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Anti-diabetic Potentials of White Mulberry

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As of 2016, the World Health Organization (WHO) estimated that around 422 million adults have a form of diabetes mellitus (WHO 2016). In the United States, the Centers for Disease Control and Prevention estimated that 30.3 million people, or about 9.4 percent of the U.S. population, have diabetes (CDC 2017). Due to the rising prevalence especially of type 2 diabetes and the condition's serious health implications, it is crucial that treatment methods are explored across every health discipline.

White mulberry (*Morus alba*) (Figure 1) is a plant known to have glucose-lowering (hypoglycemic) properties, and its leaves have been used to treat diabetes in traditional Chinese medicine. However, health care professionals in the U.S. are less familiar with white mulberry and its potential to help moderate blood sugar levels. This publication provides a comprehensive update for Virginia Cooperative Extension agents and general audiences on white mulberry's antidiabetic components and research findings on its hypoglycemic effects.

Diabetes and alpha-glucosidase

Diabetes mellitus is a disorder with multiple causes and consequences. Type 1 diabetes is characterized by the absence of insulin, a major hormone that regulates blood glucose, as a result of autoimmune damage to the pancreas. In type 2 diabetes, patients often have impaired insulin production relative to healthy individuals, along with a condition known as insulin resistance. Cells that display insulin resistance have unresponsive insulin receptors, which makes glucose transport from the bloodstream into the cell more difficult (Diabetes, n.d.). Prior to major pancreatic beta cell failure, the beta cells of individuals with type 2 diabetes often overproduce insulin in order to compensate for the insulin-resistant cells. Without normal insulin secretion or response, the human body cannot properly metabolize carbohydrates into glucose for energy.

Dietary carbohydrates can be broadly classified into various categories based on the number of sugar

Figure 1. Leaves and fruits of White mulberry (Chan et al., 2016).

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units present. Monosaccharide consists of one sugar unit, whereas disaccharide consists of two sugar units. Glucose and fructose fall in the category of monosaccharide, whereas sucrose, lactose, and maltose are types of disaccharide. When carbohydrates (starches and sugars) from food are digested, they break down into glucose molecules, which are then absorbed by the stomach and small intestine. Once glucose enters the bloodstream, it is circulated throughout the body and signals the release of insulin, allowing the glucose to be absorbed into the necessary tissues. But for diabetic patients, insulin is either absent or ineffective at this stage, so glucose remains in the bloodstream, causing frequent hyperglycemia (Diabetes, n.d.). Over time, high blood sugar levels can cause serious health problems, including heart disease, blindness, and kidney failure (CDC 2017).

Common methods for controlling blood glucose levels include injecting additional insulin and taking prescription drugs that stimulate insulin secretion, such as sulfonylureas, or hypoglycemic agents, such as metformin, either independently or in combination with other treatments. However, additional pathways that may prevent blood sugar spikes may also be found by examining the various steps of carbohydrate metabolism. One such pathway, especially for type 2 diabetes, may be achievable through the inhibition of an enzyme called alpha-glucosidase.

Alpha-glucosidase in the small intestine is critical for starting the carbohydrate metabolism cycle due to its role as the facilitator of carbohydrate digestion (Benalla, Bellahcen, and Bnouham 2010). Substances that inhibit this enzyme may prevent carbohydrates from being broken down into glucose (Gupta et al. 2016), slowing the release of glucose into the bloodstream and resulting in more stable blood glucose levels in diabetic patients. While drugs like acarbose and miglitol are capable of inhibiting this enzyme, recent research has suggested that effective alpha-glucosidase inhibitors can be found in certain plants, including white mulberry.

White mulberry and its anti-diabetic properties

White mulberry trees are found in subtropical or temperate climates in China, Japan, Korea, India, Pakistan, and other Asian countries (Hocking 1993).

White mulberry is a small to medium-sized tree with either white or light pink fruit shaped like a blackberry. Due to its mild sweetness, white mulberry fruit has been used in a wide variety of foodstuffs such as jams, wine, and flavor additives. Historically, though, the greatest demand for white mulberry leaf has been from the silk industry because the leaves are the staple food source for silkworm larvae (USDA 2003).

Apart from dietary consumption, traditional Chinese medicine uses white mulberry fruit as well as the leaves and tree bark for therapeutic treatments. Practitioners usually recommend white mulberry leaves to resolve issues such as fever, liver damage, high blood pressure, and joint pain (Chan, Lye, and Wong 2016). As for any anti-diabetic properties, those who have analyzed white mulberry's phytochemical composition credit the sugar analog 1-deoxynojirimycin (DNJ) for the plant's hypoglycemic effects (Hansawasdi and Kawabata 2006; Kimura et al. 2004).

