ROLE OF DASHAMOOLA KWATHA WITH PRAKSHEPA OF PUSKARMOOLA AND HINGU CHURNA IN THE MANAGEMENT OF DIABETIC PERIPHERAL NEUROPATHY

[1]Aparna Kumari, [2]Nitin Pandey, [3]Kalpana Rao, [4]Sanjiv Kr.Tripathi

[1]Associate Professor, [2]Professor, [3]Assistant Professor, [4]Associate Professor

Department Of Kayachikitsa

Himalayiya Ayurvedic Medical College & Hospital, Dehradun, India.

ABSTRACT:

Diabetic peripheral neuropathy (DPN) is associated with considerable morbidity, mortality and diminished quality of life, affecting up to 50% of people with diabetes. It is a nerve damaging disorder which is a consequence of diabetic microvascular injury involving small blood vessel that supplies to the nerves i.e. vasa nervorum. Its clinical manifestations include painful neuropathic symptoms and insensitivity, which increases the risk for burns, injuries and foot ulceration. In *ayurveda, Madhumeha* is described as *Vataja prameha*. When continued for a long time and in absence of adequate treatment, the resulting *dhatukshaya* and *vata prakopa* leads to production of *upadravas*. Most of the sign and symptoms are similar to that described under heading of DPN. Here, an effort is put forward to compile and critically analyze the various studies conducted on ingredients of *Dasmoola kwatha* and *Prakshepa dravya* i.e. *Puskarmoola* and *Hingu* which are pertinent for the use in Diabetic Peripheral Neuropathy.

Key words: Diabetic Peripheral neuropathy, *Madhumeha, Dhatukshaya,* Dashmoola *Kwatha, Prakshepa.*

INTRODUCTION:

According to the International Diabetes Federation, 382 million people worldwide are currently affected by diabetes, one of the leading causes of neuropathy. The distal symmetrical polyneuropathy (DSPN) is the commonest clinical form of diabetic neuropathy, affecting more than 90% of the patients[1]. Peripheral neuropathy refers to many conditions that involve damage to the peripheral nervous system, the vast communication network that sends signals between the central nervous system (the brain and spinal cord) and all parts of body. Toronto Consensus Panel on Diabetic Neuropathy recently defined DPN as a 'symmetrical, length dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycaemia exposure and cardiovascular risk covariates[2]. The direct nomenclature of diabetic peripheral neuropathy is not available in ayurvedic texts. In ayurveda, *madhumeha vyadhi* one of the types of *Vataj prameha* is compared to diabetes mellitus in respect to etiopathogenesis, clinical features and prognosis. Considering the definition of vata, the two main functions attributed to vata are *Gati* (motor functions) and *Gandhan* (sensory functions)[3]. Some of the normal functioning of *Vata* as illustrated by *Charaka* are- *Vayuh tantra yantra dharah* (vata preserves the functioning of all the organs of body), *Pravartakah chestanam* (intiator of every actions), *Sarvendriyanam udyojakah* (coordinator and stimulator of sensory system), *Sarvendriyarthanam abhivoda* (helps in propagation of sensory information)[4]. Hence the peripheral neuropathy, according to ayurveda can be considered as *Vata dosha vikriti.* Few conditions or terminology viz *Jhinjhinivata* [5] ,*Suptavata*[6] and *Sparshavata*[7] coined by the ayurvedic litterateur has similiarity with DPN up to some extent.

MATERIAL AND MEHODS

- The classical ayurvedic texts were critically analyzed for understanding pathogenesis of DPN in ayurveda and its line of treatment through ayurveda.
- All the relevant universally accepted electronic databases were searched with respect to Diabetic peripheral neuropathy, pharmacological action of Dashmoola or its individual drugs, Puskarmula and Hingu which are conforming in regard to their use in DPN.

PATHOPHYSIOLOGY OF DPN

According to modern medicine:

The pathogenesis of DPN is not fully understood. Unless recently, there were two schools of thought regarding the aetiology and pathogenesis of DPN: metabolic verses vascular. Recent studies, however, have shown that both vascular factors and metabolic interactions are involved in all stages of DPN[8]. Nerve fibre loss is the cause of insensitivity in DPN. Previous studies have reported

