cancer. The abundance of antioxidants present in M is what has the main anti-cancer preventive action.

Aanticancer properties have been confirmed by a number of investigations on various human cancer cells, including cervical cancer, lung cancer, hepatocellular carcinoma, breast cancer, and colon cancer. When compared to the other 3 plant extracts, alba leaf extract had the most cytotoxic impact on P19 embryonic cancer, with IC50 values of 273, 117, and 127 g/ml after 48, 96, and 144 hours of treatment, respectively. Nuclear factor kappa B (NF-B) gene expression was suppressed by leaf extract in a study by Fathy et al. and modulating biochemical markers alpha-fetoprotein (AFP), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (-GT), and albumin (ALB). In addition, the leaves induced morphological changes in HepG2 cells to a more mature hepatocyte shape (Fathy et al., 2013).

Morin extracted from *M. alba* leaves at 50 mM also caused morphological alterations in HeLa cells, which were then followed by the development of flocculent apoptosomes at 150 mM and globular suspensions of dead/apoptotic cells at 220 mM. This ROS-induced apoptosis, as well as the increase in death receptor expression, mitochondrial signaling, and apoptosis-associated gene expression, were all involved in this morin-induced apoptosis (Zhang et al., 2018). Fascinatingly, (Fallah et al., 2016) found that *M. alba* leaf flavonoids were more potent at inducing dose-dependent cytotoxicity in colon cancer than either doxorubicin, an established chemotherapeutic agent, or their combination (flavonoids + doxorubicin). 10 flavonoid compounds were identified as having strong cytotoxic effects on HeLa cells (IC50 = 0.643.69 M), MCF-7 cells (IC50 = 3.217.88 M), and Hep-3B cells (IC50 of 3.099.21 M). Morusin, atalantoflavone, and 30-geranyl-3-prenyl-20,40,5,7-tetrahydroxyflavone were the three principal flavonoids with the maximum cytotoxicity for each cancer cell in HeLa, MCF-7, and Hep-3B cells; 8-geranylapigenin, sanggenon K, and 30-geranyl-3-prenyl-20,40,5,7-tetrahydroxyflavone; and 30-ger. While this is going on, a new study claims that *M. alba* leaves show cytotoxic activity on a variety of substances, including morusin, morachalcone B, morachalcone C, moracin D, moracin X, chalcomoracin, and DNJ. Figure 6 depicts the chemical make-up of these molecules.

Additionally, n-hexane fractions from *M. alba* fruits had the best cytotoxicity on HCT116 (IC50 = 32.3 g/mL), whereas dichloromethane (DCM) fractions best expressed on MCF7 (IC50 = 43.9 g/mL) across the range of different extraction solvents. Furthermore, the DCM fruit fraction was recognised as being harmless because it had no effect on the Bj1 cell line, a normal cell line, but the EtOAc fraction had a 47.3 percent cytotoxic effect on Bj1. However, the extracts had little to no impact on the HepG2 (022.8%) and PC3 (039.6%) cancer cells. This demonstrated that, due to the

