Current Pharmaceutical Design, 2019, *25*, 3536-3549

REVIEW ARTICLE

Plant- and Nutraceutical-based Approach for the Management of Diabetes and its Neurological Complications: A Narrative Review

Yusuf Öztürk[1,*] and Nilgün Öztürk[2]

[1]*Department of Pharmacology, Faculty of Pharmacy, Anadolu University, Tepebasi 26120, Eskisehir, Turkey;* [2]*Department of Pharmacognosy, Faculty of Pharmacy, Anadolu University, 26120, Tepebasi, Eskisehir, Turkey*

ARTICLE HISTORY

Received: September 11, 2019
Accepted: October 8, 2019

DOI:
10.2174/1381612825666191014165633

Abstract: Diabetes is an important metabolic disease affecting many organs and systems in the body. The nervous system is one of the body systems affected by diabetes and neuropathic complications are troublesome in diabetic patients with many consequences. As diabetes has deleterious influences almost on bodily systems, an integrative approach seems to be necessary accepting the body as a whole and integrating body systems with lifestyle and living environment. Like some traditional health systems such as Ayurveda, integrative approach includes additional modalities to overcome both diabetes and diabetic complications. In general, these modalities consist of nutraceuticals and plant products. Prebiotics and probiotics are two types of nutraceuticals having active ingredients, such as antioxidants, nutrient factors, microorganisms, *etc*. Many plants are indicated for the cure of diabetes. All of these may be employed in the prevention and in the non-pharmacological management of mild-to-moderate diabetes. Severe diabetes should require appropriate drug selection. Being complementary, prebiotics, probiotics, plants and exercise may be additive for the drug therapy of diabetes. Similarly, there are complementary approaches to prevent and cure neurological and/or behavioral manifestations of diabetes, which may be included in therapy and prevention plans. A scheme is given for the prevention and therapy of comorbid depression, which is one of the most common behavioral complications of diabetes. Within this scheme, the main criterion for the selection of modalities is the severity of diseases, so that personalized management may be developed for diabetic patients using prebiotics and probiotics in their diets, plants and drugs avoiding possible interactions.

Keywords: Diabetes, diabetic neuropathy, prebiotics, probiotics, nutraceuticals, plants, microbiome, antioxidants.

1. INTRODUCTION

Life is simply based on homeostasis, which is a precise and complex balance between internal conditions of living organisms and external conditions in the environment. In cells, similar balances are present between the organelles at cellular and molecular levels. In higher organisms, there is also a balance between cells, tissues and physiological systems. Counterpoises within the autonomic nervous system [1, 2], between hormones [3-5], autocoids [6-8], and chemokines [9-11], are long-known examples of balances in molecules to systems. Interacting with each other through many endogenous factors, approximately 37 trillion body cells plus 100 trillion gut microflora cells, altogether participate in physiological tasks of daily life [12, 13]. In terms of etiopathogenesis of diseases, the disturbances in body systems or their tissues are expected to cause a disease. Disturbances in a group of cells involved in specific physiological tasks may cause diseases as in the case of diabetes [14, 15]. Certain diseases like diabetes may affect almost all tissues and systems of the living body [16, 17]. An integrative or holistic approach, which treats the human body as a whole including environmental and preparatory factors, has been gaining importance for rational therapy as well as in biomedical research [18-21]. Starting from psychiatric diseases evolving to personalized medicine [18, 21], the integrative approach has been combined to the microbiota as well as gaining assistance from alternative and complementary medicine [20] to solve today's complex medical problems, as well as to perform biomedical research.

*Address correspondence to this author at the Department of Pharmacology, Faculty of Pharmacy, Anadolu University, Tepebasi 26120, Eskisehir, Turkey; Tel: +90-222-3350750; Ext: 3602; E-mail: yozturk1958@gmail.com

2. THE INTEGRATIVE APPROACH IN MEDICINE

The terms "holistic approach" and "integrative approach" have been introduced independently by Dunbar [18] and Coleman [19]. Crosstalk mechanisms between gut and brain started to establish by the discovery of the presence of gut hormones in the brain as neurotransmitters or neuromodulators [22, 23]. The discovery of the presence of the same peptides both in neurons of the gastrointestinal tract and the central nervous system has led to understand the nature of the brain-gut axis [24-27]. So, neuromodulators and hormones in the gastrointestinal tract seem to be responsible for the modulation of gastrointestinal motility, water-electrolyte transport between lumen and blood circulation and absorption, while neuromodulators within the specific regions of brain are mainly responsible for the regulation of nutritional habits and appetite [28, 29]. After studying gut hormones and neurotransmitters, it has been understood that this axis is also important in terms of blood glucose metabolism and diabetes mellitus. A similar complex regulation also seems to be related to the pathogenesis of depression [30, 31].

An important part of the integrative approach for the neurohumoral regulation of the brain-gut axis is the immune system. It has been long-known that psychological stress causes suppression of the immune system through a corticosteroid-mediated mechanism [32]. Along with cortisol secretion, cytokine (chemokine)-regulation is now well-known to play a central role in the suppression of immune system [33, 34], and consequently, in the etiopathogenesis of a variety of diseases, such as Alzheimer's disease [35], depression [36], diabetes mellitus [37, 38], and even diabetic complications [39-41]. Although the relationship between stress-induced immunosuppression with diabetes seems paradoxical, which has autoimmune aspects, recent scientific evidence has

1873-4286/19 $58.00+.00

Table 1. Variations in microbial numbers and composition across the length of the alimentary tract [42-44].

	Segment of Alimentary Tract	Number of microorganisms	Names of Microorganisms
Proximal	Mouth	10^8	*Actinobacteria, Bacteroidetes, Chlamydiae, Chloroflexi, Euryarchaeota, Firmicutes, Fusobacteria, Proteobacteria, Spirochaetes, Synergistetes, Tenericutes*
	Eusophagus		
	Stomach	10^1	*Lactobacillus, Veillonella, Helicobacter*
	Duodenum	10^3	*Bacilli, Streptococcacea, Actinobacteria, Actinomycneae, Corynebacteriaceae*
	Jejunum	10^4	
	Ileum	10^7	
Distal	Colon	10^{12}	*Lachnospiraeae, Bacteroidates*

suggested diminished glucocorticoid and mineralocorticoid responses of stress condition in diabetic patients [37]. There is also a scientific emphasize on the bidirectional pathophysiological link between stress, depression and type 2 diabetes resulting from insulin resistance due to diurnal changes in blood cortisol levels, possibly through immune system mediation [38].

Every part of the gastrointestinal tract, skin and some other parts of the body have abundant amounts of symbiotic microorganisms. Among these, the alimentary tract exhibits an interesting situation: Microbiota in every part of the gastrointestinal tract have symbiotic microorganisms different in number and composition. Ranging from mouth to colon, the diversity and the number of microorganisms tend to increase, except for the mouth, which is an abundant source of symbiotic and saprophytic microorganisms (Table **1**). Most probably due to its strong acidic condition, the stomach hosts the smallest number and low diversity of microorganisms.

Irrespective of the composition of the microbiota in the alimentary tract, there are evident physiological tasks for it, providing a positive effect on the host-microbiome symbiosis [42, 43]:

- Upholds a healthy gastrointestinal tract,
- Confers the resistance to colonization of pathogen microorganisms,
- Regulates most systems of the body, esp. nervous system, cardiovascular system,
- Supports host immune defense functions,
- Suppresses the inflammation,
- Provides additional metabolic potential,
- Increases antioxidant and redox capacities,
- Helps the detoxification of xenobiotics and biotransformation.

Almost two millenniums before the pioneering invention of the microscope by a Dutch scientist, Antonie van Loewenhook [45], the importance of intestine has been noticed by Hippocrates stating his famous quotation “death sits in the bowels” and “bad digestion is the root of all evil” in 400 B.C. [42]. There have been more than fifty years from the discovery that it was observed that symbiotic microorganisms in gut microbiota play an important role in the biotransformation of biogenic compounds or xenobiotics to yield their active or inactive (detoxified) forms [46-48]. The microbial transformation of biogenic compounds provides invaluable nutritional factors, vitamins, neurotransmitters, endogenous regulatory factors, *etc*. [13, 47]. Gut microbiota not only provide microbial transformation of biogenic compounds and xenobiotics but also help build and maintain the immune system of the body. The immunogenic properties of intestinal microflora on gut mucosal epithelium have been found [49-51]. Interesting enough, some of these microorganisms (some bacteria species) have been reported to exhibit electrochemical activities and produce electricity in the gut, so that these bacteria seem to help in the regulation of spontaneous contractile functions in response to electrophysiological activity provided by Auerbach’s or Meissner’s intestinal plexa [52-54].

Microbiome-gut-brain axis has been used as a more integrated concept in recent biomedical literature [13, 55]. In addition to brain, disturbances in gut microbiota have been reported to be involved in the pathogenesis of a wide range of diseases, such as different infections [56], immunity disorders [57, 58], wound healing [58], atherosclerosis [59], obesity [60], diabetes mellitus [61], anorexia nervosa [62], anxiety, depression, and other similar mood disorders [63, 64] *viz.* autism spectrum disorder [64-66] and schizophrenia [65, 67, 68]. Therefore, it is necessary to look at diabetes and its neuro-psychiatric complications from a wider perspective treating the nutrition as an integral part of them.

3. NUTRACEUTICAL APPROACH FOR DIABETES AND ITS NEUROLOGICAL COMPLICATIONS

Nutrition is a vital part of our lives, which involves consuming appropriate foods as daily meals. By and large, foods contain various nutritional elements, some active constituents, prebiotics, probiotics, *etc*. Among these, nutritional elements, such as proteins, carbohydrates, lipids, *etc*., are necessary for metabolism as an essential part of life, while the consumption profile of these elements themselves may cause some diseases or is a key to prevent them, as in the case of gestational diabetes [69] and other diseases [70]. As integral parts of foods, prebiotics and probiotics are frequently confused definitions.

Prebiotics are in general leafy and non-digestible parts of foods resisting breakdown by gastrointestinal enzymes and absorption from lumen. A vast majority of prebiotics are found naturally in different fruits and vegetables. There are three indispensable criteria for prebiotics: They are 1) non-hydrolysable and absorbable components of foods, 2) provide a selective substrate/medium for symbiotic microorganism in the colon, such as *Bifidobacterium*, and 3) produce beneficial local and/or systemic effects within the host though their fermentation [71, 72]. Beyond these criteria, the appropriate use of probiotics has following helpful effects on health, most of which may also be beneficial against pathophysiological consequences of the gastrointestinal diabetic neuropathy:

- Support the regulation of mineral absorption from gastrointestinal tract,
- Reinforce intestinal microflora and suppress pathogenic microorganisms,
- Protect cellular damage in the intestine,
- Support host immune defense functions,

- Limit energy intake,
- Regulate glucose and lipid metabolisms,
- Improve overall bowel functions.

