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# A COMPREHENSIVE REVIEW OF POST GRADUATE DISSERTATIONS ON AYURVEDIC MANAGEMENT OF DIABETIC DISTAL SYMMETRICAL POLYNEUROPATHY

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**Abstract:** ***Objective:*** Review postgraduate clinical trials on effectiveness of Ayurvedic medicaments for Diabetic polyneuropathy. ***Methods:*** Electronic searches and Hand search strategies were used to identify studies. The quantitative analysis is depicted in PRISMA chart. The Methodological quality was assessed by using JADAD score. The Population included in the study, Interventions used, with or without Control, and Outcome measures are presented in Table of PICO analysis. The results of outcome measures were summarized under Primary & Secondary end points. ***Results:*** Hand Searches procured six theses out of 14 researches done in post graduate sector. Electronic searches revealed abstracts of two DHARA articles, three from PUBMED and Med know and one from AYU journal. ***Conclusion:*** Among six clinical studies Niranjan 2011 stood apart in methodological precision with Jadad score four out of five. Results were better when combined with internal than use of external medicaments alone. The electrophysiologically beneficial effects of *Bhunimbaadi choorna* by Nisha 2007 propose hope for drugs showing probable action on nerve regeneration. *Dashamoola* used in various forms like *dashamoola ghana vati, dashamoola qwatha,* dashamoola rasayana compound, showed statistically significant results compared to others. As dashamoola is vatahara, efficacy of drug implies the role of vata in the very pathology of DPN.

**Keywords:** Diabetic peripheral neuropathy, Diabetic neuropathy, Distal Symmetric Polyneuropathy, *Madhumeha, Madhumehajanya Upadrava* .

## Introduction

Diabetic Distal Symmetrical Polyneuropathy (DPN) is a common microvascular complication of diabetes mellitus (DM) that accounts for more hospitalizations than all other diabetic complications combined, are responsible for 50-75% of nontraumatic amputations **(Holzer SE, 1998; Caputo GM, 1994).**

The direct nomenclature of DPN is not available in *Ayurvedic* texts. The explanation of symptoms are scattered in the *Purvarupa* and *Upadrava* of *Madhumeha.* This disease could be included under the broad head of *Madhumeha janya Upadrava* as it manifests secondary to DM. The available treatment in contemporary science is beyond satisfaction. As per current strategies for the treatment of DPN, control of main disease is highlighted among treatment protocol. Even the same holds good in the management of *Upadrava* afflicted diseases. But this alone might not be sufficient, as it manifests in *Vyadhi pariklista shareera*. So dual management lines directed towards both *upadrava* and *pradhana vyadhi* is needed **(Charaka, 2000).** Lack of response and unwanted side-effects of conventional drug treatments force many sufferers to try alternative therapies.

Multifaceted etiology of DPN poses boundless challenges to basic research and clinical intervention. Here a contribution of *ayurveda* will be a boon to the sufferers. So this paper attempts to bring available data of *ayurvedic* DPN treatment

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in postgraduate sector, under one roof. Key data of six research works was extracted and reviewed. The quantitative analysis is depicted in PRISMA chart. The Methodological quality was assessed by using JADAD score. Arithmetic Mean used in data calculation. Additional supporting facts of six articles also provided. With an attempt to understand the multifactorial etiopathogenesis of the disease DPN, scholars have coined this disease by various names like *Twakgata vata, Jhinjhinivata, Shonitaavruta vata, Medaavruta vata, Vatanadi pradhana Shotha, Madhumehajanya upadrava* etc. The disease presents with varied *doshic* symptomatology like *daha, soochibireva toda, supti, stabdata* etc, which have made the treatment conclusive based on *dosa.* This review indirectly tries to specify which pathological constraint in treatment showed better results in patient complaints.

## Why it is important to do this review

Evidence based practice is important for refining practice so that goal of assuring patient safety is met. There is a constant need for better treatments for DPN. At present, available treatment alleviates pain and can control some associated symptoms, but the process is generally progressive. Patients with diabetes and other common chronic medical conditions are more likely to use Complementary and Alternative Medications (CAM) than individuals in the general population **(Egede, 2002; Garrow, 2006).** As a complication, there is an increased risk of injury to the feet because of loss of sensation. Small infections can progress to ulceration and this may require amputation especially in developing countries like India.[1] A study showed that the prevalence of amputation with neuropathy (82%) was high than peripheral vascular disease (35%).[2] According to (CDCP) 2005, *National Diabetes Fact Sheet*-Nearly 82,000 people with diabetes had lower-limb amputations in 2002.[3] This review is intended to update proved beneficial effects and possible adverse effects if any, of *Ayurvedic* medications used in DPN clinical trials. *Ayurvedic* treatments if found effective, give an additional management option for persons with DPN.

If studies are not with high methodological quality it would highlight the gaps in our knowledge and possibly lead to the conduct of adequate RCTs.

Thus aims to promote applicability high quality randomized controlled trials (RCTs) and Controlled Clinical Trials (CCTs), power calculations to detect treatment effects, include good numbers of participants and use appropriate statistical methods, which deter standards of *Ayurvedic* clinical trials.

## Objectives:

- Ø In all patients with DPN; which among the multiple treatment methods followed in the selected clinical studies, could hit the pathological constraint.
- Ø Based on response from therapy, better analyze which among the various hypothetical nomenclature claimed by authors can explain DPN, thereby aid for effective management and improve the quality of life i.e. patient satisfaction.

## Methods

### *Search strategy*

Electronic and Hand search strategies were used to identify studies. All available studies which used *Ayurvedic* management were assessed for changes in predictive value of diagnostic tests, signs and symptoms of DPN.

