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Nutrition importance and health benefits of mulberry leaf extract: A review

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Abstract
Mulberry (*Morus*) belongs to the *Moraceae* plant family, native of China. The leaves of mulberry plant are the major food source for the silkworm. The leaf consists of minerals, vitamins, dietary fibre, amino acids, phytosterols, flavonoids and other functional components, mainly 1-DNJ (1-Deoxynojirimycin) which acts as an anti-diabetic drug. In countries like China, Korea and Japan the preparations from mulberry leaves are used as medicine for increasing the immunity of the human body, cough relief and to lower the blood sugar and blood pressure. The high nutritional value of leaves is used as a functional food, mostly in the form of herbal tea, smoothie, yoghurt, salads, nutritional masala biscuits, capsules, dry powder, oil, dietary supplement *etc.* This manuscript mainly focuses on the nutritional importance and health benefits of mulberry leaves extract. The leaves extract may help to lower blood sugar (diabetes), inflammation levels, cholesterol and fighting against heart disease.

Keywords: Antidiabetic, heart disease, herbal tea, nutritional value, silkworm

1. Introduction
The word "Mul" in mulberry came from a Latin "mor-us" which means oddly enough. Ecologically the leaves of mulberry plant are the sole food source of silkworm, *Bombyx mori* L. Apart from its luscious and a mouth-watering fruit, the leaf is intensively used in food, pharmaceutical and also in cosmetics industries (Rohela *et al*. 2020) [52]. The mulberry leaf (*Morus alba* L.) is used as a silkworm food, animal feed and medicine particularly in eastern countries. For example, the active compounds in mulberry leaves are used to treat fever and to protect the liver in Chinese diagnosis (Zhishen *et al*. 1999) [67]. In Japan and Korea, mulberry leaves of a particular species are consumed as anti-hyperglycaemic nutraceutical foods for diabetes mellitus patients (Kim *et al*. 2003) [29]. Dates back to almost 659 AD the utilization of mulberry leaves in the medical field was introduced by the Chinese. Mulberry leaves were illustrated as fruitful for mitigating coughs and also high blood pressure. When the leaves are dried under the sun and brewed, the emanated tea is known as "The immortal mountain wizard tea" (Radhakrishna 2013) [51].

1.1. Mulberry varieties
The native red mulberry (*Morus rubra*), the east Asian white mulberry (*Morus Alba*) and the south western Asian black mulberry (*Morus Nigra*) are the three prime types of mulberry trees (Yigit *et al*. 2010) [63]. In India, the major mulberry cultivation areas are in the tropical (Karnataka, Andhra Pradesh and Tamil Nadu) and sub-tropical (West Bengal, Himachal Pradesh and the North-Eastern) zone and some parts of the temperate region. Perhaps, *Morus indicia* is the most cultivated species of *Morus.* The most cultivated varieties are Kanva-2, S-54, S-36, V-1, DD, S-34, S-13, MR-2, S-1, Goshoerami, G-4 *etc*. These varieties are generally across the South Indian states, Eastern, North East region as well as Jammu & Kashmir both under Irrigated and Rain-fed condition (Datta 2000) [10]. In China, major cultivated varieties of mulberry are Tong Xiang Qing, Hong Cang Sang, Hu Sang 197, Hu Sang 199, Nong Sang 8, Yu 2, Xiao Guan Sang, Da Hua Sang, Hei You Sang, *etc*. Mostly cultivated across the North, North West, Yellow river and Yangtze river regions (Huo 2000) [22].

1.2. Production, Utilization and Export of mulberry in India
Bhat *et al*. (2019) [4] reported that the traditional states like Karnataka, Andhra Pradesh and West Bengal are the major shareholders for the production of the mulberry in India. During the silkworm rearing period the mulberry is utilised as a fodder, fertilizer and fuel. The left over branches and leaves are used as a fuel wood.