Increased calcium, magnesium and iron absorptions by the help of prebiotics have been reported in animal experiments [72-74]. Increased absorption of calcium results in bone calcium resorption [72, 73], while increased absorption leads to an improvement in hematological parameters [72, 74]. Prebiotics are also fermented by the microbiota of the intestine enabling selective stimulation of the growth and/or activity of the intestinal microorganisms [75-77]. They usually target the activity of microorganisms like *Lactobacillus*, *Bifidobacterium* and *Bacteroides* [78, 79], which have been reported to be important for the suppression of antibiotic-resistant pathogenic bacteria, such as *Clostridium perfringens* [79]. In the gastrointestinal tracts of experimental animals, probiotics have been reported to protect cellular damage induced by chemical, such as trinitrobenzenesulfonic acid [72, 80]. Increased immunoglobulin production and secretion along with increased immunoglobulin receptor expressions have been reported in response to probiotics in the gastrointestinal tract [81, 82]. Several human studies have demonstrated limiting effects of prebiotics on the energy intake due to the sense of satiety and satiation, which may be beneficial for the glycemic control and the prevention of diabetic complications including neuropathy [72, 83, 84]. Both the animal experiments and human studies have stated positive effects of prebiotics on glucose and lipid metabolism, which may also beneficial for the control of diabetes and its long-term complications. Decreased glycaemia after oral glucose tolerance test, fasting blood glucose concentrations and improvement in the efficacy of antidiabetic drugs have been reported in mice given prebiotics [85]. In clinical studies, peak glucose response and insulin secretion of human subjects have been reported to be lower after consuming prebiotics [86]. In rats, decreased liver triglyceride content and malondialdehyde activity have been observed following the administration of prebiotics [87]. Another clinical report has specified decreases in postprandial triglyceride responses to probiotics in normolipidemic, obese and hyperlipidemic subjects on high fat diet [72]. Last but not the least, probiotics improve bowel functions by increasing gastrointestinal transit time in healthy subjects [88] and in patients suffering from constipation [89, 90]. The later effect may also be beneficial for the diabetic patients with gastrointestinal neuropathy, in which delayed gastrointestinal transit has been reported in rats with diabetic gastrointestinal neuropathy [91].

Probiotics are beneficial microorganisms for the life that are naturally created by the process of fermentation in foods. There are many variations in probiotic products and none of them can be substituted for each other. Table **2** summarizes the most common fermented dairy products. Some of these products, such as yogurt *etc*., exhibit a wide variety depending on locality and historical background [92-100]. It has now been well-documented that regular probiotic intake has a beneficial influence on various diseases, and infections mainly in the gastrointestinal and genitourinary tracts [101]; diseases of respiratory tract, ear, nose and throat [102]; dermatological disorders including eczema, psoriasis, lactational mastitis, acne, reactive skin, UV radiation damage [103]; cardiometabolic disorders including obesity, type 2 diabetes, dyslipidemia, cholesterolemia, stroke, gout, non-alcoholic liver diseases, polycystic ovary syndrome [104]; mental and neurological diseases including anxiety, attention-deficit/hyperactivity disorder, autism, and depression [105, 106].

There are many active compounds in the plant kingdom and in nutraceuticals, which may affect physiological systems of the body and promote health. By preventing and curing, they may help fight against various diseases including diabetes and its complications. Infact, food ingredients of different chemical classes, such as rutin [107], quercetin [108], polyphenols [109], lycopene [110], α-lipoic acid [111], resveratrol [112], curcumin [113], capsaicin [114], vitamin D [115], folic acid [116] *etc*., have been found to be effective against different types of diabetic neuropathies. Therefore, all foods/nutraceuticals containing these ingredients have the potential for the management of diabetic neuropathies and glycemic control. Another important issue, which needs to be emphasized here, is the fact that most of these food ingredients are also ingredients of plants effective against diabetic neuropathy.

By the help of exercise, changes in dietary style have been known to delay the onset of diabetes [117]. As in the case of Mediterranean diet, diet itself may prevent type 2 diabetes and improve glycemic control and risks of cardiovascular complications in people with established diabetes [118, 119]. Both experimental and clinical studies have demonstrated that gut microbiota may play an important role in maintaining glycemic control and preventing metabolic diseases like diabetes [61, 120-122]. In addition, nutritional intervention through gastrointestinal microbiome seems likely to help glycemic controls in diabetes [120, 122]. Improvement of gut microbiome may also have beneficial influences on long-term diabetic complications such as gastroenteropathy [123], microvascular and cardiovascular complications [124], retinopathy [125], neuropathy [126], *etc*. Until recently, almost nothing has been known about the mechanism of action of probiotics on the nervous system. However, findings of novel studies have indicated that the retrograde transport of small and large molecules from the intestines to the brain leads to both physiological and pathological consequences, highlighting both beneficial or harmful effects on the nervous system [127-129]. Fig. (**1**) summarizes mechanisms of the main effects of probiotics in the intestine. Although paracrine and endocrine effects of probiotics on the intestine have been known for quite long, retrograde transport mechanisms have been established recently. However, there are limited information available on the nature of effects produced by probiotic microorganisms having different types of actions in the intestine.

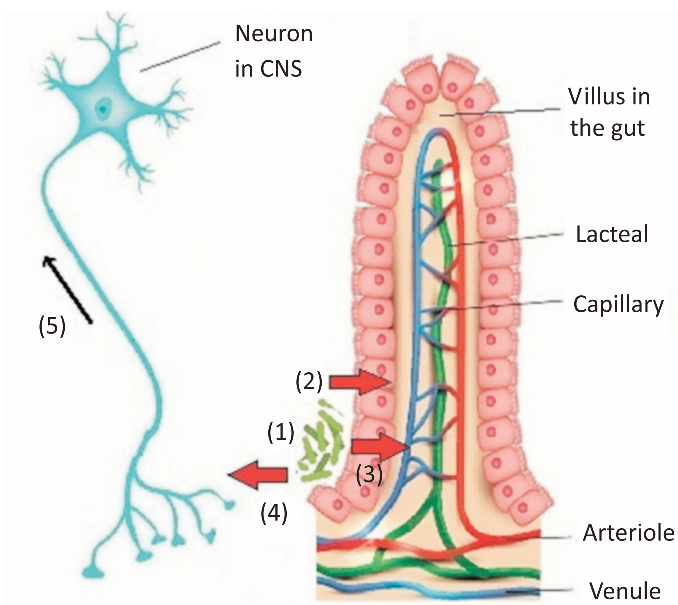

Fig. (1). Schematic representation of the mechanism of action of probiotics in the intestine. (1) Probiotic microorganisms on the villi have direct local effects, (2) Autocrine effects of factors released from probiotics both through muscles and enteral nerves, (3) Endocrine effects of factors released from probiotics after absorption from intestinal capillaries, (4) Effects of the autonomic nerve endings or uptake by them in the intestine, (5) Retrograde transport of factors by the autonomic nerve to the central nervous system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 2. Some fermented dairy products [92-100].

Name of Probiotic Product	Starting Material	Locality of Origin	Probiotics Involved
Curd	Buffalo's or cow's milk	India	*L. lactis* subsp. *lactis, L. delbrueckii* subsp. *bulgaricus, L. plantarum, Streptococcus lactis, S.thermophilus, S. cremoris*
Yoghurt	Buffalo's or cow's milk	Mesopotamia (5000 B.C.)[1]	*L. acidophilus, S. thermophilus L. bulgaricus*
Airan (Ayran, Yoghurt drink)	Buffalo's or cow's milk	Bulgaria, Turkey, Central Asia	
Cultured butter milk	Buffalo's or cow's milk	US[2]	*S. lactis subsp. diacetylactis, S. cremoris*
Lassi	Buffalo's or cow's milk	India	*L. bulgaricus*
Acidophilus milk (Acidophiline)	Cow's milk	Russia	*L. acidophilus*
Bulgarian butter milk	Cow's milk	Bulgaria	*L. delbueckii* subsp. *bulgaricus*
Shrikhand (Shikhrini)	Buffalo's or cow's milk	India	*S. thermophilus, L. bulgaricus*
Kumiss (Koumiss, Kumys)	Mare's, camel's or donkey's milk	Central Asia (2000 B.C.)	*L. acidophilus, L. bulgaricus, Saccharomyces micrococci*
Kefir	Sheep's, cow's, goat's or mixed milk	China/Caucasia	*S. lactis, Leuconostoc sp., Saccharomyces kefir, Torula kefir, Micrococci*
Leben	Goats, sheep's milk	Iraq	*S. lactis, S. thermophilus, L. bulgaricus,* Lactose fermenting yeast
Cheese	Cow's, Buffalo's, goat's milk, sheep milk	Ancient Egypt (6000 B.C.)	*L. lactis* subsp. *lactis, L. lactis* subsp. *cremoris, L.lactis* subsp. *diacetylactis, S. thermophilus, L. delbueckii* subsp. *bulgaricus, Priopionibacterium-shermanii, Penicillium roquefortie*tc.
Dahi (A version of Curd)	Cow's, Buffalo's, goat's milk	India (6000-4000 B.C.)	*L. lactis, S. diacetylactis, S. cremoris, L. delbrueckii* subsp. *bulgaricus, S.thermophilus.*
Chhash, (Ghol, Moru, Ale, Laban, Buttermilk)	Cow's, Buffalo's, goat's milk	India (6000-4000 B.C.)	(A diluted version of Dahi)
Laban zeer (Khad, Laban rayeb)	Buffalo's or cow's milk	Egypt, Sudan (5000-3000 B.C.)	*Lactobacillus* (30 different strains), *Leuconostoc* (18 different strains)
Zabadi	Cow's milk	Egypt, Sudan (2000 B.C.)	Natural type (strained or unstrained) yoghurt
Cultured cream	Buffalo's or cow's milk	Mesopotamia (1300 B.C.)	*L. acidophilus, S. thermophilus, L. bulgaricus*
Shrikhand	Cow's, Buffalo's, goat's milk	India (1300 B.C.)	Sweetened and concentrated Dahi
Kishk	Cow's milk, goat's milk	Egypt and Arab World	Dry fermented product from labanzeer and parboiled wheat
Mast	Sheep milk	Iran	Natural type of yoghurt with flavor
Viili		Finland	*Geotrichumcandidum, L. lactis* subsp.*cremoris, Lactococcus lactis* subsp. *lactis* biovar.*diacetylactis, Leuconostoc mesenteroides* subsp.*cremoris*.

(Table 2) Contd....

Name of Probiotic Product	Starting Material	Locality of Origin	Probiotics Involved
Taette	Cow's milk	Norway	*S.lactis* var. hollandicus, *Saccharomyces taette, L.taette, Bacillus acidactislogus*
Lagfil (Tattemjolk)	Cow's milk	Sweden	-
Ymer	Cow's milk	Denmark (1937 A.D.)	*Lactococcus lactis*
Skyr	Cow's milk	Iceland (870 A.D.)	*Streptococcus thermophilus,L. delbrueckii* subsp. *bulgaricus*
Trahana (Tarana, Tarhana)	Cow's milk + grain	Balkan region	*Pediococcus acidilactici, P. pentosaceus, Streptococcus thermophilus, L. fermentum, L. plantarum, L. delbrueckii* spp. *bulgaricus, L. paraplantarum, L. casei, Leuconostoc citreum, Leuconostoc pseudomesenteroides, Enterococcus faecium, Weissella cibaria.*
Yakult	Buffalo's or cow's skimmed milk	Japan (1935 A.D.)	*Lactobacillus paracasei*

[1] Although the term "yoghurt" has been derived from Turkish "yoğurt", the exact origin and inventors have not been known. It has been defined in many old inscriptions of different ancient cultures. [2] First commercial production has been made in 1920.