### *Electronic searches*

The following sources used for the identification of trials-

**International Journal of *Ayurvedic* Research;** MEDLINE (until Jan 16, 2012); **EMBASE** (until Jul 12, 2011); **AMED** (until 14 October 2011); The Cochrane Library (issue 10, 2011); ABIM which revealed Bibliography of seven titles **(ABIM)**; Articles on systematic reviews in *ayurveda;* **(Systematic reviews in *Ayurveda)*** Controlled vocabulary of *Ayurveda* search terms Complementary and alternative medicine articles on camquest **(CAMQUEST);**

Complementary and alternative medicine articles on pubmed**; (Pubmed); Central Council for Research in *Ayurveda* and *Sidha* (CCRAS); Medknow; The National library of Medicine; The National Center for complementary and alternative Medicine; HEALTHSTAR, JPGM;** DHARA revealed five abstracts; **The Internet Journal Of alternative Medicine;** The Ayurvedic research database (CD ROM) of IPGT & RA, Jamnagar **(Baghel MS, 2005).**

The electronic search strategy was developed from clinical MeSH headings like Neuropathy, Diabetic Neuropathy; AYUSH Headings like *Madhumeha* and text words.

Electronic search revealed abstracts of two DHARA articles, three articles from PUBMED & Medknow.

### *Hand searches*

The following sources used for the identification of trials-

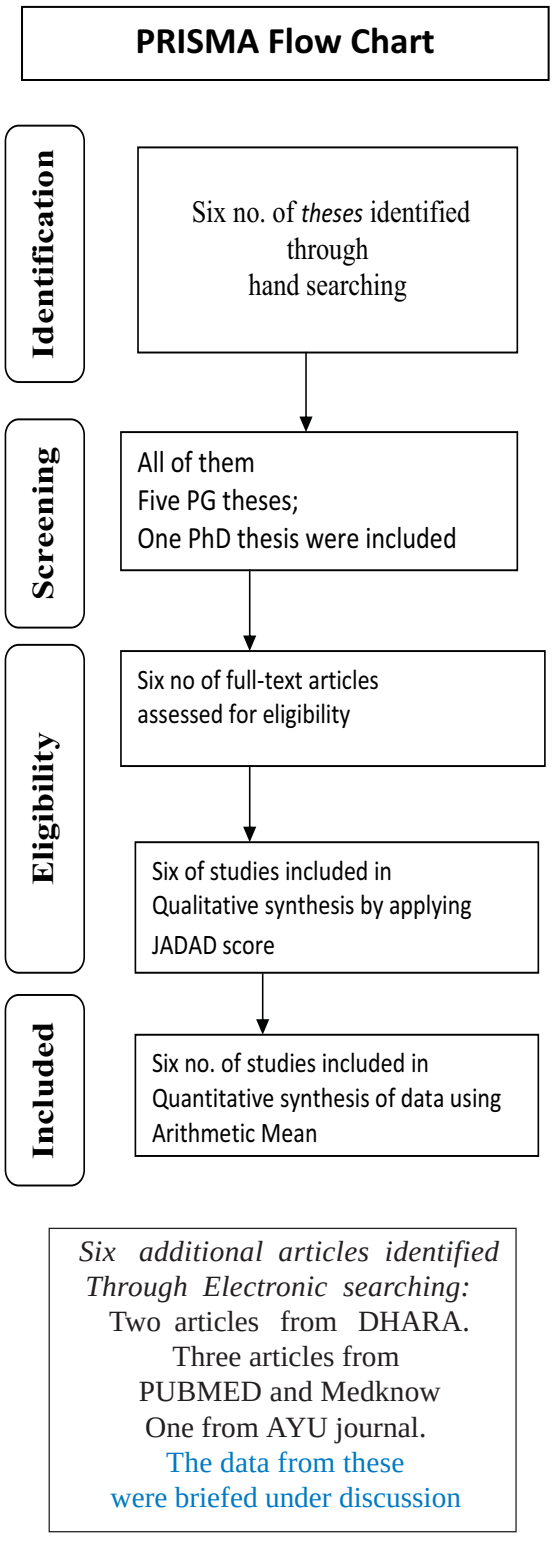
**Ayurvedic Research databases- (Baghel MS, 2005);** AYU (published quarterly by Gujarat Ayurvedic University); **AyurMedline;** The Journal of Alternative And Complementary Medicine; ***Ayurveda* newsletters and journals & magazines,** etc.

Hand searches revealed Five PG theses, one PhD thesis and one article from AYU Journal, a priliminary clinical research on Diabetic Neuropathy. **( Kalapi patel, 2011)**

### Included studies

The intention of the study was to find trials on DPN. The search revealed 5 of included studies were on DPN, except ***Nisha 2007*** which even involved autonomic forms of neuropathy also under a broad heading Diabetic Neuropathy. This was also included to extract the data due to scarcity of studies on DPN. The details of the studies included are flow charted as per PRISMA guidelines.

Ø Six (five PG and One PhD) theses testing different proprietary *Ayurvedic* drugs included for qualitative(Jadad) and quantitative analysis.



***Deepti 2008*** (**Kokane deepti, 2007)** compared *Dashamoola quatha* and *Vasanta kusumakara ras* been given in two groups(group A and B), ***Nisha 2007*** **( Nisha K., 2007 )** compared *Bhoonimbaadi Choorna* effects with a standard control, ***Karishma 2008*** **( Karishma, 2008 )** compared *Sapta Avartita Guduchi taila* given both internal and external with that of external application alone in two groups, ***Jaideep 2009*** **(Jaideep, 2009) -** *Dashamoola Ghana vati* and *Masha taila Abhyanga* as interventional group. ***V Tantri 2011*** **(Vyasraja Tantri, 2011)**- studied added effect of *Gokshuradi Guggulu*, given to group A given *Twak Choorna Lepa* with *Sahacharadi Kashaya*, group B given *Moorchita Tila Taila* and *Ela Choorna Lepa*. Both groups given *Kataka khadiradi kashaya* in common, and ***Niranjan 2011*** (**Niranjan Y 2011)** compared *Dashamoola Rasayana* Compound effect with standard control.

Altogether these studies enrolled 229 participants (189 on treatment, 40 on control). The duration of treatment ranged from minimum 21days to maximum six months. All these studies included adults with Type II DM presenting with neuropathy symptoms. The details of the studies are given in **Table 1.**

Additional Abstracts of five preclinical studies were included.

Two DHARA articles, Six from PUBMED & Medknow- Studied effect of Curcumin, Emblica officinalis, Dashamoola, Saffron and its carotenoid crocin, Eugenia jambolana, Mucuna pruriens and Tinospora cordifolia & Allium cepa and Allium sativum in experimental models of Diabetic Neuropathy.

