Original Research Paper

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CONTROL OF BLOOD GLUCOSE LEVEL AND GLYCATED HAEMOGLOBIN (HbA1C) WITH DIETARY JACKFRUIT MEAL TAKEN BY TYPE II DIABETIC PATIENTS

General Surgery

KEYWORDS: Diabetes mellitus, *Artocarpus heterophyllus*, Jack fruit, Antidiabetic activity, HbA1c

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ABSTRACT

Objective: The study was conducted to assess the anti-diabetic effect of the medicinal plant *Artocarpus heterophyllus* raw fruit meal preparation in type II Diabetes mellitus patients of South Kerala, India.

Methods: Type II Diabetes mellitus patients selected for the study were grouped into control group (18) and experimental group (18) whose blood sugars were not under control. HbA1c level was checked for both the groups and patients having HbA1c level above 6.5% were selected for the study. Patients were instructed to continue their regular medicines and lifestyle modification. Experimental group was given "Chakka Aviyal" as side dish with lunch for three months. Their daily calorie intake was adjusted by reducing the quantity of other food items by 97 calories which was approximate caloric value of our preparation to match with the control. In both groups monthly FBG and PBG, and 4 monthly HbA1c levels were monitored.

Result: For the experimental group, the mean pre test-post test difference of HbA1c was -1.29 ± 1.93 which showed an average reduction in HbA1c level. For the control group the mean difference of HbA1c was 0.65 ± 1.06, suggestive of increase in HbA1c level. Changes in HbA1c level in both the cases were significant with a p value of <0.001.

Conclusion: The findings concluded that dietary supplementation of the *Artocarpus heterophyllus* raw fruit meal preparation has an impact in reducing type 2 diabetes. This was a pilot study on anti-diabetic effect and this should be further extended with long term analysis.

Introduction

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia resulting from defects in insulin action, insulin secretion or both. The most common type of diabetes mellitus is type 2 diabetes mellitus, which accounts for 85 to 95% of all cases and constitutes a major public health problem[1].

With regard to Diabetes, symptoms that included polyuria and polydipsia were described in the Egyptian *Ebers papyri*, Greek Epidemics Book III of Hippocrates, and the Chinese Nei Ching[2,3]. Hindu writings in the Ayurvedic texts used these same symptoms and others including glucosuria and the smell of acetone in breath to differentiate between two main types of Diabetes mellitus: One inherited and another acquired through obesity[4]. Recorded treatments for these disorders included largely diet and plant-based remedies[5].

Plants have been suggested as a rich, source of potentially useful antidiabetic drugs[6]. There is widespread use of herbal dietary supplements that are believed to benefit type 2 diabetes mellitus[7]. Scientific investigations have confirmed the efficacy of many of these preparations, some of which are remarkably effective[8,9]. Human and animal trials have been done for the seeds of the herb *Trigonella foenum-graecum* L. (fenugreek) which lowered blood glucose and cholesterol levels[10,11,12,13,14]. Oral administration of extract, fruit juice and seed powder of *Momordica charantia* (Bitter gourd) reduced blood glucose and improved glucose tolerance in normal and diabetic animals and in humans[15,16,17,18,19,20,21].

Rats induced with Streptozotocin (STZ) were commonly used in experimenting anti-hyperglycemic effect of dietary supplements. Aged garlic extract (*Allium sativa bulbus*) was tested in STZ-induced diabetic rats[22] and Alloxan-induced diabetic rabbits[23]. The extract of *Murraya koenigii* (curry leaves) leaves showed hypoglycemic activity in normal and Alloxan-induced diabetic rabbits[24]. Experimental diabetic-rats also proved anti-hyperglycemic effect in the dietary supplements of herbs such as leaves of *Psidium guajava* (Guava)[25], dried herbal drink of *Prunella vulgaris* L (self-heal)[26] and male abortive flowers of *Punica granatum*[27]. Researchers confirmed that the water decoction of *Dioscorea opposite*[28] and *Mangifera indica*[29] have anti-hyperglycemic effect to experimental diabetic mice.The rhizomes of *Curcuma longa* L. (turmeric), has been reported to possess anti-diabetic properties in experimental animal models[30]. Hou *et al.*[31] conducted a meta-analysis to study the effect of garlic intake in humans in lowering glucose levels. Results showed that administration of garlic resulted significant reduction in FBG concentrations while effectiveness of garlic on HbA1c and PPG were not proven.

