

# 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

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**Hamid Saleh, Gamal S Abd El Aziz**

Department of Anatomy, King Abdulaziz University, Saudi Arabia

**Correspondence:** Hamid Saleh, Department of Anatomy, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia, Email [hsaleh@kau.edu.sa](mailto:hsaleh@kau.edu.sa)

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**Abbreviations:** DM, diabetes mellitus; DPN, diabetic peripheral neuropathy; ROS, reactive oxygen species; GB, ginkgo biloba; MC, *momordica charantia*; MO, *moringaoleifera*; TF, *trigonellafoenum*; PG, *punicagranatum*; CP, *calotropisprocera*; AD, *artemisia dracunculus*; CC, *citrullus colocynthis*; TC, *tinoporacordifolia*; 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 230million people worldwide, and this number is expected to reach 350million by 2025.<sup>1,2</sup> 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.<sup>3,4</sup> 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,<sup>5,6</sup> demyelination or axon atrophy.<sup>7</sup> 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).<sup>3,8-10</sup>

It was reported that DPN is an incapacitating problem of both types of DM, which affects more than 50% of diabetic patients.<sup>11-13</sup> 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.<sup>14</sup> Moreover, it was reported that DPN is the leading cause of non-traumatic limb amputation<sup>15</sup> and development of develop foot ulcers.<sup>16</sup>

Currently, DPN management depends on the conservative therapy, which includes mainly analgesics and anti-inflammatory drugs. Other approaches include neurotrophic factors and antioxidants.<sup>12,17,18</sup> 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.<sup>19,20</sup>

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

## Momordica charantia (MC)

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

## Moringaoleifera (MO)

The methanol extract of MO dried fruit powder has been shown to stimulate insulin release from rodent pancreatic  $\beta$ -cells and to inhibit cyclooxygenases and lipid peroxidation.<sup>25</sup> The administration of 50-100mg 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.<sup>26</sup>

## Trigonellafoenum (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.<sup>27</sup> Extract from the seed of

TF, when administered to rats at 100 and 200mg/kg orally for 7days, was found to offer protection against thermal hyperalgesia, while 15days' administration restored motor nerve conduction velocity.<sup>28</sup>

### **Punicagranatum (PG)**

PG flower extract improved postprandial hyperglycemia in type 2 diabetes by inhibiting  $\alpha$ -glucosidase activity.<sup>29</sup> 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.<sup>30</sup>

### **Calotropisprocera (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.<sup>31</sup> Administration of methanolic and ethyl acetate extracts of the root, stem, and leaf of CP at 100 and 250mg/kg doses for 14days significantly attenuated hyperalgesia, tactile allodynia, and HbA1C% levels in STZ diabetic rats.<sup>32</sup>

### **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 (500mg/kg/d for 7weeks) normalized glycemia, alleviated nerve conduction slowing and sensory neuropathy in the peripheral nervous system.<sup>33</sup>

### **Citrullus colocynthis (CC)**

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

### **Tinospora cordifolia (TC)**

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

### **Olea europaea (OE)**

Treatment with olive leaf extract (300 and 500mg/kg/d) ameliorated hyperalgesia, inhibited caspase-3 activation, and decreased bcl-2-likeprotein4 (Bax)/B-cell lymphoma 2 (Bcl-2) ratio.<sup>38</sup>

### **Gymnema sylvestre (GS)**

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

### **Catharanthus roseus (CR)**

The oral administration of aqueous extract (250mg/kg) of the flowers, leaves, roots, and stems of CR and its alkaloid-free fraction (300mg/kg) significantly reduced blood glucose in diabetic mice. Their hypoglycemic activity was comparable to that of the tolbutamide-treated group. It was demonstrated that CR can be used as a prophylactic agent against complications and abnormalities associated with DN.<sup>41</sup>

## **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.

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## **Conflict of interest**

Author declares that there is no conflict of interest.

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