Concentrated in young white mulberry leaves (0.03-0.17 percent in dry leaves) and shoots (0.3 percent in dry shoots) (Vichasilp et al. 2012), DNJ itself is a potent alpha-glucosidase inhibitor capable of reducing glucose levels following carbohydrate consumption. The content of DNJ is approximately 0.1 percent in dry tea (about 1 mg per tea bag), and the biologically effective dose of DNJ is 6 mg per 60 kg (about 130 pounds) of human body weight (Gao et al. 2016).

In addition to DNJ, white mulberry has many other bioactive compounds, including polysaccharides, polyphenols, and flavonoids (Liu et al. 2015). Together, these compounds are able to protect the body against damage caused by oxidative stress (Burlando, Clericuzio, and Cornara 2017). This can be especially beneficial for patients with diabetes who are at risk of developing serious complications, such as cardiovascular disease and kidney dysfunction, as a result of prolonged oxidative stress on small blood vessels.

Research Findings

Researchers have investigated the hypoglycemic effects of white mulberry, white mulberry products, and white mulberry's bioactive components using cell culture, animal, and human experiments.

Animal studies that have examined white mulberry's anti-diabetic properties often used white mulberry extracts derived from leaves or fruit. A single oral administration of white mulberry leaf extract (3.75 g per kg of body weight) was effective enough to reduce glucose response after diabetic rats were fed maltose and sucrose (Park et al. 2009). Longer treatments (greater than four weeks) have also shown a significant reduction in fasting blood glucose levels among diabetic rats treated with white mulberry leaf extract or leaf powder (Cai et al. 2016; Salemi et al. 2016).

In addition to lowering blood glucose levels, many animal studies observed white mulberry extract decreased oxidative stress and inflammation in parts of the body typically vulnerable to diabetic complications. A rat study tested a white mulberry alcohol extract that contained a high number of polyphenols and reactive oxygen species-scavenging activities. Sixteen weeks of treatment with white mulberry alcohol extract (100 mg per kg of body weight) reduced oxidative stress markers in the retinas and lowered pro-inflammatory markers in diabetic rats, suggesting a protective effect against diabetic retinopathy (Mahmoud, Abd El-Twab, and Abdel-Reheim 2017). Another rat study examined four types of wine — white, red, mulberry, and jamun (or plum) — containing high amounts of polyphenols and flavonoids. The study reported that treatment of both grape wine and non-grape wine for six weeks increased antioxidant enzyme activities in diabetic rats by the end of the trial and significantly improved kidney function (Srikanta et al. 2016). However, that same study could not find a correlation between white mulberry wine and any effects on lowering blood sugar.

Clinical trials involving white mulberry have also observed trends of decreasing glucose levels after carbohydrate consumption that indicate alpha-glucosidase inhibition. A trial with healthy individuals measured the glucose response of a single oral administration of white mulberry leaf powder enriched with DNJ (0, 6, 12, and 18 mg) followed by sucrose intake (50 g). The study showed that administration of 12 and 18 mg of DNJ-enriched powder significantly suppressed the elevation of blood sugar and secretion of insulin, suggesting that the DNJ-enriched powder can be used as a dietary supplement for glycemic control (Kimura et al. 2007).

Another study involving healthy women tested various ratios of white mulberry leaf extract and sugar in Japanese confections (yokan, mocha, and chiffon cake) for their effects on the blood glucose and insulin levels after carbohydrate consumption. The study found that white mulberry leaf extract-containing confections for which the ratio of extract and sugar is 1-to-10 (3 g of extract to 30 g of sucrose) effectively suppressed subjects' resulting blood glucose and insulin levels by inhibiting the intestinal sucrase (an enzyme secreted in the small intestine that breaks down sucrose into glucose and fructose) (Nakamura, Nakamura, and Oku 2009). These results suggest that the development of confections with white mulberry leaf extract can contribute to blood sugar control.

In order to test the efficacy of white mulberry on blood sugar levels in people with type 2 diabetes, one study enlisted 20 participants: 10 healthy subjects and 10 type-2 diabetes patients. Each subject was randomly given either white mulberry leaf extract (1 g) followed by sucrose (75 g), or a placebo followed by sucrose. After monitoring blood glucose levels for 120 minutes, both the healthy subjects and diabetic patients who received mulberry leaf extract had lower blood glucose levels throughout the time interval compared with those who had the placebo (Mudra et al. 2007).

