

HERBAL DRUGS FOR DIABETES MELLITUS

Parish Chauhan¹, Kirti Kaushal², Shalini Vashisht³, Jyoti Gupta⁴

1. Parish Chauhan, Student of Bachelor of Pharmacy, IEC University, Baddi
2. Kirti Kaushal, Assistant Professor, IEC School of Pharmacy, IEC University, Baddi
3. Shalini Vashisht, Assistant Professor, IEC School of Pharmacy, IEC University, Baddi
4. Jyoti Gupta, Associate Professor, HOD, IEC School of Pharmacy, IEC University Baddi

Abstract

The World Health Organization estimates that 80% of people in underdeveloped countries still rely on folk medicine for sickness prevention or treatment. People used to rely on plants to meet all of his requirements, including those for food, clothing, medicine, tastes and scents, and shelter. Since people's lifestyle preferences have drastically changed during the past century, chronic diseases have become more prevalent. The use of traditional and herbal remedies may be widespread because, due to their lower cost, they are often preferred for the treatment of disorders linked to a sedentary lifestyle (such as hypertension and diabetes mellitus). A public health issue, diabetes mellitus eventually causes major problems including insulin-dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM), is a widespread condition. The irregularity of carbohydrate metabolism, which is connected to low blood insulin levels or insulin resistance in the target organs, is what leads to diabetes mellitus. For diabetes mellitus, traditional plant treatments have been used all over the world. Thorough analysis of the material on medicinal plants used to treat diabetes mellitus and plants are a possible source of anti-diabetic medications through reports of various plants that may have such potential. The goal of this review is to look at several significant plant species and their components, highlighting their health benefits such as possible antidiabetic activity that can be utilized to manage diabetes. In this review for the treatment of diabetes mellitus using herbal remedies to manage diabetes. Herbs are utilized to treat the problems of Type I and Type II diabetes. Researchers, scientists, and academics working in the fields of pharmacology and therapeutics to produce anti-diabetic medications may find this study to be helpful.

Keywords: Diabetes mellitus, Insulin, Medicinal plants Herbal remedies

Introduction

The Diabetes Care Organization estimates that the prevalence of diabetes for all age groups worldwide will increase from 2.8% in 2000 to 4.4% by 2030[1]. Long-term exposure causes numerous micro and macro vascular complications. Micro vascular problems brought on by diabetes harm the kidneys, eyes, and brain. The early warning signals of those issues in type 1 diabetes may appear throughout adolescence, especially if the body is not producing enough insulin. Patients with type-2 diabetes may experience similar complications in their later years (T2DM). Throughout the past few decades, low- and middle-income nations have seen the largest increases in the prevalence of type 2 diabetes [5]. Unfortunately, the prevalence of T2DM is rising at an alarming rate worldwide, and the Philippines is no exception to this at the moment, where diabetes affects 4.6% (3.9 million) of the population and is expected to quadruple by 2030. An evaluation of the anticipated effects of the widespread presence of diabetes from the number of people it has affected then to now should lead to proper planning and resource allocation. Oral hypoglycemic medications, such as insulin sensitizers (biguanides, thiazolidinediones), insulin secretagogues (sulfonylureas, meglitinides), -glucosidase inhibitors, incretin agonists, and dipeptidyl peptidase-4 inhibitors, are currently the most extensively used medications for treating diabetes, aside from insulin [2]. In spite of the fact that oral hypoglycemic medications and insulin therapy can control early-onset complications of diabetes, many patients experience serious late-onset complications [3]. Additionally, some of the current medications have side effects that can occur during clinical use, including hypoglycemia, abdominal pain, and fluid retention in the extremities. Hence, study for new antidiabetic medicines with more effectiveness and less negative effects are continuously under pursuit. Antioxidants have been demonstrated to stop the peroxidation chain reaction from destroying β - cells, hence protecting against the onset of diabetes [4]. Several researches have demonstrated the ability of antioxidants to effectively neutralise free radicals, according to De Gruyter (2019). Moreover, it works well against diabetic complications [5].

Mechanism of action of Herbal -Drug Interaction

Drug-herb interactions are a significant problem for the clinical therapeutic effectiveness of pharmacological therapy. Herb-drug interactions can result in toxicities or therapeutic failure by affecting the pharmacokinetic or pharmacodynamic activities of medications. Many investigations have been done on the pharmacokinetic interactions of numerous regularly used Chinese medicinal plants and other herbal formulae with some commonly used mainstream medications. Most pharmacokinetic interactions are primarily caused by changes in the activity of membrane transporters, particularly the efflux transporter P-gp, and metabolic enzymes, particularly the CYP isozymes. Herb-drug interactions in pharmacodynamic are far less researched than those in pharmacokinetics. This area needs more consideration and work. Herbal-drug interactions can affect both pharmacokinetics and pharmacodynamic, which can have an impact on the clinical results. The safety of people receiving medical services is seriously threatened by ignorance of possible harmful interactions between herbs and drugs. Contrarily, some interactions might have therapeutic advantages [6-16].

