Complementary and Alternative Medicine in Association with Type 2 Diabetes Mellitus

Pranati Chavan¹, Pushpa Karale², Pratibha Thaware³, Pranaya Misar⁴

¹Department of Pharm D, Shivilingeshwar College of Pharmacy, Almala, Latur, Maharashtra-413520, India; ²Department of Pharmacology, Swami Ramanand Teerth Marathwada University, Nanded- 431606, Maharashtra, India; ³Department of Pharmacognosy, Dagadojirao Deshmukh College of Pharmacy, Almala, Latur, Maharashtra-413520 India; ⁴Department of Pharmacology, Vilasrao Deshmukh Foundation, Latur, Maharashtra-413512, India.

ABSTRACT

Background: Type 2 Diabetes Mellitus is a clinical condition that is associated with energy metabolism, particularly carbohydrate and fat management in the organism. An increase in the prevalence of diabetic population and the association of decreasing patient compliance and medication adherence leads to prefer a new concept for the management of disease complications. The use of complementary and alternative medicine (CAM) has proved to be effective for controlling diabetes.

Objectives: The purpose of this review is to perform an overview of CAM use, to emphasize its importance for managing diabetic complications and to get outfits of CAM.

Discussion: A literature survey was done by using various articles related to CAM and Diabetes mellitus. The focus was kept on the frequency of CAM use, the methods they use, the factors related to the use of CAM, the sources of information about CAM treatment, and the effect of the method used for disease management.

Conclusion: This review concluded that CAM therapy found to have adept at reducing blood glucose, maintaining a healthy body, and relieving symptoms of DM. From the study, the relevance of CAM for managing Diabetic complications was verified and the future need to perform scientific researches on CAM use was analyzed.

Key Words: Complementary And Alternative Medicine, Type 2 Diabetes Mellitus, Neutraceuticals, Mind-body interventions, Health

INTRODUCTION

Type 2 Diabetes Mellitus is a disease condition that is linked to energy metabolism, particularly carbohydrate and fat management in the organism. In the last decades, there was an explosive increase in the number of people diagnosed with diabetes worldwide due to ageing as well as the increasing prevalence of obesity and physical inactivity. The total number of people with diabetes is projected to rise from 347 million in 2008 to 552 million in 2030 as per data. Although medical advancements are there, therapeutic outcomes are often unreachable. An unsatisfied population can shift to nontraditional medicine or further alternatives. Many professionals considered Complementary and alternative medicine as the best option for minimizing diabetic complications. Therefore, this study focuses mainly on complementary and alternative medicine utilization in diabetic complication management.

Complementary and alternative medicine

Complementary and alternative medicine (CAM) can be defined as an alternative health-care approaches besides mainstream Western, or conventional medicine. It reflects two words, “complementary” meaning used together with, and “alternative” meaning used in place of conventional medicine. As per the guidelines from National Center for Complementary and Alternative Medicine (NCCAM), Na-
tional Institutes of Health defines complementary and alternative medicine as “health care approaches with a history of use or origins outside of mainstream medicine.”

**Objectives**
The purpose of this review is

A) To present an overview of the use of complementary and alternative therapies in association with diabetes.
B) To emphasize the importance of CAM for the management of diabetes and reducing its complications.
C) To obtain the benefits of various therapies involved in CAM approaches.

**Categories**
As per the National Center for Complementary and Alternative Medicine, CAM therapies are broadly categorized into two main categories like I) Natural therapies and II) Mind-body intervention\(^1\-^3\).

**Natural therapy or biological-based therapies**
Certain conditions like infections, microvascular and macrovascular complications of diabetes may occur due to deficiencies of the microelements, vitamins, and nutrients. Such events can be minimized by the administration of these essentials. Vitamins and minerals proved helpful for the enhancement of the immune status of patients so they can easily overcome the clinical conditions. Biologically based therapies indicate substances coming from nature that includes herbs, essential oils, typical diet, nutritional and food supplements, and other products such as cartilage\(^20\).

The following are some findings obtained from natural therapy utilization for CAM significance and outcomes obtained from them as mentioned in table no.1.