One article from AYU Journal (***Kalapi 2011)*** **(Kalapi patel, 2011)** – studied the effect of Bhumiamalaki and Atibala roots in single group.

## Criteria considered in this review

### *Types of studies included*

All available clinical trials on diabetic neuropathy with or without controlled group.

Irrespective of treatment duration all studies were included, minimum treatment duration ranged from 21 days to maximum of six months.

### *Types of intervention*

Ø *Intervention*

· Clinical trials in which Internal or external/ both interventions were administered were selected;

· Trials with *Ayurvedic* treatment, with or without ayurvedic oral anti hyperglycemic drugs;

· The intervention of *Ayurvedic* treatments may include extracts from botanicals, single botanical agents, *Ayurvedic* proprietary medicines(both herbal and mineral) or a mixture of the above, prescribed by an *Ayurvedic* practitioner (individualized treatment).

Ø Control

· Placebo;

· Standard;

· Non-pharmacological intervention (for example exercise, diet or both);

· Any active intervention used with the intention of reducing the neuropathy symptoms

· No intervention.

### *Types of outcome measures*

Primary clinical outcomes /end points

### Subjective Criteria

Paresthesia like burning Sensation, pricking pain, Tingling,Numbness, Sharp Shooting/lanciating pain, feeling of walking on cotton/wool, Gloves and Stockings, Muscle weakness, Pain in the distal part of the foot, were assessed by all authors. Autonomic Evaluation-Indigestion, Constipation, Dizziness (***Nisha 2007)***

### Objective criteria:

Ø Measurement of deep tendon reflexes, vibration and pressure sense measurement by tuning fork, thermal sense by using hot and cold test tubes, monofilament 10gm for **quantitative sensory testing.**

Ø *Karishma 2008* used Biothesiometer & Neuropathy Analyzer Machine for quantitative Sensory testing

Ø Reliable Michigan Neuropathy Screening Instrument was used only in ***Niranjan 2011.***

Ø Quality of Life(QoL) assessment

**Table I.** Table of PICO Analysis : Shows interpretation of Population included, Intervention given, Control selected and Outcome measures assessed.

| Source | Author | Population showing Neuropathy Symptoms | Intervention | Control | Control Outcome Measures | Ayurvedic Nomenclature |
|---|---|---|---|---|---|---|
| **Studies Excluded** | | | | **Due to Non availability** | | |
| PG Thesis | Dwivedi KN 1986 | Adults with type 2 DM - | *Dashamoola* | - | - | *Madhumeha Janya Upadrava* |
| PhD Thesis | Dwivedi KN 1996 | Adults with type 2 DM | Jeeveneeya & balya drugs | - | - | *Madhumeha Janya Upadrava* |
| PG Thesis | Vijaya K 2003 | Adults with type 2 DM - | *Takradhara* - 7 days with a gap of 7 days in between the two courses. & *Shamanousha Shuddha Shilajitu* 500gms BD *+Triphala choorna* 3gms BD, *+ Ashwagandha Choorna* 3gms B.D , after food 30 days. | - | Subjective Criteria | - |
| PG Thesis | Sawant Manish 2008 | Adults with type 2 DM | *Ardhamatrika basti* | - | - | *Vatanadi Pratana Shosha* |
| PG Thesis | Nandeshwar Manisha 2006 | Adults with type 2 DM | *Anuvasana Basti with Amritadi Gritam* | - | - | *Madhumeha Janya Upadrava* |
| PG Thesis | Kumar Sanjay 2009 | Adults with type 2 DM | *Naimittika Rasayana Shilajatu & Mamajjaka* | - | - | - |
| PG Thesis | Tiwari Priyaranjan 2007 | 6patients in each group Adults with type 2 DM | **Group A** *Dashamoola Ghana vati, Dashamoola, +Madhyama panchamoola, +Vanga bhasma.* For 2 months | **Group B** Methyl-cobalamin (500mcg) BD - | **Group C** Mixed - | -- |
| PG Thesis | Manish Jain 2010 | Adults with type 2 DM | Nishoshiraadi tailam External application | - | - | - |

Only two works assessed QoL - **Nottingham Health Profile QoL by *Karishma 2008* and WHO BREF QoL by *Niranjan*.**

Ø *Agni bala, chesta bala ,deha bala* were assessed in only one thesis by ***Niranjan 2011***.

Ø **Electrophysiological investigations for Nerve conduction velocity-Only *Nisha K 2007* used Electrophysiological investigations for** Motor nerve conduction velocity (MNCV) and Sensory nerve conduction velocity (SNCV) **for assessment of nerve damage.**

**Table I.** Continued …….

| Source | Author | Population Showing Neuropathy Symptoms | Intervention | Control | Control Outcome Measures | Ayurvedic Nomenclature |
|---|---|---|---|---|---|---|
| **Studies Excluded Due to Non availability** | | | | | | |
| Clinical Trial Included in Present Review | | | | | | |
| PG thesis | Kokane Deepti 2008 | 12patients in each group Adults with type 2 DM | **Group A** *Dashmoola Kwatha* 40ml Bid *Anupana*:Water For 21 days | **Group B** *Vasantkusumakarrasa*125mg, *Anupana: Godugda* For 21 days | **Subjective Criteria** Pricking Pain, Paraesthesiae, Pain in the distal part of the foot, Burning Sensation | *Madhumeha janya Upadrava* |
| PG thesis | Nisha K 2007 | 10 patients Adults with type 2 DM | **Trial** *Bhoonimbadi choorna 1 karsha Anupana –Madhu* and *gritha* in each group For 6 months | Control Gabapentin (300mg + Methylcobalamine (500mcg) + gamma-linolenic acid (50mg) + alpha lipoic acid (50mg) For 6 months | **Subjective Criteria** Pain in the distal part of the foot ,Numbness, Tingling,walking on cotton/wool,Muscle weakness,Stumble while walking, Autonomic Evaluation, Indigestion, Constipation ,Dizziness. **Objective criteria:** Diminished Touch Perception, Diminished Pain Sensation Vibration, Thermal Sensation, Neuropathy Symptom Score, Electrophysiological investigations, Nerve Conduction Velocity . | *Madhumeha Janya Upadrava* |
| PG thesis | Jaideep 2009 | 22 patients Adults with type 2 DM | **Trial** *Dashamoola Ghana Vati 500mg Dashmool extract 50mg Pushkarmool extract 25mg HinguDose Dose -One capsule TID & Masha taila for local Abhyanga for 6 weeks* | Nil | **Subjective Criteria** Burning Sensation, Pricking Pain, Pain in the distal part of the foot, Paraesthesiae, Numbness, Tingling, Gloves and Stockings. **Objective criteria** DeepTendon, Reflexes, Thermal, Pain and Vibration Sensation | *Jhinjhinivata* |
| PG thesis | Vyasaraj Tantri 2011 | 20 patients in each group Adults with type 2 DM | **Group A** *Gokshuradi Guggulu 2 tab tid+ Twak Choorna* Lepa Both *Kataka khadiradi khashaya* 15ml tid in both groups | **Group B** *Sahacharadi Kashaya* 15ml tid with *Moorchita Tila Taila* 5ml after food + *Ela Choorna Lepa* Both *Kataka khadiradi khashaya* 15ml tid in both groups | **Subjective Criteria** Burning Sensation, Pricking Pain, Pain in the distal part of the foot, Paraesthesiae, Muscle weakness,Glove and Stockings, **Objective Criteria** Deep reflexes Thermal sensation, Vibration Sensation | *Madhumeha Janya Upadrava* |

