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Review Article

Applications of Mulberry Leaves: An Overview

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AA presented the concept, designed the experiments and wrote the manuscript. HMT and Azizullah supervised the study, and reviewed and edited the manuscript. SA did formal analysis and investigation. MFB contributed reagents. MS and MFB analysed and interpreted data. MS and AHG performed experiments.

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Abstract | Mulberry plants belonging to the *Morus* genus are widely planted across Asia. Almost all parts of these economically and medically important plants including fruits, root bark, stem and leaves are of equal importance in terms of uses but their leaves are the most excessively used part. Traditionally leaves have been used in different folk remedies, dietary supplements and herbal medicine. Commercially these are used in sericulture to feed silkworms. Leaves are also used in Indian spices, poultry feed and to feed herbivores. Moreover, mulberry leaves are rich in medicinal potentials and found effective against many infections and diseases. Extract of mulberry leaves can be prepared in various solvents and contain different bioactive substances including flavonoids, phenols and alkaloids. Mulberry leaves extracts have also shown significant pharmacological activities including anti-inflammatory, antioxidant, antibacterial, anticancer, anti-diabetic and antidepressant activities. Further studies should explore the mulberry leaves potentials as these plants have got the attention of both the pharmacological and commercial industries.

Novelty Statement | The mulberry leaves possess various therapeutic potentials. In this study, we have summarized all the therapeutic potentials of different mulberry leaves extracts. Moreover, the important phytochemicals of mulberry leaves and their biological activities are also discussed in details.

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Introduction

Moraceae is an ecologically important flowering plant family consisting of 60 genera and 1500 species (De Sousa *et al*., 2016; Elish *et al*., 2023). Furthermore, it is one of the most abundant plant families (García-Cox *et al*., 2023). Plants belonging to this family are distributed across a vast range of evergreen forests in tropical regions (De Sousa *et al*., 2016). Genus *Morus* of this family has 24 species with at a minimum 100 known varieties (Negro *et al*., 2019; Rodrigues *et al*., 2019). Plants of this genus grow under cultivation and also in the wild in different areas particularly in Asia, Southern Europe, America and several areas of Africa (Ionica *et al*., 2017). Mulberry plants belong to this particular genus and are distributed in different climatic conditions across the globe, ranging

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from temperate to tropical areas (Yuan *et al*., 2015; Pel *et al*., 2017). The origin of most mulberry species can be traced back to China, Japan and the Himalayan foothills (Mallick and Sengupta, 2022). China and India have the largest reserves of mulberry plants, spreading over 626,000 ha and 280,000 ha, respectively (Mohan *et al*., 2020). The white mulberry (*Morus alba*) and black mulberry (*Morus nigra*) are the most common species of this genus.

Mulberry plants are monoecious or dioecious and shrubs or average sized trees with cylindrical stem that can be 10-12 m high. On the other hand root of these plants is astringent, while bark is brown and rough (Mall, 2017). These plants contain a milky sap and bear the fruit for which they are named. Fruit color is a prominent trait to identify different species but fruits are not available throughout the year that causes considerable confusion. However, species can be easily distinguished by comparing their leaf morphology (Erarslan *et al*., 2021). Leaves of different mulberry species also differ in size, shape, color, length, lobe structure, margins, apex, base and basal nerves (Bagachi *et al*., 2013). The flowers are greenish; while the male and female spikes or sexes are on different branches or trees (Kirtikar and Basu, 1975). These plants can easily grow in different soil types but loamy to clayey loamy soil with 6.2-6.8 pH and at least 50 cm depth are best for its growth (Tuigong *et al*., 2015). The optimum temperature and atmospheric humidity required for the growth is 24 to 29°C and 65 to 80%, respectively (Munir *et al*., 2018).