**Table 1: Clinical trials showing CAM significance and outcomes**

| Neutropceuticals     | Clinical findings                                                                 |
|-----------------------|----------------------------------------------------------------------------------|
| **Vitamin A**         | Type 2 diabetics of elderly age group showed low plasma concentrations of vitamin A and carotenoids\(^4\), with lower carotene and higher RBP than controls, the study done by administering retinoic acid in diabetic mice has been shown to reduce RBP4 (Retinol binding protein 4), as well as the reduction in retinol to RBP4 ratio, and found to improve insulin sensitivity\(^29\). |
| **Vitamin B6**        | In humans, the combination of pyridoxine with thiamine has been shown to decrease DNA glycation in leukocytes of diabetic patients\(^3\). |
| **Niacin**            | Niacin administration in the diabetic population results in the reduction of monocyte adhesion to endothelial cells\(^4\). |

**Table 1: (Continued)**

| Neutropceuticals     | Clinical findings                                                                 |
|-----------------------|----------------------------------------------------------------------------------|
| **Biotin**            | A study on biotin and chromium picolinate supplementation that showed anti-diabetic effects in type 2 diabetic rats, and appear to prevent insulin resistance in skeletal muscle by an increase in the expression of the glucose transporter protein GLUT4\(^30\)\(^-\)\(^39\). |
| **Cyanocobalmine**    | In type 2 diabetes due to oxidative stress deficiencies of vitamin B12 and folic acid results in hyperhomocysteinemia\(^40\)-\(^45\), which may further result in peripheral neuropathy\(^40\)-\(^45\). |
| **Folate, Folic Acid or B9** | Folic acid level reduction in type 2 diabetest patient’s sound to be associated with vitamin B12 deficiency and consequent hyperhomocysteinemia. Supplementation of pyridoxine, folate, and vitamin B12 are also associated with the development of positive effects in diabetic retinopathy patients\(^40\). |
| **Vitamin C or Ascorbic Acid** | From the study Glycosylated haemoglobin, fasting, and postprandial blood glucose, and oxidative stress showed the inverse correlation with plasma vitamin C concentration. Vitamin C has also been shown to reduce anxiety levels in diabetes. Three-month supplementation of vitamins C and E decreases hypertension, blood glucose while increasing superoxide dismutase and glutathione levels\(^4\). |
| **Vitamin D**         | The expression of calbindin-D28K has demonstrated a protective effect on beta cells from cytokine-mediated cell death, reducing the risk of T2DM. |
| **Vitamin E**         | The effect of vitamin E on risk of diabetes and its complications is most probably due to its role as an antioxidant; a decrease in plasma tocopherol was noted in diabetic patients with chronic state relates to total cholesterol, central type obesity, lipid peroxidation, and cardiovascular complications. |
| **Vitamin K**         | Vitamin K affects insulin sensitivity, glucose metabolism in diabetes. |
| **Multivitamin**      | In the study of multivitamin effect in type 2 diabetes patients, the study population was administered with multivitamins and minerals for one year resulted in reduced incidence of infections in patients with subclinical micronutrient deficiency\(^4\). |

Data was obtained from articles showing Clinical trials conducted on herbs like Cinnamon [Cinnamomum verum], **Chavan et al.: Complementary and alternative medicine in association with type 2 diabetes mellitus**
bitter gourd [Momordica charantia], fenugreek [Trigonella foenum-graecum], Crepe Ginger [Costus speciosus] and ivy gourd [Coccinia grandis]. Clinical outcomes and mechanisms of the antidiabetic effect of these herbs were summarized and mentioned in Table no.2.