**Table I.** Continued …….

| Source | Author | Population Showing Neuropathy Symptoms | Intervention | Control | Control Outcome Measures | Ayurvedic Nomenclature |
|---|---|---|---|---|---|---|
| **Studies Excluded** | | | **Due to Non availability** | | | |
| PG thesis | Karishma 2008 | 30 patients<br>15 patients in each<br>Adults with type 2 diabetes mellitus | Group A<br>Sapta Avartita Guduchi taila<br>Oral administration (10 -20drops B.D. )<br>Anupana – Warm milk<br>For one month | Group B<br>Sapta Avartita Guduchi taila<br>Oral administration (10 -20drops B.D. )<br>Anupana – Warm milk.<br>and Padabhyanga with Sapta Avartita Guduchi taila<br>at bed time.<br>For one month | **Subjective :** Burning Sensation<br>Pricking Pain, Pain in the distal part of the foot, Paraesthesiae<br>Numbness, Sharp Shooting /lanciating pain, bjectivecriteria: Neuropathy Symptom Score<br>**Quantitative Sensory** testing(Monofilament,Biothesiometer, HCP sensitometer)<br>Quality of Life (Nottingham Health Profile) | Twak gata vata |
| PG thesis | Kalapi Patel et al AYU Journal Jul –Sep 2011 | 33 patients<br>Adults with type 2 diabetes mellitus having symptoms of DPN | Trial<br>Bhumiamalaki choorna 3gm twice a day and decoction of 10gm of atibala mula twice a day for 30 days | Nil | Objective criteria: Neuropathy analyzer machine for analyzing cold, hot, vibration sensations before and after treatment | Vridda vata and Pitta |
| PhD thesis | Niranjan 2011 | 30 patients<br>in each group<br>Adults with type 2 diabetes mellitus | Trial<br>Dashamoola Rasayana Compound tab<br>Dose:3 tab (500mg) BD,after food<br>Anupana: Sukhoshna jala<br>For 8 weeks | Control<br>Cap Pregabalin 75mg<br>Methylcobalamin 750mcg<br>Dose –One cap OD<br>For 8 weeks | **Objective criteria**<br>Neuropathy , Symptom Score<br>Michigan, Neuropathy<br>Screening , Instrument<br>Subjective criteria,<br>Deep reflexes<br>Thermal sensation<br>Vibration Sensation<br>Monofilament testing<br>Quality of Life<br>(WHO Bref)<br>Agni bala,deha and chesta bala | Madhumeha<br>Janya<br>Upadrava |

## Secondary outcomes Measures

### *Glycaemic control Measurement*

- Ø Glycosylated hemoglobin A1c (HbA1c) - Was assessed by ***Niranjan 2011***
- Ø FBS & PPBS - Levels of fasting blood glucose levels and post prandial blood sugar levels were assessed by 4 authors only.
- Ø Lipid Profile
- Ø Weight or body mass index (BMI) changes;
- Ø Others like Blood Count ,Urine analysis etc

## Data extraction and management

Two reviewers assessed trial quality using the JADAD score which evaluates the quality of

Randomization, Blinding and reasons for withdrawal.

### *Assessment of methodological quality*

For Methodological Precision CONSORT statement 2010 was adopted by ***Niranjan 2011*** alone. The Jadad score was used as the 'gold standard' to assess the methodological quality of studies. This validated score lies in the range 0-5. 'poor trials' = Jadad score of 1-3 'good trials' = Jadad score of four or five. Out of the selected six theses for review only one thesis by ***Niranjan 2011***satisfies the current standard of methodological Quality of trials, which scored 4 whereas the others matched the scores of poor trials – one ***(Deepti 2008***), two (***Karishma 2008***), three ***(Nisha K 2007***),two (***Jaideep 2009)***, two (***vyasraj Tantri 2011)***.The Jadad score was not applied to ***Kalapi 2011***, as the article did not provide sufficient data on withdrawal, randomization etc. Sequence generation and concealment of randomization was adequate in ***Niranjan 2011***only, while in the others, randomization methods were not described. None of the studies were double-blind, neither the outcome assessors were blinded. The percentage of randomized participants completing the study ranged from 76% to 100%. No drop-outs were reported in three studies. The outcomes studied in these studies were not same. The results were not provided in a uniform manner. This calls for a need for upgrading Methodological quality of the research in *ayurveda* for Global Acceptance.**(Table 2)**