Generally, from 10000 square metre of mulberry garden yields 12100 kilogram of mulberry sticks and generated around 116440.72 kilojoule of energy. In central and north-east India, the mulberry fruits and woods are used for juice, jam, liquor preparation and furniture making. Sometimes, *M. serrata* species of mulberry plants are used for manufacturing of agricultural implements, carving and sports goods (Datta 2000) [10]. Mote *et al*. (2014) [39] reported that the raw silk production in India is around 14.91per cent of the global production. During 1998-99 to year 2006-07 the export earnings of the raw silk was increased but after that the export earing was decreased.

2. Nutrition importance of mulberry extract

The consumption of mulberry leaf extract (125 and 250 milligram) resulted in significant reduction in blood sugar level (Lown *et al*. 2017) [36]. About 23 people with high cholesterol were treated with 280 milligram of mulberry leaf supplements thrice a day. After 12 weeks, the low-density lipoprotein (bad) cholesterol was dropped by 5.6 per cent, while the high-density lipoprotein (good) cholesterol was increased by 19.7 per cent (Aramwit *et al*. 2011) [1]. Research studies have proven that mulberry leaf extract also combat inflammation and oxidative stress. Additional health benefits of mulberry leaves include anti-carcinogenic effect, reduction of liver inflammation as well as reduction of patches of dark skin were also reported (Naowaratwattana *et al*. 2010; Lim *et al*. 2019 and Freitas *et al*. 2016) [42, 34, 35, 16]. But after the consumption of mulberry leaf tablet, there were some mild side effects in some people were shown by Aramwit *et al*. (2011) [1]. According to the report the side effects were mild diarrhea (26 per cent), dizziness (8.7 per cent), bloating, and constipation (4.3 per cent). Although, Li *et al*. (2018) [31] examined the toxicological profile of mulberry leaves extract and certified it as a safe food for consumption. The nutritional components and their quantity present in mulberry leaves are summarized in Table 1.

Table 1: Nutritional composition of mulberry leaves

Sl. No.	Nutritional Components and phytochemicals	Quantity	Reference
1	Total phenolic (TP)	8.76–20.26 mg gallic acid equivalents (GAE) per g dry weight (dw)	(Yu *et al*. 2018) [65]
2	Total flavonoid content (TF)	21.36–56.41 mg rutin equivalents (RE) per g dry weight (dw)	(Yu *et al*. 2018) [65]
3	Total soluble sugars (TSS)	58.71–150.31 mg per g dry weight (dw)	(Yu *et al*. 2018) [65]
4	1-Deoxynojirimycin (1-DNJ)	0.20-3.88 mg per g	(Ji *et al*. 2016) [24]
5	Total phenols	12.81-15.50 mg gallic acid equivalents (GAE) per g dry weight (dw)	(Sanchez *et al*. 2015) [54]
6	Caffeoylquinic acids	6.78-8.48 mg per g dry weight (dw)	(Sanchez *et al*. 2015) [54]
7	ABTS	10.6-13.15 mg Trolox per g dry weight (dw)	(Sanchez *et al*. 2015) [54]
8	DPPH	10.62-12.64 mg Trolox per g dry weight (dw)	(Sanchez *et al*. 2015) [54]
9	Total soluble carbohydrates	3.1 g per 100 g fresh weight (fw)	(Dimitrova *et al*. 2015) [11]
10	Reducing sugars	1.5 g per 100 g fresh weight (fw)	(Dimitrova *et al*. 2015) [11]
11	Fructose and glucose	0.3 g per 100 g fresh weight (fw)	(Dimitrova *et al*. 2015) [11]
12	Sucrose	1.1 g per 100 g fresh weight (fw)	(Dimitrova *et al*. 2015) [11]
13	Crude proteins	15.31-30.91 per cent	(Butt *et al*. 2008) [6]
14	Crude fat	2.09-7.92 per cent	(Butt *et al*. 2008) [6]
15	Crude fibre	9.9-13.85 per cent	(Butt *et al*. 2008) [6]
16	Neutral dietary fibre	27.6-43.6 per cent	(Butt *et al*. 2008) [6]
17	Total ash	11.3-17.24 per cent	(Butt *et al*. 2008) [6]
18	Ascorbic acid	100-200 mg per 100 g	(Butt *et al*. 2008) [6]
19	Beta-carotene	8.44-13.13 mg per 100 g	(Butt *et al*. 2008) [6]
20	Oxalates	183 mg per 100 g	(Butt *et al*. 2008) [6]
21	Phytates	156 mg per 100 g	(Butt *et al*. 2008) [6]
22	Tannic acid	0.13-0.36 per cent	(Butt *et al*. 2008) [6]
23	Iron (Fe)	19-50 mg per 100 g	(Butt *et al*. 2008) [6]
24	Zinc (Zn)	0.72-3.65 mg per 100 g	(Butt *et al*. 2008) [6]
25	Calcium (Ca)	786.66-2,726.66 mg per 100 g	(Butt *et al*. 2008) [6]
26	Phosphorus (P)	970 mg per 100 g	(Butt *et al*. 2008) [6]
27	Magnesium (Mg)	720 mg per 100 g	(Butt *et al*. 2008) [6]

