International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 30, Issue 8, August 2024 pp 229-242. **ijppr.humanjournals.com** ISSN: 2349-7203

Role of Antioxidants and Vitamin Supplements in Diabetic Neuropathy

Talloju Tejasri*, Jorige Archana

1. Department of Pharmacology, RBVRR Women's College of Pharmacy, Barkatpura, Hyderabad 500027 India.

Received: 2024-08-01 Revised: 2024-08-05 Accepted: 2024-08-10

ABSTRACT

The most common complication of the diabetics is diabetic neuropathy that is Paraesthesia as a microvascular consequence of hyperglycaemia. This condition causes pain, numbness, a number of other uncomfortable manifestations, and severely affected the Quality of Life. Reactive oxygen species which are generated during detoxification of free radicals has been postulated to be one of the causes of diabetic neuropathy. Free radicals have been considered for use in therapy due to the reduction in oxidative stress and the therapeutic agents include antioxidants, vitamins supplements. Alpha-lipoic acid, N-acetylcysteine, coenzyme Q10, Vitamin E, Vitamin C, and B vitamin the particular B1, B6, and B12 due to their effectiveness in reducing oxidation and improving the function of nerves in complications related to diabetes. This review highlights the multifactorial involvement of different pathways in development of DN review will attempt to do the following: Identify how antioxidants and vitamins exert their neuroprotective roles, and clinical trials that equate their efficacy, and evaluate the additives relevance to diabetic neuropathy. This review comprehensives the etiopathology & promising therapeutic interventions in pictorial and tabular representation. These could be promising, more large, long terms controlled clinical trials are needed to know the fixed doses, duration and the final outcomes of these supplements in the DN. Therefore, if a patient with diabetes mellitus takes antioxidant/ vitamin treatment together with usual medical treatment for diabetes, the development of diabetic neuropathy may be prevented completely.

Keywords : Diabetic neuropathy, Antioxidants, Vitamins , Hyperglycaemia , Free radical

INTRODUCTION

DPN is a chronic intricacy of diabetes that causes significant distress in diabetic patients.[1,2] Around 50% of individuals with diabetes will develop diabetic peripheral neuropathy, a prevalent condition affecting 50% of patients with type 1 or type 2 diabetes mellitus.[3,4] The increase in morbidity, distress, and healthcare costs is a direct consequence of this situation. [5] DN development is influenced by various risk factors such as hyperglycaemia, abdominal adiposity, creatinine levels, and high white blood cell count.[6] DN's clinical signs vary depending on which nerve fibres are impacted. [7] Hyperalgesia and allodynia are the primary signs of a nerve disease, which can progress to the degradation and dysfunction of large myelinated nerve fibres, leading to sensory ataxia and impaired perception. Chronic DM in rodents is associated with thermal and mechanical hypoalgesia, motor dysfunction, axonal damage and demyelination.[8,9] Sensory loss leads to delays in treatment, foot injury, ulcers and infections and therefore the patients may require lower limb amputation because of recurrent infections and ulcers. Neuropathy is primarily treated with pharmacological therapy, followed by interventional strategies like nerve blocks and neuromodulators. The most extensively researched pharmaceuticals for neuropathic pain are antidepressants and antiepileptics, including those with confirmed efficacy. [10] Despite numerous conventional treatments aimed at improving the quality of life for neuropathic pain patients, over two-thirds of them have not achieved sufficient pain relief. [11] This review explores etiopathology and therapeutic interventions for diabetic neuropathy, suggesting large, long-term controlled clinical trials are needed to fully understand the effects of antioxidant/vitamin treatment in diabetes patients.

Molecular mechanisms of diabetic neuropathies:

The pathogenesis of microvascular complications in patients with DM that are induced by hyperglycaemia is influenced by a variety of mechanisms. The primary pathogenic factors are inflammation, mitochondrial dysfunction, and oxidative stress, as summarised.[12]

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 30, Issue 8, August 2024 pp 229-242. ijppr.humanjournals.com ISSN: 2349-7203

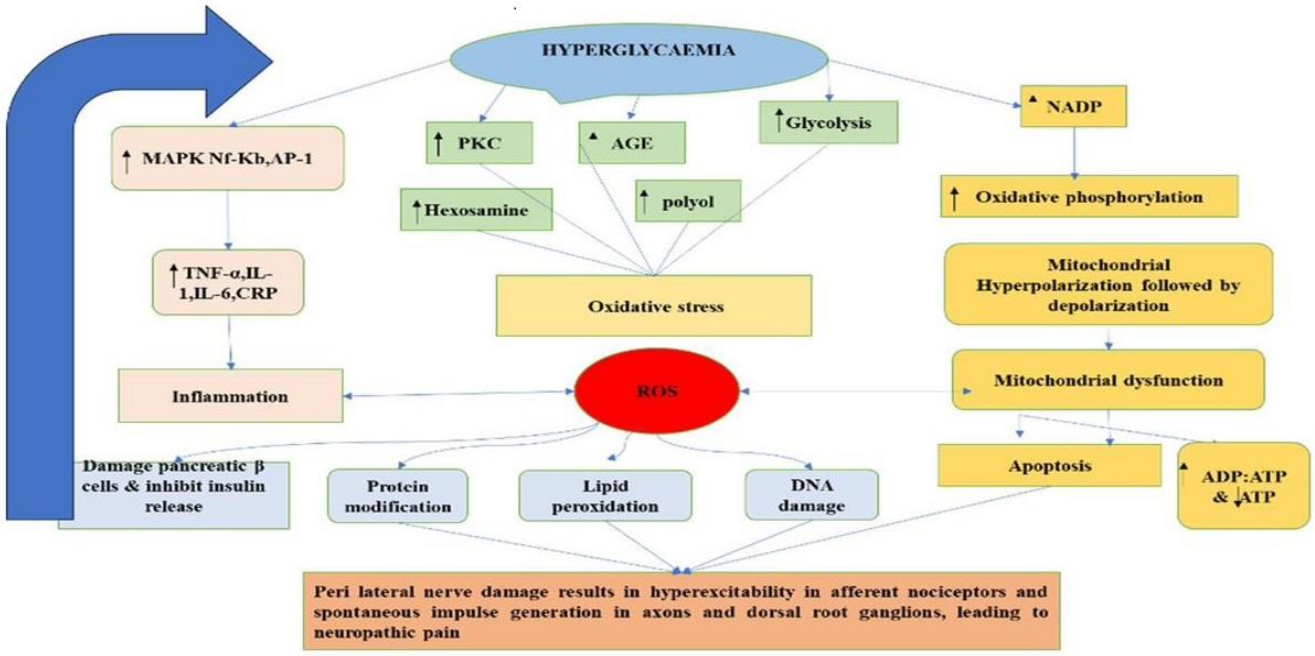

FIGURE 1

FIGURE 1: Molecular processes of diabetic neuropathy caused by hyperglycaemia

This graphic illustrates the role of oxidative stress, inflammation, and mitochondrial dysfunction in diabetic neuropathy development, highlighting the role of AGE, AP-1, CRP, MAPK, NADH, NF-kappa B, PKC, and RAGE.

