



# 1-Deoxynojirimycin from *Morus* species: An overview of its chemistry, sources, contents, pharmacology, and clinical studies

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## ABSTRACT

In this article, the chemistry, sources, contents, pharmacology, and clinical studies of 1-deoxynojirimycin (DNJ) are reviewed. DNJ is a polyhydroxylated piperidine alkaloid azasugar or iminosugar commonly found in the leaves of *Morus* (mulberry) species, notably *Morus alba*. The chemical structure of DNJ resembles that of glucose except that the oxygen atom of the pyranose ring in glucose is replaced with an imino group (–NH–). The pyranose ring has a hydroxymethyl (–CH<sub>2</sub>OH) moiety and three hydroxyl (–OH) groups. Also known as moranoline or duvoglustat, DNJ has a molecular formula of C<sub>6</sub>H<sub>13</sub>NO<sub>4</sub> and a molecular weight of 163 g/mol. Major pharmacological properties of DNJ from mulberry are anti-diabetic, anti-obesity, cardioprotective, and anti-cancer activities. Other properties of DNJ are hepatoprotective, neuroprotective, antimicrobial, anti-inflammatory, hypolipidemic, and nephroprotective activities. Most clinical studies of DNJ are focused on its anti-diabetic and related activities. Other clinical studies of DNJ included its effect on serum triglyceride, starch digestion and absorption, stable angina pectoris, and atherosclerotic lesion. Further research on DNJ is suggested.

## 1. INTRODUCTION

Commonly known as white mulberry, *Morus alba* L. of the family Moraceae is native to China and Korea [1,2]. The species is now widely cultivated and has naturalized in tropical, sub-tropical, and warm temperate countries of Asia, Europe, and America. A fast-growing species, *M. alba*, can grow up to 20 m in height. Under cultivation with regular harvesting of leaves and fruits, the trees are reduced to bushes. The bark of *M. alba* is dark grey-brown with lenticels and fissures. The leaves are ovate, alternate, glossy green at the upper surface, cordate at the base, and acuminate at the apex (Fig. 1). Leaf margins of leaf blades are serrated, and the petioles are long and slender.

From the same tree, leaf shape can vary from unlobed to almost palmate. Mulberry plants are mainly dioecious, i.e., having male and female trees. Trees are sometimes monoecious, i.e., having male and female flowers on the same plant. Flowers are inconspicuous male and female catkins, pendulous, and greenish. Fruits are sorosis formed from multiple flowers. They are white when young, red on maturing, and purplish black when ripe (Fig. 1). Ripe fruits are sweet and edible [1,2].

Traditionally, the foliage of mulberry is the primary fodder for silkworms (Fig. 1) and has long supported the silk industry [2–4]. Mulberry leaves are also used as fodder for livestock, and mulberry fruits have been used to produce functional food products such as fruit juice, jam, wine, liquor, dried fruits, and canned fruits. The main chemical components in *M. alba* are alkaloids, flavonoids, phenolic acids, terpenoids, anthocyanins, polysaccharides, carbohydrates, vitamins, and coumarins [4–6]. In China, *M. alba* is a major traditional Chinese medicine. Leaves, twigs, and roots are harvested for their antioxidant, analgesic, anti-inflammatory, anti-cancer,

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**Figure 1.** Leaves (left), silkworms (middle), and fruits (right) of *Morus alba*.

hypoglycemic, hypolipidemic, antibacterial, anti-asthma, and diuretic properties [6–8]. Fruits are used as medicine to treat age-related and metabolic disorders such as obesity, diabetes, cardiomyopathy, neurodegeneration, and hepatic steatosis.

In this article, the chemistry, sources, contents, pharmacology, and clinical studies of DNJ from *Morus* species are reviewed. In the Introduction, the botany, chemical constituents, and traditional uses of *M. alba* are described. This is then followed by highlights of the chemistry, pharmacological properties, and clinical studies of DNJ. Results of pharmacological and clinical studies of mulberry leaf extract (MLE) and DNJ are furnished with numerical values wherever possible.