Traditional uses

Mulberry leaves are traditionally used for diverse purposes (Arfan *et al*., 2012). Mulberry leaves having better quality proteins are mixed in wheat flour; this mixture has storage stability of 2 months and used to prepare parathas in certain areas of India (Srivastava *et al*., 2003). In Japan and Korea, mulberry leaves are dried and then used in making tea, infusions and juices (Buhroo *et al*., 2018; Sarkhel *et al*., 2022). Leaves of mulberry plant are utilized as a supplement in a variety of diets with low protein content. Mulberry plant is being used as indigenous system of medicine by tribals of many countries to treat various ailments (Devi *et al*., 2013; Bagachi *et al*., 2013). Various parts of these plant such as leaves, fruits and root bark are used to treat different diseases in folk remedies (Chan *et al*., 2016). In China, mulberry leaves have long been used to protect the liver, treat fevers, improve eyesight, regulate dendritic cell maturation and strengthen joints (Xue *et al*., 2015; He *et al*., 2018). In toothache mulberry is chewed so that further capitation and destruction of the tooth can be avoided (Gunjal *et al*., 2015).

Commercial uses

Mulberry leaves are used commercially in sericulture, since the silk producing insects (*Bombyx mori*) feed on leaves of mulberry plant at their caterpillar stage (Samami *et al*., 2019). Silkworms eat mulberry leaves to make cocoons, which is used to obtain silk fibers, and the leaf protein content is correlated with the cocoon production (Urbanek *et al*., 2022; John *et al*., 2023). Different amino acids (valine, threonine, methionine, phenylalanine, leucine, lysine, arginine and histidine) present in these leaves are essential for silkworm growth (Borah and Praban, 2020). This growth of silkworms and silk quality depends upon the mulberry leaves quality, which is closely related to cultivation practice and environmental conditions (Kumar *et al*., 2014). In China, about 15–18 kg of mulberry leaves are required for production of 1 kg cocoons at farm level.

Pakistan, a sub-tropical country having diverse environmental conditions is ideal to grow mulberry and silkworm even by local farmers at small scales (Masiga *et al*., 2022). Sericulture is more popular in countries with abundant labor and is more profitable as compared to other cash crops (Tuigong *et al*., 2015; Sharma and Kapoor, 2020). That is why sericulture was first introduced in Taxila now transferred to different forest localities with large mulberry plantations such as Daphor, Chichawatni, Changa-Manga, Khanewal, Kamalia, Bhagat, Jauharabad and Kundian in Punjab, Pakistan (Hyder, 2017). About 9000 households in Punjab are linked with this profession. In Pakistan almost 18660 acres of land have mulberry tree plantation and about 1053 acres of land have bush type plantation but overall annual production of silk is almost 300 to 400 metric tons, so an equal amount of silk imported every year to fulfill the needs (Ahmad and Shami, 1999; Mubin *et al*., 2013; Hyder, 2017).

Leaves are used to feed different herbivorous animals as these are highly nutritious and palatable (Sánchez-Salcedo *et al*., 2017). Mulberry leaves are rich source of vitamin supplements, so can be mixed in the poultry diets to improve egg production (Tuigong *et al*., 2015). These are also used in preparation of different unique spices as well as in various Indian recipes (Srivastava *et al*., 2006). In Korea, mulberry leaves powder is also used as an ingredient in ice-cream (Polumackanycz *et al*., 2021). Production of jam, jelly, marmalade, paste, ice cream, frozen desserts, pulp, juice and wine are the important purposes for cultivation of the mulberry plants worldwide (Keskin *et al*., 2022; Salih *et al*., 2022). Furthermore, mulberry plants have become an integral part of the landscaping in different countries (Rohela *et al*., 2020).

Medicinal uses

Mulberry plants have a rich history in medicinal uses as most of its parts are still being used in various medications (Kadam *et al*., 2019). *M. alba* is used in the indigenous system of medicine to treat diseases like cough, asthma, insomnia, edema, bronchitis, diabetes, wound healing, eye infections, influenza and nosebleeds. It increases humoral immunity and as well as cell mediated immunity (Bharani *et al*., 2010; Lee *et al*., 2011). Its leaves have some potential clinical application and contain important bioactive constituents (Li *et al*., 2021; Aurade *et al*., 2023). *M. nigra* exhibited diverse array of pharmacological and biological effects including protective activities on different human organs and organ systems against oxidative damage (Lim and Choi, 2019). It is used for the treatment of different infections such as inflammatory disorders. It has also been used in various folk medicines due to diuretic, analgesic, anxiolytic, sedative and hypotensive properties (Kumar and Sing, 2020; Wei and Hsieh, 2023).