The tree, *Artocarpus heterophyllus* Lam. is an integral part of common Indian diet and is freely available in Indian sub-continent. The plant is reported to possess antibacterial, anti-inflammatory, anti-diabetic, anti oxidant and immunomodulatory properties[32]. Hot water extract of mature jack leaves is recommended by Ayurvedic and traditional medical practitioners as a treatment for Diabetes mellitus[33]. It is already indicated that an extract of *Artocarpus heterophyllus* improves the glucose tolerance in normal human subjects and diabetic patients[34]. The leaves and stem show the presence of sapogenins, cycloartenone, cycloartenol, ß-sitosterol, and tannins[35].

The extracts of jack fruit could inhibit the glycation of haemoglobin (HbA1c) which may be caused by the presence of phytochemical constituents such as ascorbic acid, β-carotene and lycopene[36]. A random cross over design was carried out to study the nutrient compositions of cooked jackfruit meals. Results showed rich starch and dietary fibre content in seeds of jackfruit. The meal is categorized as a low glycaemic index (GI) meal. The low GI could be due to the collective contributions from dietary fibre, slowly available glucose and un-gelatinised starch granules in the seeds[37].

Many TCM/TIM (Traditional Chinese Medicine (TCM) and Traditional Indian Medicine (TIM)) possess anti-diabetic activities. The oral efficacy and safety profiles, nutritional supplement status, low cost, and easy access of TCM/TIM herbs such as ginseng, mulberry, and *Radix coptidis* could lead them as excellent candidates for long-term use for the prevention and treatment of Type 2 diabetes[38]. The present study was made to investigate the anti-diabetic activity of raw *Artocarpus heterophyllus* (Jackfruit) meal preparation in patients with Type 2 Diabetes mellitus. The study is also aimed to quantitatively evaluate the effect of the raw *Artocarpus heterophyllus* fruit preparation on glycemic control measurements such as Fasting Blood Glucose, Postprandial Blood Glucose and Glycated Haemoglobin levels.

Methods

Sampling

Blood samples of Type II Diabetes mellitus patients (T2DM) within

an age group of 30 to 70 years were collected in Saraswathy hospital, Parassala for analyses. Totally 36 T2DM patients were selected for the study 18 patients were maintained as control and 18 were experimental patients.

Eligibility Criteria

The inclusion and exclusion criteria of selection of patients were listed under; Inclusion criteria: Diabetic for > 5 years, Treatment with insulin and/or OHA, HbA1c of > 6.5%, Urea level of 20-40mg/dl and Creatinine 0.6-1mg/dl and Willingness of patients was also taken into account. Exclusion criteria: Critically ill and patients with gastro paretic symptoms were not selected for study.

Study Variables

Data collection was done through interviews and lab investigations. Demographic profile with age, gender, duration of illness and type of treatment were gathered from patients based on interview method. Laboratory results like HbA1c level, the monthly level of FBG and PBG were also obtained.

Artocarpus heterophyllus fruit meal preparation

Raw jack fruit (*Artocarpus heterophyllus*) of 100g was used for the preparation. 20 g of coconut (*Cocos nucifera*) was scrapped and half tea spoon turmeric powder (*Curcuma longa*), 3 or 4 Shallots (*Allium cepa*), 3 to 4 green chillies (*Capsicum annum*), 2 to 3 garlic cloves (*Allium sativa*),1 spring curry leaves (*Murraya koenigii*) and a pinch of table salt (Sodium chloride) were grinded and mixed well. The flesh in the raw fruit of *Artocarpus heterophyllus* was removed and boiled with 100 ml water under high heat for 10 minutes. All the other ingredients were added and kept under low heat until all the water was removed. The nutritional value of 100g of raw *Artocarpus heterophyllus* flesh was also evaluated.

Data Extraction and Outcome measure

HbA1c level was checked and noted for both control and experimental groups. The experimental group was given 100 g of *Artocarpus heterophyllus* fruit meal preparation at lunch. The study was performed for 4 months where data were collected once in every month. The calorie intake in the experimental group was adjusted to be equal to that of control group by reducing 97 calories in other food items which is the calorific value of the jackfruit meal.

The outcome measure in both control and experimental groups were FBG and PBG which were recorded and HbA1c was done before and four months after the study.