3. Health benefits of mulberry leaf extract

The ability of mulberry leaf for peak-to-trough fluctuations in blood glucose was significantly observed by Mudra *et al*. (2007) [40]. The results revealed that mulberry leaf extract with 75-gram sucrose significantly reduced the increased blood glucose within 120 minutes. The insulin inhibition ability of fahomine in mulberry leaves is also a strategic purpose of consumption. This can putatively reduce lipid peroxidation. Moreover, there are some thoughtful health problems that can be healed by consumption of mulberry leaf extract.

3.1. Antidiabetic properties of mulberry leaf

The problem in diabetic patients is lack of response or very less production of insulin, which causes “hyperglycemia”, the blood-glucose disease. Naowaboot *et al*. (2009) [41] reported that the mulberry leaves extract consists of anti-hyperglycaemic, antioxidant and anti-glycation activities and can be an excellent beverage for the treatment of “hyperglycemia”. Further, they also experimented with the effect of antihyperglycemic, antioxidant and antiglycation activities of mulberry leaf extract on animal models and

observed a significant positive result against hyperglycemia. Sharma *et al*. (2010) [55] reported the effect of red mulberry leaves extract on rat's health. The 1- Deoxynojirimycin (DNJ) played a key role in the reduction of the blood sugar. It acts as an inhibitor of intestinal α-glucosidases which reduces the blood sugar level (Hansawasdi *et al.* 2006) [18]. Furthermore, Lown *et al*. (2017) [36] studied the improvement of the glucose tolerance level by mulberry leaf extract. Results showed that the extract of mulberry leaf considerably reduced total blood glucose upsurge after ingestion of maltodextrin (Maize starch) over 120 minutes.

The mulberry leave's hybrid 1-Deoxynojirimycin (DNJ) and a polysaccharide aids in modulating the expression of the hepatic gluconeogenic enzymes, glucokinase, glucose 6-phosphatse and phosphoenolpyruvate carboxykinase (Li *et al*. 2011) [32]. The alpha-amylase is a key enzyme which catalyses the initial steps for hydrolysis of starch into smaller oligosaccharides. Usually, the mulberry leaves extract exhibit significant alpha-amylase inhibitory activity as reported by Sudha *et al*. (2011) [58]. In addition, Doi *et al*. (2000) [12] reported that extracts of mulberry leaf were effective in scavenging the DPPH radical and inhibiting the oxidative modification of rabbit and human low-density lipoprotein (LDL). Recently, Bajpai and Rao (2014) [3] pointed that the 1-Deoxynojirimycin (DNJ) in mulberry leaves have active pharmaco-kinetic principles with the potential capability of inhibiting hyperglycemia.