### Observations and discussion

**Age Incidence**: In majority of theses the scatter of patients was observed more between the age group of 50- 60 yrs which goes with the clinical finding is in similarity with Pittsbrugh

| | | | | | |
|---|---|---|---|---|---|
| words such as randomly, random, and randomization)? | | | | | |
| Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)? | 0 | 0 | 0 | 0 | 0 |
| Was the study described as double blind? | 0 | 1 | 0 | 0 | 0 |
| Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)? | 0 | 0 | 0 | 0 | 0 |
| Was there a description of withdrawals and dropouts? | 0 | 1 | 0 | 1 | 1 |
| Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc). | 0 | 0 | 0 | 0 | 0 |
| **Total** | 1 | 3 | 3 | 2 | 2 |

epidemiology study of diabetes where 58% of diabetics above 50 yrs of age had diabetic neuropathy. Survey of NIDDM in Dutch community also revealed high prevalence of neuropathy in older age groups **(Table 4).**

**Sex Incidence:** In majority of the studies the incidence of Males (63%) patients outnumbered Females (37.05%). Male patients with type 2 DM may develop DPN earlier than female patients. **(Table 5 ).**

**Prakriti:** The incidence of *vatapitta* (46.61%) was comparatively higher than *vatakapha* (36.84%) and *kaphapitta* (15.29%).The symptom manifestation like *data, toda*, etc are more towards the involvement of *vata* & *pitta*, the *prakriti* is even favoring the disease **(Table 6)**

**Table 3.** Primary End Points

| Primary End points | Deepti et al | Deepti et al | Jaideep et al | V Tantri et al | V Tantri et al | Nisha et al |
|---|---|---|---|---|---|---|
| | Group A | Group B | | Group A | Group B | Trial |
| | % of Improvement | % of Improvement | % of Improvement | % of Improvement | % of Improvement | % of Improvement |
| Burning Sensation | 100% relief | 86.13% | 82.35% | 60.00% | 45.00% | |
| Pricking Pain | 96.31% | 62.90% | 83% | 0% | 0 | |
| Pain in the distal part of the foot | 98.70% | 74.08% | 100% | 75.00% | 55.00% | 70% |
| Paraesthesiae | 86.90%% | 81.10% | 0 | 70.00% | 60.00% | |
| Numbness | None | None | 59.09% | None | None | 70% |
| Tingling | None | None | 76.47% | None | None | 90% |
| Gloves and Stockings | None | None | 50% | None | None | |
| Vibration | None | None | 19.81% | None | None | 30% |
| Pin sensitivity | None | None | 83% | None | None | |
| Thermal Sensation | None | None | 44.44% | None | None | 50% |
| Deep tendon reflexes | None | None | 42.87% | None | None | |
| Sharp Shooting/lanciating pain | None | None | None | None | None | None |
| walking on cotton/wool | None | None | None | None | None | 22% |
| Muscle weaknewss | None | None | None | 70.00% | 80.00% | 62.50% |
| Stumble while walking | None | None | None | None | None | 44.40% |
| Diminished Touch Perception | None | None | None | None | None | 80% |
| Diminished Pain Sensation | None | None | None | None | None | 70% |
| Cold Perception | None | None | None | None | None | None |
| Hot perception | None | None | None | None | None | None |
| Autonomic Evaluation -Nisha | None | None | None | None | None | Autonomic |
| Indigestion | None | None | None | None | None | 87.50% |
| Constipation | None | None | None | None | None | 80% |
| Dizziness | None | None | None | None | None | 66.60% |
| Neuropathy Symptom Score | None | None | None | None | None | None |
| Michigan Neuropathy History Questionarre | None | None | None | None | None | None |
| Michigan Neuropathy Physical Examination | None | None | None | None | None | None |
| Agni Bala | None | None | None | None | None | None |
| Abhyavarana Shakti | None | None | None | None | None | None |
| Jarana Shakti | None | None | None | None | None | None |
| Ruchi Aharakale | None | None | None | None | None | None |
| vata mootra retasam mukti | None | None | None | None | None | None |
| Deha Bala | None | None | None | None | None | None |
| Bala vriddi | None | None | None | None | None | None |
| Deha Bala-Swara varna yoga | None | None | None | None | None | None |
| shareera Upachaya | None | None | None | None | None | None |
| Chesta bala | None | None | None | None | None | None |
| Nidra labho yathakalam | None | None | None | None | None | None |
| Feeling of well being | None | None | None | None | None | None |
| Vaikarikaanam swapnanaam darshanam | None | None | None | None | None | None |
| Mano Buddi Indriyam Avyapatti | None | None | None | None | None | None |

**Table 3.** Primary End Points continued …

| Primary End points | Nisha et al | Karishma et al | Karishma et al | Nirnjan et al | Nirnjan et al | Kalapi et al |
|---|---|---|---|---|---|---|
| | Control | Group A | Group B | Trial | Control | |
| | % of Improvement | % of Improvement NS* | % of Improvement NS* | % of Complete Relief | % of Complete Relief | % of Improvement |
| Neuropathy Symptom Score | Not Assessed | Not Assessed | No Change, Remained same at end | 97.93% | 89.15% | None |
| Michigan Neuropathy History Questionarre | None | None | None | 71.03% | 72.18% | None |
| Michigan Neuropathy Physical Examination | None | None | None | 84% | 69.39% | None |
| Agni Bala | None | None | None | Agni Bala | Agni Bala | None |
| Abhyavarana Shakti | None | None | None | 33.90% | 22.41% | None |
| Jarana Shakti | None | None | None | 44.15% | 41.67% | None |
| Ruchi Aharakale | None | None | None | 16.28% | 23.08% | None |
| vata mootra retasam mukti | None | None | None | 33.96% | 22.73% | None |
| Deha Bala | None | None | None | Deha Bala | Deha Bala | None |
| Bala vriddi | None | None | None | 56.63% | 58.44% | None |
| Deha Bala-Swara varna yoga | None | None | None | 47.76% | 50.00% | None |
| shareera Upachaya | None | None | None | 0.00% | 3.33% | None |
| Chesta bala | None | None | None | Chesta bala | Chesta bala | None |
| Nidra labho yathakalam | None | None | None | 32.08% | 33.33% | None |
| Feeling of well being | None | None | None | 55.29% | 54.67% | None |
| Vaikarikaanam swapnanaam darshanam | None | None | None | 5.41% | 11.76% | None |
| Mano Buddi Indriyam Avyapatti | None | None | None | 48.53% | 47.37% | None |

