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DIABETIC NEUROPATHY-A REVIEW

G. Avinash Kumar Reddy*, Ch. Sai Saranya, B. Priyanka, S. Prathyusha

Sree Vidyanikethan College of Pharmacy, Tirupati, Andhra Pradesh – 517102, India.

ABSTRACT

More than 80% of patients with clinical diabetic neuropathy have a distal symmetrical form of the disorder. In this neuropathic pattern, signs and symptoms start and remain more pronounced in the feet, and go on to affect more-proximal parts of the lower limbs and eventually the distal parts of the upper limbs, indicating that the longest nerve fibers are affected first. Shorter sensory axons subsequently become involved, accounting for neuropathic manifestations in more-proximal parts of the limbs and eventually the anterior trunk. This is often referred to as a length-dependent pattern. In this review, I will consider the clinicopathological aspects of the various patterns of diabetic neuropathy, starting with diabetic polyneuropathy, which is by far the most common type of diabetic neuropathy. I will also consider the focal diabetic neuropathies, and discuss the diagnosis of chronic inflammatory demyelinating polyneuropathy, which should not be missed or confused with diabetic neuropathy when it occurs in patients with diabetes.

Keywords: Diabetic neuropathy, Pain and trophic ulcers, Treatment.

INTRODUCTION

Diabetic neuropathy is a condition where peripheral nerve dysfunction occurs in diabetics apart from other causes like traumatic, metabolic, hereditary, compressive, infectious, toxic, nutritional, neoplastic, immune mediated and secondary to other systemic illnesses. Peripheral neuropathy is mostly caused by long term diabetes, a heterogeneous group of disorders that alter neuronal function in the body. Pain and trophic ulcers are the most common symptoms of diabetic neuropathy, associated with morbidity and disability [1].

Epidemiology

Epidemiologic studies estimate that the prevalence of neuropathy in diabetic patients is approximately 20% in community patients and 30% in hospital patients [2]. The United Kingdom Prospective

Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT) reported that the overall annual incidence of neuropathy was ~2%.(3) In 1977 it was found that roughly 7% of diabetics had neuropathy, in case of patients with diabetes for more than 25 years, the incidence was 50%(4) 2% in conventionally treated patients, and 0.56% in intensively treated type 1 diabetes mellitus patients.

The UKPDS could not support a correlation between the incidence of neuropathy and glycemic control in type 2 diabetes patients, but the progression of disease relies on glycemic control in both type 1 and 2 diabetes patients, the pathologies being similar [2, 3, 6]. Other risk factors include duration of diabetes, age, height, alcoholism, smoking, hypertension and hypercholesterolemia [2,7].

Pathogenesis

The possible synergistically acting pathogenetic factors suggested include, hyperglycaemia, non-enzymatic glycation, polyol pathway, free radical and oxidative stress [8].

a. Hyperglycaemia and polyol pathway

Diabetes Control and Complications Trial (DCCT) results prove that long-standing hyperglycaemia is the main cause for diabetic neuropathy to occur [9]. The enzymes aldose reductase and sorbitol dehydrogenase convert excess glucose shunted into the polyol pathway into sorbitol and fructose [10].

b. Advanced glycation end products (AGE)

In the presence of hyperglycaemia, due to an unregulated glycation reaction glucose is non-enzymatically incorporated into proteins. There is a tight control of blood glucose in patients with normal blood sugar. Levels of glycated serum proteins fall to approximately 40% if plasma glucose is normal for a week [11]. Cross-linked fluorescent protein products called advanced glycation end products (AGEs) are formed from non-enzymatically glycated proteins whose formation is driven by age and excess glucose concentration. Patients with long standing diabetes have levels twice to those of normal subjects [12]. Impairment of nerve conduction may be because of the glycation of myelin protein [13].

c. Miscellaneous

i. Free radical and oxidative stress

In diabetic tissues, free radical generation is enhanced by both non-enzymatic glycation and polyol pathway, while the ability to neutralize the same is reduced because NADPH is consumed through increased activity of aldose reductase [14]. These oxygen free radicals damage nerves by inhibiting nitric oxide (NO) production by the endothelium, or by being directly toxic which in turn reduce nerve blood flow.