To analyze both the long-term and immediate effects of white mulberry consumption, one research group designed two randomized double-blind trials with a total of 88 participants (Asai et al. 2011). The first was a short-term study that gave 12 healthy participants a single dose of white mulberry leaf extract (3, 6, or 9 mg of DNJ) followed by cooked rice. The mulberry leaf extract reduced blood sugar levels in a dose-dependent manner. The second study was carried out over 12 weeks with white mulberry leaf extract enriched with DNJ (6 mg) given daily to participants with impaired glucose metabolism. By the end of the trial, the leaf extract had helped regulate after-meal blood sugar levels; however, fasting blood glucose levels, as well as hemoglobin A1C levels (a measurement of average blood sugar levels over two to three months) were largely unaffected by the treatment. Similar results were observed by another randomized double-blind trial (Kim et al. 2015). This study tested a white mulberry leaf water extract (5 g per day) in 36 subjects who had impaired fasting blood glucose, and it found that four weeks of white mulberry leaf extract supplementation improved after-meal blood sugar control.

In a study examining how white mulberry interacts with other hypoglycemic drugs, researchers gave type 2 diabetes patients sulfonylureas (an antidiabetic drug that stimulates insulin release from the pancreas) along with either jelly with white mulberry leaf extract (3.3 g) or a placebo jelly. After taking glucose readings 30 minutes following consumption, the group that received the leaf extract jelly with the sulfonylureas had lower glucose levels compared with the placebo group (Nakamura et al. 2011).

Finally, a meta-review of 13 clinical studies totaling 436 participants concluded that white mulberry may decrease postprandial (after-meal, or after consuming carbohydrates) blood glucose levels and supports white mulberry as an alpha-glucosidase inhibitor. But apart from postprandial glucose levels, the meta-review could not correlate white mulberry with other beneficial trends, such as lower blood glucose levels after fasting, lower A1C levels, or improved insulin sensitivity (Phimarn et al. 2017).

Side effects of white mulberry have not been reported in clinical studies, but not many studies have looked at side effects. Because white mulberry might lower blood glucose levels in people with diabetes, they need to be aware of the potential for developing low blood sugar (hypoglycemia), watch for its signs, and monitor blood glucose carefully.

How to Use

In the U.S., dried or powdered white mulberry leaves or shoots are mostly used for tea. These tea products recommend 1 teaspoon to 1 tablespoon of tea per cup of boiling water and to take before or with each meal. Mulberry leaf powder can also be mixed into smoothies, juices, oatmeal, yogurt, and other foods and beverages. Fresh mulberry leaves are available from stores carrying Southeast Asian products. In Asian countries, mulberry leaves are used as a food ingredient that may be blanched, fried, steamed, pickled, etc. Anyone with diabetes should consult with a healthcare professional before supplementing their diet with white mulberry products.

Summary

White mulberry is native to China and has been used in parts of the world to help treat diabetes. Among many anti-diabetic components, DNJ acts as an alpha-glucosidase inhibitor that inhibits glucose digestion in the small intestine and lowers glucose levels in the bloodstream. Both animal and clinical studies have demonstrated that the phytochemicals in white mulberry make the plant a viable alpha-glucosidase inhibitor. These findings suggest that white mulberry leaves or shoots, white mulberry extract, and DNJ-enriched products may help prevent or treat impaired glycemic control. This quality could potentially make white mulberry products an effective supplement for people with type 2 diabetes in their daily glucose control regimen. Although no side effects have been reported by researchers, individuals who introduce white mulberry into their diet should still be aware of potential hazards like hypoglycemia and should consult with a healthcare professional before starting any mulberry supplementation. Products derived from white mulberry can effectively contribute to the reduction in glucose levels after carbohydrate consumption, although large-scale trials need to be conducted to confirm these findings and provide clinical guidelines for their use.

References

Asai, Akira, Kiyotaka Nakagawa, Ohki Higuchi, Toshiyuki Kimura, Yoshihiro Kojima, Jun Kariya, Teruo Miyazawa, and Shinichi Oikawa. 2011. "Effect of Mulberry Leaf Extract with Enriched 1-Deoxynojirimycin Content on Postprandial Glycemic Control in Subjects with Impaired Glucose Metabolism." Journal of Diabetes Investigation 2 (4):318-23. https://doi.org/10.1111/j.2040-1124.2011.00101.x.