Oxidative stress and diabetic neuropathy

There is a chance of development of diabetic neuropathy in more than half of the patients with diabetes, DN is a nerve degeneration in peripheral and autonomic system deficits; it is the major cause of amputation and of failure of the autonomous system[13] Diabetes mellitus patients stand a 15% lifetime risk of one or multiple amputations.[14] In diabetic states, the synthesis of superoxide, accumulation of sorbitol through polyol-pathway, formation of AGEs, activation of protein kinase C, and the hexosamine flux path affect the cellular function adversely. This along with the metabolic and vascular derangement leads to the dysfunction in neurons and neurotropic support loss may lead to apoptosis of the Schwann cells and glial cells.[15] The results of the experimental diabetes studies on animals have shown that they have reduced levels of the nerve growth factor, neurotrophin-3, colliery neutrophil factor and insulin like growth factor-I and all of them is associated with neuropathy.[16] The neural indicators include motor and sensory nerve conduction velocities, reduced blood circulation, reduced NGF and neuropeptide levels.[17] In regard to the prevention of diabetes complications and in particular of neuropathy, many clinical trials have demonstrated significant efficacy. Though, single antioxidants in large doses such as vitamin E or vitamin C are used in DN. Chen and Lin also established that using antioxidant therapies along with trace elements and vitamins enhance the mode of treatment. It is well possible to assess patients' antioxidant surveillance, and seeing that which could be lowered through modifying the therapeutic antioxidant prophyll.[18]

Clinical features of diabetic peripheral neuropathy

DPN is a length-dependent, distal, sensorimotor neuropathy, that may affect the autonomic system with different severity. Mainly it is sensory with dilated extremities being the only areas involved in sensation and motor systems, often, upper extremity manifestations are thought to be due to mononeuropathy.[19] Sensorimotor syndrome, that is delineated by diabetic retinopathy or nephropathy, definite by evidences of electrophysiological change and can therefore be hard to differentiate from other sorts of

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 30, Issue 8, August 2024 pp 229-242. ijppr.humanjournals.com ISSN: 2349-7203

neuropathies.[20] If Retinopathy and/or Nephropathy are not visible then other causes for polyneuropathy should be considered. Symptomatic, distal sensitiveness and sensorimotor, symmetric polyneuropathy in the lower limbs, chronic hyperglycaemia, and exclusion of other contributing factors should be used to diagnose diabetic peripheral neuropathy in patients with DM.[21]

Pathogenesis of diabetic neuropathy

The pathogenic mechanism behind diabetic neuropathy (DN) is unclear, but current theory suggests it is primarily caused by hyperglycaemia, polyol activation, advanced glycation end products (AGEs), hexosamine, diacylglycerol/protein kinase C (PKC), oxidative stress, nitric oxide, and inflammation. Oxidative stress elevates blood sugar levels, leading to the activation of AGE pathway and polyol pathway. Hyperglycaemia in neurons causes saturation of the regular glycolytic pathway, leading to increased polyol production. This leads to intracellular hyperosmolarity, decreased PKC and Na+/K+-ATPase activity, axonal transport impairment, and structural nerve deterioration. Consumption of NADPH is linked to the conversion of glucose to sorbitol by aldose reductase, which exacerbates oxidative stress. The synthesis of fructose from sorbitol leads to a significant redox imbalance by increasing AGEs, promoting glycation, and depleting NADPH. The pathogenic mechanisms behind DN remain unclear, but these processes are crucial in understanding the development of DN. [22-47]