ii. Biochemical abnormalities

Gamma linolenic acid (GLA) is an important constituent of neuronal membrane and a substrate for prostaglandin E and prostacyclin formation as well, which are required for preservation of nerve blood flow. d-6-desaturase is an essential enzyme in the conversion of linoleic acid to gamma linolenic acid. Insulin deficiency and hyperglycaemia inhibit the activity of the enzyme resulting in a fall in gamma-linolenic acid (GLA) levels. Nerve conduction velocity increases when GLA is supplemented [15]. In diabetic patients, there is impaired formation and metabolism of GLA, leading to diabetic neuropathy [16].

iii. Vascular and haemorrhological abnormalities

The endoneural vessels get blocked because of hyperplasia and swelling of endothelial cells, thickening of vessel wall with debris from degenerative pericytes as well

as basement membrane material caused due to AGE-induced pericyte apoptosis by generation of reactive oxygen species (ROS), and subsequent occlusion of the capillary lumen by fibrin or aggregated platelets contributing to neuropathy [17].

iv. Defects in nerve regeneration:

Neurotrophins play an important role in promoting neuronal survival, differentiation, function, and repair. It is well established that they regulate axonal growth in sensory neurons, both regenerative growth in response to injury and collateral sprouting of uninjured nerve terminals. Diabetic patients with neuropathy show low levels of circulating nerve growth factor (NGF) concentration [17]. This reduction in one of the neurotrophins and support contributes, in part, to the failure in axonal regeneration.

Of all the factors mentioned above, chronic hyperglycaemia has a pivotal role in the pathogenesis of diabetic neuropathy. Intensive control of blood sugar reduces the occurrence of clinical neuropathy. However, once diabetic neuropathy is established, significant recovery usually does not occur, even with good glycaemic control.

Diagnosis

The diagnosis of DN can be made on clinical examination but subsequently it needs to be confirmed by investigations.

There are two approaches for diagnosis of DN

(i) Traditional (ii) Newer.

(i) Traditional Approach

Clinical examination

“Signs” of sensory, motor and autonomic function deterioration were assessed.

Test of sensory function

In-depth sensory examination is required because routine clinical examination will only detect abnormalities at a relatively advanced stage and selective involvement of fiber occurs in routine clinical examination.

a. Vibration perception threshold (VPT)

Bithesiometer, vibrometer are used to perform this test. The risk of foot ulceration is increased 3-4 fold if the vibration perception threshold exceeds 25 volts.

b. Light touch sensation

A series of increasingly thick Nylon Semmes Weinstein mono-filaments are tested, and the threshold at which the first one can be felt when buckling is noted. The inability to feel the 10 gm filament indicate that patient is prone to foot ulceration.

c. Thermal thresholds

Warm and cold sensations should be tested separately. Pain threshold can be determined either by application of high or low temperature or by using the “Pinchometer” or a series of weighted needles.

d. Tests for autonomic function

Bedside cardiovascular tests have been developed to evaluate cardiovascular autonomic neuropathy.

e. Electrophysiology

Electrophysiology, particularly conduction velocity alone, may provide a poor measure of early dysfunction in some patients, because there is little demyelination in the early stages [18,19].

(ii) New approaches

Skin punch biopsy and immune histochemical Staining

Skin punch biopsy specimens (3-4 mm in diameter) obtained with the patient under local lidocaine anaesthesia under aseptic techniques is fixed in formalin, cut into 50 mm frozen sections and processed for immunohistochemistry. By this fiber density can be readily quantified [20].

Quantitative sensory testing (QST)

It can be measured by

- i) Computer assisted sensory evaluation
- ii) Physitemp NTE-2a thermal tester
- iii) Tactile circumferential discriminator.

Abnormalities in QST reflect axonal pathology or alteration in sensory transduction.

Treatment

The treatment of diabetic neuropathy can be broadly divided into two major groups:

- (i) Symptomatic treatment
- (ii) Treatment for nerve regeneration.

SYMPTOMATIC TREATMENT

Pain

Pain is the most common symptom, which could be superficial, deep, or aching. The following measures can be taken in order of preference for pain relief :

Tricyclic anti-depressants (TCA)

Double blind trials of the tricyclic anti-depressants have demonstrated significant benefits in reducing pain that is burning, aching, sharp, throbbing [21].