Ethical Clearance

The ethical committee was provided with the consent obtained from the patients and ethical clearance was obtained from Institute Ethics Committee (IEC) (IEC No. 102/15).

Results

I. Glycemic Control

Changes in HbA1c (Glycosylated haemoglobin) Level

The mean post and pre-test difference of HbA1c in experimental group was noted as -1.29 ±1.93 which showed an average reduction in Glycated Haemoglobin level. The control group measured 0.65 ±1.06 HbA1c (Figure 1). The change in the Glycated Haemoglobin levels in control and experimental groups were subjected to statistical analysis and were found to be significant (p value <0.001).

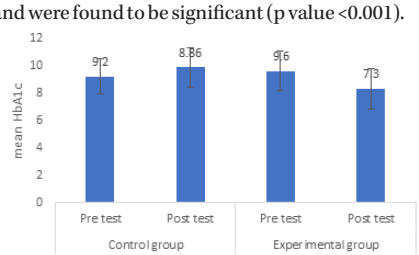

Fig. 1: Comparison of HbA1c levels of control and experimental group

Changes in FBG (Fasting Blood Glucose)

The fasting blood glucose levels were observed every month for both control and experimental group of T2DM patients. Mean of all 18 patients in each group were determined and the levels were plotted in figure 2. First month readings of experimental group supplemented with the prepared diet showed 159.88±44.98 which was reduced significantly to 124.72±16.25 in the fourth month of study.

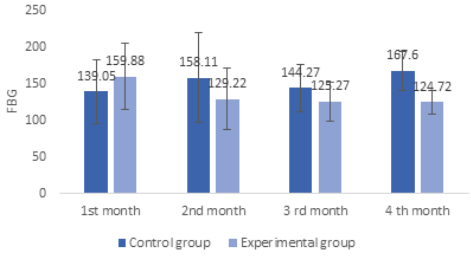

Fig. 2: Comparison in levels of FBG of control and experimental group

Changes in PPG (Postprandial Glucose)

The PPG level reduced in experimental group from 214.27±70.25 to 161.55±33.32 during a period of four months of observation (Figure 3). Average of all control patients showed an increase in postprandial glucose level which is tabulated (Table 1).

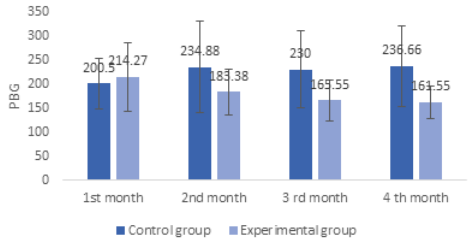

Fig. 3: Comparison in levels of PBG of control and experimental group

Table.1 Study variables at baseline and after intervention period

Variables	Control	Experimental		
	Pre test	Post test	Pre test	Post test
HbA1c	9.2±1.28	8.86±1.47	9.6±1.42	7.3±1.47
FBG	139.05±43.01	167.16±26.42	159.88±44.98	124.72±16.25
PBG	200.5±53.41	236.66±83.76	214.27±70.25	161.55±33.32

II. Chemical composition of 100g raw fruit of Artocarpus heterophyllus

The nutritive elements like energy, carbohydrate, protein, fat, fibre, vitamins and minerals were quantified in 100 g of raw fruit of *Artocarpus heterophyllus* and are listed in table 2. The dietary fibre, which can help managing type 2 diabetes was recorded as 1.5 g.

Table.2 Nutritional value per 100 g (3.5 oz) of *Artocarpus heterophyllus* fruit

Energy – 95 kcal Carbohydrates – 19.08 g Dietary Fibre – 1.5 g Fat – 0.64 g Protein – 1.72 g	**Vitamins** Vitamin A equiv – 5 µg B- Carotene – 61 µg Lutein zeaxanthin – 157 µg Thiamine (B1) – 0.105 mg Riboflavin (B2) – 0.055 mg Niacin (B3) – 0.92 mg Pantothenic acid (B5) – 0.235 mg Vitamin B6 – 0.329 mg Folic acid (B9) – 24 µg Vitamin C – 13.8 mg Vitamin E – 0.34 mg	**Minerals** Calcium – 24 mg Iron – 0.23 mg Magnesium – 29 mg Phosphorus – 21 mg Potassium – 448 mg Sodium – 2mg Zinc – 0.13 mg