that the pathophysiology of early sensory neuropathy in diabetes may involve activation of the apoptosis cascade associated with mitochondrial dysfunction[9]. Several theories have been proposed to explain the pain related to the diabetic neuropathy, such as changes in blood vessels that supply the peripheral nerves; metabolic and autoimmune disorders accompanied by glial cell activation, changes in sodium and calcium channels expression and most recently, central pain mechanisms, such as increased thalamic vascularity and imbalance of the facilitatory/ inhibitory descending pathways[10]. There is emerging evidence that nerve tissues in diabetes undergo a pro-inflammatory process that presents symptoms and enhances the development of neuropathy. Indeed, diabetic nerves contain macrophages, occasionally lymphocytes and release increased TNF-α or interleukins (IL) in humans and animals. Inhibition of cytokine release or macrophage migration was associated with the improvement of Nerve conduction velocity delay and structure in streotozocin induced diabetic rats treated with *N*-acetylcysteine or pioglittazone[11]. Several recent studies have implicated poor glycaemic control, duration of diabetes, hyperlipidaemia (particularly hypertryglyceridaemia), elevated albumin excretion rates, drinking alcohol, cigarette smoking and obesity as risk factors for the development of DPN[12].

ACCORDING TO AYURVEDA

Emanation of *Madhumeha* occurs in two ways:-

i. ***Avrita vata janya Madhumeha***- In condition of *avrita vata janya Madhumeha*, etiological factors aggravates *Kapha*, *Pitta*, and causes vitiation of *Meda* and *Mamsa.* They further causes *avarana* to *vata dosha*, and hence leads to aggravation of *vata.* In this type of *samprapti*, symptoms of vitiated Vata or *avaraka Pitta*, *Kapha Meda or Mamsa* (*harsha, pipilika eva sanchara* i.e tingling sensation seen in *Mamsavrita vata*)[13] are seen frequently. When *Avarana samprapti* extend for a longer period, *Dhatukshaya avastha* develops and continues in further disease progress.

ii. ***Dhatu kshaya janya Madhumeha***- On consuming *Vata prakopaka nidana, Vata* gets vitiated and leads to *Agnivaishamya*. Agnivaishamya causes hampered *dhatuposhana karma* and leads to *dhatukshaya* condition. *Vata prakopaka nidana* and *dhatukshaya* further aggravates Vata and this aggravated vata causes deracination of *Pitta* and *Kapha* from their normal site to different place. This phenomenon is called as *Ashayapakarsha* by ayurvedic scholars. *Bheda, daha, shrama* and *daurbalya* symptoms are developed in that *sthana* in *Pittapakasrsha*[14], and *Shoola,* Shaitya, Stambha, Gaurava are produced in condition of Kaphapakarsha[15].

Vata prakopa along with dhatukshaya together are responsible for development of Upadrava i.e. complication of madhumeha which produces symptoms like *Daha, Suptata, Angasada, Harsha, Sosha, Daurbalya, Kampa, Shoola* which are almost similar symptoms as per explained under heading of Diabetic Peripheral Neuropathy[16].

CLINICAL PRESENTATION

Diabetic Peripheral Neuropathy (DPN) is characterized by tingling, burning, sharp, shooting and lancinating or even as electric shock sensations. It is usually considered moderate to severe and often worse at night, causing sleep disturbance. The pain can be constant and accompanied of cutaneous allodynia, which can substantially affect the quality of life of patients, impacting the ability to perform daily activities and having a negative influence on mood. The pain may also be a reason of withdrawal of recreational and social activities with depression[17].

Following symptoms of diabetic peripheral neuropathy are found in terms of ayurveda- *Sparsha vaigunya* (paraesthesia), *Daha* (burning sensation), *Harsha* (tingling sensation), *Suptata* (numbness), *Kampa* (tremor), *Toda* (pricking sensation), *Stambha* (stiffness), sosha (wasting), *Daurbalya* (weakness), *Angasada* (lassitude) etc, which are almost similar symptoms as explained under heading of DPN.

MODERN PHARMACOLOGICAL TREATMENT OF DPN:

The pharmacological treatments with exception to those targeted to glycaemic control, are symptomatic, not focused on the pathophysiological mechanisms, limited by side effect and by development of tolerance. Glycaemic control and addressing cardiovascular risk is now considered important in the overall management of the neuropathic patient[18]. Currently, the drug which are used are Tricyclic antdepressants, Selective serotonin reuptake inhibitors, Anticonvulsants, local anaesthetic arrhythmic agents, opioid analgesics etc[19], but only three agents are approved in the United States for the treatment of DNP: Duloxetin, a selective serotonin and norepinephrine reuptake inhibitor, pregabalin, an anticonvulsant, and the dual- effect drug tapentadol, an opiod receptor agonist and norepinephrine reuptake inhibitor[20].