It should be started at low doses of 10 to 20 mg every night and increased gradually until pain control is achieved or dose limiting side effects occur. Achievement of pain relief may require as much as 150 mg of the drug per day for 3 to 6 weeks. Withdrawal from amitriptyline must be gradual so as to prevent rebound insomnia. These drugs act on the central nervous system, preventing the reuptake of norepinephrine and serotonin at synapses involved in pain inhibition.

TREMORS

Anti-convulsants

Carbamazepine, clonazepam, phenytoin, and gabapentin are used in common. Among anti-convulsants, carbamazepine is the most commonly used drug. When initiating carbamazepine, it is advisable to begin with a

low dose of 100 mg and then increase gradually until there is significant relief of symptoms or side effects are encountered. Complete blood counts and liver functions should be checked at the onset and then on a monthly basis over the first three months because leukopenia is a common complication [22].

Postural Hypotension

Mild postural hypotension can be managed with simple measures such as a high sodium diet, raising the head end of bed during sleep and wearing of whole body stockings. The pharmacological treatments include the use of mineralo-corticoids like fludrocortisone, sympathomimetic agents (midodrine, clonidine, yohimbine), β blockers with or without intrinsic sympathomimetic activity (propranolol, pindolol), pressor agents (dihydroergotamine, caffeine), prostaglandin synthesis inhibitors (indomethacin, ibuprofen, naproxen) and antiserotonergic agents [23].

Gastrointestinal Problems

Autonomic damage to the upper gastrointestinal tract is often asymptomatic. The prokinetic drugs used for the management of gastroparesis are metoclopramide (10-20 mg 6 hourly), domperidone (10-20 mg 4-6 hourly), cisapride (10 mg 8 hourly), and erythromycin (250 mg 8 hourly). Enteropathy includes both diarrhea and constipation.

The pathogenesis of diabetic diarrhea includes abnormalities in gastrointestinal motility, decreased gut transit time, reduced fluid absorption, bacterial overgrowth, pancreatic insufficiency, coexistent coeliac disease, and abnormalities in bile salt metabolism. The pathophysiology of diabetic constipation is poorly understood but may reflect loss of post-prandial gastrocolic reflex [24].

Loperamide, diphenoxylate, or codeine phosphate are used for symptomatic treatment of diabetic diarrhoea, while clonidine is used to reduce α_2 adrenergic receptor mediated intestinal absorption.

Aldose reductase inhibitors (ARI)

The aldose reductase inhibitors like alrestat, tolrestat, epalrestat, sorbinil, and zopolrestat prevent conversion of glucose to sorbitol in presence of hyperglycaemia [25,26].

Gamma linolenic acid (GLA)

Gamma linolenic acid (GLA) is an important constituent of neuronal membrane phospholipids as well as a substrate for prostaglandin E and prostacyclin formation, which may be important for preservation of nerve blood flow. In diabetic patients, conversion of linolenic acid to GLA and subsequent metabolism is impaired, possibly contributing to the pathogenesis of diabetic neuropathy.

A recent trial used GLA for one year and this resulted in significant improvements in both clinical measures as well as electrophysiologic test results [27].

Nerve regeneration

The agents used for nerve regeneration are known as neurotrophic factors. The neurotrophic factor is defined as a naturally occurring protein that is released by target tissues of responsive neurons, binds to specific receptors and is retrogradely transported to the cell body where it regulates gene expression through the actions of second messenger systems [28].

HERBAL REMEDIES

First of all to prevent exaggeration of the situation, the sugar levels should be monitored regularly to keep things under control. There are various herbal remedies for diabetic neuropathy described in Ayurveda-the ancient healthcare system of India. These herbs are effective in restoring the sensation in feet, healing the ulcers and keeping the sugar levels under control without causing any side effects. The herbs act together to keep nourishing the nerves damaged by diabetic neuropathy. These herbal remedies are combination of various herbal supplements which are otherwise useful in many other ailments like sexual weakness, erectile dysfunction, lack of stamina and strength, ageing related problems. The herbs can also be used by females to restore libido, fatigue, general weakness and pain in the calf muscles due to diabetic neuropathy as well as high sugar levels.

Among herbs, nerve tonics such as Skullcap (*Scutellaria lateriflora*), Cramp bark (*Viburnum opulus*) and Oat seed (*Avena sativa*) can be used to treat muscle weakness, nerve damage, and numbness. St. John's Wort (*Hypericum perforatum*) can either be massaged topically or taken internally for its antiviral and nervous system tonic properties [29].