NS* Statistically Not significant

**Table 4.** Age limit as inclusion criterion

| Age Incidence | Groups | Age on onset | % patients |
|---|---|---|---|
| Niranjan | Trial | 56-60yrs | 29.58% |
| Karishma | Trial | 51-55yrs. | 76.60% |
| Deepti | Trial | 55-60 yrs | 37.50% |
| Vyasraj | Trial | 46-55yrs | 35.00% |
| | Control | 56-65yrs | 35.00% |
| Jaideep | Trial | 51-60yrs | 47.82% |
| Nisha | Trial | >50yrs | 80.00% |
| | Control | >50yrs | 70.00% |

**Table 5.** Sex Incidence as inclusion criterion

| Sex | Males | Females |
|---|---|---|
| Vyasraj | 77.50% | 22.50% |
| Jaideep | 34.78% | |
| Nisha Trial | 90.00% | 10.00% |
| Nisha Control | 80.00% | 20.00% |
| Karishma | 50.00% | 50.00% |
| Deepti | 58.34% | 41.66% |
| Niranjan | 50.00% | 50.00% |
| Total | 63.00% | 37.05% |

**Table 6.** Prakriti of Patients

| Prakriti | Deepti | Jaideep | Vyas | Nisha (T) | Nisha (C) | Karishma | Total |
|---|---|---|---|---|---|---|---|
| Vatakapha | 50.00% | 26.08% | 05.00% | 50.00% | 70.00% | 20.00% | 36.84% |
| Vatapitta | 41.66% | 52.17% | 72.50% | 50.00% | 30.00% | 33.33% | 46.61% |
| Kaphapitta | 08.34% | 21.73% | 15.00% | 00.00% | 00.00% | 46.67% | 15.29% |

T= Trial C= Control

**Table 7.** Diet of subjects

| Diet | Vegetarian | Mixed |
|---|---|---|
| Deepti | 25.00% | 75.00% |
| Jaideep | 78.27% | 21.73% |
| Vyasraj | 32.50% | 67.50% |
| Nisha | 20.00% | 80.00% |
| Karishma | 25.00% | 75.00% |
| Niranjan | 77.47% | 16.00% |
| Total | 43.04% | 55.87% |

**Table 8.** Duration of Diabetes

| Duration of Diabetes | | |
|---|---|---|
| Authors | No of years of Diabetes | % of patients |
| Jaideep | 10.5yrs | 52.17% |
| Nisha | 10.5yrs | 40.00% |
| Nisha Control | 10.5yrs | 80.00% |
| Karishma | 10yrs | 50.00% |
| Niranjan | 8yrs | 30.99% |
| Deepti | 3yrs | 45.84% |
| Total | 10.04yrs | 55.40% |

**Table 9**. Family history of diabetes.

| Family history of Diabetes | Present | Absent |
|---|---|---|
| Deepti | 58.34% | 41.66% |
| Jaideep | 36.37% | 63.63% |
| Nisha | 70.00% | 30.00% |
| Nisha Control | 60.00% | 40.00% |
| Niranjan | 49.30% | 50.70% |
| Total | 54.80% | 45.20% |

**Diet:** It was observed that in majority of the studies the incidence of mixed diet (55.87%) was higher than that of vegetarian diet (43.04%) **(Table 7)**

**Duration of DM:** Showed mean duration of 10.04yrs; with 50.44% of subjects, which is in line with the recent study showing incidence of Diabetes Neuropathy is more common with increasing age and severity and duration of DM. (**Table 8)**

**Family History:** Positive family history of DM was found in most of the studies with a percentage of 54.80% and that of negative family history in 45.20% of patients which supports the higher familial inheritance in diabetics **(Table 9)**

## Results

Data of Clinical studies – Primary Outcomes are detailed in **Table 3.**

**Deepti 2008** -Only Subjective Criteria was used. The subjective feeling of burning, pricking, pain, paraesthesiae reduced significantly in both the groups but *Dashamoola Qwatha* Group showed better results than the *Vasasnta kusumakara ras* administered group.

**Kalapi 2011** - Showed statistically highly significant improvement in subjective criteria like numbness, tingling, burning & pain in lower limbs. Objective symptoms like vibration improved by 31% in right foot, 32% in left foot i.e. from severe to moderate range, cold sensation improved by 19.7% in right foot and 23% in left foot which came to normal range, hot perception by 6.85% in right foot and 3.9% in left foot i.e. from moderate to mild range improvement.

**V Tantri 2011** - Only subjective criteria used. The subjective feeling of pain, altered sensation reduced considerably in both the groups, but statistically it is highly significant in Group B and non-significant in Group A. The reduction of burning sensation was highly significant in both groups whereas the reduction of weakness in both groups was non-significant. The Group-B which was given with *Sahacharadi*

*kashaya* with *murchita tila taila* and *Ela lepa* has shown a better result than that of Group-A given *Gokshuradi guggulu* and *twak lepa.*

**Jaideep 2009**- Subjective along with objective criteria was used in assessment. The objective criteria like vibration (tuning fork 125hz), deep tendon reflexes, pin sensitivity, thermal sensation were assessed additional to the above. There was statistically significant improvement in all modalities of sensation examined except for the vibration sense.

**Nisha 2007** - Assessed diminished touch, pain and stumble while walking additionally. Revealed significant improvement in all criteria; except for burning which showed statistically insignificant improvement. Comparatively *Bhonimbadi Choorna* showed better results than that of standard control of Gabapentin (300mg) Methylcobalamine (500mcg), gamma-linolenic acid (50mg) & alpha lipoic acid(50mg). In this even the autonomic involvement was also assessed which showed statistically significant improvement in indigestion, dizziness and constipation.

**Karishma 2008** - Showed statistically insignificant improvement in all subjective criteria like pain, numbness, burning, hyperalgesia, sharp shooting and lanciating pain and tingling and pin sensitivity. Satisfactory response was seen in Group B than Group A (given external application *saptaarutha guduchi taila* alone) clinically. This shows that the effect of *saptaavruta guduchi taila* both internally and externally is much beneficial in counteracting the pathogenesis.