Table 2: Clinical outcomes and mechanisms of the antidiabetic effect of herbs

| Herb                           | The mechanism utilized in diabetest |
|--------------------------------|------------------------------------|
| Cinnamomum Verum/Cinnamon      | Cinnamon facilitates glucose entry into cells by increasing the amount of GLUT4 [Glucose transporter type 4] receptors, Insulin Receptor (IR), and Insulin Receptor substrate[α,γ]. Cinnamon increases the expression of PPAR [ Peroxisome proliferator-activated receptors] (alpha) and PPAR (gamma), that help to improve insulin sensitivity[α]. |
| Momordica charantia (MC) (Bitter gourd or bitter melon) | MC extract increases cellular glucose uptake by enhancing cellular insulin signalling pathways through up-regulation of GLUT 4 [Glucose transporter type 4] and P13K [Phosphoinositide 3-kinase], as well as up-regulating PPAR [ Peroxisome proliferator-activated receptors] gamma, MC preserves islet beta cells and has shown to stimulate glycogen storage by liver and insulin secretion by islets of Langerhans[γ]. |
| Trigonella foenum-graecum (Fenugreek) | Fenugreek helps diabetic patients by enhancing glucose uptake into the cells and also by stimulating the tyrosine phosphorylation of the insulin receptor[β]. |
| Costus speciosus (Crepe Ginger) | The Hypoglycemic effect was accompanied by an increased hepatic hexokinase activity and liver glycogen content in diabetic rats. |
| Coccinia grandis (Ivy gourd) | Pectin, isolated from the fruit of Coccinia grandis has hypoglycemic properties in rats[ε] by correcting elevated levels of glucose-6-phosphatase and lactate dehydrogenase [κ]. The plant extract found to increase activation of peroxisome proliferator-activated receptor-gamma activity [ε]. Triterpenes, isolated from Coccinia spp may have the ability to reverse beta-cell damage induced by Alloxan in experimental diabetic rats [ε]. |

**Mind-body therapies**

The therapies including holistic perspectives or mind body spirit evaluation techniques to enhance the mind’s ability to affect body functions and symptoms are known as mind-body therapies. Its broad category approach to be considered to include various therapies like visualization, guided imagination, progressive muscle relaxation, meditation, prayer, music therapy, light therapy, art therapy, journaling, storytelling, biofeedback, hypnosis, humour, animal-assisted therapy, tai chi, qigong, and yoga[20].

**Manipulative and body-based therapies**

Application of pressure for manipulation or movement of one or more body parts can be considered in this therapy. The following are some examples that can interpret the idea of manipulative and body-based therapies as chiropractic medicine, osteopathic manipulative medicine, movement therapy, and Rolfing i.e. a form of soft-tissue manipulation[20].

**Energy therapies**

This kind of complementary and alternative medicine works on the belief that a vital energy flows through the human body. They aimed to balance the energy flow in the patient by modification, manipulation, enhancement, and supporting the energy fields for reducing stress, anxiety, and promotion of well being[21]. Energy therapy can be known by various names as per various regions and by different countries and considered to work by light therapy or energy infusion therapy[1,22]. Energy therapies may include healing touch, therapeutic touch, Reiki, acupuncture or acupressure, and reflexology[1]. A data on randomized controlled trial in patients with diabetic peripheral neuropathy, foot reflexology resulted in a reduction of A1C and FPG, and improve pain scores along with nerve conduction velocity[39].

**Traditional Chinese Medicine**

Traditional Chinese medicine work as a holistic system consisting of a combination of natural medicines, massage therapy, diet changes, acupuncture, and some practices like breathing exercises, movement therapies, and mind stabilizing therapies[19].

**Systems of Care**

There are some categories of treatment which become distinct from other approaches of disease management that shows their work based on systems of care like homoeopathy, Ayurveda, Chinese medicine, a folk system of medicine and can be proved to be effective for improving the health status of the patients[1,21].

**Yoga**

Yoga consists of various exercises, asanas, and meditation. Yoga harmonizes the body with our mind and breath. It identifies one with different levels of consciousness and understanding resulting in gaining perspective and peace. Yoga interns proved to obtain a healthy mind and a healthy body. In the case of the diabetic population some studies on yoga
for reducing complications type 2 diabetes showed better effects of controlling glycemic levels, regulation of lipid and BP profile, again to reduce A1C, fasting, and postprandial glucose values.

**DISCUSSION**

An article among Non-Hispanic White, Mexican American, and Vietnamese American Type 2 Diabetic Patients on Complementary and Alternative Medicine (CAM) Use concluded that CAM use may result in improved diabetes management with long-term health outcomes as per race and ethnicity. It also reflected low levels of thiamine and increased renal clearance in both Type 1 and type 2 diabetic patients. Better clinical outcomes found to be obtained on thiamine supplementation among those patients.