3.2. Anti-oxidative properties of mulberry leaf

The name "antioxidant" indicates the mitigation of oxidation properties in the human body. The presence of different types and the wide range of flavonoids in mulberry leaves gives a good anti-oxidative property. Mulberry leaves contain a huge amount of anti-oxidative properties, *i.e.*, phenolics and flavonoids, which were found to be excellent antioxidants. Studies proved that the fractions of mulberry leaves extract containing the higher values of phenolic and flavonoid compounds exhibited the stronger anti-oxidative property (Iqbal *et al*. 2012 and Flaczyk *et al*. 2013) [23, 15]. The mulberry leaves extract has the highest antioxidant (DPPH and Hydrogen peroxide radical scavenging) properties compared to petiole, ripe fruit, unripe fruit and stem (Lim *et al*. 2019) [34, 35]. It was also reported that higher amount of quercetin in the leaves of mulberry were responsible for the reduction of oxidation process (Enkhmaa *et al*. 2005; Chen *et al*. 2007; Katsube *et al*. 2010 and Iqbal *et al*. 2012) [13, 8, 27, 23]. The ethanolicas and aqueous extract of mulberry leaves, contains oxyresveratrol and 5,7-dihydroxycoumarin 7-methylether. Basically, it helps to scavenge superoxide and have antioxidant potential (Oh *et al*. 2002) [45]. Samuel *et al*. (2016) [53] studied mulberry leaves aqueous extract of four varieties (S-146, AR-14, BR-2 and S-1) and the results had shown highly significant anti-oxidant activity by attenuating both malondialdehyde (50.49 per cent, 36.14 per cent, 41.36 per cent, 37.13 per cent) and superoxide dismutase (54.01per cent, 40.18 per cent, 34.82 per cent, 29.74 per cent) levels in the brain of experimented animals. Iqbal *et al*. (2012) [23] suggested the pre-eminence of *M. Nigra* over the other species of mulberry concerning their disease preventive potential. The existence of phenolics, DPPH radical and ABTS radical cations scavenging potential provides *M. Nigra* an edge over other species. Commonly, the DPPH and ABTS radicals scavenging activity are the two measures for the determination of anti-oxidant properties in mulberry leaves. Yigit *et al*. (2008) [64] also determined DPPH radical scavenging ability and lipid peroxidation inhibition activity of mulberry leaves and expressed that there was a statistically significant correlation between DPPH radical scavenging and total phenolic compounds.

3.3. Cardiovascular diseases

Cardiovascular disease commonly known as CVD is a disease related to heart or blood vessels (Mendis *et al*. 2011) [38]. Kadam *et al*. (2019) [25] reported that the mulberry leaves contain high amount of iron (Fe) and this helps for better distribution of oxygen by boosting the production of red blood cells. Another important flavonoid present in mulberry leaves is resveratrol, which directly helps to remove constriction in blood vessel which significantly reduces the chance of heart failure and also increases the production of nitric oxide, which is a vasodilator. This means that it relaxes blood vessels and reduces chances of blood clot formation and subsequent heart issues like strokes or heart attacks. Doi *et al*. (2000) [12] and Oh *et al*. (2007) [46] reported that the leaf extracts of the mulberry (*Morus Alba* and *Morus bombycis*) shown to reduce hypertension in rodents, decreases serum cholesterol and prevent atherosclerosis. Consequently, Ma *et al*. (2019) [37] also reported that the 1-Deoxynojirimycin (DNJ) in mulberry leaves improved the stable angina pectoris (SAP) of coronary heart disease (CHD) and blood stasis syndrome (BSS) patients by elevating their antioxidant and anti-inflammatory capacities.