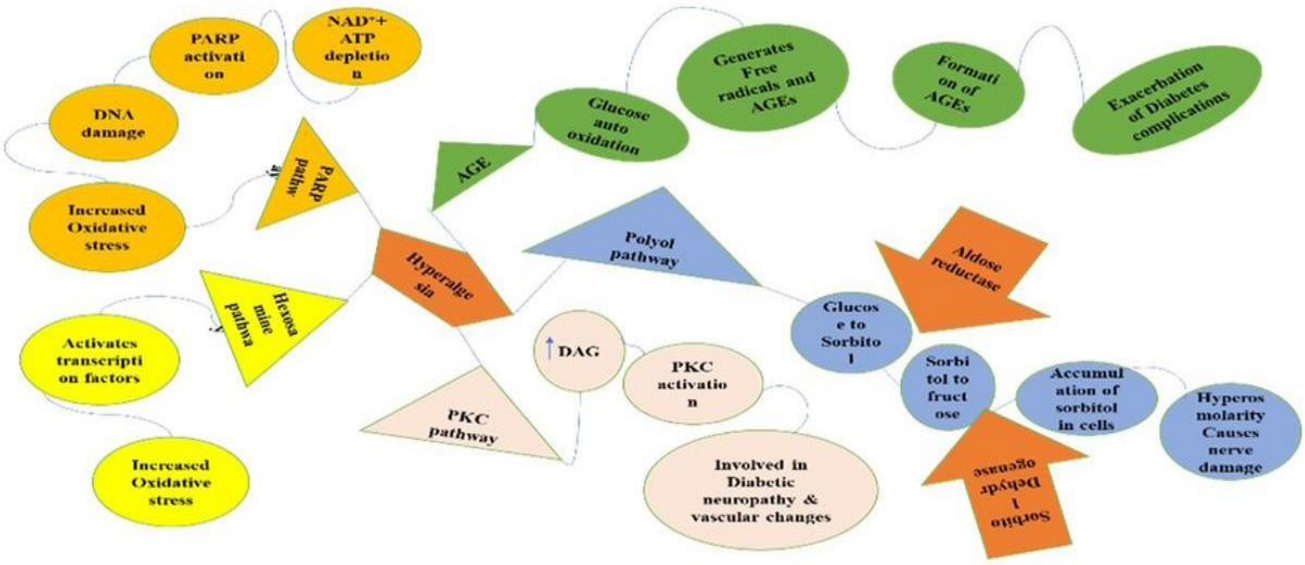

FIGURE 2: Pathways involved in the progression of DN

Diabetic neuropathy and antioxidants

The antioxidant constitute the central interests of the search for an effective and efficient treatment of nerve dysfunction in diabetes over the past decade because oxidative stress has been demonstrated to play crucial roles in the development of DN. More and more, antioxidants and other agents which mimic the antioxidant system, have been tested in vivo and in vitro by using animal experimental models.[48-55] However, there are some antioxidants that can be noted: curcumin, α-lipoic acid, melatonin, acetyl-L-carnitine, and flavonoids. At the present, only a few antioxidants are under different stages of testing in human intervention trials and there are some that have been pulled out of trials because of issues on safety or efficacy.[56] Currently, antioxidant treatment for DN has not been approved by the United States Food and Drug Administration. However α-lipoicacid, which demonstrated the highest efficacy in clinical studies has been approved in few of the European countries.[57-59]

Vitamins and supplements

vitamins and supplements reduce oxidative damage and peroxidation of lipids markers in diabetics and animals, while deficiencies in beta-carotene, vitamin C, and E are document.[60,61] Conflicting findings on blood levels during experimental diabetes suggest that

vitamin C and vitamin E are key antioxidant vitamins. Vitamin E disrupts lipid peroxidation, while vitamin C scavenges radicals. They function synergistically, with vitamin E oxidized to tocopherol and reduced back to tocopherol. Vitamin C is the most potent physiological antioxidant, protecting protein thiol groups from oxidation. High vitamin C and E intake from supplements is linked to an increased risk of cardiovascular disease mortality in postmenopausal women with diabetes.[62]

TABLE I: Role of antioxidants & vitamin supplements in preclinical studies

Sl.no	Antioxidant	Source of antioxidants	Model	Duration& parameters	Study outcomes	References
1	N-acetylcysteine (1.5g/kg/day)	Sunflower seeds, legumes, yoghurt, cheese, poultry, and turkey	Streptozotocin 65mg/kg I.v Male S.D Rats	4 weeks Parameters Behavioural assessments: Mechanical sensitivity Paw withdrawal threshold Western blot analysis Plasma TNF- α, IL-6, SOD-1, SOD-2, MDA, and 15-f2t-isoprostane measurement Statistical analysis	The paw withdrawal thresholds and latencies of the diabetic rats decreased compared to those in the control group. The protein expression of CXCR4 and p-CXCR4, IL-6, and TNF-α in the spinal cord and prefrontal cortex of the diabetic rats increased markedly. NAC treatment clearly increased the expressions of CXCR4 and p-CXCR4 proteins in both the spinal cord and prefrontal cortex. Moreover, normal levels or decreased to that noted for healthy control rats were observed for IL-6 and TNF-α protein expressions in both the spinal cord and prefrontal cortex. The PWLs, PWTs, plasma IL-6 level, TNF-α level, SOD1 level, SOD2 level, MDA level.	Li S, Li X *et al.*, 2021
2	Resveratrol (10 and 20 mg/kg. I.P)	All nuts including peanuts and pistachios, grapes particularly the raisins, red and white wine, blue berries, cranberries cocoa and dark chocolate	streptozotocin (STZ) at a dose of 55 mg/kg (I.P)	8 weeks Motor & nerve conduction velocity Sciatic nerve blood flow Plasma glucose levels Lipid peroxidation TNF α & IL-6 levels Immunohistochemistry Statistical analysis	Resveratrol reduced p65 and IjB-α expression in rats. Resveratrol could attenuate TNF-α, IL-6 and COX-2. It could also reduce MDA in nerves potentially decreasing neuro-inflammation. The activity of NF-jB inhibitory and anti-inflammation of resveratrol might be related to the neuro-protection effect on the development of diabetic neuropathy besides its anti-oxidant effects.	Kumar A *et al.*, 2010
3	Resveratrol (10 and 20	All nuts including peanuts and pistachios,	STZ 55mg/kg I.p	8 weeks Parameters Plasma glucose level	The study also showed that resveratrol treatment in diabetic rats decreased DNA damage, which indicates the possible use	Kumar A *et al.*, 2007.

	mg/kg.I .p)	grapes particularly the raisins, red and white wine, blue berries, cranberries cocoa and dark chocolate		Motor nerve conduction velocity Assessment of blood flow in the sciatic nerve Thermal hyperalgesia Measurement of allodynia Measurement of lipid peroxidation Measurement of peroxynitrite Measurement of catalase Measurement of DNA fragmentation	of resveratrol as a therapeutic agent for diabetic neuropathy. The possible role played by the reduction in DNA damage and oxidative stress in high-fat diet-induced mitochondrial dysfunction was suggested, supporting resveratrol as a promising agent for treating diabetic neuropathy.	
4	Alpha lipoic acid(20, 50,100 mg/kg) 5 times per week ,I.p	Red meat, carrot, beets, spinach, broccoli & potatoes	Streptozotocin (20,50,100mg/kg)	3 months Lipid peroxidation Leukocytes & Catecholamine oxidation Nerve blood flow GSH	Resveratrol reduced the protein levels of p65 and increased the levels of IjB-α in the model rats. Resveratrol could effectively decrease TNF-α, IL-6 and COX-2 which could reflect via MDA level of nerves that resveratrol might reduce nerve-endothelium inflammation. The effect to suppress NF-jB and to inhibit inflammatory reaction of resveratrol perhaps was associated with its protective effect on diabetic neuropathy except anti-oxidative.	Low PA *et al.*, 1997
5	CoQ10 (100mg orally)& Alpha lipoic acid(100mg orally)	Oily fish such as salmon& tuna, organ meat such as liver & whole grain	STZ (45mg/kg , I.P)	5 weeks Parameters Reactive oxygen species (ROS) Measurement of lipid peroxidation Assessment of glutathione The determination of the previously defined Adenosine Di Phosphate (ADP) and Adenosine Tri Phosphate (ATP). Western blot	The DNA damage in the diabetic rats treated with resveratrol were decreased, implying the potential application of resveratrol as therapeutic agent for diabetic neuropathy. The possible role of reduction in DNA damage and oxidative stress plays in high-fat diet-induced mitochondrial dysfunction were discussed to strengthen resveratrol as a potential agent for the treatment of diabetic neuropathy.	Galeshkalami NS *et al.*, 2019