The association between diabetes and bacterial infection has been recognized for many years. A prospective study showed a higher incidence of bacteremia in diabetic patients compared to non-diabetics. Surgical wound infection may also be associated with diabetes mellitus. In a study calculating rate of wound infection for total hip replacement surgeries among diabetic and nondiabetic populations with similar circumstances found to obtain a higher percentage for diabetic people and a very low fraction for non-diabetics. In the study i.e. Effect of Antioxidants and B-Group Vitamins on Risk of Infections in Patients with Type 2 Diabetes Mellitus, the provision of nutrient supplementation to diabetic subjects was done and improvement in the disease-related complications was noted. In some studies relating to vitamin D and chronic inflammatory status of T2DM patients, outcomes helped to conclude that vitamin D acts on inflammatory mediators and modulates the effects of mediators like cytokines and nuclear transcription factors such as NF-κB. This results in improving insulin sensitivity and promoting pancreatic β-cell survival.

Studies on Systems like yoga, tai chi showed an effect on glycemic control in people with type 2 diabetes and in lowering A1C levels.

In a preclinical study for outcomes of nutrient therapy for the management of diabetes, it was reported that external supplementation like Calcium, zinc, chromium, magnesium, vitamins found to increase insulin sensitivity, reduced vascular resistance and induced partial regurgitation, increased HbA1c, fasting glucose and insulin level, decreased lipid peroxidation, reduction in serum triglycerides, and VLDL reduction in type 1 and type 2 diabetes.

**CONCLUSION**

Total of 18 articles relating to complementary and alternative medicine was included in the study, out of which 4 reviews found to be showing the significance of CAM for the reduction of blood glucose level, improving insulin utility, and minimizing diabetic complications. One preclinical study on diabetic rats indicates Diagnostic parameters improved in MVT treated male rats but not in streptozocin treated female rats. In another prospective observational study, varying rates of CAM use were analyzed. A descriptive cross-sectional study containing differential statistical questionnaires came with outcomes as Herbs proved to be effective for reducing blood glucose, maintaining a healthy body, and relieving symptoms of DM. As such numbers of studies were taken into consideration for finding the beneficial outcomes for utilization as well as finding safety parameters of CAM for managing diabetic complications. Some of which are shown in table no 3.

**Table 3: Different clinical trials showing CAM significance in the diabetic population**

| Articles          | Type of study       | Study parameters                           | Clinical outcomes                                                                 |
|-------------------|---------------------|--------------------------------------------|----------------------------------------------------------------------------------|
| Uslu et al. 2018, 71 | Review              | CAM for children with T1DM                | Use of CAM reduces diagnosis duration, lowers blood glucose level, improves insulin utility, minimizes diabetic complications |
| Sarkozy et al. 2014, 14:72 | Preclinical case-control study | MVT administration in diabetic rats        | Diagnostic parameters improved in MVT treated male rats but not in streptozocin treated female rats |
| Khalaf et al. 2010, 10:35 | Prospective observational study | CAM use for Diabetes                      | High rates of CAM users for managing diabetes                                        |
| Niswah et al. 2014 | A descriptive, cross-sectional study | Differential statistical questionnaire for herb use | Herbs proved to be effective for reducing blood glucose levels, maintaining proper health, and relieving symptoms of DM |
| Medagama et al. 2014, 13:102 | Review              | Cinnamon, bitter guard, fenugreek, crepe ginger, ivy guard as a CAM | Effects of 5 CAM for minimizing diabetic complications |

19. Chavan et al. Complementary and alternative medicine in association with type 2 diabetes mellitus
**Table 3: (Continued)**

| Articles | Type of study | Study parameters | Clinical outcomes |
|----------|---------------|------------------|-------------------|
| Debra Kramlich. 2014, 6 | Research article | CAM use and significance | To emphasis the benefits of nonpharmacologic therapies for critically ill patients |
| L.D. Grossman et al. 2018, 42 | Case-control study | NHP and CAM | Reduction of co-morbidities and complications of diabetes, including lipids and blood pressure (BP) in diabetes, as well as CVD, nephropathy, retinopathy and peripheral neuropathy |
| Valdes Ramos et al. 2015, 15 | Review | Vitamins and Type 2 Diabetes Mellitus | Neutrophueuticals shows effectiveness for management of C-reactive protein, HDL cholesterol, triacylglycerides, serum Homocysteine, blood pressure and incidence of diabetes |
| Nguyen et al. 2014, 25(4) | California Health Interview Survey | CAM | CAM use may influence diabetes management behaviours |
| Salah Gariballa et al. 2013, 5 | Randomized trial | Dietary supplementation | Need to do more clinical studies for better clinical outcomes |
| Ghulam Jilany Khan et al. 2014, 21(6) | A cross-sectional, inter-view-based survey | CAM | CAM can be used for disease management |