Table 3. Plants and nutraceuticals indicated for the treatment of diabetes [136-138].

Plant Name	Plant Scientific Name	Parts Used	Effect	Side Effects	Contraindications	Interactions
Alfalfa	*Medicago sativa*	Whole-plant, seeds	Decreases lipid absorption, lowers blood glucose (STZ)	Hypokalemia	Gout, Sytemic lupus Pregnancy	Azathioprine Cyclosporine Prednisone Anticoagulants
Alpine Ragwort	*Senecio nemorensis*	Herb	Lowers blood glucose	Hepatotoxicity Carcinogenicity	Not known	Not known
Bean Pod	*Phaseolus vulgaris*	Pods and beans; also used as Food	Diuretic, Lowers blood glucose	Not known	Not known	Not known
Behen	*Moringo oleifera*	Seeds	Lowers blood glucose	Not known	Pregnancy (possibly abortive)	Not known
Bilberry	*Vaccinium mytillus*	Fruits and leaves; also used as food	Lowers blood glucose and regulates lipids; proctects some diabetic complications	Longer use at higher amounts causes gastrointestinal complaints	Pregnancy and lactation	Anticoagulants, antithrombotics
Bitter melon	*Momordica charantia*	Fruits; also used as food	Lowers blood glucose	Not known	Pregnancy (possibly abortive) and lactation	Antidiabetic drugs possibly potentiate cholesterol-lowering drugs

(Table 3) Contd....

Plant Name	Plant Scientific Name	Parts Used	Effect	Side Effects	Contraindications	Interactions
Black Catnip	*Phyllantus amarus*	Whole Herb	Lowers blood glucose	Not known	Not known	Not known
Centaury	*Centaurium erythraea*	Aerial parts	Lowers blood glucose	Not known	Not known	Not known
Cocoa	*Theobroma cocao*	Seeds and seeds' skin; also used as food	Lowers blood glucose	Uses at large amounts may cause constipation, cns stimulation, palpitation etc.	Not known	Not known
Cranberry	*Vaccinium macrocarpon*	Fruits; also used as food	Lowers blood glucose	Uses at large amounts may cause gastrointestinal complaints	Aspirin allergy, atrophic gastritis, hypochlorhydria, kidney stones, safety in pregnancy is not known	Warfarin, H2 receptor blockers, proton pump inhibitors
Dandelion	*Taraxacum officinale*	Roots and leaves	Lowers blood glucose, increases bile secretion	Mild gastric complaints, prolonged use may cause hyperkalemia	Bile duct obstruction, safety in pregnancy is not known	Anticoagulants, antithrombotics, fluoroquinolones
Divi-Divi	*Caesalpinia bonducella*	Seeds	Lowers blood glucose	Not known	Not known	Not known
Eucalyptus	*Eucalyptus globulus*	Essential oil	Lowers blood glucose	Gastrointestinal complaints, skin rushes, pruritis	Hypersensitivity conditions, Liver diseases; safety in pregnancy is not known	Antidiabetic drugs, Barbiturates
European Golden Rod	*Solidago virgaurea*	Aerial parts	Lowers blood glucose	Not known	Cases of edema due to cardiac and/or renal functions; safety in pregnancy is not known	Not known
Garlic	*Allium sativum*	Bulb; also used as food	Lowers blood glucose	Anaphylaxis, gastric complaints, headache, myalgia, etc.	Surgery (increases bleeding risk), breastfeeding	Anticoagulants, Protease inhibitors, Antithrombotics, Indomethacin, Chlorzoxazone
German Sarsaparilla	*Carex arenaria*	Dried rhizomes	Lowers blood glucose	Not known	Not known	Not known
Goat's Rue	*Galega officinalis*	Leaves, flowering branches	Lowers blood glucose	Not known	Not known, possibly safe during lactation	Antidiabetic drugs
Greek Sage	*Salvia triloba*	Leaf	Reduces glucose absorption	Not known	Not known	Not known
Guar Gum	*Cyamopsis tetragonoloba*	Whole plant	Reduces glucose absorption	Gastrointestinal complaints, hypoglycemia symptoms	Diseases of esophagus, stomach and intestine	Not known

(Table 3) Contd....

Plant Name	Plant Scientific Name	Parts Used	Effect	Side Effects	Contraindications	Interactions
Jambol	*Syzigium cumini*	Bark, seed kernels	Regulates pancreatic functions	Not known	Not known	Not known
Kudzu	*Pueraria lobata*	Roots	Corrects insulin resistance, blood lipid profile, lowers blood glucose	Not known	Not known	Possibly interacts with estrogens, antiarrhythmics, antihypertensive drugs
Mountain Ash Berry	*Sorbus aucuparia*	Fruits; also used as food	Lowers blood glucose	Not known	Not known	Not known
Noni	*Morinda citrifolia*	Leaf, fruit, root; also used as foot	Lowers blood glucose	Not known	Not known	Not known
Oats	*Avena sativa*	Fruits, leaf, stem	Regulates blood glucose and lipid profile	Not known	Celiac disease	Statins
Onion	*Allium cepa*	Bulb	Regulates blood glucose and lipid profile	Gastric complaints	Not known	Not known
Plantain	*Musa paradisiaca*	Fruits	Regulates blood glucose and lipid profile	May trigger migraine attacks	Not known	Not known
Poley	*Teucrium polium*	Whole herb	Lowers blood glucose	Not known	Not known	Not known
Reed Herb	*Phragmites communis*	Stem and rhizome	Lowers blood glucose	Not known	Not known	Not known
Stevia	*Stevia rebaudiana*	Leaves	Increase glucose metabolism rate	Adverse CV and genito-urinary effects reported	Not known	Not known
Wild Service Tree	*Sorbus torminalis*	Fruits; also used as food	Lowers blood glucose	Not known	Not known	Not known

4. PLANT-BASED APPROACH FOR DIABETES AND ITS NEUROLOGICAL COMPLICATIONS

Being approved in 1958 for diabetes therapy, metformin, the today's miraculous antidiabetic drug, has been produced from *Galega officinalis*, whose antidiabetic properties have been known since the 18thcentury [130]. After this innovation, many investigators around the globe have investigated many plants to develop novel modalities for the treatment of diabetes [131-135]. Unfortunately, except for metformin, there are no active constituents of plants developed as a drug up to date, despite extensive research in this area. Some of these plants have been approved for the treatment of diabetes as a therapeutic indication (Table **3**). Generally, they have been used as over-the-counter drugs for the management of mild diabetes or as an adjunct for the dietary management of diabetes.

Many plants have been reported to be effective against diabetic neuropathy. Among these plants, *Trichilia catigua* [139], *Boswellia serrata* [140], *Ligustrum vulgare* [141], *Rosmarinus officinalis* [142], *Eruca sativa* [143], *Juglans regia* [144], and *Dillenia indica* [145] are quite recent examples reported to ameliorate diabetic neuropathy in experimental models of diabetes.

There are several plants and plant mixtures, which have been reported to be effective against diabetic wounds, which is a complex phenomenon of diabetes involving vasculopathy, neuropathy and delayed wound repair due to deformed collagen production [146]. Among these plants, *Hypericum perforatum* (St.-John's

Wort), as a long-known cure for wounds, has been reported to accelerate wound healing in diabetes [147], possibly through a mechanism depending on collagen production of fibroblasts [148, 149]. The same plant has also been reported to correct some psycho-neuropathic complications, while it normalizes elevated blood glucose levels in experimental diabetes. *H. perforatum* ameliorates pain perceptions in streptozotocin-diabetic rats [150]. As *H. perforatum* decreases blood glucose levels, it may be advantageous to use in patients with diabetic neuropathy and/or psychiatric complications [151].

The Plant kingdom has many active compounds in different chemical classes affecting both diabetes and diabetic complications. One of the most important groups in this context is antioxidants and antiradicals. Both nutraceuticals [152, 153] and plants [154, 155] may have active molecules having antioxidant and antiradical activities, which are helpful in to correcting either impaired carbohydrate metabolism in diabetes or diabetic complications, since oxidative stress seems to play a role in the pathogenesis of diabetes [16, 156, 157] and in the development of diabetic complications including neuropathy [158-160]. These molecules may protect tissues from damages, which are due to diabetes or other factors. In diabetes, these damages usually result in diabetic complications. For example, phenolic compounds, a class of antioxidant molecules, have been reported to reduce the risk of cardiovascular diseases [161, 162]. They are quite common in plant species and foods, like *Thymus* sp. [163], *Achillea* sp. [164] Pomegranate [165], *Crataegus* sp. [166], *Anethum graveolens* [167] and *Hypericum* sp. [168].

Neuroprotection and neuroplasticity are important restorative factors in neuronal damages such as diabetic neuropathy [169]. There are good examples for neuroprotective compounds and extracts both from nutraceuticals and plants, which may consequently induce neuroprotection. For instance, isofuranodiene, an active ingredient of wild celery (*Smyrnium olusatrum*), has been reported to induce neurite growth of PC-12 cells as a clear evidence of for the neuroprotection and neuroplasticity [170]. Similarly, curcumin and epigallocatechin gallate have also been observed to exhibit neuroprotection by stimulating neurite growth and they have an additive interaction in terms of this action [171]. Among these two nutritional constituents, curcumin has been repeatedly reported to possess antidiabetic/antihyperglycemic activities [172, 173] and beneficial effects on comorbid neurological manifestations of diabetes [174-176]. Epigallocatechin gallate is another phytonutritional constituent having a beneficial effect on diabetes [177, 178] and neurological comorbidities of diabetes [179, 180]. From previous reports, it seems to have beneficial effects on various psycho-neurological manifestations, such as Alzheimer's disease [181], schizophrenia and bipolar disorders [182], various types of memory and cognitive deficits [183], *etc*. Other compounds from this group, gallic acid has been reported to correct diabetic neuropathy [184] in animal models. Another example of neuroprotection is the neurite growth of the same cells induced by the extract of gentian (*Gentiana lutea*) [185, 186], whose beneficial effects on neurological functions have been reported previously in animal experiments [187]. Its effect on diabetic neuropathy may be expected based on a study reporting its inhibitory action on aldose reductase [188]. There are certain plants and nutraceuticals, which have been reported to inhibit key enzymes involved in the development of diabetic complications including neuropathic pain. These are aldose reductase inhibitors from plants such as *Acacia catechu*, *Alangium salvifolium*, *Allium sativum*, *Carum carvi*, *Gentiana lutea*, and advanced glycation end products (AGEs) inhibiting plants, such as *Agrimonia eupatoria* [188, 189]. Also, there are also well-known examples of topical management of neuropathic pain, which include capsaicin containing extracts and *Citrullus colocynthis* extract oil [190]. All these plants and nutraceuticals may be utilized for the proper management of diabetic neuropathy.