				analysis Thus, the results obtained by morphometric analysis of DRG neurons investing in histopathological Measurement of motor function Statistical analysis		
6	Benfotiamine (10, 30,100, 300mg, orally)	Onion, garlic etc	Wistar rats Streptozotocin (50mg/kg. I.P)	6 weeks Parameters Formalin test Evaluation of antiallodynic activity	Anti-inflammatory effect of benfotiamine was proved in both diabetic and non-diabetic rats with inflammation induced (10–30 mg/kg) and neuropathic (75–300 mg/kg) pains. Oral benfotiamine may help reduce tactile allodynia in rats of different origins and it is proposed for diverse people to take this drug for reducing neuropathic and inflammatory pains.	Sánchez-Ramírez GM *et al.*, 2016
7	Vitamin B (B1, B6, B12) 20:20:0.2 mg/kg 60:60:0.6 mg/kg 180:180:1.8 mg/kg S.c	B1: whole grains Sunflower seeds Legumes B6: poultry Salmon Potatoes Non citrus fruits B12: Meat (liver, beef) Fish Cheese, eggs	S.D rats Streptozotocin (50mg/kg, I.p)	5 weeks Parameters Formalin test Nerve conduction velocity Tissue preparation for lipid and protein oxidation Measurement of lipid peroxidation Malondialdehyde 4- hydroxyalkenal assay measurements DNP derivated protein assay TNF α assay Cyclooxygenase assay Statistical analysis	Vitamin B plays a crucial role in managing diabetic neuropathy by shielding and repairing nerves, lowering homocysteine levels, and preserving the myelin layer for healthy nerve function. It also aids in neurotransmitter production and antioxidant properties, reducing oxidative stress and supporting healthy nerves. Studies have shown that vitamin B1, B6, and B12 can reduce sensory dysfunction in diabetic rats, including hyperalgesia and allodynia. Repeated daily administration of the B vitamin cocktail can enhance sensory nerve conduction velocity and alleviate hyperalgesia and tactile allodynia.	Jolivalt CG, Mizisin LM *et al.*, 2009.
8	Edaravone (3 mg/kg, i.p	Synthetic compound	S.D Rats Streptozotocin	8 weeks Parameters	The findings of the present investigation demonstrate that edaravone therapy enhances NCV and nociception in the	Saini AK, *et al.*, 2007

	twice a week		50mg/kg i.p	Motor nerve conduction velocity Nerve blood flow Thermal stimuli : cold & hot immersion Measurement of lipid peroxidation Measurement of SOD & catalase Statistical analysis	diabetic rats and free radicals impair this process. Motor nerve conduction velocity and nerve blood flow, as well as mechanical allodynia, determined by the tail flick latency, were significantly decreased in the diabetic rats in comparison to non-diabetic ones. Edaravone also modulates lipid peroxidation, anti-oxidant enzymes, lowers blood pressure and vascular resistance to further prove the preventative and curative roles of edaravone on nerve function and oxidative stress.	
9	Taurine 1%	Breast milk, Meat (poultry, veal, lamb, etc.) FishShellfish Milk and dairy products Eggs	Wistar rats streptozotocin 45mg/kg i.p	6 weeks. Parameters NGF ELISA MDA plus 4-HA. GSH and GSSH. DHAA and AA	Taurine exerts neuroprotective effects through the reduction of the oxidative stress and inflammation and is useful in the treatment of diabetic neuropathy. It regulates calcium levels in the body and helps maintain the stability of the neuronal membranes; also, it helps to correct insulin resistance. It is alleged that ascorbate antioxidant shields taurine counteracts oxidative stress and NGF shortcoming.	Obrosova *et al.*, 2001

I.v- Intravenous, Ip- intraperitoneal, TNF- Tumour nuclear factor, IL-Interleukin, SOD- Superoxide dismutase, MDA-Malondialdehyde, STZ- Streptozotocin, COX- Cyclooxygenase, GSH- glutathione , CoQ10- co enzyme Q10, ROS- reactive oxygen species, ADP- adenosine di phosphate, ATP- adenosine tri phosphate, DRG- Dorsal root ganglion, NCV- Nerve conduction velocity, NGF- Nerve growth factor, ELISA-enzyme-linked immunosorbent assay, AA-Amino acid.

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 30, Issue 8, August 2024 pp 229-242. **ijppr.humanjournals.com** ISSN: 2349-7203

TABLE II: Role of antioxidants and vitamin supplements in clinical studies

Sl.no	Antioxidant	Model	Duration	Study outcomes	Reference
01	Vitamin B12 (1000mg/kg) Oral	Randomized controlled trails 90 patients	12 Months Sural nerve conduction velocity (SNCV) Sural nerve potential amplitude (SNAP) Vibration perception threshold (VPT) Sudomotor function Michigan neuropathy screening instrument questionnaire and examination Pain score	Deficiency of Vitamin B12 harms nerve function; it supports myelin sheath formation, reduces homocysteine, and aids nerve impulse conduction. It also has neuroprotective benefits it alleviates pain and other symptoms associated with neuropathy. Daily, one mg of oral methyl cobalamin for 12 months may be of benefit.	Didangelos T *et al.*, 2021
02	Vitamin C 200 mg oral	open-label, parallel-arm, interventional study 300 patients	12 weeks VAS (visual analogue scale)score	The authors established that it is safe and economical to add vitamin C to treat DN peripheral neuropathy pain. The results indicated a mean VAS difference of less than five points in favor of the intervention group compared to the control group; thus, the proposed vitamin C therapy appeared to be valuable and inexpensive.	Bai A, *et al.*, 2021
03	Benfotiamine (300,600mg/kg) Oral	Double-blind, randomised, placebo-controlled phase-III study 181 patients	6 weeks NSS (neuropathy symptom score) TSS (total symptoms score) NDS (neuropathy disability score) Turning fork test left side & right side	This research revealed a positive change in the NSS in six weeks after taking benfotiamine while there was no change in Total Symptom Score. Thus, the improvement was dose dependent and was found to be more so at higher doses and it also appeared to be time dependent. As it can be inferred, the discomfort symptom was the most effective among all of the symptoms investigated. As a result, noting the characteristics of benfotiamine as a prodrug it can be suggested that this substance has great view to the extension of the opportunities of treatment of diabetic polyneuropathy.	Stracke H, *et al.*, 2008