**CONCLUSION**

This study focuses on complementary and alternative medicine, its significance, and utilization for minimizing diabetic complications. As per the data collected from various articles CAM therapy proved beneficial for the diabetic population by various mechanisms. CAM therapies include natural therapies like Yoga, mind-body intervention, energy therapy, reiki, tai chi, behavioural therapies, and utilization of natural medicines like herbs, vitamins, minerals, nutrients for disease management. CAM therapy shows its significance not only on disease outcomes but also improves the patient’s physical, psychological, and social health. CAM utilization in type 2 diabetes was found to be associated with the reduction of plasma glucose levels, it also helps by maintaining HbA1c, improving insulin sensitivity, and again it can minimize comorbid states by maintaining biological markers and improves the health status of the patient.

This review concluded that CAM therapy found to have adopt at reducing blood glucose, maintaining a healthy body, and relieving symptoms of DM. From the study, the relevance of CAM for managing Diabetic complications was verified and the future need to perform scientific researches on CAM use was analyzed.

**Acknowledgement:** Authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors / editors / publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed.

**Conflict of interest:** None

**Source of funding:** None

**REFERENCES**

1. National Center for Complementary and Alternative Medicine. Complementary, alternative, or integrative health: what’s in a name? National Institutes of Health. http://nccam.nih.gov/health/whatiscam?nav=gsa. 2008
2. Cuellar NG. Conversations in Complementary and Alternative Medicine: Insights and Perspectives from Leading Practitioners. Sudbury, MA: Jones and Bartlett Publishers 2006.
3. Snyder M, Lindquist R. Complementary & Alternative Therapies in Nursing. New York, NY: Springer Publishing Co 2010: 6.
4. Roxana VR, Guadarrama-López AL, Martínez-Carrillo BE, Benítez-Arciniega AD. Vitamins and Type 2 Diabetes Mellitus, Endocrine, Metabolic & Immune Disorders - Drug Targets 2015; 15, 54-63.
5. Zimmet P, Alberti KGMM, Jonathan S. Global and societal implications of the diabetes epidemic. Nature 2001; 414:782–787.
6. Astrup A, Finer N. Redefining type 2 diabetes: ‘diabesity’ or ‘obesity dependent diabetes mellitus’. Obes Rev 2000;1: 57–59.
7. Danaei G, Mariel MF, Yuan Lu, Singh GM, Melanie JC, Christopher JP, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet 2011;378: 31–40.
8. Whiting DR, Leonor G, Clara W, Jonathan S. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011;94: 311–312.
9. Farvid MS, Mahmoud J, Fereydoun S, Mostafa H. Comparison of the effects of vitamins and/or mineral supplementation on glomerular and tubular dysfunction in type 2 diabetes. Diabetes Care 2005;28: 2458–2464.
10. Kohda Y, Hisashi S, Kazahtoko Y, Kaoru O, Tatsuji K, Fumio T, et al. Prevention of incipient diabetic cardiomyopathy by high dose thiamine. J Toxicol Sci 2008;33: 459–472.
11. Chen H, Rajaram JK, Gail H, Umberto C, Julio AP, Richard OC, et al. High-dose oral vitamin C partially replenishes vitamin C levels in patients with Type 2 diabetes and low vitamin C levels but does not improve endothelial dysfunction or insulin resistance 2006; 290:H137–H145.
12. Takuya K, Hirooka Y, Akihiro M, Koji I, Yoshikuni K, Kosuke I, et al. Vitamin C improves attenuated angiotensin II-induced endothelium-dependent vasodilation in human forearm vessels. Hypertens Res 2003;26: 953–959.

13. Von Hurst PR, Welma S, Jane C. Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient a randomized, vehicle-controlled trial. Br J Nutr 2010;103: 549–555.