Herb with anti diabetic properties

There are many plants with anti-diabetic properties, according to Ayurveda. Only a small number of these have been established scientifically, and many more need to be investigated and verified. Many plants, including *Momordica charantia*, *Gymnema sylvestre*, *Allium sativum*, *Trigonella foenum graecum*, *Pterocarpus marsupium*, *Ocimum sanctum*, and *Ficus religiosa*, have demonstrated varied degrees of hypoglycemic action [17, 18, 19]. Moreover, it has been claimed that these plants aid in the management of diabetes-related problems. Future research might concentrate on isolating, purifying, and characterising the bioactive substances found in these plants. The results of these investigations could serve as a springboard for the creation of potential anti-diabetic medications. The management of diabetes may benefit from this review.

Common herbal-drug interactions in diabetes

Aloe Vera

In addition to its use in health and beauty products, aloe (*Aloe Vera L.*, Liliaceous family) contains antioxidant, anticancer, anti-inflammatory, laxative, and anti-atherosclerosis effects. It has 75 active ingredients, including Lignin, salicylic acid, carbohydrates, vitamins, enzymes, minerals, and icamino acids [20, 21]. There are numerous significant ingredients, including Aloe-emodin, Aloe Acid, Anthranol, Barb loin, Manna and its derivatives, Alkaline phosphates, amylase, bradykinase, carboxypeptidase, catalase, cyclooxygenase, cyclooxygenase, lipase, oxidase, phosphoenolpyruvate, carboxylase, superoxide dismutase, 8-C-glucosyl-(2'-O-cinnamoyl), and 7-O-methylal Auxins, Gibberellins, Calcium, Chlorine, Chromium, Copper, Iron, Magnesium, Steroids, Mannose, Glucose, L-Rhamnose, Aldopentose, Vitamin A, B12, C, E, Choline, and Folic Acid have all been identified [22]. Diabetic animal models had better glycoprotein metabolism after receiving oral Aloe Vera leaf gel extract for 21 days [23]. Aloe Vera can be used to control the glucose metabolism, according to evidence. [24, 25] Although Aloe Vera has been shown to have hypoglycemic effects [26,27]. The number of people at risk for type 2 diabetes is rising. Simple and readily available treatments are necessary on the one hand [28, 29].



Figure 1: Aloe Vera

Fenugreek

Limiting the prevalence of prediabetics is an excellent method for reducing the effects of T2DM on the world [30]. Our goal is to find new, highly effective treatment drugs that are both inexpensive and low-toxic and that may be administered often to slow the progression of T2DM in the population of prediabetics. So, it would be ideal to use dietary supplements that can alter glucose homeostasis and possibly enhance lipid characteristics. Despite the fact that several herbs have been claimed to have anti-diabetic properties, a large body of research and traditional use point to fenugreek seeds (*Trigonella foenumgraecum*) as being among the finest in terms of security and effectiveness [31]. Fenugreek seeds are a great source of fiber and are great for diabetic individuals [32]. Fenugreek seeds help individuals with diabetes lower their blood glucose, according to research conducted over the previous 20 years. Its effectiveness as an anti-diabetic was demonstrated by better glucose tolerance in human volunteers and a decrease in fasting blood glucose levels [33]. Fenugreek is being offered as a nutraceutical with the promise of lowering blood sugar levels [34]. An affordable, low-risk intervention focused on food that aims to normalise the patient's metabolic environment may be beneficial for patients who already show irregularities in their glucose handling. Fenugreek is a dietary supplement that shows some potential in this area. Fenugreek's hypoglycemic and hypolipidemic effects have been studied in T2DM animal and human models, but no research has been done on prediabetics. Also, it's critical to discuss with the patient the limited evidence supporting the long-term health advantages of pharmaceutical intervention over lifestyle management [35].



Ginger

One of the most popular spices in the world, ginger is an underground rhizome of the plant *Zingiber officinale* from the Zingiberaceae family. It has a long history of usage as herbal medicine to treat a range of illnesses, including indigestion (dyspepsia), pain, cold-induced syndromes, nausea and vomiting, and constipation. More recently, it was discovered that ginger has antioxidant, anti-inflammatory, anti-cancer, and anti-clotting properties because it can scavenge superoxide anion and hydroxyl radicals [37].

In addition to sesquiterpenes like beta-bisabolene and (-)-zingiberene and monoterpenes like geranial and volatile oils like gingerols and their related dehydration products, the shogaols, are known to be present in ginger [39]. Furthermore, studies on phytochemistry have revealed that the primary components of ginger include gingerol, shogaol, zingerone, and paradol. According to reports, the two main gingerols and shogaols found in the rhizome are 6-gingerol and 6-shogaol [36].