04	N-Acetylcysteine (600 mg/ twice a day, oral	RTCs 102 patients	8 weeks Parameters Mean of pain, Effect on sleep disturbance SIS, PGIC, CGIC serum interferon levels. for TAC, TTG, CAT, NO, and MDA.	The pain scores were reduced and SIS of all patients improved with no reported side effects of NAC. On the entire sample of clients, NAC demonstrated a relatively higher improvement on PGIC and CGIC than on the baseline. The MDA and NO levels decreased while at the same time increasing the TAC, TTG and CAT levels, whereas pregabalin on the other hand was inclined to decrease all of these levels , and at the same time increase the TAC only.	Sajedi F, *et al.*, 2024
05	Vitamin E 900mg Oral	Randomized ,double-blinded placebo 21 patients	6 months Electrophysiological study (median & posterior tibial motor nerve) Ortho odromic median and sural nerve sensory conduction studies	Protects cell membranes from oxidative damage Suppresses the levels of oxidative stress. There is a disagreement on how to better the nerve among the stakeholders, the media, and the public.	Tütüncü NB *et al.*, 1998
06	Vitamin E Evion-400 capsule, oral	RTCs 92 patients	3 months Parameters: NPS questionnaire & RAND Random blood sugar levels & glycated haemoglobin Neuropathic pain scale	Vitamin-E therapy significantly reduces pain scores in diabetic neuropathy patients by the 12th week, possibly due to its antioxidant function. This therapy can help reduce oxidative stress, favoring regeneration over degeneration, and improve antioxidant tone in diabetics with compromised antioxidant capacity due to an active polyol pathway. Vitamin E also prevents endoneural damage caused by free radicals, enhancing nerve signal transmission. The study suggests that vitamin E, a naturally occurring antioxidant, can help diabetic neuropathy sufferers feel less discomfort.	Rajanandh MG, *et al.*, 2014
07	Vitamin E 200mg/kg Twice a day Oral	Randomizes ,double blind, placebo controlled	8 weeks Parameters Sensory nerve action potential Conduction velocity	DPN, determined by neuro conduction velocity in sensory, sural, and tibial motor nerves, could be improved with Tocovid, which is tocotrienol rich source	Ng YT *et al.*, 2020

		88 patients	Serum NGF,MDA,TNFR-1,VCAM-1 & TXB2 levels Renal profile, lipid profile & live function test. Statistical analysis	of vitamin E. Plasma NGF concentration raised when taking Tocovid pill for eight weeks; hence Tocovid operates through NGF channel. More investigation is required for other disorders with comparable procedures to comprehend the correct pharmacokinetics of Tocovid.	
08	Vitamin E 600 mg/day Oral	488 patients RCTs	Meta analysis	The authors of a meta-analysis of eight RCTs concluded that could observed that patients who received vitamin E supplementation in a dose of 600 mg/day had a lower risk of CIPN than patients in the placebo group. Patients undergoing cisplatin chemotherapy also discovered that the vitamin E treatment lessened peripheral neuropathy, however, no enhancement was established after six cycles.	Miao H *et al.*, 2021

RTCs- Randomized control trials, SNCV- Sural nerve conduction velocity, SNAP- Sural nerve potential amplitude, VPT- Vibration perception threshold, VAS- Visual analogue score, NSS- neuropathy symptom score, TSS- Total symptom score, NDS- neuropathy disability score, SIS- Sleep impact scale, PGIC- Patient Global Impression of Change, CGIC- Clinical Global Impression of Change, TAC- Total antioxidant capacity, TTG- tissue transglutaminase, CAT- Catalase, NO-Nitric oxide, MDA-Malondialdehyde, NPS-Net promoter score, NGF- Nuclear growth factor, VCAM-1 Vascular cell adhesion molecule-1, TXB2- Thromboxane B2

List of Abbreviations

DN- Diabetic neuropathy, DPN- Diabetic peripheral neuropathy, PKC -Protein kinase C, MNCV- Motor nerve conduction velocity, AGE- Advanced glycation end product.

CONCLUSION

In conclusion the antioxidants and vitamin supplements in diabetic neuropathy play a crucial part in lowering oxidative stress and enhancing nerve quality. Specifically, researches have demonstrated the effectiveness of the prevention and treatment of various complications of diabetes with these supplements. Medications like alpha-lipoic acid, N-acetylcysteine, coenzyme Q10, and vitamins E, C, and B have helped many patients in the quest to minimize oxidation and boost nerves. In this case, various clinical trials have had positive results on the mixture of these supplements with standard medical treatment for diabetes. More large, long-term controlled clinical trials are required to look at the ideal dose, length of use of the above-mentioned supplements and the effectiveness in diabetic neuropathy. Therefore, chances are high that patients with diabetes, who consume antioxidant and vitamin supplements, can either prevent or handle diabetic neuropathy well.