PRESUMED MANAGEMENT PROTOCOL FOR DPN:

- *Pramehahara chikitsa* (main line of treatment of *Prameha*)
- *Kledashoshaka chikitsa*
- *Srotoshodhaka chikitsa*
- *Agnideepana chikitsa*
- *Vatanulomana chikitsa*
- *Treatment of Anubandh dosha/ Avaraka/Ashayapkarsha*
- *Shothahara* and *Vedanashamaka*
- *Rasayana chikitsa*

DISCUSSION

PROPERTIES AND ACTION OF DASHMOOLA QWATHA(Accountable for its use in DPN) :

Dashmoola kwath with Prakshepa of Puskarmoola and Hingu churna is indicated in *Jhinjhinivata* in *Bhaisajya ratnavali*[21], and in *Suptavata* condition in *Chakradatta*[22].*Dashmoola* is a popular, important and traditional multidrug ayurvedic formulation widely used for pain, arthritis and inflammatory disorders. According to ayurveda *dashmoola* is considered as *tridosha shamaka* and chiefly *vatashamaka*, *shothahara* (anti-inflammatory) and *ama-pachaka* (antioxidant or free radical scavenging property).

Table 1: Phytochemical constituents and Pharmacological actions of Dashamoola drugs

S.no	Plant name	Chemical constituents in the root	Karma[23]	Pharmacological action of the plants
1.	*Aegle marmelos* (L.) Corr (*Bilva*)[24]	Marmin, marmesinin, umbeliiferone, skimmianine and β-sitosterols and luperol.	*Vata-sleshmahara, balya,deepana pachana*	Antidiabetic, antioxidant, anti-inflammatory, analgesic, antihyperlipidaemic.
2.	*Premna integrifolia* linn.(*Agnimantha*)[25]	Premnazole, luteolin, 1β,3α,8β-trihydroxy-pimara-15-ene, 6α,11, 12,16 tetrahydroxy-7-oxobieta -8,11,13-triene, 2 α, 19-dihydroxypimara-7,15 diene.	*Kapha-vatahara, shothahara, deepana, aampachana*	Analgesic/antinociceptive, anti-inflammatory, antidiabetic, immunomodulatory, neuroprotective, antioxidant, longevity promoting, anti-hyperlipidaemic, cardioprotective.
3.	*Oroxylam indicum* (L.) Vent *(Shyonaka)*[26]	Chrysin, baicalein, biochanin-A, ellagic acid, 2,5-dihydroxy-6,7-dimethoxy flavones and 3,7,3',5'-tetramethoxy-4'-hydroxyflavone	Tridoshahara, deepana, amapachana	Analgesic, anti-inflammatory, antidiabetic, immunomodulatory, nephroprotective, antioxidant
4.	*Stereospermum suaveolens* (Roxb.) DC *(Patala)*[27]	*p*-coumaric acid, triacontanol, cetyl alcohol, oleic, palmitic, stearic acid, lapachol, dehydro-alpha-lapachone and dehydrotectol, β-sistosterol and n-triacontal.	*Tridoshahara , shothahara*	Analgesic, anti-inflammatory, antidiabetic, antioxidant, neuroprotective, immunomodulator.
5.	*Gmelina arborea* Roxb. *(Gambhari)*[28]	Cluytylferulate, *n*-octacosanol, gmelinol, arboreol, 2-0-methyl arboreal, 2-0-ethyl-arboreol, isoarboreol,gmelanone, β-sito-sterol, paulownin, 6"-bromoisoarboreol, 4-hydroxysesamin, 4,8-dihydroxy-ses-amin, 1,4-dihydroxy-sesamin (gummadiol), 2-piperonyl-3-(hydroxyl-methyl)-4 (α-hydroxy-3-,4-methyl-enrdioxybenzyl)-4-hydroxy tetrahydro furan (1), 4-epigummadiol-4-0-glucoside, 1,4-dihydroxy-2,6-dipiperonyl-3,7-dioxa-bicyclo [3,3,0]-octane, gmelanone, palmitic, oleic and linoleic acids, stigmasterol, stigmastanol, campesterol, α-2-sitosterol,butulinol.	Deepana, pachana, shothahara, brinhana,vrishya, rasayana, daha-trisha-vata-rakta-kshat-kshaya nashaka	Analgesic, antidiabetic, antioxidant, immunomodulator, cardioprotective.
6.	*Desmodium gigenticum* (L.) DC. (*Shalaparni*)[29]	Gangetin, gangetinin, desmodin, N, N- dimethyltryptamine, hypaphorine, hordenine, candicine, N- methyltyramine, β-phenylethylamine, desmocarpin.	Tridoshaghna, soshahara, brinhana, rasayana	Anti-inflammatory, anti-nociceptive antioxidant, antidiabetic, lipolytic, cardioprotective.
7.	*Uraria picta* Desv. (*Prishna-parni*)[30]	Alkaloids, flavonoids, steroids, terpenoids, phenols and saponins.	*Tridoshaghna,, dahashamaka,deepana, vrishya*	Anti-inflammatory, antioxidant, anti depressant.
8.	*Solanum indicum Linn/ S. anguivi* Lam. (*Brihati*)[31]	Alkaloids, flavonoids, tannins, saponins, glycosides, proteins, carbohydrates, coumarins & phytosterols, glycoprotein, solanigrosides C-H, degalactotigonin, nigrumnins I and II, ethyl b -D –theveto-pyranosyl-(1-4)- b- D oleandropyranoside and ethyl b- D -thevetopyranosyl-(1-4)-a – Doleandropyranoside.	*Kapha-vata shamak, deepana*	Analgesic, anti-inflammatory, antioxidant, immune-stimulant, anti-hyperlipidemic, cardioprotective.
9.	*Solanum xanthocarpum*	Carpesterol, gluco alkaloid solanocarpine, solanine-S,	*Kapha-vata shamak, deepana, pachana*	Adaptogenic, hypoglycaemic.