14. Upritchard JE, Wayne HJ, Jim IM. Effect of supplementation with tomato juice, vitamin E, and vitamin C on LDL oxidation and products of inflammatory activity in type 2 diabetes. Diabtes Care 2000;23: 733–738.

15. Zemel MB, Zemel PC, Bryg RJ, Sowers JR. Dietary calcium induces regression of left ventricular hypertrophy in hypertensive non-insulin-dependent diabetic blacks Am J Hypertension. 1990;3: 485–486.

16. Guerrero-Romero F, Rodriguez-Moran M. The effect of lowering blood pressure by magnesium supplementation in diabetic hypertensive adults with low serum magnesium levels: a randomized, double-blind, vehicle-controlled clinical trial. J Hypertens 2009;23: 245–251.

17. Blostein FA, DiSilvestro RA, Frid D, Katz C, Malarkey W. Short-term zinc supplementation in women with non-insulin-dependent diabetes mellitus: effects on plasma 5'-nucleotidase activities, insulin-like growth factor I concentrations, and lipoprotein oxidation rates in vitro. Am J Clin Nutr 1997;66: 639–642.

18. Anderson RA, Cheng N, Bryden NA, Polansky MM, Cheng N, Chi J, et al. Elevated intakes of supplemental chromium improve glucose and insulin variables in individuals with type 2 diabetes. Diabetes 1997;46: 1786–1791.

19. Loren D, Robert R, Anita R. Complementary and Alternative Medicine for Diabetes. Diabetes Canada Clinical Practice Guidelines Expert Committee, Clinical Practice Guidelines, Can J Diabetes 2018;42; S154–S161.

20. Debra Kramlich. Introduction to Complementary, Alternative, and Traditional Therapies, Critical Care Nurse 2014;34(6).

21. Snyder M, Lindquist R. Complementary and Alternative Therapies in Nursing. New York, NY: Springer Publishing Co 2010; 6.

22. Crino A, Masao K, Yoshiaki T, Yuku C, Toshihiro T, MAO Ji, et al. A two-year observational study of nictotnamide and intensive insulin therapy in patients with recent-onset type 1 diabetes mellitus. J Pediatr Endocrinol Metab 2005;18: 749–754.

23. Fontaine KL. Complementary and Alternative Therapies for Nursing Practice. Upper Saddle River, NJ: Pearson Prentice Hall 2005; 2.

24. Hannah N, Darla HS, John B, Sherrrie HK, Sheldon G, Quyen NM. Complementary and Alternative Medicine (CAM) Use among Non-Hispanic White, Mexican American, and Vietnamese American Patients with Type 2 Diabetes, November 2014;25(4): 1941–1955.

25. Bryan CS, Reynolds KL, Metzger WT. Bacteremia in diabetic patient’s comparison of incidence and mortality with nondiabetic patients. Diabet Care 1985;8: 244–249.

26. Delamaire M, Maugendre D, Moreno M, Goff MC, Allannic H, Genetet B. Impaired leucocyte functions in diabetic patients. Diabetic Medicine 1997;14: 29–34.

27. Salah G, Bachar A, Mamoon AH, Javed Y, Awad A. Effect of Antioxidants and B-Group Vitamins on Risk of Infections in Patients with Type 2 Diabetes Mellitus, Nutrients 2013;5, 711-724.

28. Seshadri KGT and Rajendran BA. Role of Vitamin D on Diabetes. J. Endocrinol. Metab 2011;1(2), 47-56.

29. Smolek MK, Notaroberto NF, Jaramillo AG, Pradillo LR. Intervention with vitamins in patients with nonproliferative diabetic retinopathy: a pilot study. Clin Ophthalmol 2013;7, 1451-1458.

30. Sahin K, Mehmet T, Cemal O, Nurhan S, Osman K, Ibrahim HO, et al. Anti-diabetic activity Of chromium picolinate and biotin in rats with type 2 diabetes induced by high-fat diet and streptozotocin. Br. J. Nutr 2013;110(2), 197-205.

31. Yuka S, Hideyuki S, Shin K, Muneshige S, Hitoshi S, Yasuo K et al. Administration of biotin prevents the development of insulin resistance in the skeletal muscles of Otsuka Long-Evans Tokushima Fatty rats. Food Funct 2012;3(4), 414-419.