## 2. CHEMISTRY

1-Deoxynojirimycin (DNJ) or 2-(hydroxymethyl) piperidine-3,4,5-triol is a polyhydroxylated piperidine alkaloid azasugar or iminosugar commonly found in the leaves of mulberry species Gao *et al.*, Wang *et al.* [9,10]. Also known as moranoline or divoglustat, DNJ has a molecular formula of  $C_6H_{13}NO_4$  and a molecular weight of 163 g/mol [11].

The chemical structure of DNJ (Fig. 2) is very similar to that of glucose except that the oxygen atom at position C1 of the pyranose ring in glucose is replaced with an imino group ( $-NH-$ ) in DNJ [9,12,13]. There is a hydroxymethyl ( $-CH_2OH$ ) group at position 2, and three hydroxyl ( $-OH$ ) groups at C3, C4, and C5 [14]. DNJ was first isolated from the mulberry tree by Yagi [15]. DNJ is distributed in all parts of mulberry trees, the leaf being the main source.

## 3. SOURCES AND CONTENTS

From dried leaves of different varieties of *M. alba* in China, the content of DNJ ranged from 0.20 to 3.88 mg/g [16], 1.39–3.48 mg/g [17], and 0.13–1.46 mg/g [18]. The DNJ content of *M. alba* leaves sold as traditional medicine in China was 0.20–3.88 mg/g [16]. In Thailand, *M. alba* leaves of different ages showed that the DNJ content was higher in mulberry leaf shoots (2.24–3.08 mg/g) than in young (0.62–1.61 mg/g) and mature (0.47–0.96 mg/g) leaves [19]. A more recent study in Thailand affirmed that the DNJ content in mulberry leaves was highest in the leaf shoots (3.12 mg/g), followed by young leaves (1.54 mg/g) and mature leaves (0.80 mg/g) [20]. The study also reported that a cup of mulberry tea (230 ml) contains 6.5 mg of DNJ. In Japan, mulberry leaf products (e.g., tea leaves,

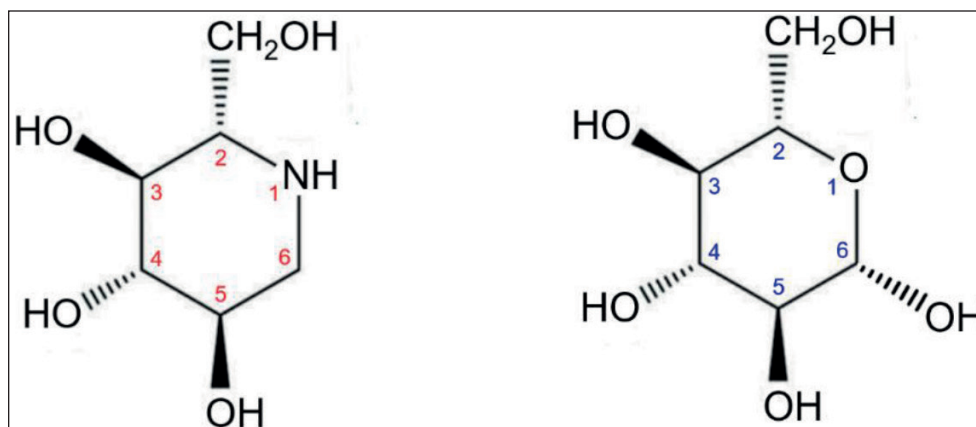
leaf powder, and tablets) can be purchased from the general market, and their DNJ contents are 0.18%, 0.20%, and 0.48%, respectively [21]. Besides the leaves, DNJ has been reported in the root [22], root bark [23], and latex of *M. alba* [24].

Leaves of all nine mulberry species of *Morus* studied contained DNJ with contents of the following descending order: *M. australis* > *M. atropurpurea* ~ *M. wittiorum* > *M. multicaulis* ~ *M. laevigata* ~ *M. alba* ~ *M. mizuho* ~ *M. cathayana* > *M. bombycis* [18]. The highest content was in *M. australis* (1.02 mg/g) while the lowest was in *M. bombycis* (0.50 mg/g). In leaves of *M. bombycis* harvested in July, there was a strong correlation between DNJ content and  $\alpha$ -glucosidase inhibition [25]. Among the major alkaloids in twigs of *M. alba*, the content of DNJ (39%) was the highest [26]. DNJ is also found in fruits of *M. atropurpurea* and *M. wittiorum*, with young fruits having higher content than mature fruits [27].