	Schrad. & Wendl./ *Solanum surattense* Burm.f *(Kantakari)*[32]	solasodine, solasonine, solamargine, cycloartanol, stigmasterol, campesterol, cholesterol, sitosteryl-glucoside, stigmasteryl glucoside, solasurine, isochlorogenic, neochlorogenic, coumarins, scopolin, scopoletin, esculin, esculetin, carpesterol, tomatidenol, norcarpesterol, and solasonine.		
10.	*Tribulus terrestris* Linn.*(Goksh-ura)*[33]	furostanol and spirostanol saponins of tigogenin, neotigogenin, gitogenin, neogitogenin, hecogenin, neohecogenin, diosgenin, chlorogenin, ruscogenin, and sarsasapogenin, protodioscin and protogracillin.	*Vastishodhana, Balya, Deepana, Vrishya, Pustida*	Anti-inflammatory, analgesic, antioxidant, antidiabetic, hypolipidemic, immuno-modulator, antidepressants, anxiolytic, cardioprotective.

Table 2: Phytochemical Constituents and Pharmacological properties of Prakshepa Dravya

S. No.	Plant name	Chemical constituents in the root	constituents Chemical in the root	Pharmacological action of the plants
1	*Inula racemosa* Hook.F *(Puskarmoola)*[34]	*Inula racemosa* yields large amounts of sesquiterpene lactones as-Alantolactone (ALT) and isoalantolactone (IALT), Dihydroalantolactone, dihydroisoalanto-lactone, inunolide, dihydroinunolide, neoalantolactone, isoalloalantolactone, alloalantolactone, inunal, isoinunal, alantodiene and isoalantodiene.	*Kapha-vata shamak, shophagna*	Anti-inflammatory, analgesic, antioxidant, antimutagenic and antiapoptotic, adaptogenic, hypogycaemic, cardioprotective.
2.	*Ferula asafoetida* Linn. (*Hingu)*[35]	The resin portion contains coumarins, sesquiterpene coumarins, and ferulic acid and its esters and other terpenoids. The gum portion includes 1-arabinose, rhamnose, glucose, galactose, glucuronic acid, polysaccharides, and glycoproteins. The volatile fraction contains monoterpenes, sulfur-containing compounds, and other volatile terpenoids. Three main sulfur constituents which have been identified include 2-butyl 1-propenyl disulfide, 1-(methylthio) propyl 1-propenyl disulfide, and 2-butyl 3-(methylthio)-2-propenyl disulfide,	*Vatakaphashamaka, pittavardhana, balya, shulanashaka*	Antidiabetic, antioxidant, anxiolytic.

THE PHARMACOLOGICAL POTENTIAL (PUBLISHED SCIENTIFIC EVIDENCES)

BILWA (*Aegle marmelos*)[36]:

- Marmin, a caumarin isolated from the roots of *Bilwa* (1g/kg p.o.) showed anti-inflammatory effect against carrageenan induced inflammation induced rats. Marmin, marmesin, umbelliferine and skimmianine are identified from the bark and roots which contribute to the anti-inflammatory property of *Bilwa*. Lupeol, a pentacyclic triterpenes showed reduction in paw swelling by 39% compared to 35% by indomethacin.

