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Current anti-diabetes mechanisms and clinical trials using *Morus alba* L.

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Abstract *Backgrounds:* Diabetes mellitus, especially type 2 diabetes, with its fast-rising prevalence, has become a global epidemic. Mulberry (*Morus alba* L.) leaf has been known to have hypoglycemic effects since ancient times. In Asia mulberry leaf is used as tea to complement the treatment of diabetes mellitus. The methods by which mulberry leaf affects the body and its mechanism when combined with chemical agents have been studied extensively.
Conclusions: We summarize the possible mechanisms of the anti-diabetic effects of mulberry leaf based on extraction procedures, *in vitro* and *in vivo* experiments, and clinical trials. We also discuss the hypothesis that crosstalk and "critical nodes" may be useful for a deeper molecular understanding of the treatment and prevention of diabetes with mulberry leaf.

Introduction

Diabetes mellitus is a disease that affects the body's regulation of blood glucose, the main symptoms of which include thirst, frequent urination, hunger, and weight loss. Diabetes, especially type 2 diabetes metillus (T2DM), is increasingly prevalent worldwide according to the WHO, calling for a monitoring of diabetes rates and researches into cost-effective treatments to slow its rise.

As for the medicinal interventions, certain traditional plants have been proved to retard the development of diabetic mice induced by streptozotocin (STZ).[1] Traditional Chinese herbs have been shown to have beneficial effects over Western pharmaceutical medications in treating diabetes, including duration effect, moderate hypoglycemic effects, and fewer side effects.[2]

In China, mulberry (*Morus alba* L.) leaf has been used to treat various illnesses since ancient times. Its use was first recorded in *Divine Husbandman's Classic of Materia Medica* (*Shennong Bencao Jing*; 200–220 CE), which is the earliest materia medica in China. The herb was described as being

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able to eliminate cold and heat in the body, promote perspiration, and have detoxifying properties.[3] With the wider use of mulberry leaf, more properties and effects were recorded in *Comprehensive Outline of the Materia Medica* (*Bencao Gangmu*; 1590), an extensive summary of Chinese herbal pharmacology. The author, Li Shizhen, indicated that brewed mulberry tea can treat wasting and thirsting (*xiao ke*) syndrome. It is now recognized that diabetes falls under this syndrome.

Pharmacological experiments have shown that the active compounds in mulberry leaf with hypoglycemic effects including alkaloids, flavonoids, polysaccharides, amino acids, simple phenylpropanoids, and phenols.[4] In this brief review, we present the mechanisms of the anti-diabetic effects of mulberry leaf from perspectives of extracts, their compounds, molecular mechanisms, and clinical trials. We hope that this manuscript provides a summary for future research on mulberry leaf as an herbal supplement for T2DM.

Extraction conditions resulting in the best anti-diabetic effects *in vitro* and *in vivo*

In ancient China, dried mulberry leaf was brewed in hot water to make a tea for treating diabetes. Modern extraction methods are now able to maximize treatment hypoglycemic effects with increased glucose uptake attributed to various factors during extraction, such as brewing time, concentration of organic solution, and extraction solution temperature.

Water extracts

Chen et al[5] compared two extracts from mulberry leaf on STZ-induced diabetic mice, and found that hot water extracts exhibited more potent hypoglycemic effects than ethanol or n-butanol fractions. Attila et al[6] investigated the dichloromethane-soluble fraction from the hot water extract of mulberry leaf had the potentiality to exert anti-diabetic activity on the 3T3-L1 adipocytes. Powder of dried mulberry leaf was given to diabetic rats by gavage, showing no traces of lenticular opacity in diabetic-mulberry group and no significant differences of blood glucose in normal group.[7] When a mixture of mulberry leaf and mulberry tea was steeped in hot water (98°C) for 3—5 min, a stronger inhibitory effect on α-glucosidase was observed in a Caco-2 cell culture experiment, compared with other extraction conditions.[8]

Ethanolic and other extracts

Aside from the water extract, the ethanol extract of mulberry leaf is effective at treating diabetes in STZ-induced rats,[9,10] So is the acetone extract, however, it is not so well as the ethanolic.[11,12] From these studies, it is clear that the mulberry extraction method plays a crucial role in preventing diabetes, and each extract has different hypoglycemic effects.

Mechanisms of the anti-diabetes effects of mulberry leaf *in vivo*

After confirming that crude extracts from mulberry leaf have hypoglycemic effects, additional extracts are purified for mechanistic studies. In these studies, various extracts from mulberry leaf are separated with reagents under different conditions, and active constituents are detected and enriched. Here we summarize these mechanistic studies with respect to their extracts.

Inhibition of α-glucosidase

Alkaloids

Total alkaloids from mulberry leaf have hypoglycemic effects in streptozotocin- (STZ-) induced diabetic mice.[13] Some alkaloids in mulberry leaf are potent inhibitors of mammalian digestive glycosidases.[14] These mulberry alkaloids, especially 1-deoxynojirimycin (DNJ), decrease α-glucosidase activity by competitive inhibition through binding to the enzyme active site to mimic natural substrates.[15]

DNJ-enriched mulberry extract may be useful in controlling postprandial hyperglycemia in pre-diabetic or mild diabetic individuals.[16] Oral administration of 0.24% DNJ and its derivatives was found to inhibit absorption of sucrose and polysaccharides in human and rat intestinal tissue samples.[17] Other investigations on the pharmacokinetics and bioavailability of DNJ showed that oral mulberry DNJ administered to rats is absorbed intact from the gastrointestinal tract, diffuses into the liver, and is then excreted with a short half-life.[18,19] Thus, studies such as the aforementioned on the metabolism of DNJ help lay the foundation for developing mulberry leaf as a dietary supplement for diabetes. As such, extracting the highest DNJ content as possible from mulberry is a high priority. In studies that investigated extraction of DNJ, when temperature was sustained at 98°C for 400 s, 95% of DNJ in dry mulberry tea was extracted[20] and water extraction versus extraction using different concentrations of ethanol produced varying contents of DNJ.[21] Other studies are exploring ways to increase production of DNJ during fermentation of mulberry leaf, such as inoculating the fermentation broth with the fungus ganoderma (*Ganoderma lucidum*).[22]

Flavonoids

Flavonoids from mulberry leaf also have *in vitro* inhibitory effects on α-glucosidase activity and can suppress blood glucose level after oral administration of starch and sucrose in Kunming mice.[23] Two flavonoids (isoquercitrin and astragalin) were shown to inhibit α-glucosidase as for the laboratory experiment.[24] Furthermore, chlorogenic acid (a phenylpropanoid) and rutin were found to play an important role in preventing diabetes, but not isoquercitrin.[25]

Polysaccharides

Polysaccharides from mulberry leaf have been shown to decrease blood glucose level, improve glucose tolerance,