3.4. Anticancer effects

Cancer or the abnormal growth of cells in the human body is a curse. The abnormal cell growth has a potential to spread through other parts of our body and can cause death (WHO 2018 and National Cancer Institute 2007) [43]. Although there is no proper treatment for cancer, due to presence of excellent anti-oxidant and other beneficial properties the mulberry leaves can be a great option to mitigate or reduce the probability of cancer. The ethanol extract of mulberry leaf can eliminate neuroblastoma stem cell-like population, which is a key reason behind this deadly disease (Park *et al*. 2012) [49]. Around 10-40 microgram per millilitre of mulberry leaf extract efficiently improved differentiation by elongating neurites, reducing clonogenicity and sphere formation. This was shown by the decreased expression of stem cell markers and increased expression of differentiation markers. Yang *et al*. (2012) [62] reported that the cell proliferation, invasion and metastasis of tumours can be inhibited by polyphenols presence in mulberry leaves. Also, cell death of hepatocellular carcinoma cells can be performed by mulberry leaf polyphenols extract. Another interesting fact is mulberry leaf extract attack the proliferation signal pathway of the inflammatory response of adipocytes in hepato celluar carcinoma (HCC) and able to prevent obesity-mediated liver cancer (Chang *et al*. 2017) [7]. Similarly, Fallah *et al*. (2018) [14] reported that an Iranian mulberry leaves deoxyribonucleic acid (DNA) can be used as an anti-cancer drug. Experimental results showed that mulberry extracted oxidative flavonoids were very effective for increasing the life span of a tumour rat.

3.5. Anti-inflammatory effects

Inflammation is a biological process or responds to remove some harmful or irritating effects in parts of our body or in other way body trying to heal itself. The anti-inflammatory properties are mostly present in barks and roots of mulberry tree, but the leaf contain a very few amounts of this property.

Due to diaphoretic and emollient effects present in mulberry leaf extract it can be helpful for making a decoction that can be used as a gargle and significantly reduced throat inflammation.

Lim *et al*. (2013) [33] studied some anti-inflammatory effect of mulberry leaf extract with a high-fat diet-induced obese mice. After 12 weeks without any liver toxicity this treatment reduced protein levels of oxidative stress markers (manganese superoxide dismutase) and inflammatory markers (inducible nitric oxide synthase) in adipose tissue and liver. Additionally, the mulberry leaves contain inducible nitric oxide synthase (iNOS) inhibitory properties (70 per cent with 10 micro grams per millilitre) which are very effective for inflammation (Hong *et al*. 2002) [20]. Park *et al*. (2013) [50] reported the use of mulberry leaves as an anti-inflammatory agent to inhibit nuclear factor kappa-light-chain-enhancer of activated B cells or NF-kB-mediated inflammatory response, the activities of pro-inflammatory mediators and cytokines can be applied to ameliorate the disease conditions.

3.6. Neurological disorders, skin diseases, gastrointestinal disorders

Alzheimer is a kind of neurological disorder associated with brain-plaque by amyloid beta peptides. Niidome *et al.* (2007) [44] and Khaengkhan *et al*. (2009) [28] reported that mulberry leaves contain kaempferol -3-O-glucoside, and kaempferol -3-O-(6-malonyl) glucoside and its consumption help to avoid peptide formation inside the brain. The methanol extract of leaf has anti-dopaminergic effect which blocks the Dopamine (D_2) receptors (Yadav *et al*. 2008) [61]. Kang *et al*. (2006) [26] showed that the gamma-aminobutyric acid (GABA) present into the extract has ability to provide protection from various free hydroxyl radical and protect the PC_{12} (model for neural differentiation) cells. Shih *et al.* (2010) [56] also mentioned about the role of anti-oxidant in defence and improving the defence system in human body. The oxyresveratrol (tyrosinase inhibitor) present in mulberry leaf extract act as a neuroprotective component (Zhang and Shi 2012) [66] and it is an impending medicine to cure acute ischemic stroke (Horn *et al*. 2003) [21]. Breuer *et al*. (2006) [5] showed that the oxyresveratrol was capable to cross the blood-brain barrier for the direct protection of the brain.