Other sources of DNJ include silkworms (*Bombyx mori*) that feed exclusively on mulberry leaves as their staple diet. The high concentration of DNJ in silkworms was 2.7-fold more than that in the mulberry leaves, probably through accumulation following ingestion [23,28]. The average DNJ content in silkworm larvae was 16.1 mg/100 g [29] and can be as high as 96.4 mg/100 g dry weight [30]. In the larvae of some species of silkworms in Thailand, higher DNJ content was reported in the early instar, while in others, higher DNJ content was reported in the older instar [31]. The high DNJ contents in the larvae of some silkworm species are comparable to those of mulberry supplements produced from leaf shoot or young leaves, suggesting the potential of using silkworm larvae as supplementary food. In Thailand, the third day of the fifth instar of the Nangnoi and Samrong varieties yielded the highest DNJ contents (3.11 and 1.96 mg/g) [32]. These larval varieties also yielded the highest  $\alpha$ -glucosidase inhibitory activity.

## 4. PHARMACOLOGICAL PROPERTIES

Including those reviewed by Ramappa *et al.* [14] and Tricase *et al.* [33], major pharmacological properties of DNJ are anti-diabetic, anti-obesity, hypolipidemic, cardioprotective, and anti-cancer activities (Table 1). Other properties of DNJ are hepatoprotective, neuroprotective, antimicrobial, anti-inflammatory, and nephroprotective activities. Minor properties are the inhibition of vascular smooth muscle cells (VSMCs),



**Figure 2.** Chemical structure of DNJ (left) and glucose (right).

inhibition of human umbilical vein endothelial cells (HUVECs), and amelioration of gastric ulcer (GU).

ABCA1 = ATP-binding cassette transporter A1, AD = Alzheimer's disease, AGEs = advanced glycation end-products, Akt = protein kinase B, AL = atherosclerotic lesion, AMP = adenosine monophosphate, AMPK = AMP-activated protein kinase, AOM = azoxymethane, ARG = arginine, BDNF = brain-derived neurotrophic factor, BSS = blood stasis syndrome, BVDV = bovine viral diarrhea virus, C/EBP $\alpha$  = CCAAT-enhancer-binding protein, CCR = creatinine-clearance rate, CHD = coronary heart disease, db/db = diabetic, DV = dengue virus, DHE = dihydroethidium, DNA = deoxyribonucleic acid, DNJ = 1-deoxynojirimycin, DPM = DNJ and polysaccharide mixture, DSS = dextran sodium sulfate, ECM = extracellular matrix, FAG = fagomine, FAK = focal adhesion kinase, GAL = 2-O- $\alpha$ -D-galactopyranosyl; GFR = glomerular filtration rate, GLUT4 = glucose transporter 4, GU = gastric ulcer, HCM = hypertrophic cardiomyopathy diabetes mellitus, HFD = high-fat diet, HL = hepatic lipase, HOMA-IR = homeostasis model assessment insulin resistance diabetes mellitus, HSL = hormone sensitive lipase, HUVEC = human umbilical vein endothelial cells, IKK $\beta$  =  $\kappa$ B kinase  $\beta$ , IRS-1 = insulin receptor substrate 1, JAK = Janus kinase, LDL = low-density lipoprotein, LEF = lymphoid enhancer factor, LF = liver fibrosis, LPL = lipoprotein lipase, LXRA = liver X receptor  $\alpha$ , MA = *Morus alba*, MAPK = mitogen-activated protein kinase, MIC = minimum inhibitory concentration, MLE = mulberry leaf extract, MMP = matrix metalloproteinase, NASH = non-alcoholic steatohepatitis, NF = nuclear factor, NF- $\kappa$ B = nuclear factor  $\kappa$ B, NIR = neuronal insulin resistance, NRF2 = nuclear factor-like 2, OGG1 = 8-oxoguanine DNA glycosylase, PDX-1 = pancreatic and duodenal homeobox factor-1, PI3K = phosphatidylinositol 3-kinase, PPAR $\gamma$  = peroxisome proliferator-activated receptor gamma, QG = quercetin glucuronide, ROS = reactive oxygen species, SAP = stable angina pectoris, SREBP = sterol regulatory-element binding protein, STAT = signal transducer and activator of transcription, STZ = streptozotocin, T2DM = type 2 diabetes mellitus, TG = triglyceride, TGF = transforming growth factor, TNF = tumor necrosis factor, and VSMC = vascular smooth muscle cells.