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Discussion

Table 1 shows the fasting blood glucose, post prandial glucose and HbA1c variables and corresponding differences of these variable for normal group and the *Artocarpus heterophyllus* fruit diet preparation consumed experimental group. All the three variables of the experimental group were significantly reduced after the intervention compared with the baseline values. The glycated haemoglobin level HbA1c was significant with a p value of 0.001. The observations were made withnormal medication, hence significant increase in blood glucose level was noted in control group of diabetic patients.HbA1c of 6.5% is recommended as the cut off point for diagnosing diabetes.A value less than 6.5% does not exclude diabetes diagnosed using glucosetests. The expert group concluded that there is currently insufficient evidenceto make any formal recommendation on the interpretation of HbA1c levelsbelow 6.5%[39]. Hence for the present study, the patients having HbA1c level above 6.5% were selected.

Our results show that consuming 100 g of the *Artocarpus heterophyllus* fruit meal preparation per day for four months lead to quantitative reduction in FBG, PBG and HbA1c compared with the baseline. The HbA1c decreased by 13.59%, FBG by 22.68% and PBG also decreased by 25.69%.The present observations were made for a period of four months. A study by Hahm*et al.*[40]was done using stem of *Opuntia humifusa* in which the stem was suspended in distilled water and administered orally for 7 weeks and significant reduction in fasting blood glucose and triglyceride levels were observed with a p value < 0.05.

The reduction in blood glucose were observed only in experimental group of Diabetic mellitus patients while the control group patients showed significant increase in blood glucose level. The observed reduction in HbA1c in the present study was found to be more than in a similar study of cinnamon supplementation where the glycated haemoglobin reduced by 6.12%[41]. A meta-analysis also proved the efficacy of cinnamon improving FBG and HbA1c in diabetic patients[42,43]. Hou*et al.*[31] shows an overall decrease of 95% of FBG in a pooled analyses of garlic intake by T2DM patients.

In majority of cases, type 2 diabetes could be prevented by the adoption of a healthier lifestyle[44]. The nutritive supplementation has been considered as the cheap and effective method in controlling T2DM[45]. A research with 150 diabetic patients was conducted to study the dietary supplementation of T2DM patients with minerals, vitamins, dietary fibre and fatty acids. It was reported that highest percentage of patients took magnesium and B group vitamins while insufficient intake of K, Ca, Mg, Vitamin E, folic acid, Vitamin D were assessed[45].The daily calorie intake in the experimenting patients in the present study were adjusted to 385 calories. The nutritive value of the dietary supplement prepared for the present analysis has been monitored and tabulated (Table 2). *Artocarpus heterophyllus*fruit preparation has sufficient quantity of energy, carbohydrates, fat and protein. The dietary fibre content is an important factor to control blood glucose level and was found to be rich in the fruit of the medicinal plant *Artocarpus heterophyllus.* Eleven types of essential vitamins including folic acid and vitamin E, minerals were also found to be the added nutritive value of the fruit.

Conclusion

From the findings above, it is proven that the *Artocarpus heterophyllus* meal preparation reduces blood sugar in T2DM patients. The limitations of the study include the smaller sample size and short duration (4 months) of study. Hence the study should be extended with more number of patients with large scale clinical trials to confirm the safety and efficacy of *Artocarpus heterophyllus* fruit preparation.

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Conflict of interest

No conflict of interest.

