Effects of *Dioscoreae Rhizoma* (*SanYak*) on Peripheral Neuropathy and its Safety

Min-jung Kim¹, Hyunkyung Sung², Kwon-eui Hong*¹

¹ Department of Acupuncture & Moxibustion, Oriental Hospital of Daejeon University, Daejeon, Korea
² Department of Oriental Pediatrics, Oriental Hospital of Daejeon University, Daejeon, Korea

Key Words
*Dioscoreae Rhizoma* (DR), peripheral neuropathy, safety, effects

Abstract

Objectives: This study aimed to evaluate the evidence available in the literature for the safety and efficacy of *Dioscoreae Rhizoma* (DR) for the treatment of peripheral neuropathy.

Methods: Literature searches were performed in MEDLINE and three Korean medical databases up to April 2013. All studies evaluating the effects on peripheral neuropathy or the safety of DR monopreparations were considered.

Results: Three studies - DR extract per os (po) on diabetic neuropathy in mice, DR extract injection on the peripheral sciatic nerve after crush injury in rats and DR extract injection to patients with peripheral facial palsy proved that DR treatments were effective for the treatment of nerve injuries.

Conclusions: In conclusion, we found the DR has a strong positive potential for the treatment of peripheral neuropathy, but studies addressing direct factors related to the nerve still remain insufficient.

1. Introduction

In Korea, *Dioscoreae Rhizoma* (DR) is widely used as a herbal medicine or food product with potential health benefits [1, 2]. The major components of DR are known to be saponins [3] and sapogenins [4], starch [5], purine derivatives, and muclage [6]. DR extract was approved by the Korean Food and Drug Administration (KFDA) in 2011. The KFDA claimed that the extract at a dose of 900 mg/day effectively regulated the blood sugar level [7]. In addition, the protective effect of DR against diabetic neuropathy has been demonstrated by induction of nerve growth factor (NGF) [2].

Diabetic neuropathy is the most common condition associated with peripheral neuropathy [8], which is the most common form of nerve damage and may be caused by diseases or trauma to the nerves or by the side effects of systemic illness [9]. Frequently, the causes and treatments of neuropathy cannot be identified, and it is designated as being idiopathic [8]. In this report, the authors aimed to evaluate the effects of DR on the peripheral nervous system.

2. Materials and Methods

A literature search was performed in MEDLINE and three Korean medical databases (Korean Studies Information, DBPIA - DataBase Periodical Information...
Academic, and Korean Pharmacopuncture Institute Information) up to April 2013 without language restriction. All studies evaluating either the effects of DR monopreparations (Dioscoreae Rhizoma or San yak) on peripheral neuropathy or the safety of those DR monopreparations were considered. An initial assessment was made by the reading abstracts. Articles that appeared to be appropriate were then investigated in full by two authors, who then discussed the articles and made the decision to include or exclude them.

3. Results

3.1. Safety of DR

3.1.1. RCT with DR pharmacopuncture

Randomized controlled clinical trials (RCT) with DR pharmacopuncture was published to evaluate its safety in 2013. A total of 25 participants were divided into the following three groups by a medical statistics expert according to block randomization: 10 participants for the distilled saline DR group (DDG), 10 participants for the alcohol extracted DR group (ADG), and five participants for the control (normal saline) group (NSG). Each treatment was performed three times a week, for a total of 10 times. The participants fasted for at least 14 hr and underwent a liver function test, a complete blood cell count, and urinalysis before the injection and after completing 10 rounds of pharmacopuncture. After injections, the total protein level in the liver function tests and the hematocrits changed within normal limits. DR pharmacopuncture did not cause any severe physical responses or subjective symptoms. DR pharmacopuncture was demonstrated to be safe according to this study [10].

3.1.2. Clinical cases with DR allergen

Two patients with DR allergy were evaluated. Patient 1 complained of severe urticaria and angioedema following indigestion of DR with water as a health supplement. She had been suffering from multiple food allergies, including shellfish and peaches, and from allergic rhinitis. Patient 2 had been working as a merchant dealing in several herbal materials including DR. She had dyspnea with sudden onset following exposure to DR. She was allergic to foodstuffs, including chestnuts and potatoes, and was suffering from allergic rhinitis [11]. Therefore, long-term use of DR or its use by an allergy-sensitive person should be treated with extra caution.

3.2. Effects of DR on peripheral neuropathy

3.2.1. Effects of DR extract po on diabetic neuropathy

The protective effects of DR extract against diabetic neuropathy were shown by induction of nerve growth factor (NGF) [2]. NGF is essential for the development and phenotypic maintenance of neurons in the peripheral nervous system [12].

Mice (ICR mice, 7-week-old) were administered samples by po. Control group (n = 3): 0.1 ml Vehicle po, DR extract 1 group (n = 3): 1 mg/kg DR extract po, DR extract 3 group (n = 3): 3 mg/kg DR extract po, DR extract 10 group (n = 3): 10 mg/kg DR extract po, DR extract 30 group (n = 3): 30 mg/kg DR extract po, DR extract 100 group (n = 3): 100 mg/kg DR extract po, and DR extract 300 group (n = 3): 300 mg/kg DR extract po. Sciatic nerves and salivary glands were collected after 16-h administrations of the samples by po. The NGF levels in the mice were investigated by using the Enzyme-linked immunosorbent assay (ELISA) method in each section. DR extract increased the endogenous NGF levels in the salivary gland and the sciatic nerve of a mouse, although not in proportion.