Benalla, Wafaa, Said Bellahcen, and Mohamed Bnouham. 2010. "Antidiabetic Medicinal Plants as a Source of Alpha Glucosidase Inhibitors." Current Diabetes Reviews 6 (4):247-54.

Burlando, Bruno, Marco Clericuzio, and Laura Cornara. 2017. "Moraceae Plants with Tyrosinase Inhibitory Activity: A Review." Mini-Reviews in Medicinal Chemistry 17 (2):108-121.

Cai, Shengyu, Wen Sun, Yixin Fan, Xuan Guo, Guangyuan Xu, Tunhai Xu, Yi Hou, Baosheng Zhao, Xingzhong Feng, and Tonghua Liu. 2016. "Effect of Mulberry Leaf (Folium Mori) on Insulin Resistance via IRS-1/PI3K/Glut-4 Signalling Pathway in Type 2 Diabetes mellitus Rats." Pharmaceutical Biology 54 (11):2685-2691. https://doi.org/10.1080/13880209.2016.1178779.

CDC. 2017. "About Diabetes." https://www.cdc.gov/diabetes/basics/diabetes.html.

Chan, Eric Wei-Chiang, Phui-Yan Lye, and Siu-Kuin Wong. 2016. "Phytochemistry, Pharmacology, and Clinical Trials of Morus alba." Chinese Journal of Natural Medicines 14 (1):17-30. https://www.ncbi.nlm.nih.gov/pubmed/26850343.

Diabetes. n.d. "Diabetes and Metabolism." Diabetes.co.uk, The Global Diabetes Community. http://www.diabetes.co.uk/diabetes-and-metabolism.html.

Gao, Kuo, Chenglong Zheng, Tong Wang, Huihui Zhao, Juan Wang, Zhiyong Wang, Xing Zhai, Zijun Jia, Jianxin Chen, Yingwu Zhou, and Wei Wang. 2016. "1-Deoxynojirimycin: Occurrence, Extraction, Chemistry, Oral Pharmacokinetics, Biological Activities and In Silico Target Fishing." Molecules 21 (11). https://doi.org/10.3390/molecules21111600.

Gupta, Prachi, Manju Bala, Sanjeev Gupta, Anita Dua, Rajesh Dabur, Elisha Injeti, and Ashwani Mittal. 2016. "Efficacy and Risk Profile of Anti-diabetic Therapies: Conventional vs Traditional Drugs—A Mechanistic Revisit to Understand Their Mode of Action." Pharmacological Research 113 (Part A):636-674. https://doi.org/10.1016/j.phrs.2016.09.029.

Hansawasdi, Chanida, and Jun Kawabata. 2006. "Alpha-glucosidase Inhibitory Effect of Mulberry (Morus alba) Leaves on Caco-2." Fitoterapia 77 (7-8):568-73. https://doi.org/10.1016/j.fitote.2006.09.003.

Hocking, Drake. 1993. Trees for Drylands. New Delhi, Bombay, Calcutta: Oxford and IBH Publishing Co. PVT. LTD.

Kim, Ji Yeon, Hyang Mok Ok, Joohee Kim, Seok Won Park, Sung Won Kwon, and Oran Kwon. 2015. "Mulberry Leaf Extract Improves Postprandial Glucose Response in Prediabetic Subjects: A Randomized, Double-blind Placebo-controlled Trial." Journal of Medicinal Food 18 (3):306-13. https://doi.org/10.1089/jmf.2014.3160.

Kimura, Toshiyuki, Kiyotaka Nakagawa, Hiroyuki Kubota, Yoshihiro Kojima, Yuko Goto, Kenji Yamagishi, Shigeru Oita, Shinichi Oikawa, and Teruo Miyazawa. 2007. "Food-grade Mulberry Powder Enriched with 1-Deoxynojirimycin Suppresses the Elevation of Postprandial Blood Glucose in Humans." Journal of Agricultural and Food Chemistry 55 (14):5869-74. https://doi.org/10.1021/jf062680g.

Kimura, Toshiyuka, Kiyotaka Nakagawa, Yuko Saito, Kenji Yamagishi, Masahiro Suzuki, Kohji Yamaki, Hiroshi Shinmoto, and Teruo Miyazawa. 2004. "Simple and Rapid Determination of 1-Deoxynojirimycin in Mulberry Leaves." Biofactors 22 (1-4):341-5. https://doi.org/10.1002/biof.5520220167.