The mulberry leaf compounds with anti-diabetic properties include alkaloids such as DNJ, N-methyl-DNJ, and fagomine, and flavonoids such as morusin, chalconoracin, isoquercitrin, and kuwanon C [41,77,78]. Fruit compounds possessing strong  $\alpha$ -glucosidase inhibitory activities include quercetin, isobavachalcone, and morachalcone [79]. Their inhibitory IC<sub>50</sub> values are 8.57, 67.3, and 50.0  $\mu$ M, respectively.

The anti-diabetic mechanisms of DNJ are well-documented in the literature (Table 1). DNJ is a promising inhibitor of intestinal  $\alpha$ -glucosidase by reducing body weight, exerting an anti-obesity effect, suppressing the elevation of post-prandial blood glucose, improving fasting blood glucose levels, glucose tolerance, and plasma lipid profile, improving gut microbiota, increasing insulin sensitivity, regulating the PI3K/Akt insulin signaling pathway, and inhibiting injury induced by advanced glycation end-products (AGEs). DNJ has been shown to improve glucose metabolism by controlling the composition of gut microbiota in a streptozotocin-induced diabetic mouse model [40]. DNJ relieves gut dysbiosis and controls gut microbiota composition. The latter, depending on its type, ameliorates blood sugar levels.

The other major pharmacological properties of DNJ are anti-obesity, cardioprotective, and anti-cancer activities (Table 1). DNJ exerted anti-obesity activities by inhibiting adipogenesis, suppressing liver lipid accumulation, restoring gut dysbiosis, rebuilding gut microbiota, improving lipid-lowering efficacy, and reducing plasma triacylglycerol, epididymal adipose tissue, and low-density lipoprotein (LDL)-cholesterol levels. Improved cardiac function, reduced myocardial fibrosis, improved diabetic myocardium, attenuated cardiomyopathy, alleviated cardiac hypertrophy, and ameliorated stable angina pectoris (SAP) in patients with coronary heart disease (CHD) are some of the cardioprotective activities of DNJ. Anti-cancer activities of DNJ include inhibition of the growth of cancer cells *via* inducing G1 phase cell cycle arrest and apoptosis, decreasing metastasis and migration, and checking tumor progression.

## 5. CLINICAL STUDIES

In this article on clinical studies of DNJ, 10 studies have been described. They consist of one review paper, seven