REFERENCES

1. Townsend T. A decade of diabetes research and development. Dubai Diabetes and Endocrinology Journal. 2000;8:88-92.
2. Tandan R, Lewis GA, Krusinski PB, Badger GB, Fries TJ. Topical capsaicin in painful diabetic neuropathy: controlled study with long-term follow-up. Diabetes care. 1992 Jan 1;15(1):8-14.
3. Dyck PJ, Kratz KM, Karnes JL, Litchy WJ, Klein R, Pach JM, Wilson DM, O'brien PC, Melton Iii LJ. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. Neurology. 1993 Apr;43(4):817-.
4. Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, Lauria G, Malik RA, Spallone V, Vinik A, Bernardi L. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes care. 2010 Oct;33(10):2285.
5. Javed S, Alam U, Malik RA. Treating diabetic neuropathy: present strategies and emerging solutions. The review of diabetic studies: RDS. 2015;12(1-2):63.
6. Wang DD, Bakhotmah BA, Hu FB, Alzahrani HA. Prevalence and correlates of diabetic peripheral neuropathy in a Saudi Arabic population: a cross-sectional study. PloS one. 2014 Sep 3;9(9):e106935.
7. O'Brien PD, Sakowski SA, Feldman EL. Mouse models of diabetic neuropathy. ILAR journal. 2014 Jan 1;54(3):259-72.
8. Calcutt NA, Freshwater JD, Mizisin AP. Prevention of sensory disorders in diabetic Sprague-Dawley rats by aldose reductase inhibition or treatment with ciliary neurotrophic factor. Diabetologia. 2004 Apr;47:718-24.
9. Muller KA, Ryals JM, Feldman EL, Wright DE. Abnormal muscle spindle innervation and large-fiber neuropathy in diabetic mice. Diabetes. 2008 Jun 1;57(6):1693-701.
10. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. Pain. 2010 Sep 1;150(3):573-81.
11. Jensen TS, Baron R, Haanpää M, Kalso E, Loeser JD, Rice AS, Treede RD. A new definition of neuropathic pain. Pain. 2011 Oct 1;152(10):2204-5.
12. Alsulaimani MA, Magadmi RM, Esmat A. Mechanisms of diabetic neuropathies and antioxidant therapy. J. Pharm. Res. Int. 2020;32:28-43.
13. Porte D, Sherwin RS, Ellenberg M, Rifkin H. Ellenberg and Rifkin's diabetes mellitus. (No Title). 2002 Sep.
14. Feldman EL, Stevens MJ, Russell JW. Diabetic peripheral and autonomic neuropathy. InType 1 Diabetes: Etiology and Treatment 2002 (pp. 437-461). Totowa, NJ: Humana Press.
15. Schmeichel AM, Schmelzer JD, Low PA. Oxidative injury and apoptosis of dorsal root ganglion neurons in chronic experimental diabetic neuropathy. Diabetes. 2003 Jan 1;52(1):165-71.
16. Apfel S. Neurotrophic factors and diabetic peripheral neuropathy. European Neurology. 1999 Feb 1;41(Suppl. 1):27-34.
17. Feldman EL. Oxidative stress and diabetic neuropathy: a new understanding of an old problem. The Journal of clinical investigation. 2003 Feb 15;111(4):431-3.
18. Rahimi-Madiseh M, Malekpour-Tehrani A, Bahmani M, Rafieian-Kopaei M. The research and development on the antioxidants in prevention of diabetic complications. Asian Pacific journal of tropical medicine. 2016 Sep 1;9(9):825-31.
19. Dyck PJB, Dyck PJ. Paresthesia, pain and weakness in hands of diabetic patients is attributable to mononeuropathies or radiculopathy, not polyneuropathy: the Rochester (RDNS) and Pancreas Renal Transplant (MC-PRT) Studies. Neurology. 1998;50:A333.
20. Sinnreich M, Taylor BV, Dyck PJ. Diabetic neuropathies: classification, clinical features, and pathophysiological basis. The neurologist. 2005 Mar 1;11(2):63-79.
21. Dyck PJ, Dyck PJB. Diabetic polyneuropathy. In: Dyck PJ, Thomas PK, eds. Diabetic Neuropathy. Philadelphia. PA: WB Saunders; 1999.
22. Oyenihi AB, Ayeleso AO, Mukwevho E, Masola B. Antioxidant strategies in the management of diabetic neuropathy. BioMed research international. 2015;2015(1):515042.
23. Negre-Salvayre A, Coatrieux C, Ingueneau C, Salvayre R. Advanced lipid peroxidation end products in oxidative damage to proteins. Potential role in diseases and therapeutic prospects for the inhibitors. British journal of pharmacology. 2008 Jan;153(1):6-20.
24. Hosseini A, Abdollahi M. Diabetic neuropathy and oxidative stress: therapeutic perspectives. Oxidative medicine and cellular longevity. 2013;2013(1):168039.

25. Edwards JL, Vincent AM, Cheng HT, Feldman EL. Diabetic neuropathy: mechanisms to management. Pharmacology & therapeutics. 2008 Oct 1;120(1):1-34.
26. Mahmood D, Singh BK, Akhtar M. Diabetic neuropathy: therapies on the horizon. Journal of Pharmacy and Pharmacology. 2009 Sep;61(9):1137-45.
27. Ho EC, Lam KS, Chen YS, Yip JC, Arvindakshan M, Yamagishi SI, Yagihashi S, Oates PJ, Ellery CA, Chung SS, Chung SK. Aldose reductase–deficient mice are protected from delayed motor nerve conduction velocity, increased c-Jun NH2-terminal kinase activation, depletion of reduced glutathione, increased superoxide accumulation, and DNA damage. Diabetes. 2006 Jul 1;55(7):1946-53.
28. Francis G, Martinez J, Liu W, Nguyen T, Ayer A, Fine J, Zochodne D, Hanson LR, Frey WH, Toth C. Intranasal insulin ameliorates experimental diabetic neuropathy. Diabetes. 2009 Apr 1;58(4):934-45.
29. Jakus V. The role of free radicals, oxidative stress and antioxidant systems in diabetic vascular disease. Bratislavske lekarske listy. 2000 Jan 1;101(10):541-51.
30. Miyata T, Wada Y, Cai Z, Iida Y, Horie K, Yasuda Y, Maeda K, Kurokawa K, De Strihou CV. Implication of an increased oxidative stress in the formation of advanced glycation end products in patients with end-stage renal failure. Kidney international. 1997 Apr 1;51(4):1170-81.
31. Kalousova M, Skrha J, Zima T. Advanced glycation end-products and advanced oxidation protein products in patients with diabetes mellitus. Physiological research. 2002 Jan 1;51(6):597-604.
32. Lal MA, Brismar H, Eklöf AC, Aperia A. Role of oxidative stress in advanced glycation end product-induced mesangial cell activation. Kidney International. 2002 Jun 1;61(6):2006-14.
33. King RH. The role of glycation in the pathogenesis of diabetic polyneuropathy. Molecular Pathology. 2001 Dec;54(6):400.
34. Toth C, Rong LL, Yang C, Martinez J, Song F, Ramji N, Brussee V, Liu W, Durand J, Nguyen MD, Schmidt AM. Receptor for advanced glycation end products (RAGEs) and experimental diabetic neuropathy. Diabetes. 2008 Apr 1;57(4):1002-17.
35. Hosseini A, Abdollahi M. Diabetic neuropathy and oxidative stress: therapeutic perspectives. Oxidative medicine and cellular longevity. 2013;2013(1):168039.
36. Wolff SP, Dean RT. Glucose autoxidation and protein modification. The potential role of 'autoxidative glycosylation'in diabetes. Biochemical journal. 1987 Jul 1;245(1):243-50.
37. Turko IV, Marcondes S, Murad F. Diabetes-associated nitration of tyrosine and inactivation of succinyl-CoA: 3-oxoacid CoA-transferase. American Journal of Physiology-Heart and Circulatory Physiology. 2001 Dec 1;281(6):H2289-94.
38. Buse MG. Hexosamines, insulin resistance, and the complications of diabetes: current status. American Journal of Physiology-Endocrinology and Metabolism. 2006 Jan;290(1):E1-8.
39. Leinninger GM, Vincent AM, Feldman EL. The role of growth factors in diabetic peripheral neuropathy. Journal of the peripheral nervous system. 2004 Mar;9(1):26-53.
40. Hosseini A, Abdollahi M. Diabetic neuropathy and oxidative stress: therapeutic perspectives. Oxidative medicine and cellular longevity. 2013;2013(1):168039.
41. Li F, Drel VR, Szabo C, Stevens MJ, Obrosova IG. Low-dose poly (ADP-ribose) polymerase inhibitor-containing combination therapies reverse early peripheral diabetic neuropathy. Diabetes. 2005 May 1;54(5):1514-22.
42. Obrosova IG, Xu W, Lyzogubov VV, Ilnytska O, Mashtalir N, Vareniuk I, Pavlov IA, Zhang J, Slusher B, Drel VR. PARP inhibition or gene deficiency counteracts intraepidermal nerve fiber loss and neuropathic pain in advanced diabetic neuropathy. Free Radical Biology and Medicine. 2008 Mar 15;44(6):972-81.
43. Obrosova IG, Xu W, Lyzogubov VV, Ilnytska O, Mashtalir N, Vareniuk I, Pavlov IA, Zhang J, Slusher B, Drel VR. PARP inhibition or gene deficiency counteracts intraepidermal nerve fiber loss and neuropathic pain in advanced diabetic neuropathy. Free Radical Biology and Medicine. 2008 Mar 15;44(6):972-81.
44. Stavniichuk R, Shevalye H, Hirooka H, Nadler JL, Obrosova IG. Interplay of sorbitol pathway of glucose metabolism, 12/15-lipoxygenase, and mitogen-activated protein kinases in the pathogenesis of diabetic peripheral neuropathy. Biochemical pharmacology. 2012 Apr 1;83(7):932-40.
45. Hall KE, Sima AA, Wiley JW. Voltage-dependent calcium currents are enhanced in dorsal root ganglion neurones from the Bio Bred/Worchester diabetic rat. The Journal of physiology. 1995 Jul 15;486(2):313-22.
46. Kellogg AP, Wiggin TD, Larkin DD, Hayes JM, Stevens MJ, Pop-Busui R. Protective effects of cyclooxygenase-2 gene inactivation against peripheral nerve dysfunction and intraepidermal nerve fiber loss in experimental diabetes. Diabetes. 2007 Dec 1;56(12):2997-3005.