Type-2 diabetes mice (db/db mice, 7-week-old) were administered samples by po. Control group (n = 5): 0.1 ml Vehicle po, DR extract 10 group (n = 5): 10 mg/kg DR extract po, and DR extract 100 group (n = 5): 100 mg/kg DR extract po. Vehicle and samples were administered once a day for 30 days. The sensory nerve conductivity velocity (SNCV), the motor nerve conductivity velocity (MNCV) and thermal hyperalgesia increased in the DR-extract-treated mice compared with the control group [2].

3.2.2. Effects of DR extract injection on the peripheral sciatic nerve

DR extract (5 μL of 10 mg/mL) or an equivalent volume of saline (0.9% NaCl) was directly applied into the crush sites of the sciatic nerve for comparison. Focal application of DR extract at the injury site increased GAP-43 and Cdc2 protein levels in the distal portion of the injured nerve. DR was demonstrated to be effective for the regeneration of the peripheral sciatic nerve after crush injury in rats by using biochemical and histological analyses [13]. GAP-43 is strongly induced at the gene expression level in neurons after axonal injury and is transported into the growth cone involved in the process of regrowth [14, 15]. Cdc2 is the prototypical cell cycle protein and plays a critical role in the transition from growth phase 2 to the mitotic phase [16].

Furthermore, a quantitative analysis of axonal regeneration by counting Dil-labeled axons of neurons undergoing axonal regeneration revealed that DR treatment increased axonal regeneration. DR treatment increased staining for NF-200 in axons [13].

3.2.3. Effects of DR extract injection on patients with peripheral facial paralysis
The authors of this study conducted a retrospective investigation for a total 70 cases of patients, who were diagnosed as having peripheral facial paralysis by physical examination. For comparative analysis, the patients were divided into 11 patients treated with acupuncture and alcohol extracted DR pharmacopuncture (ADG), 25 patients treated with acupuncture and distillation DR pharmacopuncture (DDG) and 34 patients treated with acupuncture and non-DR pharmacopuncture (NDG). The changed House-Brackmann grades indicated significant improvements in all three groups, and the ADG and the DDG showed significant results after two weeks of treatment compared to the NDG. The change in Yanagihara’s score showed significant improvements in all three groups, and the ADG group showed significant results after 10 and 15 days of treatment when compared to the NDG. DR pharmacopuncture did not cause any severe physical responses or subjective symptoms except pain after application of pharmacopuncture [17].

4. Discussion

DR is a member of the Dioscoreaceae or Yam family, frequently used to treat diarrhea, cough, spermatorrhea, leucorhea, urinary frequency, and arthritis [18]. In the theories of traditional Korean medicine, the function of DR is delineated as helping to remove dampness and to promote healthy body condition [19].

Several studies have shown that DR decreases damage in renal tubules, inflammation in the central vein, and necrosis in the liver through its anti-inflammatory action [20]. The inhibitory effects of Dioscorealide B, a naphthoquinone isolated from DR, on NO and TNF-α production were also reported [21]. Recently in Korea, the hypoglycemic effect and the preventive effect of DR extract were examined in a rodent model [1, 2]. The protective effect of DR against diabetic neuropathy has been demonstrated [2]. In this study, we demonstrated the effects of DR on the nerve, as well as its safety, by reviewing previous studies.

One randomized controlled trial was performed to evaluate the safety of using DR pharmacopuncture on healthy persons. After injections, the total protein level in liver function tests and hematocrits changed within normal limits, and DR pharmacopuncture did not cause any severe physical responses or subjective symptoms in this study [10]. Another clinical study with 70 cases of peripheral facial paralysis reported that DR pharmacopuncture did not cause any severe physical responses or subjective symptoms [17]. Though DR allergy cases are very rare, two cases with DR allergy to multiple food allergies, as well as allergic rhinitis, were evaluated [11]. Therefore long-term use of DR or use by allergy-sensitive persons should be treated with extra caution.

Protective effects of DR extract against diabetic neuropathy were shown by induction of NGF. In this study, DR extract po increased the endogenous NGF level in the salivary gland and the sciatic nerve of a normal mouse. The sensory nerve conductivity velocity, motor nerve conductivity velocity and thermal hyperalgesia were increased in the DR-extract-treated type-2 db/db mice compared with the control group [2]. Another study with focal application of DR extract (5 μL of 10 mg/mL) at the injury site of the sciatic nerve showed that DR was effective for the regeneration of the peripheral nerve by using biochemical and histological analyses of GAP-43, Cdc2, Dil-labeled neurons and NF-200 [13]. Clinical research with 70 cases investigated the effects of DR on peripheral facial paralysis. The changes in the House-Brackmann grades and the Yanagihara scores in DR-pharmacopuncture-treated group indicated significant improvements compared with normal saline group [17].