References

1. Cheplick S, Kwon YI, Bhowmik P, Shetty K. Phenolic linked variation in strawberry cultivars for potential dietary management of hyperglycemia and related complications of hypertension. BioresourTechnol2010; 101: 404-413.
2. Rezabek KM. Medical nutrition therapy in type 2 diabetes. NursClin North Am 2001; 36: 203-16.
3. Cheung BM. The Cardiovascular Continuum in Asia-A New Paradigm for the Metabolic Syndrome. J Cardiovasc Pharmacol 2005; 46: 125-9.
4. Vuksan V, Sievenpipera LJ. Herbal remedies in the management of diabetes: Lessons learned from the study of ginseng. Nutr Metab Cardiovasc Dis 2005; 15: 149-60.
5. Cheng JT. Review: Drug therapy in Chinese traditional medicine. J Clin Pharmacol 2000; 40: 445-50.
6. Mukherjee PK, Maiti K, Mukherjee K, Houghton PJ. Leads from Indian medicinal plants with hypoglycemic potentials. J Ethnopharmacol 2006;106: 1-28.
7. Manaharan T, Palanisamy UD, Ming CH. Tropical Plant Extracts as Potential Antihyperglycemic Agents.Molecules 2012;17: 5915-5923.
8. Ali H, Houghton PJ, Soumyanath. A. Alpha-amylase inhibitory activity of some Malaysian plants used to treat diabetes; with particular reference to Phyllanthus amarus. J Ethnopharmacol 2006;107: 449-455.
9. Saha S, Verma R. Inhibitory potential of traditional herbs on amylase activity. Pharm Biol2012; 50: 326-331.
10. Khosla P, Gupta DD, Nagpal RK. Effect of Trigonellafoenumgraecum (Fenugreek) on blood glucose in normal and diabetic rats. Indian J PhysiolPharmacol 1995;2: 173-174.
11. Puri D, Prabhu KM, Murthy PS. Hypocholesterolemic effect of the hypoglycemic principle of fenugreek (Trigonellafoenumgraecum) seeds. Indian J ClinBiochem 1995;9: 13-16.
12. Puri D, Prabhu KM, Murthy PS. Mechanism of action of a hypoglycemic principle isolated from fenugreek seeds. Indian J PhysiolPharmacol 2002;4: 457-462.
13. Gupta A, Gupta R, Lal B. Effect of Trigonellafoenum-graecum (fenugreek) seeds on glycaemic control and insulin resistance in type 2 Diabetes mellitus: A double blind placebo controlled study. J Assoc Physicians India 2001;49: 1057-1061.
14. Vats V, Grover JK, Rathi SS. Evaluation of anti-hyperglycemic and hypoglycemic effect of Trigonellafoenum-graecum Linn, Ocimum sanctum Linn and Pterocarpusmarsupium Linn in normal and allox- anized diabetic rats. J Ethnopharmacol 2002;79: 95-100.
15. Raman A, Lau C. Anti-diabetic properties and phytochemistry of Momordicacharantia L. (Cucurbitaceae) Phytomed 1996;2: 349-62.
16. Miura T, Itoh C, Iwamoto N, Kato M, Kawai M, Park SR, et al. Hypoglycemic activity of the fruit of the Momordicacharantia in type 2 diabetic mice. J NutrSciVitaminol(Tokyo) 2001;47: 340-344.
17. Fan YL, Cui FD. Comparative studies on hypoglycemic activity of different sections of Momordicacharantia L. J Shenyang Pharm Univ 2001;18: 50-53.
18. Srivastava Y, Venkatakrishna-Bhatt H, Verma Y, Venkaiah K, Raval BH. Antidiabetic and adaptogenic properties of Momordicacharantia extract: An experimental and clinical evaluation. Phytother Res 1993;7: 285-289.
19. Ahmed I, Lakhani MS, Gillett M, John A, Raza H. Hypotriglyceridemic and hypocholesterolemic effects of anti-diabetic Momordicacharantia (karela) fruit extract in streptozotocin-induced diabetic rats. Diabetes Res ClinPract 2001;51: 155-161.
20. Ooi CP, Yassin Z, Hamid TA. Momordicacharantia for type 2 Diabetes mellitus. Cochrane Database Syst Rev2010;2:CD007845.
21. Wang F, Zhang PP, Yu XF. A clinical observation of type 2 diabetes treated by saponins from MomordicacharantiaL. PractClin J Integrated Tradit Chin West Med 1991;4:721.
22. Liu CT, Hse H, Lii CK, Chen PS, Sheen LY. Effects of garlic oil and diallyltrisulfide on glycemic control in diabetic rats. Eur J Pharmacol 2005;516: 165-173.
23. Mathew PT, Augusti KT. Studies on the effect of allicin (diallyl disulphide-oxide) on alloxan diabetes I. Hypoglycaemic action and enhancement of serum insulin effect and glycogen synthesis. Indian J BiochemBiophys 1973;10: 209-212.
24. Nayak A, Manda S, Banerji A, Banerji J. Review on chemistryand pharmacology of MurrayakoenigiiSpreng (Rutaceae). JChem Pharm Res 2010;2:286-299.
25. Maryuma Y, Matsuda H, Matsuda R, Kubo M, Hatano T, Okuda T. Study on Psidiumguajava L. (I). Antidiabetic effect and effective components of the leaf of Psidiumguajava L. (Part I) ShoyakugakuZasshi1985;39: 261-269.
26. Liu BL, Zhu DN, Wang G. The anti-hyperglycemic effect ofethanol extract of Prunella vulgaris L. to mice. J China PharmUniv1995; 26:44-46.
27. Jafri MA, Aslam M, Javed K, Singh S. Effect of Punicagranatum Linn. (flowers) on blood glucose level in normal and alloxan induced diabetic rats. J Ethnopharmacol 2000;70: 309-314.
28. Hao ZQ, Hang BQ, Wang Y. The anti-hyperglycemic effect of water decoction of DioscoreaoppositaThunb. To experimental diabetic mice. J China Pharm Univ1991;22: 158-160.
29. Miura T, Iwamoto N, Kato M, Ichiki H, Kubo M, Komatsu Y, et al. The suppressive effect of mangiferin with exercise on blood lipids in type 2 diabetes. Biol Pharm Bull2001;24: 1091-1092.
30. Eshrat MH, Hussain A. Hypoglycemic, hypolipidemic and antioxidant properties of combination of curcumin from Curcuma longa. Lnn, and partially purified product from Abromaaugusta, Linn in streptozotocin induced diabetes. Indian J ClinBiochem 2002;17: 33-43.
31. Hou LQ, Liu YH and Zhang YY. Garlic intake lower s fasting blood glucose: meta-analysis of randomized controlled trials. Asia Pac J Cl in Nutr 2015;24.
32. Jayaweera DM. Part 11. Medicinal plants used in Ceylon Sri Lanka, Colombo: National Science Council 1982; 4-89.
33. Fernando MR, Wickramasinghe SM, Thabrew MI, Ariyaratne PL, Karunanayake EH. J Ethnopharmacol 1991;31: 277-282.
34. Chackrewarthy S, Thabrew MI, Weerasuriya M, Jayasekera S. Evaluation of the hypoglycemic and hypolipidemic effects of an ethylacetate fraction of Artocarpusheterophyllus (jak) leaves in streptozotocin-induced diabetic rats. Phcog