CAPSAICIN

Majority of studies of capsaicin cream for PN have been conducted in individuals with diabetes. In a large, multicenter, double-blind, placebo controlled trial conducted by The Capsaicin Study group, 277 subjects entered the study, 252 continued for at least two weeks, and 219 completed the eight week trial. Subjects applied 0.075-percent capsaicin cream (n=100 completers) or placebo cream four times daily and were evaluated at two-week intervals for eight weeks. Pain was assessed via physician assessment as well as patient driven VAS. Statistically significant improvements were noted in physician global assessment (69.5% versus 53.4%), pain intensity (38.1% versus 27.4%), and degree of pain relief (58.4% versus 45.3 %) in the capsaicin versus placebo groups, respectively; statistically significant differences started during the fourth week [30]. Effect on daily activities was also assessed, and statistically significant

improvements in walking, working, sleep, and participation in recreational activities were noted in the capsaicin group compared to placebo [31].

Another study using the same protocol as the above studies was conducted on 22 diabetics with PN (11 in each group). Decrease in pain intensity via VAS was 16 percent in the capsaicin group and 4.1 percent in the placebo group. In an open-label continuation of the study (average follow-up 22 weeks), 50 percent of subjects experienced improvement or complete amelioration of pain, 25 percent remained unchanged, and 25 percent worsened [32]. Sensory function was tested in this same group of individuals and there were no differences between active or placebo in regard to sensations of vibration, warmth, or cold [33].

To determine the mechanism of action of capsaicin, a study was conducted on 13 subjects with diabetic PN who used 0.05-percent capsaicin for eight weeks. Cream was applied to one foot while the other foot served as a control. In addition to pain scores and vibrational and thermal thresholds, serum levels of substance P were measured. Significant improvements in total pain score and heat thresholds were noted in the treatment foot compared to the untreated foot, indicating very localized effects. Substance P levels increased initially during the first four weeks of the study, but declined to baseline by the end of the study, calling into question the long-term effect of capsaicin on substance P. [34].

CINNAMON

Cinnamon is an excellent kitchen spice, and it can be used for medicinal purposes. In fact, the oils in cinnamon contain cinnamyl acetate, cinnamaldehyde and cinnamyl alcohol, which give this spice its unique ability to heal various ailments. The phytochemical analysis indicated the presence of flavonoids and glycosides along with other major common secondary metabolites in the extract. Previous reports on α -glucosidase inhibitors isolated from medicinal plants suggest that several potential inhibitors belong to flavonoid glycoside class which has the characteristic structural features to inhibit α -glucosidase enzyme [35].

Based on the preliminary results obtained from LC-MS study, it is speculated that the presence of flavonoid glycosides might have contributed to the α -glucosidase inhibitory effect of the cinnamon extract. It effectively suppresses the maltose and sucrose induced postprandial blood glucose spikes in rats. Cinnamon extract could be used as a potential nutraceutical agent for treating postprandial hyperglycemia.

α -glucosidase inhibitors can retard the liberation of d-glucose from dietary complex carbohydrates and delay glucose absorption, resulting in reduced postprandial

plasma glucose levels and suppression of postprandial hyperglycemia. In recent years, many efforts have been made to identify effective α -glucosidase inhibitors from natural sources in order to develop a physiologic functional food or lead compounds for use against diabetes. Many α -glucosidase inhibitors that are phytoconstituents, such as flavonoids, alkaloids, terpenoids, anthocyanins, glycosides, phenolic compounds, and so on, have been isolated from plants [36].

ONIONS

Onion appears to prevent insulin from being broken down, and it is effective in either raw or boiled form. A potent antioxidant in onions, known as N-acetyl-l-cysteine, protects against diabetic neuropathy, according to a study conducted at Panjab University, Chandigarh, India. In the study, published in the January 2010 "Journal of Neurochemistry," diabetic laboratory rats were given N-acetyl-l-cysteine at a dose of 1.5 g per kg of body weight for 7 weeks. Improvements from the treatment included improved coordination, decreased hypersensitivity to pain, and decreased oxidation of lipids. The authors concluded a clear benefit of N-acetyl-l-cysteine in the prevention and treatment of diabetic neuropathy [37].

ASIAN GINSENG

Long used in Chinese medicine, this herb contains strong medicinal properties called panaxosides (or ginsenosides), which strengthen the immune system and enhance overall health. This herb helps the body to produce more insulin, reduce the level of fasting blood sugar and improve mood.