Mulberry leaves are used extensively and have the potential to perform different physiological functions including anti-hyperlipidemic, anti-inflammatory and antiviral; decreasing blood glucose, blood pressure and cholesterol; keeping excretory and digestive system healthy; resisting and preventing cancer as well as improve overall immune abilities (Ge *et al*., 2018; Jan *et al*., 2021; Ma *et al*., 2022). Other important medicinal properties of mulberry leaves include anti-obesity (Chang *et al*., 2016; Kim *et al*., 2017), neuroprotective (Sharma *et al*., 2020), antioxidant (Zhang *et al*., 2018; Ma *et al*., 2022), antimicrobial (Maqsood *et al*., 2022) and anti-hyperglycemic properties (Zhang *et al*., 2022). Mulberry leaves show anti-hyperglycemic effects as a single dose of these can suppress the high levels of glucose in body (Chan *et al*., 2016; Sheng *et al*., 2017). On the other hand, long term treatment with these leaves has potentials to normalize the insulin indexes of diabetic animals as well as glycated haemoglobin, fasting plasma glucose and fructosamine levels (Wilson and Islam, 2015; Thaipitakwong *et al*., 2018).

Mulberry leaves extracts have the ability to modify the expressions of specific genes in hepatic cells with their proteins that are responsible for glucose homeostasis (Liu *et al*., 2016). Mulberry extracts have also the ability to promote activities of different enzymes such as, phosphofructokinase, pyruvate kinase and glycolysis enzymes (glucokinase) depending upon their dose (Rodrigues *et al*., 2019). Furthermore, these extracts have the ability to activate signaling pathways of glycogen synthase kinase-3β and phosphatidylinositol-3-kinase as well as to elevate the transposing of glucose transporter-4 in adipose tissues and skeletal muscles (Kim *et al*., 2011; Liu *et al*., 2015).

Mulberry leaves have the potential to suppress body weight gain as they suppress the body fat mass and weight of visceral adipose tissues (Chang *et al*., 2016). These leaves can significantly decrease the adipocytes number as well as the size and number of lipid drops in different cells (Yang *et al*., 2014). After a long term ingestion of these leaves, there is a gradual increase of circulating cytokine called adiponectin (Tond *et al*., 2016). These cause decline in expression of important lipogenic enzymes including acetyl-coenzyme A carboxylase (ACC) and fatty acid synthase (Chang *et al*., 2016). Moreover, these leaves cause reductions in total cholesterol, triglycerides and low-density lipoprotein-cholesterol (Mahboubi, 2019; Khater *et al*., 2022). Increase in the size and number of lipid droplets in liver cells has been attenuated by the leaves of mulberry plants (Ann *et al*., 2015; Chang *et al*., 2016).

Ingestion of mulberry leaves have the potential to normalize heart rate, diastolic and systolic blood pressures as well as arterial pressure (Nade *et al*., 2013). The reduced heart rate and hypertension is due to the inhibition of angiotensin converting enzyme (Yang *et al*., 2012). Mulberry leaves can also block calcium channels, decreasing the vascular contraction (Nade *et al*., 2013). These leaves are also helpful in preserving cardiac structure and function by decreasing myocarditis and areas of myonecrosis (Thaipitakwong *et al*., 2018). In myosin induced myocarditis these leaves preserve the structure of myocardial tissues by decreasing the infiltration of fibrous tissues and inflammatory cytokines so the cardiac function is preserved by reversing the diastolic and systolic dysfunction of myocardium (Arumugam *et al*., 2012).

Mulberry leaves also possess anti-atherosclerosis activities and inhibit the transfer of LDL through atrial wall and LDL oxidative modifications during the foam cell formation procedure (Yang *et al*., 2011). In addition to decreased serum cholesterol level and improved liver functioning the volume of atherosclerotic plaque has also been significantly reduced with the persistent administration of mulberry leaves extract (Chan *et al*., 2013). Extracts of mulberry leaves have the potential to inhibit the ability of vascular smooth muscle cell lines to migrate and proliferate (Thaipitakwong *et al*., 2018; Kadam *et al*., 2019). Furthermore, treatment with mulberry leaves restores the normal level of different circulating markers of endothelial impairment such as soluble vascular cell adhesion molecule-1 (sVCAM-1), nitric oxide and fibrinogen (Sharma *et al*., 2010).