CONCLUSION

Based on the above-mentioned findings and data, it may be concluded mainly that new strategies should be followed in the management of diabetes and comorbid neurological manifestations. Nutritional factors being related to the microbiota of the body seem to be related to both controls of diabetes and its neurological complications in high degrees. Recent findings along with the notions of traditional medicine systems have indicated that the integrative approach [19] is quite important for disease management and the body should be considered as a whole in terms of the management of diabetes and its neurological comorbidities. Due to the severity of clinical situations of diabetic neuropathic pain, plants and drugs may be analgesic ones, respectively. It should be noted that appropriate nutritional interventions are indicated in every case. Exercise should also be applied as non-pharmacological interventions when indicated.

Glycated hemoglobin (HbA_{1c}) is an important parameter of long-term glycemic control and elevated HbA_{1c} levels are a clear indicator of the risk of diabetic complications including diabetic neuropathy [191]. Plant and/or nutraceutical-based approaches seem to be effective for the maintenance of HbA_{1c} levels at lower levels [192], so that prevention of diabetic neuropathy may become possible. Another important issue is the differences between prevention and therapy of diabetes/diabetic complications. The main difference between prevention and therapy is the presence of an appropriate drug. The critical point is to avoid the interaction of a drug with other components of intervention. Neuroprotection through enhanced neuroplasticity seems to have importance for the management of neurological complications of diabetes, as it may restore neuronal damages, and consequently increase the quality of life in diabetic patients. In conclusion, both prevention and therapy in diabetes/its neuropathic complications seem to need novel approaches, which should include appropriate and convenient complimentary materials. Well organized research is necessary in the future to enhance the success of the prevention and treatment of diabetes and diabetic neuropathy.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Mason DT, Bartter FC. Autonomic regulation of blood volume. Anesthesiology 1968; 29(4): 681-92. [http://dx.doi.org/10.1097/00000542-196807000-00010] [PMID: 4874153]

[2] Hoebel BG. Feeding: neural control of intake. Annu Rev Physiol 1971; 33: 533-68. [http://dx.doi.org/10.1146/annurev.ph.33.030171.002533] [PMID: 4951055]

[3] Leung PC, Armstrong DT. Interactions of steroids and gonadotropins in the control of steroidogenesis in the ovarian follicle. Annu Rev Physiol 1980; 42: 71-82. [http://dx.doi.org/10.1146/annurev.ph.42.030180.000443] [PMID: 6773470]

[4] Alberti KG, Cuthbert C. The hydrogen ion in normal metabolism: a review. Ciba Found Symp 1982; 87: 1-19. [http://dx.doi.org/10.1002/9780470720691.ch1] [PMID: 6804190]

[5] Gurer-Orhan H, Ince E, Konyar D, Saso L, Suzen S. The role of oxidative stress modulators in breast cancer. Curr Med Chem 2018; 25(33): 4084-101. [http://dx.doi.org/10.2174/0929867324666170711114336] [PMID: 28699501]
[6] Regoli D, Dion S, Rhaleb NE, Drapeau G, D'Orléans-Juste P. Vasoactive peptides and their receptors. Blood Vessels 1990; 27(2-5): 137-45. [PMID: 2173637]
[7] Oztürk Y. Kinin receptors and their antagonists as novel therapeutic agents. Curr Pharm Des 2001; 7(2): 135-61. [http://dx.doi.org/10.2174/1381612013398338] [PMID: 11172705]
[8] Stridh S, Palm F, Takahashi T, Ikegami-Kawai M, Friederich-Persson M, Hansell P. Hyaluronan production by renomedullary interstitial cells: influence of endothelin, angiotensin ii and vasopressin. Int J Mol Sci 2017; 18(12): E2701. [http://dx.doi.org/10.3390/ijms18122701] [PMID: 29236055]
[9] Graham GJ, Pragnell IB. Negative regulators of haemopoiesis-current advances. Prog Growth Factor Res 1990; 2(3): 181-92. [http://dx.doi.org/10.1016/0955-2235(90)90004-4] [PMID: 2132955]
[10] Mantovani A, Bottazzi B, Sozzani S, *et al.* Cytokine regulation of tumour-associated macrophages. Res Immunol 1993; 144(4): 280-3. [http://dx.doi.org/10.1016/0923-2494(93)80108-B] [PMID: 8378597]
[11] Stone MJ, Hayward JA, Huang C, E Huma Z, Sanchez J. Mechanisms of regulation of the chemokine-receptor network. Int J Mol Sci 2017; 18(2): E342. [http://dx.doi.org/10.3390/ijms18020342] [PMID: 28178200]
[12] Zimmer K. How many cells are in your body? National Geographics 2013; Available at: https://www.nationalgeographic.com/science/phenomena/2013/10/23/how-many-cells-are-in-your-body/
[13] Wang HX, Wang YP. Gut microbiota-brain Axis. Chin Med J (Engl) 2016; 129(19): 2373-80. [http://dx.doi.org/10.4103/0366-6999.190667] [PMID: 27647198]
[14] Cudworth AG. Type I diabetes mellitus. Diabetologia 1978; 14(5): 281-91. [http://dx.doi.org/10.1007/BF01223018] [PMID: 77236]
[15] Minkowski O, Bretzel RG. Further reports on diabetes mellitus after the exstirpation of the pancreas. J Mol Med (Berl) 2002; 80(1): 3-4. [PMID: 11862318]
[16] Oztürk Y, Altan VM, Yildizoğlu-Ari N. Effects of experimental diabetes and insulin on smooth muscle functions. Pharmacol Rev 1996; 48(1): 69-112. [PMID: 8685248]
[17] Forbes JM, Cooper ME. Mechanisms of diabetic complications. Physiol Rev 2013; 93(1): 137-88. [http://dx.doi.org/10.1152/physrev.00045.2011] [PMID: 23303908]
[18] Powell RC. Helen Flanders Dunbar (1902-1959) and a holistic approach to psychosomatic problems. I. The rise and fall of a medical philosophy. Psychiatr Q 1977; 49(2): 133-52. [http://dx.doi.org/10.1007/BF01071661] [PMID: 329311]
[19] Coleman ML. An integrative approach to individual and group psychology. Psychoanal Rev 1949; 36(4): 389-402. [PMID: 15406980]
[20] Leiby A, Vazirani M. Complementary, integrative, and holistic medicine: integrative approaches to pediatric ulcerative colitis. Pediatr Rev 2013; 34(9): 405-7. [http://dx.doi.org/10.1542/pir.34-9-405] [PMID: 24000344]
[21] Wouters EF, Wouters BB, Augustin IM, Franssen FM. Personalized medicine and chronic obstructive pulmonary disease. Curr Opin Pulm Med 2017; 23(3): 241-6. [http://dx.doi.org/10.1097/MCP.0000000000000377] [PMID: 28257315]
[22] Polak JM, Bloom SR. Peptidergic innervation of the gastrointestinal tract. Adv Exp Med Biol 1978; 106: 27-49. [http://dx.doi.org/10.1007/978-1-4684-7248-6_5] [PMID: 31074]
[23] Track NS. The gastrointestinal endocrine system. Can Med Assoc J 1980; 122(3): 287-92. [PMID: 6989456]
[24] Pearse AG. The cytochemistry and ultrastructure of polypeptide hormone-producing cells of the APUD series and the embryologic, physiologic and pathologic implications of the concept. J Histochem Cytochem 1969; 17(5): 303-13. [http://dx.doi.org/10.1177/17.5.303] [PMID: 4143745]
[25] Hughes J, Kosterlitz HW, Smith TW. The distribution of methionine-enkephalin and leucine-enkephalin in the brain and peripheral tissues. Br J Pharmacol 1977; 61(4): 639-47. [http://dx.doi.org/10.1111/j.1476-5381.1977.tb07557.x] [PMID: 597668]
[26] Gregory RA. Heterogeneity of gut and brain regulatory peptides. Br Med Bull 1982; 38(3): 271-6. [http://dx.doi.org/10.1093/oxfordjournals.bmb.a071772] [PMID: 6129024]
[27] Fujimiya M, Inui A. Peptidergic regulation of gastrointestinal motility in rodents. Peptides 2000; 21(10): 1565-82. [http://dx.doi.org/10.1016/S0196-9781(00)00313-2] [PMID: 11068106]
[28] Meguid MM, Yang ZJ, Gleason JR. The gut-brain brain-gut axis in anorexia: toward an understanding of food intake regulation. Nutrition 1996; 12(Suppl. 1): S57-62. [http://dx.doi.org/10.1016/0899-9007(95)00083-6] [PMID: 8850223]
[29] Cummings DE, Overduin J. Gastrointestinal regulation of food intake. J Clin Invest 2007; 117(1): 13-23. [http://dx.doi.org/10.1172/JCI30227] [PMID: 17200702]
[30] Latorre R, Sternini C, De Giorgio R, Greenwood-Van Meerveld B. Enteroendocrine cells: a review of their role in brain-gut communication. Neurogastroenterol Motil 2016; 28(5): 620-30. [http://dx.doi.org/10.1111/nmo.12754] [PMID: 26691223]
[31] Hoogendoorn CJ, Roy JF, Gonzalez JS. Shared dysregulation of homeostatic brain-body pathways in depression and type 2 diabetes. Curr Diab Rep 2017; 17(10): 90. [http://dx.doi.org/10.1007/s11892-017-0923-y] [PMID: 28815394]
[32] Treadwell PE, Rasmussen AF Jr. Role of the adrenals in stress induced resistance to anaphylactic shock. J Immunol 1961; 87: 492-7. [PMID: 13922363]
[33] Suzuki K, Nakaji S, Yamada M, Totsuka M, Sato K, Sugawara K. Systemic inflammatory response to exhaustive exercise. Cytokine kinetics. Exerc Immunol Rev 2002; 8: 6-48. [PMID: 12690937]
[34] McGregor BA, Murphy KM, Albano DL, Ceballos RM. Stress, cortisol, and B lymphocytes: a novel approach to understanding academic stress and immune function. Stress 2016; 19(2): 185-91. [http://dx.doi.org/10.3109/10253890.2015.1127913] [PMID: 26644211]
[35] de la RubiaOrtí JE, Sancho Castillo S, Benlloch M, Julián Rochina M, CorchónArreche S, García-Pardo MP. Impact of the relationship of stress and the immune system in the appearance of alzheimer's disease. J Alzheimers Dis 2017; 55: 899-903.
[36] Ogłodek E, Szota A, Just M, Moś D, Araszkiewicz A. The role of the neuroendocrine and immune systems in the pathogenesis of depression. Pharmacol Rep 2014; 66(5): 776-81. [http://dx.doi.org/10.1016/j.pharep.2014.04.009] [PMID: 25149980]
[37] Carvalho LA, Urbanova L, Hamer M, Hackett RA, Lazzarino AI, Steptoe A. Blunted glucocorticoid and mineralocorticoid sensitivity to stress in people with diabetes. Psychoneuroendocrinology 2015; 51: 209-18. [http://dx.doi.org/10.1016/j.psyneuen.2014.09.023] [PMID: 25462894]
[38] Joseph JJ, Golden SH. Cortisol dysregulation: the bidirectional link between stress, depression, and type 2 diabetes mellitus. Ann N Y Acad Sci 2017; 1391(1): 20-34. [http://dx.doi.org/10.1111/nyas.13217] [PMID: 27750377]
[39] Godbout JP, Glaser R. Stress-induced immune dysregulation: implications for wound healing, infectious disease and cancer. J Neuroimmune Pharmacol 2006; 1(4): 421-7. [http://dx.doi.org/10.1007/s11481-006-9036-0] [PMID: 18040814]
[40] Tesch GH. Diabetic nephropathy-is this an immune disorder? Clin Sci (Lond) 2017; 131(16): 2183-99. [http://dx.doi.org/10.1042/CS20160636] [PMID: 28760771]
[41] Jia G, Whaley-Connell A, Sowers JR. Diabetic cardiomyopathy: a hyperglycaemia-and insulin-resistance-induced heart disease. Diabetologia 2018; 61(1): 21-8. [http://dx.doi.org/10.1007/s00125-017-4390-4] [PMID: 28776083]