AGNIMANTHA (*Premna integrifolia* Linn. /*P. serratifolia* L.)

- Pretreatment with single dose of Methanolic extract of root of *Premna integrifolia* (PIM) (300 mg/kg b.w) produced significant inhibition on carrageenan induced rat hind paw edema, histamine induced wheal formation and acetic acid induced mouse vascular permeation. In a 7 day study, daily administration of PIM suppressed formalin induced paw edema and cotton pellet induced rat granuloma formation[37].
- **Antioxidant** activity of the extract of *P.integrifolia* was evaluated using the antiradical, superoxide scavenging, erythrocyte membrane stability, anti lipid peroxidation, hydroxyl radical scavenging, nitric oxide scavenging and reducing power assays. Methanolic extract of P.integrifolia showed significant antioxidant activity[38].
- **Neuroprotective** effects were evaluated by using roots of *P.serratifolia* in the experimental model of febrile seizure[39].
- **Immunomodulatory** activity was evaluated by using methanol extract of root of *P. integrifolia* in BALB/c mice.Oral administration of methanol extract (300 mg/kg × 7 days) in mice prior to immunization with sheep red blood cells resulted in a significant increase in haemagglutinating antibody titre, plaque forming cell assay and delayed type hypersensitivity to SRBS[40].
- **Analgesic** activity was also evaluated using methanolic extract of *Premna integrifolia* (MEPI) bark by writhing test in rats at doses 100 and 200 mg/kg body weight. The positive control group received Diclofenac-Na at the dose of 10 mg/kg p.o. The oral administration of both doses of MEPI significantly ($P < 0.001$) inhibited writhing response induced by acetic acid in a dose dependent manner. Antinociceptive study was performed by formalin induced pain model in rats at doses of 100 and 200 mg/kg body weight. The standard drug was used in the study is Indomethacin at 10 mg/kg, p.o. MEPI (100 and 200 mg/kg, p.o.) significantly ($P < 0.001$) suppressed the licking activity in either phase of the formalin-induced pain in rats in a dose dependent manner. But, MEPI, at the dose of 200 mg/kg body weight, showed the more licking activity against both phases of formalin-induced pain than that of the standard drug[41].

SHYONAKA (*Oroxylum indicum* L.Vent)[42]

- *Oroxylum indicum* has been used since ages as analgesic agent. Pharmacologically, the activity was reported in the butanol extract of root bark of *Oroxylum indicum*. Two assay models, viz. tail flick and acetic acid induced writhing response, were employed to detect analgesic activity. For tail flick method, Wistar albino rats of either sex 200-250 g were selected. One group of animals was administered 100 mg/kg BW, p.o., and another group was administered standard drug morphine (10 mg/kg BW, i.p.). One hour after the administration, tail of the rat was placed on nichrome wire of an analgesiometer and the time taken by the animal to flick its tail was taken as reaction time. Analgesic activity was measured at 0 and 30 min. for acetic acid induced writhing; Swiss albino mice 20-25 g were selected. The n-butanol fraction was administered 100 mg/kg BW p.o. in one group. Another group received standard aspirin (25 mg/kg BW, i.p.). One hour after the administration, the injection of acetic acid 0.6 %v/v (10 ml v/v/kg BW, i.p.) was given and thereafter, the number of writhes was observed for up to 30 minutes. Oral administration of n-butanol fraction significantly prolonged the reaction time in rats. Oral administration of n-butanol fraction also significantly reduced the number of writhing by 75.93 % as compared to aspirin 87.05 %. The analgesic activity has been attributed to the presence of flavonoids such as baicalein, ellagic acid, biochanin-A present in the roots of *Oroxylum indicum.*
- Antioxidant potential of methanolic extracts of different parts of *Oroxylum indicum* viz. root, root bark, stem, and stem bark, leaves and fruits was determined by performing DPPH, nitric oxide, superoxide anion and hydroxyl radical scavenging potential and reductive ability assay. Leaves and root bark extracts showed maximum reductive ability and highest free radical scavenging activity than stem and fruit extract.[z]
- The root bark of *Oroxylum indicum* has been shown to inhibit chronic inflammation in rats. In the acute test conducted on experimental Wistar rats, carrageenan was used to induce rat paw edema in one group of animals and cotton pellet was used to induce chronic inflammation in second group. Pre-treatment with n-butanol fraction showed significant ($p<0.05$) anti-inflammatory activity at 3 hour when compared with control group. Further, it also significantly ($p<0.05$) reduced the increase in the weight of cotton pellet when compared with the control group and the results were comparable with that of standard diclofenac treated group of animals.
- The hypoglycemic activity of extracts of *Oroxylum indicum* (L) Vent roots has been studied in Wistar albino rats.
- Oral administration of ethanolic and water extracts of roots of *Oroxylum indicum* at the dose levels of 300 and 500 mg/kg bw for 21 days and 11 days respectively in two different studies showed a significant reduction in the serum glucose, triglyceride, total cholesterol levels and a significant increase in the liver and muscle glycogen levels, when compared with diabetic control groups. Sufficient reduction in serum glucose concentration was shown by aqueous and alcoholic extracts at 500 mg/kg BW after 21 days and 11 days by 50.92 % and 49.59 % respectively.