**Table 1.** Pharmacological properties of DNJ from *Morus* species.

Bioactivity	Description of activity and effect	Reference
Anti-diabetic	DNJ from the latex of mulberry exerted anti-diabetic effects on STZ-induced diabetic mice treated for 21 days by lowering post-prandial blood glucose level and reducing fasting blood glucose level.	[24]
	DNJ isolated from silkworms reduced body weight, improved fasting blood glucose levels and glucose tolerance, exerted an anti-obesity effect, and increased insulin sensitivity in hyperglycemic rats.	[34]
	DNJ inhibited $\alpha$ -glucosidase with an $IC_{50}$ value of 9.39 $\mu$ M. The inhibitory activity of MLE was attributed to DNJ and was comparatively stronger at 7.35 $\mu$ M.	[35]
	In the treatment of diabetes, DPM was tested in alloxan-induced diabetic mice. DNJ decreased post-prandial blood glucose, protected pancreatic $\beta$ -cells, and modulated hepatic glucose metabolism and gluconeogenesis.	[36]
	The hypoglycemic effect of DPM on HFD mice and STZ-induced diabetic mice involved the regulation of hepatic glucose metabolism <i>via</i> insulin resistance and the dysfunction of pancreatic $\beta$ -cells.	[37]
	DNJ significantly alleviated insulin resistance in db/db mice by improving insulin signaling PI3K/Akt pathway in the skeletal muscle.	[38]
	Rice-coated with DNJ supplemented for 6 weeks, ameliorated hyperglycemia in db/db mice. DNJ decreased fasting blood glucose, plasma insulin, and blood hemoglobin levels.	[39]
	DNJ significantly decreased serum glucose and insulin levels, improved serum lipid levels, and reversed insulin resistance in STZ-induced diabetic mice. DNJ also improved the gut microbiota by promoting the growth of gut bacteria.	[40]
	DNJ and QG increased glucose uptake in HepG2 cells, increased PPAR $\gamma$ , C/EBP $\alpha$ , and SREBP-1 expression in 3T3-L1 cells, and inhibited AGEs-induced injury and apoptosis in GLUTag cells.	[41]
	In HFD and STZ-induced pre-diabetic mice, DNJ decreased the blood glucose level and improved insulin sensitivity. DNJ significantly reduced the relative diabetic risk in prediabetic mice by 83.7%.	[42]
	The combination of DNJ (5 mg/kg) and morin (25 mg/kg) effectively hindered the progression of T2DM in pre-diabetic mice by 88%. The mechanisms involved amelioration of insulin resistance.	[43]
	DNJ attenuated high-glucose-induced oxidative DNA damage and cell senescence in HUVEC <i>via</i> the activation of Akt-NRF2/OGG1 signaling.	[44]
	DNJ exerted hypoglycemic effects through regulation of the PI3K/Akt insulin signaling pathway in type 2 diabetic rats.	[45]
Anti-obesity	DNJ from MLE administered for 12 weeks in diet-induced mice decreased visceral fat weight and adipocyte size by suppressing liver lipid accumulation and reducing plasma triacylglycerol.	[46]
	3T3-L1 adipocytes, when treated overnight with DNJ, showed increased diet-induced cholesterol efflux, increased expression of ABCA1, and enhanced presence of LXR $\alpha$ .	[47]
	In HFD mice, supplementation of DNJ for 12 weeks significantly reduced the expression of ABCA1 in epididymal adipose tissue and reduced LDL-cholesterol levels.	[47]
	Commercial DNJ inhibited adipogenesis by directly regulating PPAR $\gamma$ and phosphorylation of extracellular regulated protein kinases 1/2 in intramuscular adipocytes.	[48]
	DNJ from mulberry leaves inhibited hypercholesterolemia induced by HFD and modulated the gut microbiota more strongly in female mice than in male mice.	[49]
	DNJ from MLE inhibited adipogenesis in white 3T3-L1 preadipocytes and promoted the conversion of white preadipocytes to beige adipocytes <i>via</i> activation of AMPK.	[50]
	Commercial DNJ improved HFD-induced NASH in male mice by restoring gut dysbiosis and rebuilding gut microbiota.	[51]
Hypolipidemic	Rice coated with DNJ supplemented for 6 weeks, ameliorated dyslipidemia in db/db mice. DNJ suppressed hyperlipidemia by reducing the weight of mesenteric, epididymal, and total adipose tissue, and by improving the plasma lipid profile.	[39]
	In HFD and STZ-induced pre-diabetic mice, DNJ ameliorated lipid metabolism.	[42]
	The combination of DNJ (5 mg/kg) and morin (25 mg/kg) effectively hindered the progression of T2DM in pre-diabetic mice by 88%. The mechanisms involved amelioration of lipid metabolism.	[43]
	The lipid-lowering efficacy of mulberry green tea (0.20% DNJ) was superior to that of mulberry black tea (0.15% DNJ) in HFD hyperlipidemic mice.	[52]
	Intake of DNJ for four weeks suppressed lipid accumulation and activated the $\beta$ -oxidation system in the liver of male rats. DNJ did not cause hepatic dysfunction and led to a decline in oxidative stress.	[53]
Cardioprotective	Mice with cardiomyopathy, when fed with commercial DNJ for 12 weeks, showed significantly improved cardiac function, reduced myocardial fibrosis, and improved diabetic myocardium by inhibition of the TGF- $\beta$ -Smad2/3 pathway.	[54]
	DNJ from MLE attenuated septic cardiomyopathy by regulating oxidative stress, apoptosis, and inflammation <i>via</i> the JAK2/STAT6 signaling pathway.	[55]
	DNJ served as a mitochondrial rescue agent for HCM. The efficacy of DNJ in promoting cardiac mitochondrial function and alleviating cardiac hypertrophy was verified using an angiotensin II-induced cardiac hypertrophy mouse model.	[56]