[42] Sekirov I, Russell SL, Antunes LC, Finlay BB. Gut microbiota in health and disease. Physiol Rev 2010; 90(3): 859-904. [http://dx.doi.org/10.1152/physrev.00045.2009] [PMID: 20664075]
[43] Kilian M, Chapple IL, Hannig M, *et al.* The oral microbiome-an update for oral healthcare professionals. Br Dent J 2016; 221(10): 657-66. [http://dx.doi.org/10.1038/sj.bdj.2016.865] [PMID: 27857087]
[44] Dewhirst FE, Chen T, Izard J, *et al.* The human oral microbiome. J Bacteriol 2010; 192(19): 5002-17. [http://dx.doi.org/10.1128/JB.00542-10] [PMID: 20656903]
[45] Duval da Silva V. van Leeuwenhoek, Antonie (1632-1723) van den Tweel JG, Ed. Pioneers in Pathology, Encyclopedia of Pathology 2017; 505-10.
[46] Das NP, Griffiths LA. Studies on flavonoid metabolism. Metabolism of (+)-catechin in the guinea pig. Biochem J 1968; 110(3): 449-56. [http://dx.doi.org/10.1042/bj1100449] [PMID: 5755325]
[47] Ramakrishna BS. Role of the gut microbiota in human nutrition and metabolism. J Gastroenterol Hepatol 2013; 28(Suppl. 4): 9-17. [http://dx.doi.org/10.1111/jgh.12294] [PMID: 24251697]
[48] Koppel N, Maini Rekdal V, Balskus EP. Chemical transformation of xenobiotics by the human gut microbiota. Science 2017; 356(6344): eaag2770. [http://dx.doi.org/10.1126/science.aag2770] [PMID: 28642381]
[49] van Bekkum DW, Knaan S. Role of bacterial microflora in development of intestinal lesions from graft-versus-host reaction. J Natl Cancer Inst 1977; 58(3): 787-90. [http://dx.doi.org/10.1093/jnci/58.3.787] [PMID: 14265]
[50] McGhee JR, Michalek SM, Kiyono H, *et al.* Mucosal immunoregulation: environmental lipopolysaccharide and GALT T lymphocytes regulate the IgA response. Microbiol Immunol 1984; 28(3): 261-80. [http://dx.doi.org/10.1111/j.1348-0421.1984.tb00679.x] [PMID: 6234450]
[51] Shi N, Li N, Duan X, Niu H. Interaction between the gut microbiome and mucosal immune system. Mil Med Res 2017; 4:14. [https://mmrjournal.biomedcentral.com/articles/10.1186/s40779-017-0122-9]
[52] Deneer HG, Boychuk I. Reduction of ferric iron by Listeria monocytogenes and other species of Listeria. Can J Microbiol 1993; 39(5): 480-5. [http://dx.doi.org/10.1139/m93-068] [PMID: 8330259]
[53] Freitag NE, Port GC, Miner MD. Listeria monocytogenes-from saprophyte to intracellular pathogen. Nat Rev Microbiol 2009; 7(9): 623-8. [http://dx.doi.org/10.1038/nrmicro2171] [PMID: 19648949]
[54] Light SH, Su L, Rivera-Lugo R, *et al.* A flavin-based extracellular electron transfer mechanism in diverse Gram-positive bacteria. Nature 2018; 562(7725): 140-4. [http://dx.doi.org/10.1038/s41586-018-0498-z] [PMID: 30209391]
[55] Dinan TG, Cryan JF. The microbiome-gut-brain axis in health and disease. Gastroenterol Clin North Am 2017; 46(1): 77-89. [http://dx.doi.org/10.1016/j.gtc.2016.09.007] [PMID: 28164854]
[56] Saha S, Tariq R, Tosh PK, Pardi DS, Khanna S. Fecal microbiota transplantation for eradicating carriage of multidrug-resistant organisms: a systematic review. Clin Microbiol Infect 2019; 25(8): 30158-2.
[57] Cheng HY, Ning MX, Chen DK, Ma WT. Interactions between the gut microbiota and the host innate immune response against pathogens. Front Immunol 2019; 10: 607. [https://www.frontiersin.org/articles/10.3389/fimmu.2019.00607/full10.3389/fimmu.2019.00607]
[58] Kurashima Y, Kiyono H. Mucosal ecological network of epithelium and immune cells for gut homeostasis and tissue healing. Annu Rev Immunol 2017; 35: 119-47. [http://dx.doi.org/10.1146/annurev-immunol-051116-052424] [PMID: 28125357]
[59] Li DY, Tang WHW. Gut Microbiota and Atherosclerosis. Curr Atheroscler Rep 2017; 19(10): 39. [http://dx.doi.org/10.1007/s11883-017-0675-9] [PMID: 28842845]
[60] Torres-Fuentes C, Schellekens H, Dinan TG, Cryan JF. The microbiota-gut-brain axis in obesity. Lancet Gastroenterol Hepatol 2017; 2(10): 747-56. [http://dx.doi.org/10.1016/S2468-1253(17)30147-4] [PMID: 28844808]
[61] BordaloTonucci L. Dos Santos KM, De Luces Fortes Ferreira CL, Ribeiro SM, De Oliveira LL, Martino HS. Gut microbiota and probiotics: focus on diabetes mellitus. Crit Rev Food Sci Nutr 2017; 57: 2296-309.
[62] Roubalová R, Procházková P, Papežová H, Smitka K, Bilej M, Tlaskalová-Hogenová H. Anorexia nervosa: gut microbiota-immune-brain interactions. Clin Nutr 2019; pii: S0261-5614(19)30137-2.
[63] Lach G, Schellekens H, Dinan TG, Cryan JF. Anxiety, depression, and the microbiome: a role for gut peptides. Neurotherapeutics 2018; 15(1): 36-59. [http://dx.doi.org/10.1007/s13311-017-0585-0] [PMID: 29134359]
[64] Li Q, Zhou JM. The microbiota-gut-brain axis and its potential therapeutic role in autism spectrum disorder. Neuroscience 2016; 324: 131-9. [http://dx.doi.org/10.1016/j.neuroscience.2016.03.013] [PMID: 26964681]
[65] Mangiola F, Ianiro G, Franceschi F, Fagiuoli S, Gasbarrini G, Gasbarrini A. Gut microbiota in autism and mood disorders. World J Gastroenterol 2016; 22(1): 361-8. [http://dx.doi.org/10.3748/wjg.v22.i1.361] [PMID: 26755882]
[66] Ding HT, Taur Y, Walkup JT. Gut microbiota and autism: key concepts and findings. J Autism Dev Disord 2017; 47(2): 480-9. [http://dx.doi.org/10.1007/s10803-016-2960-9] [PMID: 27882443]
[67] Caso JR, Balanzá-Martínez V, Palomo T, García-Bueno B. The microbiota and gut-brain axis: contributions to the immunopathogenesis of schizophrenia. Curr Pharm Des 2016; 22(40): 6122-33. [http://dx.doi.org/10.2174/1381612822666160906160911] [PMID: 27604609]
[68] Kanji S, Fonseka TM, Marshe VS, Sriretnakumar V, Hahn MK, Müller DJ. The microbiome-gut-brain axis: implications for schizophrenia and antipsychotic induced weight gain. Eur Arch Psychiatry Clin Neurosci 2018; 268(1): 3-15. [http://dx.doi.org/10.1007/s00406-017-0820-z] [PMID: 28624847]
[69] Donazar-Ezcurra M, López-Del Burgo C, Bes-Rastrollo M. Primary prevention of gestational diabetes mellitus through nutritional factors: a systematic review. BMC Pregnancy Childbirth 2017; 17(1): 30. [http://dx.doi.org/10.1186/s12884-016-1205-4] [PMID: 28086820]
[70] Slawson DL, Fitzgerald N, Morgan KT. Position of the Academy of nutrition and dietetics: the role of nutrition in health promotion and chronic disease prevention. J Acad Nutr Diet 2013; 113(7): 972-9. [http://dx.doi.org/10.1016/j.jand.2013.05.005] [PMID: 23790411]
[71] Manning TS, Gibson GR. Microbial-gut interactions in health and disease. Prebiotics. Best Pract Res Clin Gastroenterol 2004; 18(2): 287-98. [http://dx.doi.org/10.1016/j.bpg.2003.10.008] [PMID: 15123070]
[72] do Carmo MM, Walker JC, Novello D, *et al.* Polydextrose: physiological punction, and effects on health. Nutrients 2016; 8(9): E553. [http://dx.doi.org/10.3390/nu8090553] [PMID: 27618093]
[73] Legette LL, Lee W, Martin BR, Story JA, Campbell JK, Weaver CM. Prebiotics enhance magnesium absorption and inulin-based fibers exert chronic effects on calcium utilization in a postmenopausal rodent model. J Food Sci 2012; 77(4): H88-94. [http://dx.doi.org/10.1111/j.1750-3841.2011.02612.x] [PMID: 22394255]
[74] Santos EF, Tsuboi KH, Araújo MR, *et al.* Ingestion of polydextrose increase the iron absorption in rats submitted to partial gastrectomy. Acta Cir Bras 2010; 25(6): 518-24. [http://dx.doi.org/10.1590/S0102-86502010000600011] [PMID: 21120284]
[75] Gibson GR, Probert HM, Loo JV, Rastall RA, Roberfroid MB. Dietary modulation of the human colonic microbiota: updating the concept of prebiotics. Nutr Res Rev 2004; 17(2): 259-75. [http://dx.doi.org/10.1079/NRR200479] [PMID: 19079930]
[76] Florowska A, Krygier K, Florowski T, Dłużewska E. Prebiotics as functional food ingredients preventing diet-related diseases. Food Funct 2016; 7(5): 2147-55. [http://dx.doi.org/10.1039/C5FO01459J] [PMID: 26961814]
[77] Notay M, Foolad N, Vaughn AR, Sivamani RK. Probiotics, prebiotics, and synbiotics for the treatment and prevention of adult dermatological diseases. Am J Clin Dermatol 2017; 18(6): 721-32. [http://dx.doi.org/10.1007/s40257-017-0300-2] [PMID: 28681230]
[78] Slavin J. Fiber and prebiotics: mechanisms and health benefits. Nutrients 2013; 5(4): 1417-35.