Apart from the consumption as a tea, mulberry leaves extract can also be used as a natural skin care product. The leaf has a great anti-aging effects and beneficial for acne-prone skin or pimples (Cheng 2016) [9]. It reduces inflammation and skin oil secretions. Due to the presence of anti-tyrosinase activity in mulberry leaves, it is very effective for skin lightening and glowing skin (Suisse 2017**)** [58]**.** An enzyme called tyrosinase has an ability to control the production of melanin. Singh *et al*. (2013) [57] examined the effects of mulberry, kiwi, and *Sophora angustifolia* extracts on melanogenesis and melanin transfer in human melanocytes and in cocultures with phototype-matched normal adult epidermal keratinocytes. Mulberry leaf extract gives a light skin tone by suppressing tyrosinase activity.

The diseases related to the gastrointestinal tract are commonly known as gastrointestinal disorders. Mulberry leaves have a very good potential activity to improve digestion. In addition, it contained excessive amount of dietary fibres which helps to bulking of stool for digestion improvement (Kadam *et al*. 2019) [25]. Hogade *et al.* (2010) [19] explained the defensive effect on liver (rats) by inoculating mulberry leaves extract with carbon tetrachloride (induced). Mulberry leaves are also high in mineral content and vitamin C, antioxidants and have no anti-nutritional factors or toxic compounds. Hence, the bio-active components of mulberry leaves are very advantageous for boosting metabolism (Li *et al*. 2019) [30].

3.7. Antimicrobial effects

Antimicrobial means protection from microbial organism. It is very useful for the production of antibiotics. This antibiotic plays a crucial role in protection of human body from harmful microorganism. The saponins, tannins, alkaloids and flavonoids present in mulberry leaf extract shows admirable antimicrobial effects. The microbes like *E. coli, Salmonella Typhimurium, Staphylococcus epidermis, S. aureus, Candida albicans* and *Saccharomyces cerevisiae* can be prevented by the mulberry leaves flavonoid extract (Paiva *et al*. 2010) [48]. The Chalcomoracin which is a leaf phytoalexine of mulberry shows tremendous anti-bacterial activity against *Stapalococcus aureus* (Fukai *et al*. 2005) [17]. Similarly, the ethanolic extract of mulberry leaves shows protection against *Artemia salina* (L.), which cause oral toxicity to mice, was reported by Oliveira *et al*. (2015) [67]. Ayoola *et al*. (2011) [2] worked on the antibacterial activity of ethanol extracts of *M. Alba* leaves and showed that the Gram-negative bacteria such as: *Escherichia coli, Pseudomonas aeruginosa, Neisseria gonorrheae* and gram-positive bacteria *Proteus vulgaris, Staphylococcus aureus* and *Streptococcus faecium*, and fungi *Aspergillus tamari, Aspergillus Niger, Fusarium oxysporum* and *Penicillium oxalicum* can be inhibited by using mulberry leaves extract.

4. Conclusion

Several research studies have been reported on nutritional and health benefits of mulberry leaf extract for consumers. This manuscript compiles few nutritional aspects of mulberry leaves extract. Research studies have elucidated the existence of a number of active molecules in it and those compounds has shown to be effective in the treatment of various diseases. The active molecules such as 1-deoxynojirimycin (DNJ), gamma-aminobutyric acid (GABA), phytosterol, quercetin, flavonoids *etc*., helps to control blood sugar level, maintains blood pressure, reduce cholesterol, prevent liver cancer, prevent oxidation, respectively. Additionally, the vitamins such as vitamin A, B1, B2, C offer healthy eyes, body immunity, body tissue repairing and healthy skin. One important benefit is that antioxidant activity of mulberry leaves which could be used to combat free radical's formation which is the major reason for several diseases. Comparison of natural and synthetic compounds will clearly show the potential of these bio-compounds in pharmaceutical as well as in food sectors. Thus, more research is essential to exploit the potential capability of mulberry leaves extract to treat diverse health problems in human beings. It is expected that, before the end of 21st century the use of mulberry based products for combating the health issues would increase tremendously.

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