Continued

Bioactivity	Description of activity and effect	Reference
Anti-cancer	Commercial DNJ inhibited the metastasis of B16F10 melanoma cells by attenuating the expression of MMP-2/-9, enhancing MMP-2 mRNA expression, and altering cell surface-binding motifs.	[57]
	A derivative of DNJ inhibited the growth and migration of A549 lung cancer cells by inducing G1 phase cell cycle arrest and apoptosis.	[58]
	DNJ from MLE inhibited colorectal cancer induced by AOM/DSS in ICR mice by increasing mRNA expression of pro-apoptotic Bax, and decreasing mRNA expression of Bcl-2.	[59]
	Against MG63 osteosarcoma cells, DNJ disrupted the binding of integrin to ECM proteins, decreased the migration rate of metastatic cancer cells, and checked tumor progression.	[60]
Hepatoprotective	DNJ alleviated liver injury in db/db mice by improving lipid homeostasis and attenuating hepatic steatosis.	[61]
	DNJ attenuated liver fibrosis in mice <i>via</i> hypoglycemic, anti-inflammatory, and anti-oxidative effects. Treatment with DNJ in L929 cells exposed to high glucose significantly lowered ROS generation.	[62]
	DNJ alleviated resistin-induced lipid accumulation in the mouse liver by significantly inhibiting the decline in activities of HSL, HL, and LPL.	[63]
Neuroprotective	Orally administered DNJ for 3–9 months alleviated age-related changes in SAMP8 mice. A dose of 20 mg/kg/day showed significant improvement. Thus, DNJ is able to maintain brain aging.	[64]
	DNJ from MLE significantly inhibited $\beta$ -secretase expression, attenuated $\beta$ -amyloid deposition, remitted neuro-inflammation, and upregulated BDNF/tyrosine kinase receptors signal pathway in the brain of SAMP8 mice.	[65]
	DNJ attenuated tau and amyloid pathological markers of AD using SK-N-SH cells with induced NIR. DNJ displayed neuroprotective activity by reversing NIR.	[66]
Antimicrobial	DNJ from MLE acted as an anti-infective agent by demonstrating anti-adherence activity in controlling the overgrowth of <i>Streptococcus mutans</i> . Against <i>S. mutans</i> , the MIC of DNJ (15.6 mg/l) was eight times stronger than MLE (125 mg/l).	[67]
	DNJ derivatives displayed antiviral activity against BVDV with $EC_{50}$ and $EC_{90}$ values of 1.6–4.5 $\mu$ M and 14–47 $\mu$ M, respectively.	[68]
	DNJ-derived imino-sugars exerted antiviral effects on DV-infected dendritic cells with $IC_{50}$ values of 1.6–3.3 $\mu$ M after treatment for 48 h.	[69]
Anti-inflammatory	MA alkaloids with 39% DNJ exerted anti-inflammatory effects on macrophages <i>via</i> regulation of MAPK signaling. DNJ, FAG, and ARG are the main constituents of alkaloids that exert the anti-inflammatory effects.	[26]
	DNJ improved gut health, reduced villus height, inhibited inflammation, improved intestinal mucosal barrier, and regulated the composition of fatty acids in fattening white rabbits.	[70]
	DNJ treatment for eight weeks improved testosterone levels, ameliorated testicular structure damage, and improved sperm viability in obese-induced testicular inflammation mice. DNJ treatment also inhibited the IKK $\beta$ /NF- $\kappa$ B signaling pathway and reduced inflammation in obese mice.	[71]
Nephroprotective	DNJ from MLE normalized the renal function in diabetic rats by ameliorating kidney hypertrophy, CCR, and GFR.	[72]
	DNJ reduced blood glucose, improved glucose tolerance, and attenuated renal damage in rats with diabetic nephropathy.	[73]
Inhibition of VSMC	DNJ from MLE inhibited the migration of VSMC under hyperglycemic conditions by activating AMPK/RhoB and by inhibiting FAK.	[74]
Inhibition of HUVEC	DNJ from MLE attenuated high glucose-accelerated senescence in HUVEC by inactivating NF- $\kappa$ B and decreasing ROS production.	[75]
Amelioration of GU	DNJ ameliorated indomethacin-induced GU in male mice by improving antioxidant and anti-inflammatory profiles, inactivating the NF- $\kappa$ B signaling pathway, and increasing the anti-ulceration ability.	[76]

studies on anti-diabetic and related properties, and two studies on other pharmacological activities involving digestion and absorption of starch, and atherosclerotic lesion (AL).