Leaves of mulberry plant exhibit activities against oxidative stress and free radical formation induced tissue damages (Iqbal *et al*., 2012). These leaves have also shown inhibitory effects on peroxidation of lipids, suppressing the malondialdehyde (lipid peroxidation end product) formation (Thaipitakwong *et al*., 2018). Furthermore, the extracts of these leaves also promote different enzymes activities including glutathione peroxidase, reductase and *S*-transferase as well as superoxide dismutase, which are involved in the anti-oxidative defense system (Andallu and Varadacharyulu, 2003). Additionally, these extracts also have the capacity of donating electron to reduce Fe^{3+} to Fe^{2+} (Iqbal *et al*., 2012).

Mulberry leaves have potentials to suppress the inflammatory processes in a dose dependent response by down regulating the NF-κB transcription factor, that is an

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active mediator in inflammation induced by macrophage activation (Park *et al.*, 2013). Leaves extracts of mulberry significantly reduce TNF-α induced adhesion of monocytes with endothelial cell (Chao *et al.*, 2013). Anti-inflammatory activity of these leaves are due to the decreases in pro-inflammatory cytokines such as IL-6 and interleukin (IL)-1β as well as due to decrease in concentration of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS) and tumour necrosis factor-alpha (TNF-α) (Park *et al.*, 2013).

Herbal extracts

The herbal tea or extract of mulberry leaves (Tables 1 and 2) has traditionally been used as a medicine to treat various diseases. Drinking mulberry tea is gaining popularity in East and Southeast Asia as it contains 10 times more γ-aminobutyric acid (3-4.5 $mg.g^{-1}$ dry weight) than that of green tea (Yang *et al.*, 2012). Typically, different solvents such as water, acetone, ether and alcohols are used for extraction of biologically active compounds from mulberry leaves (Wen *et al.*, 2019). These extracts have shown effective biological results against rheumatic arthritis and diabetes (Park *et al.*, 2013). Moreover, these extracts have also shown good results against cancer, atherosclerosis and neurodegenerative diseases (Lim and Choi, 2019).

Table 1: Biological potentials of *Morus alba* leaves extracts.

S.	Product	Activity	Reference
1	Chloroform, petroleum ether and methanol extracts	Anti-microbial activity	(Aditya *et al.*, 2012)
2	Leaves extract	Blood glucose levels reduction and β cells regeneration	(Mohammadi and Naik, 2012)
3	Crude methanolic extract	Acetylcholine esterase inhibition	(Priya, 2012)
4	Ethanol extracts	Antioxidant and anticancer properties	(Chon *et al.*, 2009; Shahid *et al.*, 2012)
5	Aqueous extract or green tea	Stimulates the innate immune system	(Venkatachalam *et al.*, 2009)
6	Leaves extract	Production of cytokines, nitric acid and prostaglandin E2 in macrophages	(Ouyang *et al.*, 2005)
7	Flavonoid fraction of extracts	Protect kidneys from nephrotoxicants	(Nematbakhsh *et al.*, 2013)
8	Crude hydroalcoholic extract	Liver protection by decreasing the serum levels of ALT and AST	(Kalantari *et al.*, 2009)
9	Methanolic extract	Inhibition of tyrosinase activity and melanin synthesis as a skin whitening agent	(Lee *et al.*, 2002)
10	Methanolic extract	Treatment of Alzheimer's disease	(Niidome *et al.*, 2007)
11	Aqueous extract or green tea	Antidepressant without an anxiolytic-like effect	(Sattayasai *et al.*, 2008)
12	Butanolic extract	Atherosclerosis prevention and inhibition of LDL oxidative modification	(Katsube *et al.*, 2006)
12	Methanolic extract	Decreased the mutability level and ageing in the plants and animals cells	(Agabeyli, 2012)

LDL, low density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 2: Biological potentials of *Morus nigra* leaves extract.

