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Topical Remedy for Diabetic Neuropathy in Persian Medicine and Modern Phytotherapy: A Narrative Review

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ABSTRACT

One of the most common complications of diabetes, which places a significant economic burden on both patients and society, is diabetic peripheral neuropathy. Managing diabetic neuropathy is challenging due to the limited availability of effective treatment options. In recent years, numerous studies have shown that topical herbal medicines can alleviate neurological symptoms. Therefore, these products, which offer significant analgesic effects with minimal side effects, have been used to treat patients with this condition. This paper reviews six types of topical herbal medicines with analgesic effects on diabetic neuropathy and provides insights for researchers aiming to design and develop effective topical herbal treatments.

Keywords: Diabetic Neuropathies, Plants, Medicinal, Administration, Topical, Persian Medicine

1. Introduction

1.1. Diabetic peripheral neuropathy

One of the most common complications of diabetes that imposes a large economic burden on patients and society is diabetic peripheral neuropathy (DPN), which occurs in one out of five diabetic patients (1, 2). The causes of 32% to 53% of peripheral neuropathy are diabetes (3). Symptoms of DPN appear after 14.5 years in people with type 1 diabetes and after 8.1 years in people with type 2 diabetes (4). This micro-vascular complication damages the peripheral and central nervous system, and it can increase death (2, 5, 6). The DPN pain can limit the patients' daily activities and job performance, reduce their walking speed, induce falling, fractures, leg manuscript, and significantly reduce the quality of life. This is a big challenge for health care (1, 7).

Regarding DPN, it has been suggested that high blood glucose levels cause oxidative and nitrosative stress and ultimately damage the nervous system (8, 9). The management of DPN includes timely diagnosis, blood glucose control, psychotherapy, and symptomatic pain treatment (1). Many researchers have suggested that

synthetic medicines such as gabapentin, pregabalin, duloxetine, and amitriptyline are used to relieve neuropathic pain. These medicines may be taken several times a day. Therefore, frequent and long-term medication increases the side effects and drug-to-drug interaction (10-13). On the other hand, medication adherence is usually poor due to inadequate pain relief (6). These challenges highlight the need for alternative or complementary approaches.

Due to the failure of current treatments in relieving the pain of DPN, nowadays, herbal remedies are receiving more attention in research. Herbal remedies can be used to manage chronic pain (2). In recent years, growing attention has been directed toward herbal remedies, especially topical formulations, due to their lower systemic side effects, reduced risk of drug interactions, and better patient acceptance. These limitations have increased interest in complementary therapies, particularly topical herbal medicines, which may offer effective pain management with fewer systemic effects. Persian medicine is one of the important schools of complementary medicine with rich scientific resources. Based on the theories in Persian medicine and with the help of modern technologies, it is hoped that more effective and safer medicines can be produced (14). Several medicinal plants have shown promising analgesic and anti-inflammatory properties in experimental models of DPN. In traditional Persian medicine, nerve-related pain syndromes have been described in detail, and a wide range of topical treatments using herbal oils and ointments have been proposed for neuropathic conditions.

Given the limitations of current treatments and the increasing interest in integrative medicine, this narrative review aims to summarize the existing clinical evidence on the efficacy and safety of topical herbal treatments for DPN, focusing on formulations rooted in Persian medical literature. This review also seeks to identify gaps in current research and propose directions for future investigations.

1.2. DPN in Persian Medicine

"Auojae Asab" was a medical term in the medieval Persian medical literature to describe nerve-originated pain syndromes (15).

According to Avicenna (Ibn Sina), neuropathy is divided into several categories, including paralysis [Falaj], facial paralysis [Laghveh], paresis [Esterkha], sensory disturbance [Khadar], tremors [Ra'sheh], and muscle spasms [Tashannoj]. In Persian medicine, khadar (sensory neuropathy) is a general term for diseases with similar sensory symptoms such as pain, paresthesia, and hypoesthesia. Moreover, in Avicenna's opinion, sensory and motor nerves are various, or in "temperament" in Persian medicine. Hence, nerves are different in susceptibility to neuropathy, and sensory symptoms appear before motor symptoms (16).

According to Medieval Persian scholars, DNP is a type of "khadar" or "Esterkha" which is caused by the accumulation of glucose in peripheral nerves (17).

1.3. Side Effects

Among the advantages of topical herbal treatments for DPN are: lower cost, ease of use, reduced systemic absorption, and minimal drug interactions. These features make them particularly attractive for patients who require long-term pain management. However, safety considerations such as potential allergic irritation or limited absorption still need further investigation, highlighting the importance of critically reviewing current clinical evidence.

Considering the lack of a systematic review study that specifically measures the cumulative effect of peppermint essential oil on the severity of nausea and vomiting, this study aims to systematically evaluate the cumulative evidence on the effectiveness of peppermint essential oil in reducing the severity of CINV through a meta-analysis of randomized controlled trials.