In a review of clinical studies of DNJ in the twig of *M. alba* or *Ramulus mori* (RM), Chan *et al.* [80] reported that three clinical trials [81–83] were conducted in China and focused on using RM alkaloid tablets in the treatment of diabetes. RM tablets are found to be effective in lowering blood sugar in diabetic patients by reducing production [81] and delaying glucose absorption, regulating lipid metabolism [82], and improving intestinal microecology [83].

A DNJ-enriched leaf powder of *M. alba* (1.5%) was clinically tested at Tohoku University, Sendai, Japan, to determine the optimal dose to suppress post-prandial glucose (PPG) [84]. Volunteers (24 in number, average age of 25.3 years, and body mass index of 20.9 kg/m<sup>2</sup>) participated. They were divided into four groups, each received 0.0, 0.4, 0.8, or 1.2 g of DNJ-enriched leaf powder (corresponding to 0, 6, 12, or 18 mg of DNJ, respectively), followed by 50 g of sucrose in 100 ml of water. Blood samples were collected before DNJ and sucrose intake, and at 30, 60, 90, 120, 150, and 180 minutes after intake. Results showed that a dose of 0.8 and 1.2 g of the leaf powder significantly reduced PPG and secretion of insulin after 30–180

minutes. This indicates the effective dose and efficacy of the DNJ-enriched *M. alba* leaf powder in humans [84].

A clinical study evaluated the effects of DNJ-rich MLE on plasma lipid profiles in subjects at Medical Corporation Kenshokai, Osaka, Japan [85]. This single-group study comprised 10 subjects with an initial serum triglyceride (TG) level  $\geq 200$  mg/dl. Each subject ingested DNJ-rich MLE at a dose of 12 mg three times daily before meals for 12 weeks. Results showed that the TG level decreased from 312 to 269 mg/dl at week 6 and to 252 mg/dl at week 12. However, the differences were not significant. Changes in blood biochemistry that included total cholesterol, LDL-cholesterol, and high-density lipoprotein-cholesterol were also not significant [85].

At Nippon Medical School, Tokyo, Japan, the effect of DNJ-rich MLE on post-prandial hyperglycemia (PPH) was assessed in subjects having impaired glucose metabolism [86]. Study One, a carbohydrate test, was participated by 12 subjects with fasting plasma glucose (FPG) in the range of 100–140 mg/dl. They each ingested MLE with 0, 3, 6, or 9 mg DNJ on blood glucose and insulin, 2 hours after a carbohydrate meal of 200 g boiled white rice. Results showed that ingestion of the MLE significantly attenuated post-challenge acute glycemia in a dose-dependent manner. Study Two was to assess the efficacy of a 12-week MLE containing 6 mg DNJ on FPG in 76 subjects. Results showed that the serum 1,5-anhydroglucitol in the extract group increased. No differences were observed in FPG, glycated hemoglobin, and glycated albumin concentrations between the groups [86].

At Hallym University Hospital, Chuncheon, Korea, the  $\alpha$ -glucosidase inhibitory and post-prandial hypoglycemic effects of rice-coated MLE (12 mg/100 g rice) were tested for 14 days on 46 patients with impaired glucose tolerance (IGT) and on another group of 14 healthy adults [87]. The content of DNJ was 5.2 mg in 1.0 g of MLE. Results showed that MLE had significant inhibition towards PPH in both groups.  $\alpha$ -Glucosidase inhibition was four-fold higher in the IGT patients compared to the positive control. The study concluded that MLE ameliorated the hyperglycemic effect and can be used as a dietary supplement for the treatment of diabetic patients [87].

Another clinical study was conducted at the Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand [88]. The study investigated the optimal dose of DNJ in MLE and evaluated the efficacy and safety of the extract for glycemic control of obese persons with pre-diabetes and patients with borderline diabetes. Results showed that the optimal dose for long-term administration of MLE was 12 mg of DNJ to reduce PPH without any side effects except for some gastrointestinal symptoms. Overall, MLE decreased FPG, glycated hemoglobin, and ameliorated insulin resistance and inflammation. This clinical study also reported that DNJ in MLE caused gastrointestinal side effects such as symptoms including bloating, flatulence, and loose stools. Participants (50%) experienced bloating and flatulence during the first four weeks of the study [88].