S.	Product	Activity	References
1	Ethanolic extract	Antibacterial, anti-inflammatory and antioxidant activities	(Souza *et al.*, 2018)
2	Topical application of leaves	Accelerated skin wound contraction	(Zhou *et al.*, 2019)
3	Leaves	Anti-diabetic and contain a potent α-glycosidase inhibitor (deoxynojirimycin)	(Padilha *et al.*, 2010)
4	Dichloromethane extract	Antinociceptive, antidepressant and neuroprotective effects	(de Mesquita Padilha *et al.*, 2009; Dalmagro *et al.*, 2017)
5	Aqueous extract	Reduction of internal anomalies in offspring of a diabetic mother	(Volpato *et al.*, 2011)
6	Leaf extract	Inhibition of tyrosinase as a potential whitening agent	(De Freitas *et al.*, 2016)
7	Leaf extract	Hepatoprotective effect against hepatotoxicity induced by anti-rheumatic drug, MTX and paracetamol	(Qadir, *et al.*, 2014; Tag, 2015)
8	Homogenized and digested leaves	Biomonitor of air pollution in industrial and high traffic areas	(Daud *et al.*, 2011)
9	*n*-hexane and aqueous methanol extract	Anti-cancer activity against HeLa cells	(Qadir, Muhammad Imran *et al.*, 2014)

MTX, methotrexate; HeLa, Cervical cancer cells.

Table 3: Leaves constituents.

Constituent	Morus alba	Morus nigra	References
Nitrogen	2.3-3.1 g/100g	2.1-2.9 g/100g	(Sánchez-Salcedo *et al.*, 2017)
Moisture	51.3-66.9%	51.1-59.7%	
Crude Fiber	3.6-7.1 g/100g (dw)	5.1-8.4 g/100g (dw)	
Proteins	14.1-19.4%	13.4-18.7%	
Crude protein	8.01-25.72%	20.15-29.94%	(Koyuncu *et al.*, 2014)
Crude fat	1.01%	-	(Dhiman *et al.*, 2020)
Organic matter	90%	71.80%	
Hemicellulose	10.02%	-	
Dry matter	46.27%	42.20%	(Guven, 2012)
Ash	15.40%	17.50%	
Neutral detergent fiber	19.38%	22.08%	
Acid detergent fiber	17.33%	19.46%	
Total phenols	14.87-17.55 mg GAE/g (dw)	22.23-26.51 mg GAE/g (dw)	(Shahid *et al.*, 2012)
Total flavonoids	25.27-27.55 mg RE/g (dw)	-	
ABTS	5.59-6.65 mM TE/g (dw)	9.02-10.76 mM TE/g (dw)	
Carbohydrates	2.5-3.7 g/100 g (fw)	3-4.4 g/100 g (fw)	(Dimitrova *et al.*, 2015)
DPPH	3.9 mM TE/g (fw)	10.9 mM TE/g (fw)	
FRAP	4.5 mM TE/g (fw)	6 mM TE/g (fw)	

Dw, dry weight; Fw, fresh weight; -, data not available; ABTS, 2, 2′-azino-bis-(3-ethylbenzthiazoline-6-sulphonic acid; DPPH, 2, 2-diphenyl-1-picrylhydrazyl; FRAP, ferric reducing antioxidant power; RE, rutin equivalent; TEAC, Trolox equivalent antioxidant capacity.

Phytochemicals

Mulberry leaves have several bioactive compounds (Table 3) that are responsible for their pharmacological effects. These leaves are rich source of organic acids, macronutrients and micronutrients (Thaipitakwong *et al.*, 2018). Phytochemicals responsible for the bioactivities of mulberry leaves includes flavonols, glycosides, phenolic acids, alkaloids, chalcones, γ-aminobutyric acid, coumarins, prenylated stilbenes, iminosugars and aryl benzofuran derivatives (Gryn-Rynko *et al.*, 2016; Sugiyama *et al.*, 2016; D'urso *et al.*, 2019). Various other ingredients such as polysaccharides, volatile oil, plant sterols and proteins are also reported in the mulberry leaves (Wani *et al.*, 2023). There are also some mineral constituents, vitamins, food fibers and amino acid present in these leaves (Sarkhel *et al.*, 2020).