[http://dx.doi.org/10.3390/nu5041417] [PMID: 23609775]

[79] Lefranc-Millot C, Guérin-Deremaux L, Wils D, Neut C, Miller LE, Saniez-Degrave MH. Impact of a resistant dextrin on intestinal ecology: how altering the digestive ecosystem with NUTRIOSE®, a soluble fibre with prebiotic properties, may be beneficial for health. J Int Med Res 2012; 40(1): 211-24. [http://dx.doi.org/10.1177/147323001204000122] [PMID: 22429361]

[80] Witaicenis A, Fruet AC, Salem L, Di Stasi LC. Dietary polydextrose prevents inflammatory bowel disease in trinitrobenzenesulfonic acid model of rat colitis. J Med Food 2010; 13(6): 1391-6. [http://dx.doi.org/10.1089/jmf.2009.0275] [PMID: 21091252]

[81] Peuranen S, Tiihonen K, Apajalahti J, Kettunen A, Saarinen M, Rautonen N. Combination of polydextrose and lactitol affects microbial ecosystem and immune responses in rat gastrointestinal tract. Br J Nutr 2004; 91(6): 905-14. [http://dx.doi.org/10.1079/BJN20041114] [PMID: 15182394]

[82] Yamamoto Y, To M, Hayashi T, *et al.* Intake of indigestible carbohydrates influences IgA response and polymeric Ig receptor expression in the rat submandibular gland. Br J Nutr 2015; 113(12): 1895-902. [http://dx.doi.org/10.1017/S0007114515001403] [PMID: 25999025]

[83] den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J Lipid Res 2013; 54(9): 2325-40. [http://dx.doi.org/10.1194/jlr.R036012] [PMID: 23821742]

[84] Blundell JE, Lawton CL, Cotton JR, Macdiarmid JI. Control of human appetite: implications for the intake of dietary fat. Annu Rev Nutr 1996; 16: 285-319. [http://dx.doi.org/10.1146/annurev.nu.16.070196.001441] [PMID: 8839929]

[85] Stenman LK, Waget A, Garret C, *et al.* Probiotic B420 and prebiotic polydextrose improve efficacy of antidiabetic drugs in mice. Diabetol Metab Syndr 2015; 7: 75. [http://dx.doi.org/10.1186/s13098-015-0075-7] [PMID: 26366205]

[86] Konings E, Schoffelen PF, Stegen J, Blaak EE. Effect of polydextrose and soluble maize fibre on energy metabolism, metabolic profile and appetite control in overweight men and women. Br J Nutr 2014; 111(1): 111-21. [http://dx.doi.org/10.1017/S0007114513002183] [PMID: 23880340]

[87] Albarracín M, Weisstaub AR, Zuleta A, Mandalunis P, González RJ, Drago SR. Effects of extruded whole maize, polydextrose and cellulose as sources of fibre on calcium bioavailability and metabolic parameters of growing Wistar rats. Food Funct 2014; 5(4): 804-10. [http://dx.doi.org/10.1039/c3fo60424a] [PMID: 24577488]

[88] Hengst C, Ptok S, Roessler A, Fechner A, Jahreis G. Effects of polydextrose supplementation on different faecal parameters in healthy volunteers. Int J Food Sci Nutr 2009; 60(Suppl. 5): 96-105. [http://dx.doi.org/10.1080/09637480802526760] [PMID: 19107626]

[89] Costabile A, Fava F, Röytiö H, *et al.* Impact of polydextrose on the faecal microbiota: a double-blind, crossover, placebo-controlled feeding study in healthy human subjects. Br J Nutr 2012; 108(3): 471-81. [http://dx.doi.org/10.1017/S0007114511005782] [PMID: 22099384]

[90] Magro DO, de Oliveira LM, Bernasconi I, *et al.* Effect of yogurt containing polydextrose, *Lactobacillus acidophilus* NCFM and *Bifidobacterium lactis* HN019: a randomized, double-blind, controlled study inchronic constipation. Nutr J 2014; 13: 75. [http://dx.doi.org/10.1186/1475-2891-13-75] [PMID: 25056655]

[91] Ramabadran K, Bansinath M, Turndorf H, Puig MM. Streptozotocin-diabetes attenuates α 2-adrenoceptor agonist-induced delay in small intestinal transit in mice. J Auton Pharmacol 1990; 10(3): 163-71. [http://dx.doi.org/10.1111/j.1474-8673.1990.tb00015.x] [PMID: 1974257]

[92] el-Neshawy AA, el-Shafie NM. Quality of zabadi made from cow's milk fortified with whey and soy proteins. Nahrung 1988; 32(10): 939-43. [http://dx.doi.org/10.1002/food.19880321005] [PMID: 3244370]

[93] Steinkraus KH. Handbook of Indigenous Fermented Foods Revised and Expanded 1996.

[94] Prajapati JB, Nair BM. The History of Fermented Foods. Handbook of Fermented Functional Foods 2003; 1-27.

[95] Kahala M, Mäki M, Lehtovaara A, *et al.* Characterization of starter lactic acid bacteria from the Finnish fermented milk product viili. J Appl Microbiol 2008; 105(6): 1929-38. [http://dx.doi.org/10.1111/j.1365-2672.2008.03952.x] [PMID: 19120639]

[96] Yıldız F. Overview of yogurt and other fermented dairy products. Development and manufacture of yogurt and other functional dairy products 2010; 1-44.

[97] Panesar PS. Fermented dairy products: starter cultures and potential nutritional benefits. Food Nutr Sci 2011; 2: 47-51. [http://dx.doi.org/10.4236/fns.2011.21006]

[98] Saleh FA. Isolation and identification of microorganisms and antibacterial activity of Laban Zeer, an Egyptian traditional fermented milk product. Sci J Microbiol 2013; 2: 31-42.

[99] Shah NP. Novel dairy probiotic products. Adv Probiotic Technol 2015; 338-55.

[100] Gadallah MGE, Hassan MFY. Quality properties of Kishk (a dried fermented cereal-milk mixture) prepared from different raw materials. J Saudi Soc Agric Sci 2019; 18: 95-101. [http://dx.doi.org/10.1016/j.jssas.2017.02.003]

[101] Sengun IY, Nielsen DS, Karapinar M, Jakobsen M. Identification of lactic acid bacteria isolated from Tarhana, a traditional Turkish fermented food. Int J Food Microbiol 2009; 135(2): 105-11. [http://dx.doi.org/10.1016/j.ijfoodmicro.2009.07.033] [PMID: 19703719]

[102] Gasta MG, Williamson CB, Gossard CM, *et al.* Probiotics and disease: a comprehensive summary-part 4, infectious diseases. Integr Med (Encinitas) 2017; 16(2): 28-38. [PMID: 30881235]

[103] Gasta MG, Gossard CM, Williamson CB, *et al.* Probiotics and disease: a comprehensive summary-part 5, respiratory conditions of the ears, nose, and throat. Integr Med (Encinitas) 2017; 16(3): 28-40. [PMID: 30881245]

[104] Dolan KE, Pizano JM, Gossard CM, *et al.* Probiotics and disease: a comprehensive summary-part 6, skin health. Integr Med (Encinitas) 2017; 16(4): 32-41. [PMID: 30881255]

[105] Williamson CB, Burns CM, Gossard CM, *et al.* Probiotics and disease: a comprehensive summary-part 3, cardiometabolic disease and fatigue syndromes. Integr Med (Encinitas) 2017; 16(1): 30-41. [PMID: 28223906]

[106] Dolan KE, Finley HJ, Burns CM, *et al.* Probiotics and disease: a comprehensive summary-part 1, mental and neurological health. Integr Med (Encinitas) 2016; 15(5): 46-58. [PMID: 27980495]

[107] Tian R, Yang W, Xue Q, *et al.* Rutin ameliorates diabetic neuropathy by lowering plasma glucose and decreasing oxidative stress via Nrf2 signaling pathway in rats. Eur J Pharmacol 2016; 771: 84-92. [http://dx.doi.org/10.1016/j.ejphar.2015.12.021] [PMID: 26688570]

[108] Shi Y, Liang XC, Zhang H, Sun Q, Wu QL, Qu L. Combination of quercetin, cinnamaldehyde and hirudin protects rat dorsal root ganglion neurons against high glucose-induced injury through Nrf-2/HO-1 activation and NF-κB inhibition. Chin J Integr Med 2017; 23(9): 663-71. [http://dx.doi.org/10.1007/s11655-017-2405-0] [PMID: 28861887]

[109] Naseri R, Farzaei F, Fakhri S, *et al.* Polyphenols for diabetes associated neuropathy: Pharmacological targets and clinical perspective. Daru 2019. [http://dx.doi.org/10.1007/s40199-019-00289-w] [PMID: 31352568]

[110] Icel E, Icel A, Uçak T, *et al.* The effects of lycopene on alloxan induced diabetic optic neuropathy. Cutan Ocul Toxicol 2019; 38(1): 88-92. [http://dx.doi.org/10.1080/15569527.2018.1530258] [PMID: 30277087]

[111] Shay KP, Moreau RF, Smith EJ, Smith AR, Hagen TM. Alpha-lipoic acid as a dietary supplement: molecular mechanisms and therapeutic potential. Biochim Biophys Acta 2009; 1790(10): 1149-60.

[http://dx.doi.org/10.1016/j.bbagen.2009.07.026] [PMID: 19664690]

[112] Ferreira PEB, Beraldi EJ, Borges SC, Natali MRM, Buttow NC. Resveratrol promotes neuroprotection and attenuates oxidative and nitrosative stress in the small intestine in diabetic rats. Biomed Pharmacother 2018; 105: 724-33. [http://dx.doi.org/10.1016/j.biopha.2018.06.030] [PMID: 29906751]

[113] Verma S, Dey A, Kumar V. Potential of *Curcuma longa* and *Withania somnifera* for diabetes and associated comorbidities. Herbs for diabetes and neurological disease management: research and advancements oakville: CRC/Apple Academic Press 2018; 117-49.