GINGKO BILOBA

This herb is rich in terpenoids and flavonoids, which are very powerful antioxidants. Antioxidants are vital for fighting off free radicals that cause the majority of chronic illnesses we face today. Typically, ginkgo is used to enhance memory and improve circulation, but it is also one of the best herbs for diabetic neuropathy. It may help with the flow of blood out to the extremities and thus helps to keep these tissues healthy and the nerves working. Ginkgo biloba may alleviate neuropathy by means of the bilobalides in Ginkgo biloba accelerating the repair of damaged motor nerves.

GARLIC

Garlic is abundant in antioxidants and contains APDS (allyl propyl disulphide), which aids in reducing inflammation and keeping blood sugar levels low. The compound takes the place of insulin in the liver, and thus more insulin is left in the blood stream to help maintain blood sugar levels [37].

FLAVONOIDS

Flavonoids are naturally occurring phenolic compounds with a broad range of biological activities and

the beneficial effects of flavonoids have been studied in relation to diabetes mellitus, either through the inhibition of intestinal α -glucosidase enzyme or through their capacity to avoid glucose absorption and/or to improve glucose tolerance [38]. It has been shown that Calendula Oil, as an active ingredient in a pain relief product is an effective topical analgesic for diabetic neuropathy pain [39].

The inhibitory activity of six groups of flavonoids against α -glucosidase in yeast and rat small intestine was compared, and the chemical structures of flavonoids responsible for the inhibitory activity were evaluated. Rat's small intestinal α -glucosidase was weakly inhibited by many flavonoids, and slightly by the anthocyanidin and isoflavone groups [40].

Eg : *epicatechin, silymarin, isoquercitin, chrysin and rutin*

ALKALOIDS

Methanolic extract of *Adhatoda vasica* Nees was tested in screening experiments for rat intestinal α -glucosidase. Vasicine and Vasicinol, which were isolated by assay-guided fractionation of this extract, showed a high sucrase inhibitory activity. Both of these compounds were shown to be reversible inhibitors of sucrase.

Three alkaloids named piperumbellactam A, piperumbellactam B and piperumbellactam C were isolated from branches of *Piper umbellatum* and these compounds showed moderate α -glucosidase enzyme inhibition [41]. The methanolic extract from flower buds of *Tussilago farfara* showed the highest maltase inhibitory activity, with maltose as a substrate. Enzyme assay-guided fractionation of this extract afforded 3,4-dicaffeoylquinic acid, 3,5-dicaffeoylquinic acid, and 4,5-dicaffeoylquinic acid. Comparison of the activities of these three compounds with others, such as chlorogenic acid, quinic acid, and caffeic acid, suggested that the number of caffeoyl groups attached to a quinic acid core were important for the potency [42].

PHENOLICS

The dried *Terminalia chebula* (Combretaceae) fruits were extracted using 70% methanol at room temperature and its mammalian α -glucosidase inhibitory activity was investigated. It was found to have a potent rat intestinal maltase inhibitory activity. Three active ellagitannins, identified as chebulanin, chebulagic acid and chebulinic acid were isolated using bioassay-guided separation. All the three compounds were shown to possess potent intestinal maltase inhibitory activity [43].

The extraction and fractionation of 50% aqueous methanolic extracts of *Bergenian cilata* led to the isolation of two active compounds, namely, (-)-3-O-galloylepicatechin and (-)-3-O-galloylcatechin. These isolated compounds demonstrated significant dose dependent enzyme inhibitory activities against rat intestinal α -glucosidase [44].

Eg: phlorizine, marsupsin and pterostibene

CURCUMINOIDS

Natural curcumin, demethoxycurcumin and bisdemethoxycurcumin isolated from *Curcuma longa* (turmeric) were evaluated in vitro for the α -glucosidase inhibitory activity via UV and circular dichroism spectroscopy. The results indicated that natural curcuminoid compound showed a remarkable inhibitory effect [45].

TERPENOIDS

3b-Acetoxy-16b-hydroxybetulinic acid was isolated from *Fagara tessmannii*, and it was found to be a potent α -glucosidase inhibitor with IC_{50} value 7.6 ± 0.6 [46].