47. Obrosova IG, Stavniichuk R, Drel VR, Shevalye H, Vareniuk I, Nadler JL, Schmidt RE. Different roles of 12/15-lipoxygenase in diabetic large and small fiber peripheral and autonomic neuropathies. The American journal of pathology. 2010 Sep 1;177(3):1436-47.
48. Cameron NE, Cotter MA, Archibald V, Dines KC, Maxfield EK. Anti-oxidant and pro-oxidant effects on nerve conduction velocity, endoneurial blood flow and oxygen tension in non-diabetic and streptozotocin-diabetic rats. Diabetologia. 1994 May;37:449-59..
49. Cameron NE, Cotter MA. Effects of antioxidants on nerve and vascular dysfunction in experimental diabetes. Diabetes research and clinical practice. 1999 Sep 1;45(2-3):137-46.
50. Sytze van Dam P. Oxidative stress and diabetic neuropathy: pathophysiological mechanisms and treatment perspectives. Diabetes/metabolism research and reviews. 2002 May;18(3):176-84.
51. Coppey LJ, Gellett JS, Davidson EP, Yorek MA. Preventing superoxide formation in epineurial arterioles of the sciatic nerve from diabetic rats restores endothelium-dependent vasodilation. Free radical research. 2003 Jan 1;37(1):33-40.
52. Sayyed SG, Kumar A, Sharma SS. Effects of U83836E on nerve functions, hyperalgesia and oxidative stress in experimental diabetic neuropathy. Life sciences. 2006 Jul 17;79(8):777-83.
53. Kumar A, Kaundal RK, Iyer S, Sharma SS. Effects of resveratrol on nerve functions, oxidative stress and DNA fragmentation in experimental diabetic neuropathy. Life sciences. 2007 Mar 6;80(13):1236-44.
54. Negi G, Kumar A, Sharma SS. Melatonin modulates neuroinflammation and oxidative stress in experimental diabetic neuropathy: effects on NF-κB and Nrf2 cascades. Journal of pineal research. 2011 Mar;50(2):124-31.
55. Negre-Salvayre A, Coatrieux C, Ingueneau C, Salvayre R. Advanced lipid peroxidation end products in oxidative damage to proteins. Potential role in diseases and therapeutic prospects for the inhibitors. British journal of pharmacology. 2008 Jan;153(1):6-20.
56. SYDNEY Trial Authors, for the SYDNEY Trial Study Group:, Ametov AS, Barinov A, Dyck PJ, Hermann R, Kozlova N, Litchy WJ, Low PA, Nehrdich D, Novosadova M, O'Brien PC. The sensory symptoms of diabetic polyneuropathy are improved with α-lipoic acid: the SYDNEY trial. Diabetes care. 2003 Mar 1;26(3):770-6.
57. Ziegler D, Ametov A, Barinov A, Dyck PJ, Gurieva I, Low PA, Munzel U, Yakhno N, Raz I, Novosadova M, Maus J. Oral treatment with α-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. Diabetes care. 2006 Nov 1;29(11):2365-70.
58. Ziegler D, Low PA, Litchy WJ, Boulton AJ, Vinik AI, Freeman R, Samigullin R, Tritschler H, Munzel U, Maus J, Schütte K. Efficacy and safety of antioxidant treatment with α-lipoic acid over 4 years in diabetic polyneuropathy: the NATHAN 1 trial. Diabetes care. 2011 Sep 1;34(9):2054-60.
59. Hong JH, Kim MJ, Park MR, Kwag OG, Lee IS, Byun BH, Lee SC, Lee KB, Rhee SJ. Effects of vitamin E on oxidative stress and membrane fluidity in brain of streptozotocin-induced diabetic rats. Clinica chimica acta. 2004 Feb 1;340(1-2):107-15.
60. Naziroğlu M, Butterworth PJ. Protective effects of moderate exercise with dietary vitamin C and E on blood antioxidative defense mechanism in rats with streptozotocin-induced diabetes. Canadian journal of applied physiology. 2005 Apr 1;30(2):172-85.
61. Penckofer S, Schwertz D, Florczak K. Oxidative stress and cardiovascular disease in type 2 diabetes: the role of antioxidants and pro-oxidants. Journal of Cardiovascular Nursing. 2002 Jan 1;16(2):68-85.
62. Lee DH, Folsom AR, Harnack L, Halliwell B, Jacobs Jr DR. Does supplemental vitamin C increase cardiovascular disease risk in women with diabetes? The American journal of clinical nutrition. 2004 Nov 1;80(5):1194-200.
63. Li S, Li X, Xie X, Wei X, Yu C, Cheung CW, Xia Z, Tian G. N-Acetylcysteine Attenuates Hyperalgesia in Rats with Diabetic Neuropathic Pain: Role of Oxidative Stress and Inflammatory Mediators and CXCR4. Journal of Diabetes Research. 2021;2021(1):8862910.
64. Kumar A, Sharma SS. NF-κB inhibitory action of resveratrol: a probable mechanism of neuroprotection in experimental diabetic neuropathy. Biochemical and biophysical research communications. 2010 Apr 2;394(2):360-5.
65. Kumar A, Kaundal RK, Iyer S, Sharma SS. Effects of resveratrol on nerve functions, oxidative stress and DNA fragmentation in experimental diabetic neuropathy. Life sciences. 2007 Mar 6;80(13):1236-44.
66. Low PA, Nickander KK, Tritschler HJ. The roles of oxidative stress and antioxidant treatment in experimental diabetic neuropathy. Diabetes. 1997 Sep 1;46(Supplement_2):S38-42
67. Galeshkalami NS, Abdollahi M, Najafi R, Baeeri M, Jamshidzade A, Falak R, Gholami MD, Hassanzadeh G, Mokhtari T, Hassani S, Rahimifard M. Alpha-lipoic acid and coenzyme Q10 combination ameliorates experimental diabetic neuropathy by modulating oxidative stress and apoptosis. Life sciences. 2019 Jan 1;216:101-10.