### Quality of Life (QOL) assessment: *Nottingham Health Profile QOL by* Karishma 2008

Out of 30 patients, on 30$^{th}$ day, one in group B showed satisfactory response, three in group A and six in group B showed good response; 12 in group A and 8 in group B showed excellent response.

### WHO BREF QOL by *Niranjan.*

Effect of therapy was assessed on overall perception of QOL and overall perception of Health and 4 domains representing physical, psychological, social, and environmental. *Dashamoola rasayana* compound markedly improved all domains and subjective changes with statistically highly significant changes with P<0.001 than that of Standard Control.

### Neuropathy Assessment Scale: Neuropathy Symptom Score (NSS) :

**Niranjan 2011:** Group A showed 97.93% improvement in NSS, whereas control showed 89.19%of improvement, with insignificant result between groups. *Dashamoola Rasayana* compound showed better results.

**Karishma 2008:** It was noted that on 30$^{th}$ day, in both the groups the distribution remained same as that of 0 day. Though it was statistically significant, no improvement was observed. (Quantitative Sensory Testing using Biothesiometer). Michigan Neuropathy Screening Instrument **(Niranjan 2011)**

Part A (History): The pretest and post test mean improved by 71.03% in Group A and 72.18% in Group B with statistically highly significant with p<0.001. Control group showed better results in the mean values.

Part B (Physical Examination): The pre and post test mean in Group A was 84% and Group B 69.39%,showed *Dashamoola Rasayna* compound was efficient.

### Effect on *Roga bala,Chesta Bala and Deha Bala* (*Niranjan 2011*)

*Dashamoola Rasayana* Compound showed extremely effective results in improving the *Agni bala*, *Chesta Bala* and *Deha bala* with statistically highly significant improvement in both the groups and insignificance between the groups

### *Data related to electrophysiological investigations (*Nisha 2007*)*

Electrophysiologically, mild improvement in mean values of MNCV and SNCV amplitude and Conduction velocity of median nerve, ulnar nerve, common peroneal nerve, posterior tibial

nerve in both trial group and control, but were not statistically significant. It was concluded that both the groups are equally better.

### *Data of Clinical studies - Secondary Outcomes*

### Fasting Blood Glucose (FBS )

Analysis of FBS was done only in four theses, of which

· *Dashamoola Qwatha* Group of ***Deepti 2008*** showed better results than the *Vasasnta kusumakara ras* administered group,

· The *dashamoola ghana vati* of ***Jaideep2011***, showed a considerable improvement in FBS after treatment.

· The Group B(*kataka khadiradi khashaya* with *Sahacharadi Kashaya* 15ml tid and *Moorchita Tila Taila* 5ml after food+ *Ela Choorna Lepa*) of ***V.Tantri(2011)*** showed significant decrease in the mean value with P<0.001 than Group A.

· *Dashamoola Rasayana Compound* of ***Niranjan 2011***Showed significant improvement in FBS compared to that of standard control (Cap Pregabalin 75mg + Methylcobalamin 750 mcg).

The Improvement in the mean FBS before treatment was 146.38 mg/dl which showed significant reduction to 133.94mg/dl with a mean difference of 12.44mg/dl. (**Table 10)**

**Table 10.** Fasting Blood Sugar (FBS)

| Fasting Blood Sugar | | | |
|---|---|---|---|
| **Authors** | | **Before Treatment** | **After Treatment** |
| Deepti | Group A | 131.85 | 129.25 |
| | Group B | 112.95 | 118.85 |
| Jaideep | Trial | *164.68* | *131.94* |
| Vyasraj | Group A | 147.8 | 128.15 |
| | Group B | 169.05 | 129.25 |
| Niranjan | Group A | 152.66 | 141.37 |
| | Control | 145.73 | 158.77 |
| | Total mean | 146.38 | 133.94 |
| | Mean Dif | | 12.44 |

### Post Prandial Blood Glucose(PPBS)

Analysis of PPBS was done only in three theses, of which

· *Dashamoola Qwatha* Group and *Vasasnta kusumakara ras* group of ***Deepti 2008*** both showed better results and comparisons between the groups was statistically insignificant.

· Both groups of ***V.Tantri 2011*** showed statistically significant improvement and but the mean value between the groups statistically non-significant.

· *Dashamoola Rasayana Compound* of ***Niranjan 2011***showed better improvement in PPBS compared to that of Standard control (Cap. Pregabalin 75mg+Methylcobalamin 750mcg), but the improvement was statistically insignificant.

**Table 11.** Post Prandial Blood Sugar

| Post Prandial Blood Sugar | | | |
|---|---|---|---|
| **Authors** | | **Before Treatment** | **After Treatment** |
| Deepti | Group A | 210 | 190.91 |
| | Group B | 189.11 | 178.43 |
| Vyasraj | Group A | 223.55 | 188.6 |
| | Group B | 266.85 | 199.05 |
| Niranjan | Group A | 204.14 | 206.85 |
| | Control | 177.3 | 204.83 |
| | Total Mean | 211.82 | 194.77 |
| | Mean diff. | | 17.05 |

The Improvement in the mean PPBS before treatment was 211.82 mg/dl which showed significant reduction to 194.77mg/dl with a mean difference of 17.05mg/dl. (**Table 11)**

By observing these it could be said that the *ayurvedic* medication has added benefit in controlling the glucose levels and has anti hyperglycemic effects along with the action of reducing symptoms of neuropathy. Thus it could be concluded that the *Ayurvedic* medications has definite action on breaking the pathology of *Madhumeha* too.

### Glycosalated Hemoglobin

One study **(Niranjan 2011)** showed at end of study decrease in HBA1c levels (35treatmets) by 1.29% with but was statistically insignifant. But the *Dashamoola rasayana Compound* beneficial effects **in correcting glycemic status** was better than that of Control (30) group which showed a statistically significant increase in HBA1c levels by 7.55%.

### Body Mass Index (BMI)

This was assessed in only two theses. There was 52.17% of patient distribution and 52.11% of patient distribution in the range of 20 to 25 being the highest in ***Jaideep 2009***and ***Niranjan 2011***respectively. This shows the evidence of altered fat metabolism in the very pathogenesis of Diabetic Neuropathy.