Phenols

Among different bioactive chemicals of mulberry leaves, the polyphenols are unique and well known for showing multi-directional activities (Gryn-Rynko *et al.*, 2016). Most of the phenolic constituents in the leaves of mulberry plant include gallic acid, caffiec acid, protocatechuic acid, gallate as well as other phenolic derivatives such as catechin, epicatechin, gallocatechin, rutin and quercetin are bioactive and possess antioxidant properties (Radojkovića *et al.*, 2012; Panyatip *et al.*, 2022). Mulberry leaves extract rich in polyphenol like hydroxyflavin and caffeic acid has ability to limit the lipogenesis by regulating the fatty acid synthase, glycerol-3-phosphate acyltransferase and sterol regulatory element-binding proteins (Ann *et al.*, 2015; Sun *et al.*, 2015).

It has been considered that phenolic compounds of mulberry leaves are responsible for its anti-obesity effects (Sheng *et al.*, 2019). Other phenolic acids present in mulberry leaves are vanillic, gentisic, chlorogenic, *p*-hydroxybenzoic, syringic, ferulic, *m*-coumaric and *p*-coumaric acids (Thabti *et al.*, 2012). Resveratrol has got much attention due to its potential cardioprotective and neuroprotectant activities (Mir *et al.*, 2022; Duta-Bratu *et al.*, 2023). Oxyresveratrol is also being used in cosmetic and medical materials against hyperpigmentation as it inhibits tyrosinase and limits the biosynthesis of melanin (Khan *et al.*, 2019; Hong *et al.*, 2021).

Alkaloids

Alkaloids are major constituents in mulberry leaves that possess potent glycosidase inhibitory activities (He and Lu, 2013; Wang *et al.*, 2017). Alkaloids present in mulberry includes DNJ, *N*-methyl-DNJ and fagomine, while their amounts depends on the source species (Ramya *et al.*, 2022). Other polyhydroxy alkaloids present in mulberry are methylpyrrolidine carboxylic acid, *cis*- and *trans*-5-Hydroxypipecolic acids as well as pipecolic acid (Rodríguez-Sánchez *et al.*, 2011). Although, there are different iminosugar alkaloids or polyhydroxy alkaloids with inhibitory effects on the glucosidase enzymes; 1-deoxynojirimycin (DNJ) and fagomine are most prominent and glucosidase inhibitory activities are attributed to them (Parida *et al*., 2023).

DNJ, a major polyhydroxylated alkaloids of mulberry leaves (1.389–3.483 $mg.g^{-1}$) that accounts for almost 50% of the mulberry alkaloids (Liu *et al*., 2020; Yang *et al*., 2021). DNJ is a potential antihyperglycaemic compound in mulberry leaves as it inhibits glucosidase, suppress abnormally high level of blood glucose and prevent diabetes mellitus (Ramappa *et al*., 2020; Tang *et al*., 2023). Furthermore, glucose and DNJ are similar in structures that is why DNJ blocks the main active sites of glucose degrading enzymes; so inhibits the carbohydrates digestion and absorption (Momeni *et al*., 2021; Mohamed *et al*., 2023). DNJ is known as a cofactor and help in controlling postprandial blood glucose; also helps in degrading the oligosaccharides and starch to monosaccharides before their absorption (Liu *et al*., 2015). DNJ exhibits anti-microbial, cardioprotective, anti-obesity and anti-cancer properties (Ramappa *et al*., 2020).

