Phytochemicals, Management of Diabetic Peripheral Neuropathy, Experimental Evidences

Abstract

Diabetic peripheral neuropathy (DPN) is an unwanted side effect that usually occurs in both types of diabetes mellitus (DM). Like other diabetic complications, the cause of DPN is not clear. This review will provide an experimental evidences on some common phytochemicals that used for the prevention or treatment of DPN. This review will not be only useful to doctors in making decisions about the best available phytochemical therapeutic choices of DPN but also to avoid the side effects of pharmacological drugs.

Keywords: Diabetes mellitus; Diabetic peripheral neuropathy; Phytochemicals

Abbreviations: DM: Diabetes Mellitus; DPN: Diabetic Peripheral Neuropathy; ROS: Reactive Oxygen Species; GB: Ginkgo Biloba; MC: Momordica Charantia; MO: Moringa oleifera; TF: Trigonella foenum-graecum; CP: Calotropis procera; AD: Artemisia Dracunculus; CC: Citrullus colocynthis; TC: Tinospora cordifolia; OE: Olea Europaea; GS: Gymnema Sylvestre; CR: Catharanthus Roseus

Introduction

Nowadays, diabetes mellitus (DM) has become one of the most difficult health problems, where its incidence has considerably increased. It affects more than 230 million people worldwide, and this number is expected to reach 350 million by 2025 [1,2]. Diabetic peripheral neuropathy (DPN) is the most common complication of DM. It occurs in more than 60% of the diabetic patients affecting their quality of life. The most common form of DPN is a sensory polyneuropathy with symptoms such as paresthesia, hyperalgesia and reduced temperature and vibration perceptions [3,4]. Studies of DPN models have reported a decrease in impulse conduction in the peripheral nerves, interpreted as being caused by a reduction in number of large or medium-sized axons [5,6], demyelination or axon atrophy [7]. Many mechanisms have been postulated in the pathogenesis of DPN including hyperglycemia, impaired insulin activity, vascular effects, hypoxia and inflammation, which leads to increased production of reactive oxygen species (ROS) [3,8-10].

It was reported that DPN is an incapacitating problem of both types of DM, which affects more than 50% of diabetic patients [11-13]. However, recent studies showed that the progressive axonal atrophy is more severe in type 1 DM; in contrast to type 2, which shows nodal and para nodal degenerative changes [14]. Moreover, it was reported that DPN is the leading cause of non-traumatic limb amputation [15] and development of develop foot ulcers [16].

Currently, DPN management depends on the conservative therapy, which includes mainly analgesics and anti-inflammatory drugs. Other approaches include neurotrophic factors and antioxidants [12,17,18]. However, the clinical studies have failed to demonstrate the effectiveness of any drug treatment in improving nerve function, in addition to their wide spectrum of adverse effects which limit their usefulness [19,20].

Recently, many medical professions had a significant interest regarding complementary and alternative medicine by identifying natural antidiabetic and neuro-protective agents from plant origin to replace the synthetic drugs. These plants contain a large amount of phytochemicals such as polyphenols, organosulfuric compounds, limonoids, flavonoids, terpenoids and saponins. These compounds were found to have good availability with few side effects in addition to their antioxidant activity, DNA modulation effect and immune system stimulation.

As there is a plenty of new phytochemicals from plant origin that have strong effects against the neuropathic pain and the progression DPN, this mini review is undertaken to highlight some of the phytochemical-containing plants and their experimentally potential beneficial effects.

Ginkgo biloba (GB)

Extracts of GB (50 mg/kg body weight) exhibited neuroprotective effect on the ileum myenteric plexus and on the jejunal submucous plexus of STZ-diabetic rats [21]. It is well documented that GB extract particularly inhibits oxidative stress in the mitochondria [22].

Momordica charantia (MC)

It has been reported that administration of MC (200-800 mg/kg body weight for 6 weeks) caused a decrease in withdrawal latency without impacting sensory and motor functions [23]. It was demonstrated a potent neuroprotective activity of MO against neural injury and consequent neurological deficits in a diabetic mouse model [24].
**Moringa oleifera (MO)**

The methanol extract of MO dried fruit powder has been shown to stimulate insulin release from rodent pancreatic β-cells and to inhibit cyclooxygenases and lipid peroxidation [25]. The administration of 50-100 mg MO seed powder/kg body weight to diabetic rats has been reported to ameliorate DPN and to restore the normal histology of both kidney and pancreas [26].

**Trigonella foenum (TF)**

It was reported a higher GLK/glucose-6-phosphatase (G6Pase) ratio in the liver and lower levels of serum tumor necrosis factor alpha in TF-treated mice compared to controls [27]. Extract from the seed of TF when administered to rats at 100 and 200 mg/kg orally for 7 days, was found to offer protection against thermal hyperalgesia, while 15 days’ administration restored motor nerve conduction velocity [28].

**Punica granatum (PG)**

PG flower extract improved postprandial hyperglycemia in type 2 diabetes by inhibiting α-glucosidase activity [29]. PG extract and its spray dried biopolymeric dispersions with casein or chitosan were evaluated against DN and found to be effective in improving peripheral nerve function [30].

**Calotropis procera (CP)**

The administration of root extract of CP at 100 mg/kg body weight in diabetic rats attenuated the impairment of diabetic condition and reversed DPN and neuropathic pain [31]. Administration of methanolic and ethyl acetate extracts of the root, stem, and leaf of CP at 100 and 250 mg/kg doses for 14 days significantly attenuated hyperalgesia, tactile allodynia, and HbA1C% levels in STZ diabetic rats [32].

**Artemisia dracunculus (AD)**

A study performed on high fat diet induced neuropathy of prediabetes and obesity in mice reported that the ethanolic extract of AD (500 mg/kg/d for 7 weeks) normalized glycemia, alleviated nerve conduction slowing and sensory neuropathy in the peripheral nervous system [33].

**Citrus aurantium (CC)**

The oral administration of 300 mg/kg body weight ethanolic extract of dried seedless pulp of CC showed insulin-trropic actions in alloxan-induced diabetic rats [34]. Recently, 11-deoxocurcurbitacin-glucoside was isolated from the seed of a CC chloroform fraction which exerted significant in vivo anti-inflammation and analgesic activities at all tested doses [35].

**Tinospora cordifolia (TC)**

Aqueous extract of TC significantly reversed the hyperalgesia at a dose of 200 and 400 mg/kg body weight [36]. In addition, following TC administration, reduced glucokinase, insulin, and C-peptide levels were improved, showing the regeneration of insulin-secreting β-cells [37].

**Olea europaea (OE)**

Treatment with olive leaf extract (300 and 500 mg/kg/d) ameliorated hyperalgesia, inhibited caspase-3 activation, and decreased bcl-2-like protein-4 (Bax)/B-cell lymphoma 2 (Bcl-2) ratio [38].

**Gymnema sylvestre (GS)**

Administration of GS extract has been shown to ameliorate the untoward effects of DPN in experimental induced diabetic rats. GS at 100 mg/kg body weight was observed to induce attenuation in diabetes-induced biochemical and histopathological alterations in the sciatic nerves of rats [39].

**Conclusion**

In conclusion, DPN is the most annoying complication of DM. This mini review highlights some of the phytochemical-containing plants and their experimentally potential beneficial effects. The information of this review will not be only useful to doctors and patients in making decisions about the best available phytochemical therapeutic choices to improve the symptoms of DPN but also to avoid the side effects of pharmacological drugs.

**References**


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