[114] Surh YJ, Lee SS. Capsaicin in hot chili pepper: carcinogen, co-carcinogen or anticarcinogen? Food Chem Toxicol 1996; 34(3): 313-6. [http://dx.doi.org/10.1016/0278-6915(95)00108-5] [PMID: 8621114]

[115] Niu Y, Li J, Peng R, Zhao X, Wu J, Tang Q. Low vitamin D is associated with diabetes peripheral neuropathy in older but not in young and middle-aged patients. Diabetes Metab Res Rev 2019; 35(6): e3162. [http://dx.doi.org/10.1002/dmrr.3162] [PMID: 30931541]

[116] Mottaghi T, Khorvash F, Maracy M, Bellissimo N, Askari G. Effect of folic acid supplementation on nerve conduction velocity in diabetic polyneuropathy patients. Neurol Res 2019; 41(4): 364-8. [http://dx.doi.org/10.1080/01616412.2019.1565180] [PMID: 30730785]

[117] Pan XR, Li GW, Hu YH, *et al.* Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 1997; 20(4): 537-44. [http://dx.doi.org/10.2337/diacare.20.4.537] [PMID: 9096977]

[118] Esposito K, Maiorino MI, Ceriello A, Giugliano D. Prevention and control of type 2 diabetes by Mediterranean diet: a systematic review. Diabetes Res Clin Pract 2010; 89(2): 97-102. [http://dx.doi.org/10.1016/j.diabres.2010.04.019] [PMID: 20546959]

[119] Bloomfield HE, Koeller E, Greer N, MacDonald R, Kane R, Wilt TJ. Effects on health outcomes of a Mediterranean diet with no restriction on fat intake: a systematic review and meta-analysis. Ann Intern Med 2016; 165(7): 491-500. [http://dx.doi.org/10.7326/M16-0361] [PMID: 27428849]

[120] Powell-Tuck J. Nutritional interventions in critical illness. Proc Nutr Soc 2007; 66(1): 16-24. [http://dx.doi.org/10.1017/S0029665107005253] [PMID: 17343768]

[121] Cani PD, Bibiloni R, Knauf C, *et al.* Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes 2008; 57(6): 1470-81. [http://dx.doi.org/10.2337/db07-1403] [PMID: 18305141]

[122] Patterson E, Ryan PM, Cryan JF, *et al.* Gut microbiota, obesity and diabetes. Postgrad Med J 2016; 92(1087): 286-300. [http://dx.doi.org/10.1136/postgradmedj-2015-133285] [PMID: 26912499]

[123] Yarandi SS, Srinivasan S. Diabetic gastrointestinal motility disorders and the role of enteric nervous system: current status and future directions. Neurogastroenterol Motil 2014; 26(5): 611-24. [http://dx.doi.org/10.1111/nmo.12330] [PMID: 24661628]

[124] Leustean AM, Ciocoiu M, Sava A, *et al.* Implications of the intestinal microbiota in diagnosing the progression of diabetes and the presence of cardiovascular complications. J Diabetes Res 2018; 2018: 5205126. [http://dx.doi.org/10.1155/2018/5205126] [PMID: 30539026]

[125] Beli E, Yan Y, Moldovan L, *et al.* Restructuring of the gut microbiome by intermittent fasting prevents retinopathy and prolongs survival in *db/db* mice. Diabetes 2018; 67(9): 1867-79. [http://dx.doi.org/10.2337/db18-0158] [PMID: 29712667]

[126] Collier A, McLaren J, Godwin J, Bal A. Is *Clostridium difficile* associated with the '4C' antibiotics? A retrospective observational study in diabetic foot ulcer patients. Int J Clin Pract 2014; 68(5): 628-32. [http://dx.doi.org/10.1111/ijcp.12347] [PMID: 24499256]

[127] Ito K, Enomoto H. Retrograde transport of neurotrophic factor signaling: implications in neuronal development and pathogenesis. J Biochem 2016; 160(2): 77-85. [http://dx.doi.org/10.1093/jb/mvw037] [PMID: 27318359]

[128] Azizi SA, Azizi SA. Synucleinopathies in neurodegenerative diseases: Accomplices, an inside job and selective vulnerability. Neurosci Lett 2018; 672: 150-2. [http://dx.doi.org/10.1016/j.neulet.2017.12.003] [PMID: 29217261]

[129] Caleo M, Restani L. Direct central nervous system effects of botulinum neurotoxin. Toxicon 2018; 147: 68-72. [http://dx.doi.org/10.1016/j.toxicon.2017.10.027] [PMID: 29111119]

[130] Bailey CJ. Metformin: historical overview. Diabetologia 2017; 60(9): 1566-76. [http://dx.doi.org/10.1007/s00125-017-4318-z] [PMID: 28776081]

[131] Bever BO. Oral hypoglycaemic plants in West Africa. J Ethnopharmacol 1980; 2(2): 119-27. [http://dx.doi.org/10.1016/0378-8741(80)90005-7] [PMID: 7005546]

[132] Bailey CJ, Day C. Traditional plant medicines as treatments for diabetes. Diabetes Care 1989; 12(8): 553-64. [http://dx.doi.org/10.2337/diacare.12.8.553] [PMID: 2673695]

[133] Marles RJ, Farnsworth NR. Antidiabetic plants and their active constituents. Phytomedicine 1995; 2(2): 137-89. [http://dx.doi.org/10.1016/S0944-7113(11)80059-0] [PMID: 23196156]

[134] Ingle-Jadav P, Angolkar TR, Kaur G. Diabetes and phytopharmaceuticals: translational pharmacology perspective. herbs for diabetes and neurological disease management: research and advancements Oakville: CRC/Apple Academic Press 2018; 201-23.

[135] Hamza N, Berke B, Umar A, Cheze C, Gin H, Moore N. A review of Algerian medicinal plants used in the treatment of diabetes. J Ethnopharmacol 2019; 238: 111841. [http://dx.doi.org/10.1016/j.jep.2019.111841] [PMID: 30959140]

[136] Bone K, Mills S. Principles and practice of phytotherapy: modern herbal medicine. Elsevier 2013.

[137] Gruenwald J, Brendler T, Jaenicke C. PDR for herbal medicines, 4th ed. 2007.

[138] Öztürk Y. Obesity, diabetes and metabolic syndrome in terms of preventive medicine and healthcare. J Obese Weight Loss Ther 2015; 5: 44. [http://dx.doi.org/10.4172/2165-7904.S1.013]

[139] do Nascimento BonatoPanizzon CP, de Miranda Neto MH, Ramalho FV, Longhini R, de Mello JCP, Zanoni JN. Ethyl acetate fraction from *Trichilia catigua* confers partial neuroprotection in components of the enteric innervation of the jejunumin diabetic rats. Cell Physiol Biochem 2019; 53(1): 76-86. [http://dx.doi.org/10.33594/000000122] [PMID: 31192545]

[140] Pengzong Z, Yuanmin L, Xiaoming X, *et al.* Wound healing potential of the standardized extract of Boswellia serrata on experimental diabetic foot ulcer *via* inhibitionof inflammatory, angiogenetic and apoptotic markers. Planta Med 2019; 85(8): 657-69. [http://dx.doi.org/10.1055/a-0881-3000] [PMID: 30909313]

[141] Czerwińska ME, Gąsińska E, Leśniak A, *et al.* Inhibitory effect of *Ligustrum vulgare* leaf extract on the development of neuropathic pain in a streptozotocin-induced rat model of diabetes. Phytomedicine 2018; 49: 75-82. [http://dx.doi.org/10.1016/j.phymed.2018.06.006] [PMID: 30217264]

[142] Rasoulian B, Hajializadeh Z, Esmaeili-Mahani S, Rashidipour M, Fatemi I, Kaeidi A. Neuroprotective and antinociceptive effects of rosemary (*Rosmarinus officinalis* L.) extract in rats with painful diabetic neuropathy. J Physiol Sci 2019; 69(1): 57-64. [http://dx.doi.org/10.1007/s12576-018-0620-x] [PMID: 29754274]

[143] Kishore L, Kaur N, Singh R. Effect of Kaempferol isolated from seeds of *Eruca sativa* on changes of pain sensitivity in Streptozotocin-induced diabetic neuropathy. Inflammopharmacology 2018; 26(4): 993-1003. [http://dx.doi.org/10.1007/s10787-017-0416-2] [PMID: 29159712]

[144] Nasiry D, Khalatbary AR, Ahmadvand H. TalebpourAmiri F, Akbari E. Protectiveeffects of methanolic extract of *Juglans regia* L. leaf on streptozotocin-induced diabetic peripheral neuropathy in rats. BMC Complement Altern Med 2017; 17(1): 476. [http://dx.doi.org/10.1186/s12906-017-1983-x] [PMID: 28969623]

[145] Kaur N, Kishore L, Singh R. Chromane isolated from leaves of *Dillenia indica* improves the neuronal dysfunction in STZ-induced diabetic neuropathy. J Ethnopharmacol 2017; 206: 19-30. [http://dx.doi.org/10.1016/j.jep.2017.05.018] [PMID: 28506898]

[146] Soliman AM, Teoh SL, Ghafar NA, Das S. Molecular concept of diabetic wound healing: Effective role of herbal remedies. Mini Rev Med Chem 2019; 19(5): 381-94. [http://dx.doi.org/10.2174/1389557518666181025155204] [PMID: 30360709]

[147] Farsak M, Özdağli G, Özmüş D, *et al*. Effects of *Hypericum perforatum* on an experimentally induced diabetic wound in a rat rodel. Wounds 2017; 29: E10-7. [PMID: 28272017]

[148] Oztürk N, Korkmaz S, Oztürk Y. Wound-healing activity of St. John's Wort (*Hypericum perforatum* L.) on chicken embryonic fibroblasts. J Ethnopharmacol 2007; 111(1): 33-9. [http://dx.doi.org/10.1016/j.jep.2006.10.029] [PMID: 17156955]

[149] Dikmen M, Oztürk Y, Sagratini G, Ricciutelli M, Vittori S, Maggi F. Evaluation of the wound healing potentials of two subspecies of *Hypericum perforatum* on cultured NIH3T3 fibroblasts. Phytother Res 2011; 25(2): 208-14. [PMID: 20632305]

[150] Can ÖD, Öztürk Y, Öztürk N, *et al.* Effects of treatment with St. John's Wort on blood glucose levels and pain perceptions of streptozotocin-diabetic rats. Fitoterapia 2011; 82(4): 576-84. [http://dx.doi.org/10.1016/j.fitote.2011.01.008] [PMID: 21262331]

[151] Öztürk Y. Role of St.-John's Wort (*Hypericum perforatum* L.) in the management of diabetes and neurological disorders. Herbs for diabetes and neurological disease management: Research and Advancements Oakville: CRC/Apple Academic Press 2018; 1-21.

[152] Khoo HE, Ng HS, Yap WS, Goh HJH, Yim HS. Nutrients for prevention of macular degeneration and eye-related diseases. Antioxidants 2019; 8(4): E85. [http://dx.doi.org/10.3390/antiox8040085] [PMID: 30986936]

[153] Carlos-Reyes Á, López-González JS, Meneses-Flores M, *et al.* Dietary dompounds as epigenetic modulating agents in cancer. Front Genet 2019; 10: 79. [http://dx.doi.org/10.3389/fgene.2019.00079] [PMID: 30881375]

[154] Pisoschi AM, Pop A, Cimpeanu C, Predoi G. Antioxidant capacity determination in plants and plant-derived products: a review. Oxid Med Cell Longev 2016; 2016: 9130976. [http://dx.doi.org/10.1155/2016/9130976] [PMID: 28044094]

[155] Alché JD. A concise appraisal of lipid oxidation and lipoxidation in higher plants. Redox Biol 2019; 7: 101136. [http://dx.doi.org/10.1016/j.redox.2019.101136] [PMID: 30772285]

[156] Maritim AC, Sanders RA, Watkins JB III. Diabetes, oxidative stress, and antioxidants: a review. J Biochem Mol Toxicol 2003; 17(1): 24-38. [http://dx.doi.org/10.1002/jbt.10058] [PMID: 12616644]

[157] Rehman K, Akash MSH. Mechanism of generation of oxidative stress and pathophysiology of type 2 diabetes mellitus: how are they interlinked? J Cell Biochem 2017; 118(11): 3577-85. [http://dx.doi.org/10.1002/jcb.26097] [PMID: 28460155]