Flavonoids

Present abundantly in plant kingdom the flavonoids are important component of the human diet due to their diverse nutritional effects (Zhang *et al*., 2019). Flavonoids in mulberry leaves are mixtures containing various compounds such as epicatechin, isolicorices and astragalin (kaempferol 3-β-d-glucopyranoside) as well as different flavonoid glycosides (Eruygur and Dural, 2019; Hassan *et al*., 2020). It has been suggested that most of the flavonoid pharmacological effects are linked with their antioxidant activities (Ma *et al*., 2022; Zheng *et al*., 2022). Flavonoids possess different potential activities including anti-inflammatory, antithrombotic, antiviral, hepatoprotective, antiallergic and anticarcinogenic as well as they inhibit the oxidative and hydrolytic enzymes including phospholipase A_2, lipoxygenase and cyclooxygenase (Khanpara and Sojitra, 2022; Samrot *et al*., 2022). Mulberry leaves flavonoid also reduces the serum lipid levels in hyperlipidemic conditions (Mahboubi, 2019; Zhang *et al*., 2022). Moreover, these phytochemicals have ability to modulate lipid peroxidation in conditions like thrombosis, atherogenesis and carcinogenesis (Panche *et al*., 2016; Hao *et al*., 2022). Flavonoids from mulberry leaves have shown anti-fatigue activities (Cui *et al*., 2019; Sarkhel and Manvi, 2021).

Glycosides

In mulberry leaves, five major flavonol glycosides have been reported including rutin, astragalin, quercetin 3-(6-acetylglucoside), isoquercitrin and kaempferol 3-(6-acetylglucoside) (El-Sayyad *et al*., 2015; Hassan *et al*., 2020). First three of these specially rutin and quercetin 3-(6-acetylglucoside) has been identified as the major low-density lipoprotein antioxidant compounds (El-Sayyad *et al*., 2015). Furthermore, three novel glycosides have been identified including quercetin 3-*O*-β-glucoside-7-*O*-α-rhamnoside, kaempferol-7-*O*-glucoside and quercetin 3-*O*-rhamnoside-7-*O*-glucoside (Chen *et al*., 2021). Different quercetin derivatives present in mulberry leaves have shown to be effective for reducing obesity, improving lipid and glucose metabolism, enhancing β-oxidation and reducing oxidative stress (Sun *et al*., 2015). Another abundant constituent of mulberry leaves called quercetin 3- (6- malonylglucoside) has shown antiatherogenic activity (Sun *et al*., 2015). Moreover, the dietary consumption of this abundant flavonol glycoside has improved hyperglycemia in mice by promoting the expression of glycolysis related genes as well as has reduced the oxidative stress of liver by decreasing the concentrations of reactive substances such as thiobarbituric acid (Katsube *et al*., 2010).

Astragalin and quercetin have shown anti-inflammatory activities by inhibiting the expression of different inflammatory as well as have prevented both oxidative damages and cell death (Lesjak *et al*., 2018; Hu *et al*., 2022). Rutin possesses antioxidant, anti-inflammatory, hexokinase and cytoprotective activities preventing against oxidative cell destruction; also responsible for restoring the glycogen contents by increasing insulin levels and decreasing plasma glucose (Ugusman *et al*., 2014; Fideles *et al*., 2020; Arowoogun *et al*., 2021). Isoquercetin has potentials to regulate blood glucose levels, improve pancreatic islets function, and protect against lipid peroxidation (Gryn-Rynko *et al*., 2016).

Anthocyanins

Anthocyanins are natural compounds present in plants and these are responsible for the color of flower, fruits and leaves. In plants about twenty anthocyanins has been identified, but only six of these can be utilized as food additives (Hu *et al*., 2017). Anthocyanins have got attention as they possess diverse health potentials such as anti-inflammatory and antioxidant (Hu *et al*., 2017). Different anthocyanins have been identified and evaluated in mulberry (Przygoński and Wojtowicz, 2019; Smailagić *et al*., 2019). Mulberry anthocyanins have significant ability to inhibit lipid oxidation and migration of B16–F1 cells, showing antimetastasis activity (Lee *et al*., 2019). These have potentials to reduce the susceptibility to cancers and other cardiovascular diseases, showing chemoprotective activities (Samtiya *et al*., 2021). Both cyanidin 3-glucoside and cyanidin 3-rutinoside effectively inhibit the invasion and migration of metastatic cells in lung cancer, without inducing cytotoxic effects (Ku *et al*., 2015; Chen *et al*., 2021; Alsharairi, 2022).