68. Sánchez-Ramírez GM, Caram-Salas NL, Rocha-González HI, Vidal-Cantú GC, Medina-Santillán R, Reyes-García G, Granados-Soto V. Benfotiamine relieves inflammatory and neuropathic pain in rats. European journal of pharmacology. 2006 Jan 13;530(1-2):48-53.
69. Jolivalt CG, Mizisin LM, Nelson A, Cunha JM, Ramos KM, Bonke D, Calcutt NA. B vitamins alleviate indices of neuropathic pain in diabetic rats. European journal of pharmacology. 2009 Jun 10;612(1-3):41-7.
70. Saini AK, HS AK, Sharma SS. Preventive and curative effect of edaravone on nerve functions and oxidative stress in experimental diabetic neuropathy. European journal of pharmacology. 2007 Jul 30;568(1-3):164-72.
71. Obrosova IG, Fathallah L, Stevens MJ. Taurine counteracts oxidative stress and nerve growth factor deficit in early experimental diabetic neuropathy. Experimental Neurology. 2001 Nov 1;172(1):211-9.
72. Didangelos T, Karlafti E, Kotzakioulafi E, Margariti E, Giannoulaki P, Batanis G, Tesfaye S, Kantartzis K. Vitamin B12 supplementation in diabetic neuropathy: a 1-year, randomized, double-blind, placebo-controlled trial. Nutrients. 2021 Jan 27;13(2):395.
73. Bai A, Abdullah FN, Kumar J, Lal A, Abbas M, Sandesh R, Naz S, Shahid S, Anees F, Memon S. The role of vitamin C in reducing pain associated with diabetic neuropathy. Cureus. 2021 Jun;13(6).
74. Stracke H, Gaus W, Achenbach U, Federlin K, Bretzel RG. Benfotiamine in diabetic polyneuropathy (BENDIP): results of a randomised, double blind, placebo-controlled clinical study. Experimental and clinical endocrinology & diabetes. 2008 Nov;116(10):600-5.
75. Sajedi F, Abdi A, Mehrpooya M, Faramarzi V, Mohammadi Y, Sheida F. Comparison of therapeutic effects of N-Acetylcysteine with pregabalin in improving the clinical symptoms of painful diabetic neuropathy: a randomized, double-blind clinical trial. Clinical Diabetes and Endocrinology. 2024 Apr 19;10(1):15.
76. Tütüncü NB, Bayraktar M, Varli K. Reversal of defective nerve conduction with vitamin E supplementation in type 2 diabetes: a preliminary study. Diabetes care. 1998 Nov 1;21(11):1915-8.
77. Rajanandh MG, Kosey S, Prathiksha G. Assessment of antioxidant supplementation on the neuropathic pain score and quality of life in diabetic neuropathy patients–a randomized controlled study. Pharmacological Reports. 2014 Feb 1;66(1):44-8.
78. Ng YT, Phang SC, Tan GC, Ng EY, Botross Henien NP, M. Palanisamy UD, Ahmad B, Abdul Kadir K. The effects of tocotrienol-rich vitamin E (Tocovid) on diabetic neuropathy: a phase II randomized controlled trial. Nutrients. 2020 May 23;12(5):1522.
79. Miao H, Li R, Chen D, Hu J, Chen Y, Xu C, Wen Z. Protective effects of vitamin E on chemotherapy-induced peripheral neuropathy: A meta-analysis of randomized controlled trials. Annals of Nutrition and Metabolism. 2021 Jun 18;77(3):127-37.

How to cite this article:
Talloju Tejasri et al. Ijppr.Human, 2024; Vol. 30 (8): 229-242.
Conflict of Interest Statement: All authors have nothing else to disclose.

Image **Author -1**	Author Name – **Talloju Tejasri** Author Affiliation- Department of Pharmacology. RBVRR Women's College of Pharmacy, Barkatpura, Hyderabad 500027 India
Image **Author -2**	Author Name- **Jorige Archana** Author Affiliation- Department of Pharmacology. RBVRR Women's College of Pharmacy, Barkatpura, Hyderabad 500027 India