- Rats treated with n-butanol fraction (100 mg/kg bw) of *Oroxylum indicum* root bark for 22 consecutive days when challenged with sheep red blood cells (SRBC hemaglutinating antibody [HA] titter) and delayed-type hypersensitivity (DTH) reactions, showed a significant rise in antibody titre during secondary antibody responses, indicating a potentiating of certain aspects of the humeral response. The treatment also resulted in a significant rise in paw edema formation indicating increased host DTH response. Furthermore, histopathological analysis of lymphoid tissues showed an increase in cellularity such as T-lymphocytes and sinusoids, in the treatment group. The reported immunomodulatory activity might be attributed to its ability to enhance specific

immune responses (both humeral and cell-mediated) as well as its antioxidant potential[85]. The immunomodulatory properties of *Oroxylum indicum* have also been evaluated through estimation of hum oral and cell mediated immune response in broiler chicks.

PATALA (*Stereospermum suaveolens* (Roxb.) DC)[43]:

- In the anti-diabetic assay, after 30 minutes of administration the methanolic crude extract of *S.suaveolens* at 200- and 400-mg/kg b.w. reduced blood glucose level by 37.58% and 56.10%, respectively as compared to 58.53% reduced by standard glibenclamide (0.1 mg/kg b.w.).
- The central analgesic effect of methanol extract of *S.suaveolens* effectively elongated the reaction time. The percent elongation time was recorded at 30, 60 and 90 min after administration of drug samples in the experimental mice. About 30 min after administration, the methanolic crude extract, at the doses of 200- and 400-mg/kg b.w. revealed elongation of reaction time by 69.23% and 132.30%, respectively while the standard morphine (4 mg/kg b.w.) showed 200.09% of elongation. After 60 min, the tested extract exhibited highest elongation as 185.59% and 259.21%, respectively compared to 313.32% by morphine. The central analgesic property was found to increase till 60 min and then decreased with time.
- In peripheral analgesic activity study, the crude extract significantly decreased the number of acetic acid-induced abdominal writhings in mice. Statistical evaluation of the data confirmed promising analgesic activity of *S. suaveolens*. Here, the plant extract at 200- and 400-mg/kg b.w. showed 31.82% and 48.48% inhibition of writhing, respectively as compared to 65.15% inhibition produced by the standard diclofenac-Na. Both in the acetic acidinduced writhing and tail flick method, the crude methanolic extract showed significant analgesic activity. As the extract appeared to be active in both animal models of nociception, it may possess peripherally and centrally acting compounds for its antinociceptive action.
- In the screening for antioxidant activity, the aqueous soluble fraction showed the highest activity with IC_{50} value of 18.99µg/ml. At the same time, the crude methanolic extract and its chloroform soluble fraction also exhibited significant antioxidant activity with IC_{50}value of 45.6 and 46.7µg/ml, respectively. These results denote the presence of antioxidant principles in the extractives.

GAMBHARI (*Gmelina arborea* Roxb.)[44]

- Ethanolic extract of *Gmelina arborea* Roxb. bark at dose of 420mg/kg and chlorpropamide at dose of 200mg/kg ($p<0.05$) was found to reduce the increase of blood sugar in streptozotacin (50mg/kg) induced diabetes due to the increased blood GSH (Glutathione) levels reinforcing the role of GSH as free radical scavenger and in the repair of free radical caused biological damage.
- Methanolic extract of *Gmelina arborea* Roxb. and ethyl acetate fraction of methanolic extract have been found to increase the total WBC count, which was lowered by cyclophosphamide, a cytotoxic drug. The drug is also capable of normalizing the levels of neutrophils and lymphocytes. The results indicates that the *Gmelina arborea* Roxb. can stimulate the bone marrow activity.
- The analgesic activity of ethanolic and aqueous extract (test compounds) was found to be more significant on acetic acid induced test than tail flick test as compared to standard diclofenac sodium at a dose of 25mg/kg and thus it appear that the test compounds inhibit predominantly the peripheral pain mechanism.
- Effect of antioxidant activity of methanolic extracts of stem bark of *Gmelina arborea* Roxb. (MEGA) was studied using various in vitro assays method which showed free radical scavenging activity 85.20%. The activity could be at the same concentration to that of standard ascorbic acid which was 89.58% due to proton donating ability and could serve as free radical inhibitors or scavengers.