Liu, Qingpu, Xuan Li, Cunyu Li, Yunfeng Zheng, and Guoping Peng. 2015. "1-Deoxynojirimycin Alleviates Insulin Resistance via Activation of Insulin Signaling PI3K/AKT Pathway in Skeletal Muscle of db/db Mice." Molecules 20 (12):21700-14. https://doi.org/10.3390/molecules201219794.

Mahmoud, Ayman M., Sanaa M. Abd El-Twab, and Eman S. Abdel-Reheim. 2017. "Consumption of Polyphenol-rich Morus alba Leaves Extract Attenuates Early Diabetic Retinopathy: The Underlying Mechanism." European Journal of Nutrition 56 (4):1671-84. https://doi.org/10.1007/s00394-016-1214-0.

Mudra, Mitchell, Nacide Ercan-Fang, Litao Zhong, Julie Furne, and Michael Levitt. 2007. "Influence of Mulberry Leaf Extract on the Blood Glucose and Breath Hydrogen Response to Ingestion of 75 g Sucrose by Type 2 Diabetic and Control Subjects." Diabetes Care 30 (5):1272-74. https://doi.org/10.2337/dc06-2120.

Nakamura, Mariko, Sadako Nakamura, and Tsuneyuki Oku. 2009. "Suppressive Response of Confections Containing the Extractive from Leaves of Morus alba on Postprandial Blood Glucose and Insulin in Healthy Human Subjects." Nutrition & Metabolism 6:29. https://doi.org/10.1186/1743-7075-6-29.

Nakamura, Sadako, Michiru Hasgiguchi, Yoshihiko Yamaguchi, and Tsuneyuki Oku. 2011. "Hypoglycemic Effects of Morus alba Leaf Extract on Postprandial Glucose and Insulin Levels in Patients with Type 2 Diabetes Treated with Sulfonylurea Hypoglycemic Agents." Diabetes & Metabolism 2 (3):1000158. https://doi.org/10.4172/2155-6156.1000158

Park, Ji Min, Ha Yoon Bong, Hye In Jeong, Yeon Kyoung Kim, Ji Yeon Kim, and Oran Kwon. 2009. "Postprandial Hypoglycemic Effect of Mulberry Leaf in Goto-Kakizaki Rats and Counterpart Control Wistar Rats." Nutrition Research and Practice 3 (4):272-8. https://doi.org/10.4162/nrp.2009.3.4.272.

Phimarn, Wiraphol, Kittisak Wichaiyo, Khuntawan Silpsavikul, Bunleu Sungthong, and Kritsanee Saramunee. 2017. "A Meta-analysis of Efficacy of Morus alba Linn. to Improve Blood Glucose and Lipid Profile." European Journal of Nutrition 56 (4):1509-1521. https://doi.org/10.1007/s00394-016-1197-x.

Salemi, Zahra, Sepideh Barzin Tond, Soudabeh Fallah, Asie Shojaii, and Morteza Seifi. 2016. "The Effect of Morus alba Leaves Extract and Powder on Resistin Levels and Liver Transaminase Enzymes Activities in Diabetes." Cellular and Molecular Biology 62 (6):112-8.

Srikanta, Akshatha H., Anbarasu Kumar, Shinde V. Sukhdeo, Muthukumar S. Peddha, and Vijayalakshmi Govindaswamy. 2016. "The Antioxidant Effect of Mulberry and Jamun Fruit Wines by Ameliorating Oxidative Stress in Streptozotocin-induced Diabetic Wistar Rats." Food & Function 7 (10):4422-31. https://doi.org/10.1039/c6fo00372a.

USDA. 2003. "White Mulberry — USDA Plants Database." United States Department of Agriculture Natural Resources Conservation Service. https://plants.sc.egov.usda.gov/plantguide/pdf/pg_moal.pdf

Vichasilp, Chaluntorn, Kiyotaka Nakagawa, Phumon Sookwong, Ohki Higuchi, Somchai Luemunkong, and Teruo Miyazawa. 2012. "Development of High 1-Deoxynojirimycin (DNJ) Content Mulberry Tea and Use of Response Surface Methodology to Optimize Tea-making Conditions for Highest DNJ Extraction." LWT-Food Science and Technology 45 (2):226-32.

WHO. 2016. "Diabetes." World Health Organization. http://www.who.int/diabetes/en/.