### Others

Aseessed by *Niranjan 2011*only. Statistically insignificant improvement was observed. The parameters like Blood Urea, Serum creatinine, Liver profile, Lipid Profile, Hematological and urine Investigations, were within physiological limits at end of study.

### Discussion

There is great heterogeneity in available articles on approach to *Ayurvedic* management for DPN. Some treat in lines of *Twak gata vata, Rakta gata vata, Medaavaruta vata* etc. But the outcome is good in most of the studies. This could be due to extent of involvement of *rakta* and other *dhatus* in *madhumeha*. Among the works no concrete conceptual decision was made regarding *Ayurvedic* nomenclature of DPN. However an effort has been made to understand the *pathology* through various approaches. Summing up all it could be understood as the transmutation in the quantity of involvement of *dushyas(tissue elements)*; leads to variability in symptom exhibition with progression of *Madhumeha*.

The overwhelming majority of studies test herbal therapy except one of ***Deepti 2008*** which used *Vasantakusumakara Ras*, a Herbomineral preparation. Heterogeneity exists in the drug selection, criteria, mode of drug action and administration (out of more than seven different interventions screened).

There was a significant methodological shortcoming observed, specifically;

1. There were few RCTs and CCTs.
2. Studies in general were underpowered to determine even large effect sizes: many studies had an extremely small number of subjects.

The majority of the studies tested non-insulin dependent diabetes mellitus (type II) patients only. Therefore, no definitive conclusion can be drawn on the effect of these therapies on insulin dependent diabetes mellitus (type I) patients.

Despite these limitations, there is sufficient data for several herbs or herbal formulas to warrant further studies. ***Niranjan 2011*** satisfies the current standard of methodological Quality of trials, which scored 4 out of 5.Higher age incidence between 50-60yrs and male sex predominance was observed in most of the studies. With mean duration of Diabetes of 10.04 yrs, habituated to mixed diet in higher rate. Afflicting *Vata pitta prakriti* persons maximally; with high familial inheritance. Regarding the primary end points most of the authors considered subjective grading of symptoms, which poses potential risk of bias. QOL assessment was done only in ***Karishma 2008***and ***Niranjan 2011***only. Nerve conduction Studies used in ***Nisha 2007*** only. Reliable Michigan Neuropathy Scale used only in ***Niranjan 2011***. Most of them had sample size(n) of <30 except for ***Niranjan 2011***with n=65 having good sample limits. Even though randomization was mentioned the method was not precise except for ***Niranjan 2011***.

Blinding/Masking not reported in most of them. Most of the interventions used *Dashamoola* in different forms. Of the selected studies standard control was taken in ***Nisha K 2007*** and ***Niranjan 2011***only. The criterion of inclusion of forms of Neuropathy was not quite rigid as the autonomic and proximal neuropathies were also

included except for ***Niranjan 2011***selected DPN cases only.

*Bhoonimbadi choornam* (***Nisha K 2007***) found effective in reducing Neuropathy, with electrophysiological studies improved to near normal velocity, indicating remyelination, but the sample size was too small to come to a conclusion.

***V.Tantri*** showed highly significant improvement but as the clinical grading was done the results poses a risk of bias. ***Kalapi 2011*** showed highly significant improvement in objective and subjective analyzes, *Bhumiamalaki choorna* and *atibala mula qwatha* found beneficial, but methodological quality assess lacked due to insufficient data.

***Karishma 2008***, no significant change was noticed in neurological assessment. Patients receiving *Sapta-Avartita Guduchi taila* both orally and in the form of external application exhibited a significant improvement in the symptoms of DPN.

***Jaideep***, refered *Bhaishajyaratnavali*, and selected *dashamoola gahna vati* from *Jhinjhinivata chikitsa*. No control group taken. Results showed highly significant improvement but not much improvement in Glove and Stocking. No objective criterion included.

***Deepti 2008*** showed highly significant improvement with Group A better than Group B. No objective criterion included.

***Niranjan 2011:*** *The* work stands apart in methodical precision, scoring four in Jadad Scale, which showed the highly significant effects of *Dashamoola Rasayana Compound* compared with a standard control, but the difference between the two were insignificant. The recurrence was reduced in trial which showed the beneficial effects on a long run.

## Additional source survey

Preclinical data on *Curcumin* **(Kandhare AD,2012)** proved beneficial in prevention of biochemical and behavioral aberration induced by alcoholic neuropathy in laboratory animals. Combination of curcumin with gliclazide may protect against the development of diabetic neuropathy. *Emblica officinalis* corrected Functional, Biochemical and Molecular Deficits in Experimental Diabetic Neuropathy **(Attia H.N., 2012; Vinod Tiwari, 2011)**. *Dashamoola* improved the Nerve Conduction Velocity in Sensory as well as motor nerves and facilitates H spinal Reflex **(Tripati K., 1998)** *Saffron* and its carotenoid crocin was potentially useful in diabetic neuropathy by its protective effect on reactive oxygen species-mediated high glucose-induced toxicity in PC12 cells **(Mousavi SH,2010).** *Eugenia jambolana, Mucuna pruriens* and *Tinospora cordifolia* showed amelioration of experimental diabetic neuropathy and gastropathy in rats **(Grover, J.K.,2002).** Methanol extracts of *Allium cepa* and *Allium sativum* significantly ameliorated the hyperalgesia in diabetic neuropathy, in mice **(Bhanot,2012).**

## Conclusion

For the Global acceptance clinical trials should be aimed at with proper randomization, blinding, with enough sample size. Researches be directed towards establishing effects of drugs like C*urcumin, Emblica officinalis, Dashamoola, Saffron* and its carotenoid crocin, *Eugenia jambolana, Mucuna pruriens and Tinospora cordifolia* & *Allium cepa* and *Allium sativum* which have shown beneficial effects in experimental studies, in a more precise way. *Dashamoola* used in various forms like *dashamoola ghana vati, dashamoola qwatha, dashamoola rasayana compound*, showed statistically significant results compared to others. As *dashamoola* is *vatahara*, efficacy of drug implies the role of *vata* in the very pathology of Diabetic Neuropathy occurrence.

Hence, a planned approach could be executed to counter act vitiated *vata* through the various therapeutic modalities of *Ayurveda* for better therapeutic benefits.

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