SHALAPARNI (*Desmodium gangeticum* (L.)DC)

- Flavanoid and alkaloid fractions of *Desmodium gangeticum* were evaluated for anti inflammtory and antioxidant activities in carrageenan – induced inflamed rats. The flavanoid fraction of D. gangeticum possesses potent antioxidant activity compared with the alkaloid fraction and also with respect the standard drug indomethacin, in terms of augmentation of the liver and spleen superoxide dismutase(SOD), catalase(CAT), glutathione peroxidase (GPX) activities, concomitant with a reduction in lipid peroxidation[45].
- Aqueous extract of *Desmodiaum gangeticum* showed pronounced analgesic activity in the acetic acid induced abdominal writhing assay in the test animals[46]. The water decoction of root and aerial parts of *Desmodium gangeticum* was observed for anti-inflammatory and anti-nociceptive activity in experimental animals[47]. The hexane extract of root of *Desmodium gangeticum* showed significant anti-inflammatory effect both in exudative and proliferative phase of inflammation and also showed analgesic effect of the compound was significantly more prolonged in a dose of 100 mg/kg in comparison to Analgin in a dose of 500 mg/kg[48].

PRISHNIPARNI (*Uraria picta* Desv.)[49]

- *U. picta* Desv root aqueous extract significantly reduced acute and subacute inflammation, and showed effective and similar anti-inflammatory activity in rats.
- *Uraria picta* root content flavonoid is known to exhibit a range of biological activities like antiinflamma-tory, anti-thrombotic, hepatoprotective properties due to its free radical scavenging ability. The activity elicited by the extract might be due to its ability to activate antioxidant enzymes.

BRIHATI (*Solanum nigrum* Linn./ *S.anguivi* Lam.)[50]

- Ethanolic extracts of *Solanum nigrum* for analgesic activity was evaluated for its central and peripheral pharmacological actions by using Eddy's hot plate and acetic acid induced writhing respectively. The study was carried out using doses of 100, 250 & 500 mg/kg orally. The extract showed significant analgesic activity at the dose of 500 mg/kg ($P<0.01$) as compare to standard drug Diclofenac sodium (50 mg/kg).

- The methanolic extract of whole plants of Solanum nigrum L. was investigated for anti-inflammatory activity on the experimental animal models. The methanolic extract at a concentration of 100 mg/kg b.w and 200 mg/kg b.w showed the significant dose dependent anti-inflammatory activity in carrageenin and egg white induced hind paw edema in rats.

KANTAKARI (*Solanum xanthocarpum* Schrad. & Wendl./ *Solanum surattense* Burm.f**)**[51]

- The adaptogenic effects of *Solanum xanthocarpum* (Sx) whole plant extracts (Aq-methanol) and steroidal saponins in forced swimming test (FST) and cold restraint stress (CRS) models were investigated in Swiss albino mice. The adaptogenic effects of steroidal saponins were found to be better than those of the total extracts.

GOKSHURA (Tribulus terrestris Linn.)[52]

- The ethanolic extract of TT inhibited the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) in lipopolysaccharide-stimulated RAW264.7 cells. It also suppressed the expression of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-4 in macrophage cell line. Thus, the ethanolic extract of TT inhibits the expression of mediators related to inflammation and expression of inflammatory cytokines, which has a beneficial effect on various inflammatory conditions.
- **Analgesic** activities of TT were studied in male mice using formalin and tail flick test. The study indicated that the methanolic extract of TT at a dose of 100 mg/kg produced analgesic effect. This analgesic effect of the TT extract may be mediated centrally and/or peripherally. Effect of the extract was lower than morphine and higher than acetylsalicylic acid (aspirin) in both tests.
- Saponin from TT possesses hypoglycemic properties.TT significantly reduced the level of serum glucose, serum triglyceride, and serum cholesterol, while serum superoxide dismutase (SOD) activity was found to be increased in alloxan-induced diabetic mice. The decoction of TT showed inhibition of gluconeogenesis in mice.TT ethanolic extract at 2 g/kg body weight produced protective effect in streptozotocin-induced diabetic rats by inhibiting oxidative stress.
- An alcoholic extract of the whole plant of TT exhibited a significant dose-dependent increase in humoral antibody titre and delayed type hypersensitivity response, indicating increased specific immune response.