A clinical study performed at the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, found that long-term (12 weeks) supplementation of DNJ-enriched MLE

(12 mg of DNJ) prevented the progression of diabetes [89]. A total of 54 obese patients with pre-diabetes or with early diabetes participated. Compared to the control group, the treatment group had alleviated insulin resistance and reduced hemoglobin A1C (HbA1c), PPH, and FPG [89].

The effect of mulberry leaf and water-chestnut husk tea on PPG levels in 30 subjects with borderline diabetes was investigated [90]. Subjects in the tea group were given 0, 3, 6, and 9 mg of DNJ, followed by 200 g of cooked rice. Results showed that blood glucose levels in the tea group significantly decreased at 30 and 60 minutes. Insulin was also significantly lower at 30, 60, 90, and 120 minutes. With hypoglycemic and antioxidant properties, the tea is expected to be effective for patients with borderline diabetes. The high antioxidant content in water chestnut husk reduced oxidative stress associated with high blood glucose levels in patients with borderline diabetes [90].

Conducted at the Poznan University of Medical Sciences in Poland, this clinical study investigated the effects of MLE on the digestion and absorption of starch in 25 healthy subjects, 19–27 years of age [91]. Subjects ingested 50 g of cornflakes and 100 ml of low-fat milk as a test meal either with the MLE (36 mg DNJ) or the placebo. A week later, MLE subjects were given the placebo while placebo subjects received MLE. The overall dose recovery was lower for MLE (13.9%) than for placebo (17.2%). A single dose of MLE taken with the test meal reduced starch digestion and absorption (10.8%) compared to the placebo (14.1%) [91].

At First Hospital of Jilin University in Changchun, China, a clinical study investigated the effects of DNJ extracted from *M. alba* leaves on AL in patients with CHD [92]. The patients were divided into treatment and control. A total of 160 CHD patients with LDL cholesterol ( $>140$  mg/dl) were given DNJ. The DNJ group was orally administered with 150 mg of DNJ per day (one tablet with 50 mg of DNJ, three times a day). Results showed that the DNJ group had increased serum levels of DNJ, improved serum lipid profile, and reduced antioxidant, anti-inflammatory, and oxidative stress [92].

## 6. CONCLUSION

DNJ is a polyhydroxylated piperidine alkaloid azasugar or iminosugar commonly found in the leaves of *Morus* (mulberry) species. Major pharmacological properties of DNJ are anti-diabetic, anti-obesity, hypolipidemic, cardioprotective, and anti-cancer activities. Other properties are hepatoprotective, neuroprotective, antimicrobial, anti-inflammatory, and nephroprotective activities. Minor properties are inhibition of VSMCs, inhibition of HUVECs, amelioration of GU, and attenuation of AL. Clinical studies on DNJ have affirmed its anti-diabetic and related properties. They entail pre-diabetic, borderline diabetic, and early diabetic cases. Other pharmacological activities of DNJ clinical studies are the digestion and absorption of starch and atherosclerotic lesions.

Suggested research on DNJ for further studies includes 1) Studies on the structure-activity relationship (SAR) of DNJ with regard to its pharmacological properties, such as anti-diabetic and anti-cancer activities, present exciting research opportunities in understanding its mechanisms of bioactivities.

The SAR studies can be extended to other pharmacological properties of DNJ. 2) Types of bacteria and viruses that are susceptible to DNJ are important in understanding the antimicrobial activities of DNJ. 3) The development of value-added DNJ drugs with enhanced pharmacological potency, such as the anti-diabetic drug Reducose® has its commercial merits. 4) Clinical trials on other pharmacological properties of DNJ other than those of anti-diabetic and its related activities need to be done to affirm its efficacy. Overall, the potential of DNJ as a commercial drug for various diseases is worth exploring.

## 7. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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## 9. CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

## 10. ETHICAL APPROVALS

This study does not involve experiments using animals or human subjects.

## 11. DATA AVAILABILITY

All data generated and analyzed are included in this research article.

## 12. PUBLISHER'S NOTE

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## 13. USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declare that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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