Proteins

Mulberry leaves are rich source of proteins and dry mulberry leaves contain 17–25% proteins (Zhang *et al*., 2014; Sun *et al*., 2015). Mulberry leaf proteins and their hydrolysates have shown potential antioxidant and chelating activities (Sun *et al*., 2015, 2017). Different new peptides have been isolated from mulberry leaves with have higher antioxidant activities as compared to other synthetic peptides (Sun *et al*., 2019). Mulberry leaf proteins consist mostly of four fractions that are albumin, prolamin, globulin and glutelin; while maintain a balance of essential amino acids (Zhang *et al*., 2014). Glutelin and albumin are the dominant fractions and consist of higher amino acids content (300 $g.kg^{-1}$) (Sun *et al*., 2017). Albumin with much higher antioxidant or radical scavenging activity should be utilized as a potential food (Sun *et al*., 2017). Mulberry leaves also contain diverse array of amino acids including glutamine, valine, lysine, leucine glycine (Butt *et al*., 2008).

Carbohydrates

Mulberry leave polysaccharides, as the active constituents of mulberry leaves have attracted much attention as compared to other plant polysaccharides because of their diverse biological activities for example anti-tumor, anti-diabetic, anti-inflammatory and immunostimulatory activities (Yang *et al*., 2008; Li *et al*., 2010; Zhang *et al*., 2010, 2014). These polysaccharides also possess antihyperlipidemic and antihyperglycaemic potentials (Wang and Li, 2005). Mulberry leave polysaccharide is mostly comprised of Galacturonic Acid, Arabinose, Rhamnose, Glucose, Xylose and Galactose; while monosaccharides mostly consist of Mannose, Rhamnose, Glucuronic acid, Galactose, Glucose and Arabinose (Katayama *et al*., 2008; Xia *et al*., 2008).

GABA (γ-aminobutyric acid)

GABA is a widely distributed amino acid across different animals and plants such as mulberry leaves (Chen *et al*., 2016). It exhibits diverse pharmacological activities including anti-cancer, anti-inflammatory, antioxidant, anti-anxiety, pain reduction, anti-hypertensive, multiple biological neuroprotective and sleep improvement (Jin *et al*., 2022). GABA present in mulberry leaves has more anti-fatigue effect than that of taurine (Chen *et al*., 2016). The antihypertensive potentials of mulberry leaves could be due to presence of GABA in their extracts (Yang *et al*., 2012).

Terpenoids

Terpenoids present in mulberry are responsible for defense of mulberry plant as these specific chemicals protect it from insects and bacteria; these are also responsible for different physiological activities, making these chemicals suitable to be used against different human diseases (Zhang *et al*., 2020). Terpenoids are also used in different products such as insecticides, perfumes and pharmaceutical compounds (Tholl, 2015). The mulberry leaves contain monoterpens as well as triterpenes such as betulinic acid and betulin (Gryn-Rynko *et al*., 2016). Titerpenoids are secondary metabolites of plants with diverse and important physiological and pharmaceutical activities including antidiabetic, antinociceptive, antioxidant and anti-HIV (Özdemir and Wimmer, 2022). Triterpenes not only have anti-inflammatory, anti-viral and atherosclerotic activity but are also effective against diabetes mellitus; therefore, is a potential candidate for developing new diverse bioactive drugs (Nazaruk and Borzym-Kluczyk, 2015). Another terpenoid called ursolic acid with anticancer and antibacterial properties, is isolated from mulberry plant (Chen *et al*., 2018).

Conclusions and Recommendations

Mulberry plant possesses diverse array of phytochemicals and is being used extensively in Asia for a variety of purposes like food and medicine. The phytochemicals discussed in this review does not account for all the biologically active compounds present in the mulberry plant. Much of the biological activities performed by the mulberry leaves as well as their constituents are discussed in this article. The significant potentials in mulberry leaves as food, medicine and commercial commodity are increasingly being discovered. Extraction of natural products from mulberry leaves should be considered seriously in future studies to develop better ways for the extraction of various constituents. This could lead to unfolding of new potentials in mulberry leaves.

Conflict of interest

The authors have declared no conflict of interest.

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