A new triterpenoid saponin Segetalic acid 28-O- α -l-arabinopyranosyl-(1 \rightarrow 4)- α -l-arabinopyranosyl-(1 \rightarrow 3)- β -d-xylopyranosyl-(1 \rightarrow 4)- α -l-rhamnopyranosyl-(1 \rightarrow 2)- β -d-fucopyranosyl ester has been isolated and elucidated from the roots of *Gypsophila oldhamiana* and has been evaluated for its α -glucosidase inhibition activity [47].

ANTHOCYANINS

Cyanidin-3-galactoside, a natural anthocyanin, was also investigated for its α -glucosidase inhibitory activity. A low dose of cyanidin-3-galactoside showed a synergistic inhibition on intestinal α -glucosidase (maltase and sucrase) when combined with acarbose [48].

MISCELLANEOUS

Two bromophenols, 2,4,6-tribromophenol and 2,4-dibromophenol, were purified from *Grateloupia elliptica*. α -Glucosidase inhibitory activity of these compounds against α -glucosidases was determined compared with acarbose and voglibose. The IC_{50} values of compounds and against *Saccharomyces cerevisiae* α -glucosidase, which were lower than what was presented against *Bacillus stearothermophilus* α -glucosidase [49]. The α -glucosidase inhibitory activities of compound against *S. cerevisiae* and *B. stearothermophilus* α -glucosidases were also higher than that for compound.

It is to be concluded that inhibitory potencies of bromophenol increased with increasing degree of bromo-substitution per benzene ring and with decreasing degree of methyl-substitution [47]. Voglibose and acarbose had high inhibitory effects on mammalian α -glucosidase, but no inhibitory activity against *S. cerevisiae* α -glucosidase [48].

PRODUCTS IN PRESENT MARKET

Suggested Products & herbal remedies

People suffering from diabetes often have to deal with neuropathy, which is where the peripheral nerves become damaged. Symptoms may include loss of sensation, pain and the inability to control muscles. A means of fighting this is to take herbs. In every case, these herbs for diabetic neuropathy will improve your blood sugar levels.

“DIABETES CARE PACK” made of Ashwagandha, shilajit, chanderprabha was formulated by Planet Ayurveda for treating diabetic neuropathy [49].

Table 1. Herbal products for diabetic neuropathy

Product	Dose	Applications
GluControl™ 120 caps, 480 caps	6 caps per day	Improves glucose tolerance, restores hypothalamic and muscle insulin receptor-cell sensitivity, normalizes high blood sugar levels without causing hypoglycemia.
Alpha Lipoic Acid 60 caps (200mg), 90 caps (500mg)	2 caps per day	Powerful antioxidant. May prevent nerve damage caused by free radical attack in diabetic patients. Results may not be seen for several months.
Phosphatidylserine 100 Plus 45 softgels	1 capsule daily in the morning	May improve nerve function in diabetic patients.
Acetyl-L-Carnitine 60 caps (500mg)	3-6 capsules per day	ALC or L-carnitine assist the transport of fat through the cell membrane, into the mitochondria where it is oxidized to product cellular energy.
Ca-AEP (Calcium-AEP) 90 caps (500mg)	2-6 capsules per day	Studies over the past 30 years have shown that Ca-AEP is essential for neurotransmission, nerve impulse generation, and muscular contractions.

CONCLUSION

Herbal remedies claim themselves as safer, potent and economic compared to the conventional treatment as they have zero/mild side effects when used.

REFERENCES

1. Vinik AI, Park TS, Stansberry KB et al. Diabetic neuropathies. *Diabetologia*, 43, 2000, 957-73.
2. Shaw JE, Zimmet PZ. The epidemiology of diabetic neuropathy. *Diabetes Rev*, 7, 1999, 245-52.

3. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*, 329, 1993, 977-86.
4. Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973. *Diabete Metab*, 3, 1977, 97-107.
5. Vinik AI, Holland MT, Le Beau JM et al. Diabetic neuropathies. *Diabetes Care*, 15, 1992, 1926-75.
6. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonyl ureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet*, 352, 1998, 837-53.
7. Neef H, Declercq P, Laekeman G. Hypoglycaemic activity of selected European plants. *Phytother Res*, 9, 1995, 45-48.
8. Roman-Ramos R, Flores-Saenz JL, Alarcon-Aguilar F. Antihyperglycaemic effect of some edible plants. *JEthnopharmacol*, 48, 1995, 25-32.
9. Aderibigebe AO, Emudianughe Lawal BA. Antihyperglycaemic effect of *Mangifera indica* in rat. *Phytother Res*, 13, 1999, 504-507.
10. Vuksan V, Sievenpiper JL, Koo VY, et al. American ginseng (*Panax quinquefolius* L.) reduces postprandial glycaemia in nondiabetic subjects and subjects with type 2 diabetes mellitus. *Arch Intern Med*, 160, 2000, 1009-1013.
11. Hypoglycaemic effect of Saponin isolated from leaves of *Acanthopanax senticosus* (Rupr. Et Maxim.) Harms. *Chung Kuo Chung Yao Tsa Chih*, 19, 1994, 683-685.
12. Yoshikawa M, Matsuda H, Harada E, et al. A new hypoglycaemic principle from the root cortex of *Aralia elata* Seem; Structure-related hypoglycaemic activity of oleanolic acid glycosides. *Chem Pharm Bull* (Tokyo), 42, 1994, 1354-1356.
13. Park HJ, Kim DH, Choi JW, et al. A potent antidiabetic agent from *Kalopanax pictus*. *Arch Pharm Res*, 21, 1998, 24-29.
14. Kim DH, Yu KW, Bae EA, et al. Metabolism of kalopanaxsaponin B and H by human intestinal bacteria and antidiabetic activity of their metabolites. *Biol Pharm Bull*, 21, 1998, 360-365.
15. Sindurani JA, Rajamohan T. Effects of different levels of coconut fiber on blood glucose, serum insulin and minerals in rats. *Indian J Physiol Pharmacol*, 44, 2000, 97-100.
16. Faradji V, Sotelo J. Low serum levels of nerve growth factor in diabetic neuropathy. *Acta Neurol Scand*, 1990, 402-13.
17. Shabana MM, Mirhom YW, Genenah AA, et al. Study into wild Egyptian plants of potential medicinal activity. Ninth communication : Hypoglycaemic activity of some selected plants in normal fasting and alloxanised rats. *Archiv Fur Exp Veterinarmedizin*, 44, 1990, 389-394.
18. Holland NR, Stocks A, Hauer P et al. Intra epidermal nerve fibre density in patients with painful sensory neuropathy. *Neurology*, 48, 1997, 708-11.
19. Holland NR, Crawford TQ, Hauer P et al. Small fiber sensory neuropathies: clinical course and neuropathology of idiopathic cases. *Ann Neurol*, 44, 1998, 47-59.
20. Max MB, Culnane M, Schafer SC et al. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. *Neurology*, 37, 1987, 589.
21. Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus. *JAMA*, 280, 1998, 1831-6.
22. Dejgaard A, Hilsted J. No effect of pindolol on postural hypotension in type 1 (insulindependent) diabetic patients with autonomic neuropathy. A randomised double-blind controlled study. *Diabetologia*, 31, 1988, 281-4.
23. Feldman M, Corbett DB, Tamsey EJ et al. Abnormal gastric function in long-standing insulin dependent diabetic patients. *Gastroenterology*, 43, 1979, 65-75.
24. Yagihashi S, Yamagishi S, Wada R, et al. Neuropathy in diabetic mice over expressing human aldose reductase and effects of aldose reductase inhibitor. *Brain*, 124, 2001, 2448-2458.
25. Obrosova IG, Van Huysen C, Fathallah L, et al. An aldose reductase inhibitor reverses early diabetes-induced changes in peripheral nerve function, metabolism, and antioxidative defense. *Faseb J*, 16, 2002, 123-125.
26. Keen H, Paxan J, Allawi J et al. Treatment of diabetic neuropathy with gamma - linoleic acid. *Diabetes Care*, 16, 1993, 8-15.
27. Apfel SC. Neurotrophic factors in the therapy of diabetic neuropathy. *Am J Med*, 107, 1999, 34S-42S.
28. Kunt T, Forst T et al. Effect of treatment with capsaicin on daily activities of patients with painful diabetic neuropathy. Capsaicin Study Group. *Diabetes Care*, 15, 1992, 159-165.
29. Tandan R, Lewis GA, Krusinski PB, et al. Topical capsaicin in painful diabetic neuropathy. Controlled study with long-term follow-up. *Diabetes Care*, 15, 1992, 8-14.
30. Tandan R, Lewis GA, Badger GB, Fries TJ. Topical capsaicin in painful diabetic neuropathy. Effect on sensory function. *Diabetes Care*, 15, 1992, 15-18.
31. Forst T, Pohlmann T, Kunt T, et al. The influence of local capsaicin treatment on small nerve fibre function and neurovascular control in symptomatic diabetic neuropathy. *Acta Diabetol*, 39, 2002, 1-6.