Mag 2010;6: 186-190.
35. Sathyavathi GV, Gupta AK, Tandon N. Medicinal plants of India. New Delhi, India: ICMR 1987.
36. Biwaro A, Tanjung E, Iskandar, Khairina, Suhartono E.Antidiabetic and Antioxidant Activity of Jackfruit (Artocarpusheterophyllus) Extract.J Med Biol Eng 2015; 4(4).
37. HettiaratchiUPK, Ekanayake S, Welihinda J. Nutritional assessment of a jackfruit (Artocarpusheterophyllus) meal. Ceylon Med J 2011; 56: 54-58.
38. Wang Z, Wang J, Chan P. Treating Type 2 Diabetes Mellitus with Traditional Chinese andIndian Medicinal Herbs. J Evid Based ComplementaryAlternMed 2013.
39. World Health Organization. Use of Glycated Haemoglobin(HbA1c) in the Diagnosis of DiabetesMellitus Abbreviated Report of a WHO Consultation WHO/NMH/CHP/CPM/11.1. 2011.
40. Hahm SW, JieunPark,Yong-Suk Son.Opuntiahumifusa stems lower blood glucose and cholesterol levels in streptozotocin-induced diabetic rats.Nutr Res2011; 31: 479-487.
41. Vafa M, Mohammadi F, Shidfar F, Sormaghi MS, Heidari I, Golestan B, et al. (2012) Effects of cinnamon consumption on glycemic status, lipidprofile and body composition in type 2 diabetic patients. IntJ Prev Med 2012;3:531-536.
42. Akilen R, Tsiami A, Devendra D, Robinson N. Cinnamonin glycaemic control: Systematic review and metaanalysis. ClinNutr 2012;31:609-615.
43. Davis PA, Yokoyama W. Cinnamon intake lowersfasting blood glucose: Meta-analysis. J Med Food2011;14:884-889.
44. Frank B Hu MD, Joann E Manson MD, Meir J Stampfer MD, Graham Colditz MD, Simin Liu MD, Caren G Solomon MD, Walter C Willett MD. Diet, Lifestyle, and the Risk of Type 2 Diabetes Mellitus in Women.N Engl J Med2001; 345: 11.
45. Slowinska KZ, EwelinaDzielska, IwonaGryszkin,,HalinaGrajeta.Dietary Supplementation During Diabetes Therapy and the Potential Risk of Interactions.AdvClinExp Med 2014;23(6): 939-946.