5. Conclusion

We reviewed studies with DR treatments for peripheral neuropathy. There were three studies - DR extract per os (po) on diabetic neuropathy in mice, DR extract injection on the peripheral sciatic nerve after crush injury in rats and DR extract injection to patients with peripheral facial paralysis. In these studies, DR treatments were identified to be effective for the treatment of nerve injuries, but studies addressing direct factors related to the nerve still remain insufficient.

References

1. Kang TH, Choi SZ, Lee TH, Son MW, SY Kim. [Characteristics of antidiabetic effect of Dioscorea rhizome (1) -Hypoglycemic Effect-] Korean J Food & Nutr. 2008;21(4):425-9. Korean.
2. Kang TH, Choi SZ, Lee TH, Son MW, Park JH, Kim SY. [Characteristics of Antidiabetic Effect of Dioscorea rhizome (2) -Prevention of Diabetic Neuropathy by NGF Induction-] Korean J Food & Nutr. 2008;21(4):430-9. Korean.
3. Liu CZ, Zhou HY, Yan Q. Fingerprint analysis of Dioscorea nipponica by high-performance liquid chromatography with evaporative light scattering detection. Analytica Chimica Acta. 2007;582(1):61-8.
4. Akahori A. Studies on the steroidal components of domestic plants-XLIV : Steroidal sapogenins contained in
Japanese Dioscorea sp. Phytochemistry. 1965;4(1):97-106.
5. Jayakody L, Hoover R, Liu Q, Donner E. Studies on tuber starches. II. Molecular structure, composition and physicochemical properties of yam (Dioscorea sp.) starches grown in Sri Lanka. Carbohydr Polym. 2007;69(1):148-63.
6. Fu YC, Ferng LHA, Huang PY. Quantitative analysis of allantoin and allantoic acid in yam tuber, mucilage, skin and bulbil of the Dioscorea species. Food Chemistry. 2006;94(4):54-9.
7. Park CL, Lee JS. Mini Review: Natural ingredients for diabetes which are approved by Korean FDA. Biomedical Research. 2013;24(1):164-9.
8. Martyn CN, Hughes RAC. Epidemiology of peripheral neuropathy. J Neurol Neurosurg Psychiatry. 1997;62(4):310-8.
9. US National Institute of Neurological Disorders and Stroke (NINDS). Peripheral neuropathy fact sheet NIH Publication No. 04-4853 [Internet]. Bethesda (MD): National Institutes of Health; c2012. [cited 2012 Aug 10]. Available from: http://www.ninds.nih.gov/disorders/peripheralneuropathy/detail_peripheralneuropathy.htm.
10. Ko MK, Hong KE. Evaluation of the safety of Sanyak (Dioscoreae Rhizoma) pharmacopuncture according to the extraction method: a double-blind randomized controlled trial. J Acupunct Meridian Stud. 2013;6(1):41-51.
11. Hur GY, Park HJ, Kim HA, Ye YM, Park HS. Identification of Dioscorea batatas (Sanyak) allergen as an inhalant and oral allergen. J Korean Med Sci. 2008;23(1):72-6.
12. Aloe L, Bracci-Laudiero L, Bonini S, Manni L. The expanding role of nerve growth factor: from neurotrophic activity to immunologic diseases. Allergy. 1997;52(9):883-94.
13. Lee JM, Namgung U, Hong KE. Growth-promoting activity of Sanyak (Dioscoreae rhizoma) extract on injured sciatic nerve in rats. J Acupunct Meridian Stud. 2009;2(3):228-35.
14. Skene JH, Willard M. Axonally transported proteins associated with axon growth in rabbit central and peripheral nervous systems. J Cell Biol. 1981;89(1):96-103.
15. Gispen WH, Boonstra J, De Graan PNE, Jennekens FG, Oestreicher AB, Schotman P, et al. B-50/GAP-43 in neuronal development and repair. Restorat Neurol Neurosci. 1990;1(3):237-44.
16. Hunt T. Cyclins and their partners: from a simple idea to complicated reality. Semin Cell Biol. 1991;2(4):213-22.
17. Sung IS, Hong KE, Kim MJ, Song I. Clinical research of the efficacy and the safety of Dioscoreae Rhizoma (San-yak) pharmacopuncture therapy for peripheral facial paralysis patients. Pharmacopuncture. 2012;15(4):15-24.
18. Zhong X, Nishino E, Okagami N. Temperature dependence of seedling establishment of a perennial, Dioscorea tokoro. J Plant Res. 2002;115(1117):55-7.
19. The Compilation Committee of Oriental Medicine University. Herbal medicine. Seoul:Younlimsa;2004. p. 583-4.
20. Lee SC, Tsai CC, Chen JC, Lin CC, Hu ML, Lu S. The evaluation of reno- and hepatoprotective effects of huai-shan-yao (Rhizome Dioscoreae). Am J Chin Med. 2002;30(4):609-16.
21. Tewtrakul S, Itharat A. Nitric oxide inhibitory substances from the rhizomes of Dioscorea membranacea. J Ethnopharmacol. 2007;109(3):412-6.