32. Guay DR. Pregabalin in neuropathic pain: a more “pharmaceutically elegant” gabapentin *Am J Geriatr Pharmacother*, 3, 2005, 274-287.
33. Tadera K, Minami Y, Takamastu K, Matsuoka T. Inhibition of α -Glucosidase and α -Amylase by Flavonoids. *J Nutr Sci Vitaminol*, 52, 2006, 149–53.
34. Tabopda TK, Ngoupayo J, Liu J, Mitaine-Offer AC, Tanoli SA, Khan SN et al. Bioactive aristolactams from *Piper umbellatum*. *Phytochem*, 69, 2008, 1726–31.
35. Gao H, Huang YN, Gao B, Xu PY, Inagaki C, Kawabata J. α -Glucosidase inhibitory effect by the flower buds of *Tussilago farfara* L. *Food Chem*, 106, 2008, 1195–201.
36. Gao H, Huang YN, Xu PY, Kawabata J. Inhibitory effect on α -glucosidase by the fruits of *Terminalia chebula* Retz. *Food Chem*, 105, 2007, 628–34.
37. Bhandari MR, Anurakkun NJ, Hong G, Kawabata J. α -Glucosidase and α -amylase inhibitory activities of Nepalese medicinal herb Pakhanbhed (*Bergenia ciliata*, Haw.) *Food Chem*, 106, 2008, 247–52.
38. Kurihara H, Mitani T, Kawabata J, Takahashi K. Inhibitory potencies of bromophenols from Rhodomelaceae algae against α -glucosidase activity. *Fish Sci*, 65, 1999, 300–3.
39. Ivorra MD, Paya M, Villar A. A review of natural products and plants as potential antidiabetic drugs. *J Ethnopharmacol*, 27, 1989, 248-275.
40. Kurihara H, Mitani T, Kawabata J, Takahashi K. Inhibitory potencies of bromophenols from Rhodomelaceae algae against α -glucosidase activity. *Fish Sci.*, 65, 1999, 300–3.
41. Haslam E. Polyphenol-protein interactions. *J Chem Ecol*, 139, 1974, 285–8.
42. Cogoli A, Semenza G. 18 A probable oxocarbonium ion in the reaction mechanism of small intestinal sucrase and isomaltase. *J Biol Chem*, 250, 1975, 7802–9.
43. Stern JL, Hagerman AE, Steinberg PD, Mason PK. Phlorotannins-protein interactions. *J Chem Ecol*, 22, 1996, 1877–99.
44. Lam SH, Chen JM, Kang CJ, Chen CH, Lee SS. α -Glucosidase inhibitors from the seeds of *Syagrus romanzoffiana*. *Phytochem*, 69, 2008, 1173–8.
45. Anurakkun NJ, Bhandari MR, Kawabata J. α -Glucosidase inhibitors from Devil tree (*Alstonia scholaris*) *Food Chem*, 103, 2007, 1319–23.
46. Du ZY, Liu RR, Shao WY, Mao XP, Ma L, Gu LQ, et al. α -Glucosidase inhibition of natural curcuminoids and curcumin analogs. *Eur E Med Chem*, 14, 2006, 213–8.
47. Mbaze LM, Poumale HM, Wansi JD, Lado JA, Khan SN, Iqbal MC, et al. α -Glucosidase inhibitory pentacyclic triterpenes from the stem bark of *Fagara tessmannii* (Rutaceae) *Phytochem*, 68, 2007, 591–5.
48. Luo JG, Ma L, Kong LY. New triterpenoid saponins with strong α - glucosidase inhibitory activity from the roots of *Gypsophila oldhamiana*. *Bioorg Med Chem*, 16, 2008, 2912–20.
49. Adisakwattana S, Charoenlertkul P, Yibchok-Anun S. α -Glucosidase inhibitory activity of cyanidin-3-galactoside and synergistic effect with acarbose. *J Enzym Inhib Med Chem*, 24, 2009, 65–9.