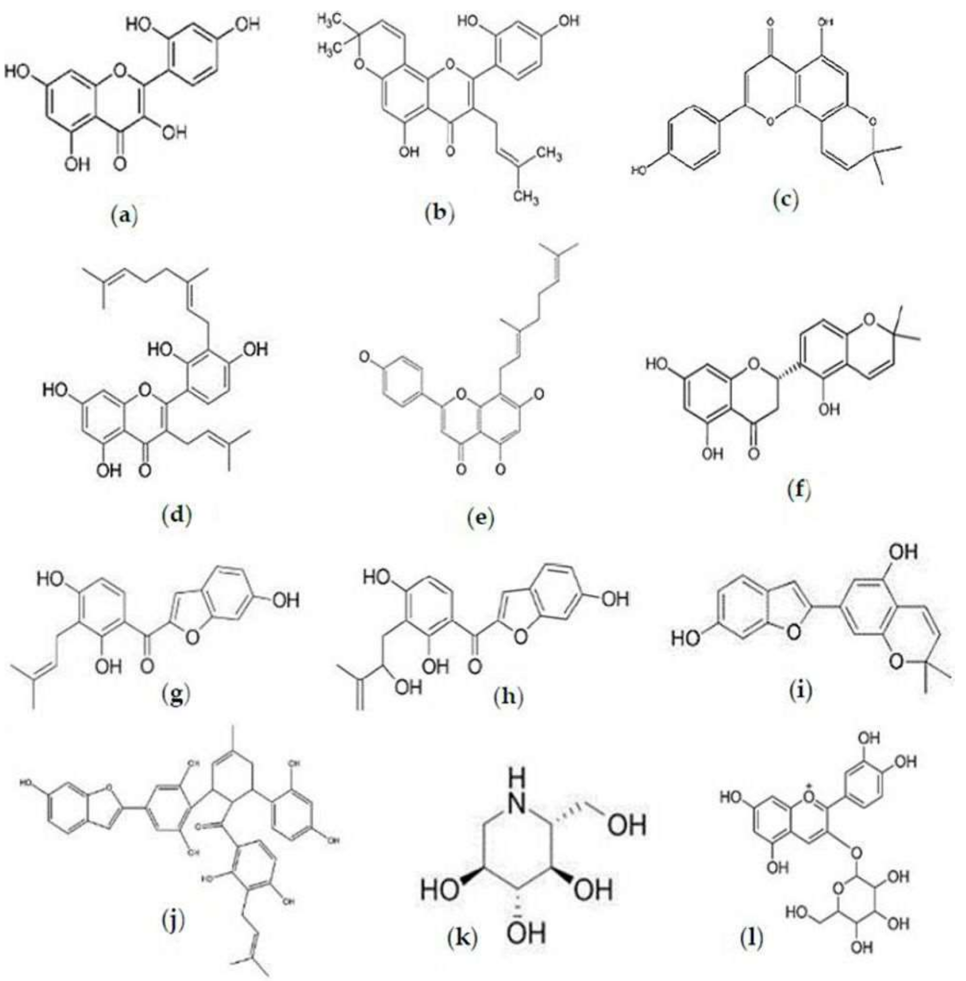

Figure 6. Natural compounds in *M. alba* with anticancer abilities. (**a**) Morin; (**b**) morusin; (**c**) atalantoflavone; (**d**) 3$'$-geranyl-3-prenyl-2$'$,4$'$,5,7-tetrahydroxyflavone; (**e**) 8-geranylapigenin; (**f**) sanggenon K; (**g**) morachalcone B; (**h**) morachalcone C; (**i**) moracin D; (**j**) chalcomoracin; (**k**) 1-deoxynojirimycin (DNJ); (**l**) cyanidin-3-glucoside. [1] Refers to compounds in *M. alba* leaves; [2] refers to compounds in *M. alba* fruit.

variable polarity of the solvents, a sample's cytotoxicity changed with the extraction yield (Jyoti et al., 2013).

The cyanidin-3-glucoside (C3G) from the *M. alba* fruit can induce cytotoxicity and dose-dependently promote human breast cancer cell death, according to research by (Cho et al., 2017).

M. alba C3G underwent active apoptosis as a result of an increase in cleaved caspase-3, a decrease in Bcl-2, and DNA fragmentation. In addition, mice with tumour grafts experienced dose-dependent tumour size reduction after 25 days on a C3G diet. This shows they can stop cancer cells from growing and proliferating in both in vitro and in vivo models (Cho et al., 2017).

An indoleacetic acid derivative from *M. alba* fruits that was recently identified exhibited dose-dependent cytotoxicity on HeLa cells. Caspase-8 and Caspase-9 activation via the mitochondrial intrinsic pathway and death receptor-mediated extrinsic pathway have been used to infer the mechanism of apoptosis (Yu et al., 2018). Interestingly, (Ramis et al., 2018) found that despite having higher total phenols, total flavonoids, and antioxidants, the cytotoxic effects of leaves on colon cancer cells were only marginally superior to those of fruits. However, hepatocellular liver cells were subjected to a cytotoxic impact that was almost identical to the fruit. The multifaceted mode of action of *M. alba*s has been the subject of numerous investigations. It involves the elimination of reactive oxygen and nitrogen species, the reduction of harmful mutations, and inflammation, the promotion of apoptosis, and the activation of the immune system. To give patients with advanced-stage tumours a better chance, it is recommended that additional research be done on in vivo studies of *M. alba* cytotoxicity in more aggressive, metastatic, or late-stage cancers.

Discussion and Conclusion

Leaves and fruits of *M. alba* are considered as a whole, they contain significant amounts of bioactive substances such phenolic acids, flavonoids, flavonols, anthocyanins, macronutrients, vitamins, and volatile aromatic compounds. The abilities of *M. alba* to prevent and treat conditions like oxidative stress, diabetes, hyperlipidemia, neurological disorders, microbial infections, and cancer are greatly influenced by these compounds. Numerous studies have been conducted on the fruits and leaves of *M. alba*, mostly to identify the bioactive components, potential therapeutic uses, and toxicological consequences. *M. alba* seeds, however, have only been the subject of a few investigations. In order to maximise the potential of *M. alba*, it is crucial to include information about the seeds.

There are a lot of unknowns about how *M. alba* leaves and fruit function, as well as their bioavailability and biochemistry in the human body. Furthermore, different *M. alba* cultivars, maturation stages, extraction circumstances, and techniques have each contained a variety of phytochemicals and bioactive components, which have resulted in heterogeneous data. This has made it challenging to evaluate and standardise their operations. In order to further understand the impact of *M. alba* leaves and fruit on human health in vivo, including their bioavailability and biological effects against enzymes, pH, and particularly gut microbiota, more suggestive scale trials with well-designed and uniform parameters will provide a significant input in obtaining homogenous data. Additionally, it has been demonstrated that using microencapsulation techniques can considerably improve the stability of *M. alba* polyphenols and protect them from destruction by heat. This outcome could provide a solid scientific foundation for additional research into their use in heat-processed products and improved industrial processing performance, hence broadening the use of *M. alba* in different food products. However, integration into the industry necessitates scaling up from the laboratory size to the pilot plant, and then to the industrial plant, to develop a bigger production scale in order to guarantee that demand can be satisfied.

Unfortunately, there are still very few research on the pilot scale-up process for *M. alba* leaves and fruit. This may be a result of how challenging it is to scale up bioprocessing. Deliberate time, efforts, experiences, in-depth research, and significant financial resources are needed. Unwanted energy and financial losses to a corporation would result from improper scale-up variables, practices, and characteristics that would significantly affect product values, qualities, and volumes.

In conclusion, *M. alba* is suited for use as a functional food ingredient and does certainly have advantageous biological qualities. However, there hasn't been much research done on how to use *M. alba's* functioning and qualities in the industrial field.

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