2. Search Strategy

In this narrative review, a literature search was conducted in the databases PubMed, Scopus, and Google Scholar using the following keywords: "Diabetic Neuropathies", "Plants, Medicinal", "Administration, Topical", and "Persian Medicine". The search included articles published up to the end of 2022, with no geographical restrictions. After screening the titles and abstracts, relevant studies were selected based on their focus on the topical use of medicinal plants and herbal formulations with potential therapeutic effects on diabetic neuropathy. This review highlights and discusses plant-based topical treatments, particularly those rooted in Persian traditional medicine, that have shown promise in alleviating or managing symptoms of diabetic neuropathy.

3. Topical Herbal Medicines

Due to DPN's adverse effect on patients' quality of life, proper treatment is very important (18). The limited efficacy and more side effects of systemic therapies for DNP, topical herbal medicines as promising alternatives. Due to their analgesic, anti-inflammatory, and neuroprotective properties, several medicinal plants have shown potential in relieving DNP-related pain (3, 19). This section reviews the effects of topical herbal treatments-capsaicin (pepper), nutmeg, bitter apple, hemp seed, turmeric, and black cumin-on DNP.

3.1. Effect of Pepper on DNP

Due to its anti-inflammatory and antioxidant properties, topical capsaicin has successfully relieved pain in patients with DNP (20-22). Capsaicin, an active ingredient of chili pepper (Capsicum annuum L.), binds to the TRPV1 (transient receptor potential vanilloid 1) channel-a membrane channel involved in pain sensation. Upon activation, this channel allows sodium and calcium influx, triggering the release of substance P. Repeated exposure

to capsaicin reduces substance P levels and a decline in TRPV1 sensitivity and function (1).

Studies on the effectiveness of low-concentration topical capsaicin cream (0.075%) have yielded conflicted results. However, the American Academy of Neurology recommends topical capsaicin cream 0.075% as a treatment option for pain relief in patients with DNP (23). Research suggested that capsaicin 0.075% provides pain relief comparable to oral amitriptyline, with a better safety profile (24). Also, the topical application of 0.075% capsaicin cream for eight weeks reduced pain in people with DNP (25). Additionally, an 8% capsaicin patch could moderately but significantly relieve the pain in patients with painful peripheral neuropathy, so it was reported as a good option for controlling DNP (26). In contrast, some studies have reported limited effectiveness of low-concentration capsaicin in DNP management (27, 28).

3.2. Effect of Nutmeg on DNP

The nutmeg (*Myristica fragrans Houtt.*) has also shown beneficial effects in relieving pain in DNP patients (1). Myristicin (an active compound in nutmeg) exhibits neuroprotective effects through the regulation of apoptosis mediators such as caspase-3, B-cell lymphoma-2 (Bcl-2), and Bcl-2-associated X protein as well as antioxidant activities (29). Another compound, allyl guaiacol, protects hippocampal cells through modulation of the NF-κB pathway and increased expression of brain-derived neurotrophic factor (BDNF) (30).

Topical use of nutmeg extract spray over four weeks significantly reduced average pain scores and improved quality of life in patients with DNP. However, there was no statistically significant difference between the nutmeg topical and placebo spray groups (31), indicating a need for further investigation.

3.3. Effect of Bitter Apple on DNP

Bitter apple (*Citrullus colocynthis* L.) is a medicinal plant native to Asia and Africa, traditionally used for pain relief due to its antioxidant, analgesic, anesthetic, and anti-inflammatory properties (1, 9, 32). The topical use of *Citrullus colocynthis* L. oil has been reported to significantly improve neurological function and reduce average pain scores in patients with DNP, thereby enhancing their overall quality of life (33).

3.4. Effect of Hemp Seed on DNP

The main bioactive components of hemp seed (Cannabis sativa L.) are *cannabinoids*, primarily *cannabidiol* (CBD) and *tetrahydrocannabinol* (THC), both known for their analgesic effects (34). In a randomized controlled clinical trial involving 30 patients with diabetic peripheral neuropathy (DPN), the use of a cannabis-based medicinal spray (Sativex) over 12 weeks showed no statistically significant improvements in neuropathic pain scale (NPS), total pain score (TPS), quality of life, or SF-36 questionnaire outcomes compared to placebo (35). However, studies in animal models have shown that cannabis extract may alleviate DPN by reducing oxidative neuronal damage, increasing nerve growth factor levels, and modulating the TRPV1 channel (2).

3.5. Effect of Turmeric on DNP

Turmeric (*Curcuma longa* L.), a widely used spice and medicinal plant from the *Zingiberaceae* family, contains active constituents such as curcumin (diferuloylmethane) and several volatile oils (e.g., atlantone, tumerone, zingiberone) (19). Curcumin is known for its antioxidant and anti-inflammatory effects, contributing to its pain-relieving potential (36). The studies have shown that topical curcumin cream, either alone or combined with capsaicin, can reduce pain associated with DNP (37). Furthermore, using curcuminoids topically helps avoid the low oral bioavailability and may reduce the likelihood of drug interactions (2).