[158] Calderon GD, Juarez OH, Hernandez GE, Punzo SM, De la Cruz ZD. Oxidative stress and diabetic retinopathy: development and treatment. Eye (Lond) 2017; 31(8): 1122-30. [http://dx.doi.org/10.1038/eye.2017.64] [PMID: 28452994]

[159] Herder C, Roden M, Ziegler D. Novel insights into sensorimotor and cardiovascular autonomic neuropathy from recent-onset diabetes and population-based cohorts. Trends Endocrinol Metab 2019; 30(5): 286-98. [http://dx.doi.org/10.1016/j.tem.2019.02.007] [PMID: 30935671]

[160] Victorio JA, Davel AP. Perivascular adipose tissue oxidative stress on the pathophysiology of cardiometabolic diseases. Curr Hypertens Rev 2019. [http://dx.doi.org/10.2174/1573402115666190410153634] [PMID: 30968777]

[161] Réus GZ, Carlessi AS, Silva RH, Ceretta LB, Quevedo J. Relationship of oxidative stress as a link between Diabetes Mellitus and major depressive disorder. Oxid Med Cell Longev 2019; 2019: 8637970. [http://dx.doi.org/10.1155/2019/8637970] [PMID: 30944699]

[162] Lutz M, Fuentes E, Ávila F, Alarcón M, Palomo I. Roles of phenolic compounds in the reduction of risk factors of cardiovascular diseases. Molecules 2019; 24(2): E366. [http://dx.doi.org/10.3390/molecules24020366] [PMID: 30669612]

[163] Öztürk N. Phenolic composition and antioxidant activity of the different extracts from *Thymus longicaulis* C Presl. subsp. *longicaulis* var. *longicaulis* and *T. longicaulis* C. Presl. subsp. *longicaulis* var. *subisophyllus* growing in Turkey. Pak J Pharm Sci 2015; 28(2): 465-72. [PMID: 25730781]

[164] Agar OT, Dikmen M, Öztürk N, Yilmaz MA, Temel H, Türkmenoğlu FP. Comparative studies on phenolic composition, antioxidant, wound healing and cytotoxic activities of selected *Achillea* L. species growing in Turkey. Molecules 2015; 20(10): 17976-8000. [http://dx.doi.org/10.3390/molecules201017976] [PMID: 26437391]

[165] Dikmen M, Öztürk N, Öztürk Y. The antioxidant potency of *Punica granatum* L. Fruit peel reduces cell proliferation and induces apoptosis on breast cancer. J Med Food 2011; 14(12): 1638-46. [http://dx.doi.org/10.1089/jmf.2011.0062] [PMID: 21861726]

[166] Öztürk N, Tunçel M. Assessment of phenolic acid content and in vitro antiradical characteristics of hawthorn. J Med Food 2011; 14(6): 664-9. [http://dx.doi.org/10.1089/jmf.2010.0063] [PMID: 21554133]

[167] Orhan IE, Senol FS, Ozturk N, Celik SA, Pulur A, Kan Y. Phytochemical contents and enzyme inhibitory and antioxidant properties of *Anethum graveolens* L. (dill) samples cultivated under organic and conventional agricultural conditions. Food Chem Toxicol 2013; 59: 96-103. [http://dx.doi.org/10.1016/j.fct.2013.05.053] [PMID: 23764360]

[168] Sagratini G, Ricciutelli M, Vittori S, Oztürk N, Oztürk Y, Maggi F. Phytochemical and antioxidant analysis of eight *Hypericum* taxa from Central Italy. Fitoterapia 2008; 79(3): 210-3. [http://dx.doi.org/10.1016/j.fitote.2007.11.011] [PMID: 18178326]

[169] Mao XY, Jin MZ, Chen JF, Zhou HH, Jin WL. Live or let die: Neuroprotective and anti-cancer effects of nutraceutical antioxidants. Pharmacol Ther 2018; 183: 137-51. [http://dx.doi.org/10.1016/j.pharmthera.2017.10.012] [PMID: 29055715]

[170] Mustafa AM, Maggi F, Papa F, Kaya E, Dikmen M, Öztürk Y. Isofuranodiene: A neuritogenic compound isolated from wild celery (*Smyrnium olusatrum* L., Apiaceae). Food Chem 2016; 192: 782-7. [http://dx.doi.org/10.1016/j.foodchem.2015.07.079] [PMID: 26304411]

[171] Dikmen M, Kaya-Tilki E, Engür S, Öztürk Y. Neuritogenic Activity of epigallocatechin gallate and curcumin combination on rat adrenal pheochromocytoma cells. Fresenius Environ Bull 2017; 26: 4726-33.

[172] Poolsup N, Suksomboon N, Kurnianta PDM, Deawjaroen K. Effects of curcumin on glycemic control and lipid profile in prediabetes and type 2 diabetes mellitus: a systematic review and meta-analysis. PLoS One 2019; 14(4): e0215840. [http://dx.doi.org/10.1371/journal.pone.0215840] [PMID: 31013312]

[173] Azhdari M, Karandish M, Mansoori A. Metabolic benefits of curcumin supplementation in patients with metabolic syndrome: A systematic review and meta-analysis of randomized controlled trials. Phytother Res 2019; 33(5): 1289-301. [http://dx.doi.org/10.1002/ptr.6323] [PMID: 30941814]

[174] Lee HJ, Seo HI, Cha HY, Yang YJ, Kwon SH, Yang SJ. Diabetes and Alzheimer's disease: mechanisms and nutritional aspects. Clin Nutr Res 2018; 7(4): 229-40. [http://dx.doi.org/10.7762/cnr.2018.7.4.229] [PMID: 30406052]

[175] Sun J, Chen F, Braun C, *et al.* Role of curcumin in the management of pathological pain. Phytomedicine 2018; 48: 129-40. [http://dx.doi.org/10.1016/j.phymed.2018.04.045] [PMID: 30195871]

[176] Lopresti AL. Curcumin for neuropsychiatric disorders: a review of in vitro, animal and human studies. J Psychopharmacol (Oxford) 2017; 31(3): 287-302. [http://dx.doi.org/10.1177/0269881116686883] [PMID: 28135888]

[177] Ferreira MA, Silva DM, de Morais AC Jr, Mota JF, Botelho PB. Therapeutic potential of green tea on risk factors for type 2 diabetes in obese adults - a review. Obes Rev 2016; 17(12): 1316-28. [http://dx.doi.org/10.1111/obr.12452] [PMID: 27443447]

[178] Casanova E, Salvadó J, Crescenti A, Gibert-Ramos A. Epigallocatechin gallate modulates muscle homeostasis in type 2 diabetes and obesity by targeting energetic and redox pathways: a narrative review. Int J Mol Sci 2019; 20(3): E532. [http://dx.doi.org/10.3390/ijms20030532] [PMID: 30691224]

[179] Raposo D, Morgado C, Pereira-Terra P, Tavares I. Nociceptive spinal cord neurons of laminae I-III exhibit oxidative stress damage during diabetic neuropathy which is prevented by early antioxidant treatment with epigallocatechin-gallate (EGCG). Brain Res Bull 2015; 110: 68-75. [http://dx.doi.org/10.1016/j.brainresbull.2014.12.004] [PMID: 25522867]

[180] Baluchnejadmojarad T, Roghani M. Chronic oral epigallocatechin-gallate alleviates streptozotocin-induced diabetic neuropathic hyperalgesia in rat: Involvement of oxidative stress. Iran J Pharm Res 2012; 11(4): 1243-53. [PMID: 24250559]

[181] Amit T, Avramovich-Tirosh Y, Youdim MB, Mandel S. Targeting multiple Alzheimer's disease etiologies with multimodal neuroprotective and neurorestorative iron chelators. FASEB J 2008; 22(5): 1296-305. [http://dx.doi.org/10.1096/fj.07-8627rev] [PMID: 18048580]

[182] Loftis JM, Wilhelm CJ, Huckans M. Effect of epigallocatechin gallate supplementation in schizophrenia and bipolar disorder: an 8-week, randomized, double-blind, placebo-controlled study. Ther Adv Psychopharmacol 2013; 3(1): 21-7. [http://dx.doi.org/10.1177/2045125312464103] [PMID: 23983989]

[183] Lee B, Shim I, Lee H, Hahm DH. Effects of epigallocatechin gallate on behavioral and cognitive impairments, hypothalamic-pituitary-adrenal axis dysfunction, and alternations in hippocampal BDNF expression under single prolonged stress. J Med Food 2018; 21(10): 979-89. [http://dx.doi.org/10.1089/jmf.2017.4161] [PMID: 30273101]

[184] Abdel-Moneim A, Yousef AI, Abd El-Twab SM, Abdel Reheim ES, Ashour MB. Gallic acid and p-coumaric acid attenuate type 2 diabetes-induced neurodegeneration in rats. Metab Brain Dis 2017; 32(4): 1279-86. [http://dx.doi.org/10.1007/s11011-017-0039-8] [PMID: 28573601]

[185] Mustafa AM, Maggi F, Caprioli G, *et al.* Evaluation of neuritogenic activity of cultivated, wild and commercial roots of *Gentiana lutea* L. J Funct Foods 2015; 19: 164-73. [http://dx.doi.org/10.1016/j.jff.2015.09.018]

[186] Mustafa AM, Maggi F, Öztürk N, *et al.* Chemical and biological analysis of the by-product obtained by processing *Gentiana lutea* L. and other herbs during production of bitter liqueurs. Ind Crops Prod 2016; 80: 131-40. [http://dx.doi.org/10.1016/j.indcrop.2015.11.041]

[187] Oztürk N, Başer KH, Aydin S, Oztürk Y, Caliş I. Effects of *Gentiana lutea* ssp. *symphyandra* on the central nervous system in mice. Phytother Res 2002; 16(7): 627-31. [http://dx.doi.org/10.1002/ptr.998] [PMID: 12410542]

[188] Akileshwari C, Muthenna P, Nastasijević B, Joksić G, Petrash JM, Reddy GB. Inhibition of aldose reductase by *Gentiana lutea* extracts. Exp Diabetes Res 2012; 2012: 147965. [http://dx.doi.org/10.1155/2012/147965] [PMID: 22844269]

[189] Alam F, Shafique Z, Amjad ST, Bin Asad MHH. Enzymes inhibitors from natural sources with antidiabetic activity: a review. Phytother Res 2019; 33(1): 41-54. [http://dx.doi.org/10.1002/ptr.6211] [PMID: 30417583]

[190] Yang XD, Fang PF, Xiang DX, Yang YY. Topical treatments for diabetic neuropathic pain. Exp Ther Med 2019; 17(3): 1963-76. [PMID: 30783472]

[191] Darivemula S, Nagoor K, Patan SK, Reddy NB, Deepthi CS, Chittooru CS. Prevalence and its associated determinants of Diabetic Peripheral Neuropathy (DPN) in individuals having type-2 diabetes mellitus in rural South India. Indian J Community Med 2019; 44(2): 88-91. [PMID: 31333282]

[192] Rezaeiamiri E, Bahramsoltani R, Rahimi R. Plant-derived natural agents asdietary supplements for the regulation of glycosylated hemoglobin: A review of clinical trials. Clin Nutr 2019; pii: S0261-5614(19)30058-5.