32. Manolescu DC, Aurelia S, Pangala VB. All-trans retinoic acid lowers serum retinol-binding protein 4 concentrations and increases insulin sensitivity in diabetic mice. J. Nutr 2009;140(2), 311-316.

33. Tijpto BW. Effectiveness of acupuncture as adjunctive therapy for diabetes mellitus: A randomized controlled trial. Med Acupunct 2014;26:341–5.

34. Lee MS, Jun JH, Lim HJ, Lim HS. A systematic review and meta-analysis of tai chi for treating type 2 diabetes. Maturitas 2015;80:14–23.

35. Yan JH, Gu WJ, Pan L. Lack of evidence on Tai Chi-related effects in patients with type 2 diabetes mellitus: A meta-analysis. Exp Clin Endocrinol Diabetes 2013;121: 266–71.

36. Wandell PE, Arnlov J, Andrenasson AN, Andersson K, Tornkvist L, Carlsson AC. Effects of tactile massage on metabolic biomarkers in patients with type 2 diabetes. Diabetes Metab 2013;39: 411–17.

37. Andersson K, Wandell P, Tornkvist L. Tactile massage improves glycemic control in women with type 2 diabetes: A pilot study. Pract Diabetes Int 2004;21: 105–9.

38. Wandell PE, Carlsson AC, Andersson K, Gafvels C, Tornkvist L. Tactile massage or relaxation exercises do not improve the metabolic control of type 2 diabetics. Open Diabetes J 2010;3: 6–10.

39. Dalal K, Maran VM, Pandey RM, Tripathi M. Determination of efficacy of reflexology in managing patients with diabetic neuropathy: A randomized controlled clinical trial. Evid Based Complement Alternat Med 2014;843036.

40. Cao H, Polansky MM, Anderson RA. Cinnamon extract and polyphenols affect the expression of tristetraprolin, insulin receptor, and glucose transporter 4 in mouse 3T3-L1 adipocytes. Arch Biochem Biophys 2007;459(2):214–222.

41. Bolin Q, Masaru N, Ming R, Gustavo B, Yoshiharu O, Yuzo S. Cinnamon extract (traditional herb) potentiates in vivo insulin-regulated glucose utilization via enhancing insulin signalling in rats. Diabetes Res Clin Pract 2003;62(3):139–148.

42. Sheng X, Zhang Y, Gong Z, Huang C, Zang YQ. Improved insulin resistance and lipid metabolism by cinnamon extract through activation of peroxisome proliferator-activated receptors. PPAR Res 2008;581348:9.

43. Ahmed I, Lakhani MS, Gillett M, John A, Raza H. Hypotriglyceremic and hypocholesterolemic effects of anti-diabetic Monodormica charantia (karela) fruit extract in streptozotocin-induced diabetic rats. Diabetes Res Clin Pracet 2001;51: 155–161.

44. Yibchokanun S, Adisakkattana S, Yao CY, Sangvanich P, Roengsumran S, Hsu WH. Slow acting protein extract from the fruit pulp of Momordica charantia with insulin secretagogue and insulin-mimetic activities. Biol Pharm Bull 2006;29(6):1126–1131.

45. Vijaykumar MV, Singh S, Chhipa RR, Bhat MK. The hypoglycemic activity of fenugreek seed extract is mediated through the stimulation of an insulin signalling pathway. Br J Pharmacol 2005;146:41–48.

46. Kuriyan R, Rajendran R, Bantwal G, Kurpad AV. Effect of supplementation of Coccinia cordifolia extract on newly detected diabetic patients. Diabetes Care 2008;31(2):216–220.
47. Kamble SM, Kamlakar PL, Vaidya S, Bambole VD. Influence of Coccinia indica on certain enzymes in glycolytic and lipolytic pathway in human diabetes. Indian J Med Sci 1998;52(4):143–146.

48. Sato M, Tai T, Nunoura Y, Yajima Y, Kawashima S, Tanaka K. Dehydrotrametenolic acid induces preadipocyte differentiation and sensitizes animal models of non-insulin-dependent diabetes mellitus to insulin. Biol Pharm Bull 2002;25(1):81–86.