PHARMACOLOGICAL ACTION OF PRAKSHEPA DRAVYA :

PUSKARMULA (*Inula racemosa* Hook.F)[53]

- It has been reported that alcoholic extract of the roots of I.racemosa lowers blood glucose level and enhances liver glycogen without increasing plasma insulin level in rats. Antidiabetic effect of I.racemosa was performed in 15 patients of age above 35 years suffered from complications of Diabetes mellitus were treated with 1 table spoonful of I.racemosa root powder three times a day for three months duration. After the treatment blood glucose level of all patients found to be normal. Chronic treatment with methanol root extract of I.racemosa produced significant reduction in blood sugar level in alloxan induced hyperglycaemia model as compared to alloxan treated animals. The body weight, food intake, water intake and urine output were significantly reversed to normal by methanol extract of I.racemosa treatment.
- Aqueous extract of the roots of *I. racemosa* showed maximum inhibition (60%) at a dose of 400 mg/kg, b.w. after 8 h of drug administration in carageenan-induced paw edema in rats, whereas standard drug indomethacin (20 mg/kg) produced 69% of inhibition.
- Analgesic effect of aqueous extract of the roots of *I. racemosa* was performed in albino mice of either sex by acetic acid-induced writhing and tail immersion methods. Aqueous extract of plant at a dose of 400 mg/kg showed higher latency of percentage protection in acetic acid-induced writhing model (63%), whereas in tail immersion model the highest enhanced reaction time was observed at 400 mg/kg (8.65 ± 1.63 at 3 h).
- Antiapoptotic effect of aqueous root extract of *I. racemosa* (400 mg/kg, b.w.) was measured by the use of Annexin V-FITC assay kit. 4-NQO-induced genetic damage in mice was modulated by aqueous root extract of *I. racemosa via* effective restoration of micronuclei and apoptotic cells formations. The potential protective effects might be due to the synergistic effects of secondary metabolites present in aqueous root extract of *I. racemosa.*
- Adaptogenicity potential of 90% ethanol roots extract of *I. racemosa* was investigated in the forced swim test model in albino mice. The animals treated with 100 mg/kgand 200 mg/kg of ethanol root extract of *I. racemosa* showed a significant decrease in the immobility period with simultaneous increase in antioxidant markers, adrenaline and serotonin levels.
- Antioxidant activity of 70% ethanol extract of the roots of *I. racemosa* was performed in Albino rats. The effect of daily oral administration of alcoholic extract (suspended in 1% gum acacia) of the roots of *I. racemosa* to rats for 21 days was investigated for lipid peroxide formation and reduced glutathione (GSH) content. The level of GSH in blood and liver was found significantly higher in treated animals as compared to control (1% gum acacia). Result showed that *I. racemosa* has antioxidant properties because greater availability of GSH to the cell would lead to higher rate of destruction of deleterious hydrogen peroxide and lipid peroxides by glutathione peroxidase.

HINGU[54]

- It has proved that the effect of *Asafetida* on the secretion function of the pancreas is a result of their direct correlation with the cell membrane. Through carrier, Glut-2 the glucose enters to beta cell of the pancreatic islet Langerhans, where during metabolism adenosine triphosphate (ATP) created. Then, the production of ATP stimulate the insulin secretion by changing the membrane

potential, which finally ensure the Ca++ ion flow into cytoplasm. *Asafoetida* has a high concentration of calmodulin which transport calcium in beta cell. The sensitivity of the beta cell to Ca++ is increased by the action of other secondary messenger. Calcium stimulates the tyrosine kinase leading to activation of insulin and its secretion from the cell.

- Antioxidant activity of the essential oil components from the *F. Asafoetida* was examined by *in vitro* 1,1-Diphenyl-2- picryl-hydrazyl (DPPH) and nitric oxide radical scavenging assay, reducing power, linoleic acid and iron ion chelation power, and establishing usefulness of this plant. The extract from aerial parts of *F. asafoetida* showed good but different levels of antioxidant activity in all the models studied.

CONCLUSION

From this review we can conclude that DPN can be very well managed with *Dashmoola qwatha* with *prakshepa* of *puskarmula* and *hingu churna*. Its ingredients have been tested in various experimental models and proves efficacious in breaking pathogenesis of DPN at different levels.

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