3.6. Effect of Black Cumin on DNP

Black cumin (*Nigella sativa L.*) and its primary active compound, thymoquinone (TQ), exhibit a broad range of neurological benefits, including anti-inflammatory, antioxidant, analgesic, anti-anxiety, and neuroprotective effects (38). Topical applications of Nigella sativa have demonstrated efficacy comparable to oral gabapentin in reducing pain and improving clinical outcomes in DNP patients (39, 40). Additionally, topical black cumin oil has shown clinical efficacy similar to topical diclofenac in women with periodic mastalgia, suggesting a broader potential for pain management (41).

3.7. Other Herbal Oils in Persian Medicine

Traditional Persian medicine also highlights herbal oils such as olive oil, garlic oil, flaxseed oil, saffron oil, castor oil, and chamomile oil for nerve protection. These oils are praised for their anti-inflammatory and antioxidant properties, offering a safe and effective complementary approach for managing neuropathic pain (20, 42).

4. Discussion

4.1. Etiology of DNP

DNP is caused by increased production of free radicals and oxidative stress (2). There is increasing evidence that hyperglycemia reduces glutathione, increases the production of reactive oxygen species, induces oxidative stress, increases the production of advanced glycation end products (AGEs), and causes neuronal hypoxia (i.e., changes in the electrical stability and function of sensory nerves) (1). Hence, inflammatory cytokines and growth factors cause inflammation and nerve damage. Also, activating pro-inflammatory cascades increases the release of serotonin and norepinephrine. Finally, the pain threshold is lowered, which causes severe pain in DNP (1).

4.2. Management of DNP in Persian Medicine

The humeral and temperamental approach of Persian medicine can help to find preventive and therapeutic solutions for neuropathy. According to this theory, the accumulation of inappropriate humor and its imbalance in

the body can cause disorders. From Avicenna's point of view, the prevention and treatment of neuropathy include a couple of measures discussed below.

a. Lifestyle modification

In the second part of the first volume of the *Canon of Medicine*, Avicenna has stated the main factors of lifestyle affecting body health. He refers to six basic items (or Asbab-e-Settah-e-Zaruriah) as preventive/therapeutic factors. His treatment strategy assumes that any disturbance in these factors changes one's temperament and makes the body susceptible to various diseases.

b. Medication

The main strategy that Avicenna recommended for treating neuropathy is to correct the temperament of the nerve. Several topical or oral herbal remedies are recommended in the *Canon of Medicine* for treating nerve pain. He has also suggested non-pharmacological interventions for the next stage of the disease **(16)**.

In summary, the different treatment strategies that are mentioned in the sources of Persian medicine for the management of nerve-originated pain syndromes are; a) lifestyle modification and temperament modification, b) ointments based on hot-natured plants such as pepper, chamomile and thyme, c) herbal syrups such as the one made from lavender, d) warm compress (Takmid), and e) cauterization by special devices, as the last option for severe pains that are resistant to treatment **(15)**.

DNP is difficult to relieve, and current medications for it are insufficient. The pathogenesis mechanisms involved in DNP are multidirectional and complex, including microvascular damage, metabolic disturbances, and alterations in the interaction of the nervous and immune systems. Most people in the world rely on traditional and complementary medicine for their daily health care needs. In this regard, it is to be noted that the World Health Organization (WHO) recommends traditional medicine, and a quarter of all medical prescriptions are herbal formulations or synthetic analogs derived from plants. As one of the comprehensive schools of traditional medicine, Persian medicine provides guidelines on types of neuropathy and managing their symptoms.

5. Conclusion

According to this review, although topical herbal medicines such as pepper, nutmeg, bitter apple, hemp, turmeric, black cumin, and traditional Iranian oils demonstrate varying degrees of effectiveness in managing DNP, they generally possess favorable safety profiles and offer complementary therapeutic benefits. Their low cost, ease of access, fewer side effects, lack of interaction with oral medications, acceptable efficacy, and historical use in traditional medicine make them attractive options, particularly in cases where systemic treatments are poorly tolerated. However, well-designed clinical trials are essential to confirm their efficacy, optimize therapeutic formulations, and develop standardized treatment protocols.

6. Declarations

6.1 Acknowledgments

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6.2 Ethical Considerations

The authors are committed to the correctness of the research results. The manuscript has not been sent to several journals at the same time. It has not been published elsewhere in any form or language (partially or completely). In writing an article, no data, text, or theory is presented by others as if it were the author's own ("plagiarism").

6.3 Authors' Contributions

S.A.KH, H.N, R.R, N.N, and M. M.K. contributed equally to the research's conception and design; S.A.KH, H.N, R.R, N.N, and M. M.K. drafted the manuscript. All authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

6.4 Conflict of Interest

The authors have no conflict of interest.

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6.6 Using Artificial Intelligence Tools (AI Tools)

The authors were not utilized AI Tools.

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