The pretreatment with ginger prevented the development of induced hyperglycemia and hypoinsulinemia [40]. Several researchers have demonstrated ginger's ability to lower cholesterol [41]. According to other studies, the dose concentration of ginger components affects how the body reacts to it [42, 43]. The validity of several experimental studies on ginger's anti-diabetic, hypolipidemic, and anti-oxidative qualities that have been published is debatable, but more research may shed more light on its effectiveness in preventing and treating metabolic disorders [38]. In order to determine the effects of ginger powder supplementation on serum levels of fasting blood sugar (FBS), haemoglobin A1c (HbA1c), apolipoprotein B (apo B), apolipoprotein A-I (apo A-I), Apo B/A-I, and malondialdehyde (MDA) in type 2 diabetes patients.



Garlic

One of the world's first plants to be domesticated, garlic is valued both as a food and a traditional remedy. Due to its antibacterial, antioxidant, anticarcinogenic, antimutagenic, antiasthmatic, immunomodulatory, and prebiotic actions, garlic extract has been shown to be helpful for human bodies [44, 45]. It has already been shown in earlier studies that it can lower blood pressure and prevent cardiovascular events in people with severe hypertension [46, 47]. Although the effects were not entirely established, it may also be beneficial in the primary prevention of cardiovascular mortality and colorectal cancer [46, 48]. At the moment, garlic extract is one of the medications that have undergone the most thorough research. Throughout the years, a number of high-quality randomized controlled trials (RCTs) have been conducted to examine its effectiveness in treating T2DM [49- 58]. If garlic's potential as a traditional food and medicine were to be proven, along with its potential benefits of multiple targets, widespread distribution, low cost, and infrequent complications. However, a thorough and quantitative study with high reliability is still lacking due to the small sample size and validated results. In order to evaluate the effectiveness and safety of garlic supplements in the management of T2DM on blood glucose as well as blood fluids including total cholesterol, triglyceride, high density lipoprotein (HDL), and low density lipoprotein (LDL) regulation.



Bitter Gourd

The indigenous populations of Asia, South America, India, the Caribbean, and East Africa frequently employ *Momordica charantia* (*M. charantia*), also known as bitter melon, karela, balsam pear, or bitter gourd, to treat diabetes-related conditions[59,60]. Because of the fruit's distinctively bitter flavour, which becomes more intense as it ripens, it is also known as a bitter melon or a bitter gourd. Many facts and theories explaining the anti-diabetic properties of *M. charantia* have been generated through biochemical and animal model investigations. Clinical investigations using human patients, in contrast, are few and of poor design quality. The clinical condition known as diabetes mellitus has a number of long-term consequences, including retinopathy, neuropathy, nephropathy, etc. Pharmaceutical biology is well known to be significantly influenced by natural products [61]. Understanding particular plants can help with strategic consumption and sustainable use. With the

discovery of active components derived from many plant species, the alternative medical system is currently gaining ground [62]. *M. charantia* can be used as an adjuvant with allopathic treatments of medicine to treat diabetes and to prevent the late consequences of diabetes due to its considerable antidiabetic and hypolipidemic activity.

Conclusion

Modern medicine has made several synthetic pharmaceutical medications available, including biguanides, thiazolidinediones, biguanides, and insulin, which had been shown to have anti-diabetic characteristics. However, these medications frequently bring on a number of side effects, including hypoglycemia, nephrological diseases, exhaustion, and gastrointestinal discomfort (upset stomach, diarrhoea, and vomiting). Diabetes is treated with a variety of medicinal plants around the world. Due to their bioactive compounds, including flavonoids, tannins, phenolics, and alkaloids, the plants mentioned in this study are proven to have natural antioxidants and are used as an effective herbal medicine in diabetes mellitus. These compounds help the pancreatic tissues function better by increasing insulin secretion or decreasing the absorption of glucose through the intestinal tract. The many anti-diabetic plants discussed in this article and been found to have some utility in the prevention and treatment of Diabetes Mellitus. According to certain research, the benefits of these plants may rectify metabolic imbalances and postpone the onset of diabetes consequences. It has also been highlighted that there are a number of potential ways by which these herbs may work to reduce blood sugar levels. The mechanisms of action may, in general, be connected to the plant in question's (or its active principle's) capacity to reduce plasma glucose levels by interfering with some glucose homeostasis-related processes. Examining the findings of experimental investigations on the hypoglycemic properties of plants and their bioactive components that were conducted in different regions of Asia and other parts of the world is the main topic of the current review. The kind of diabetes, associated physiological abnormalities, and readily available plants with antidiabetic properties are briefly outlined. The profiles of the plants with hypoglycemic qualities mentioned in the literature are presented this review paper. The development of evidence-based alternative medicines or dosage formulations to treat various types of diabetic problems with herbal remedies may benefit researchers, scientists, and academics. When developing medications and treating the hyperglycemic issues associated with diabetes mellitus, extracts separated and derived compounds from various natural resources play a very important role. Consequently, the researcher can draw the conclusion that the medicinal plants indicated above can be utilized for the treatment and prevention of diabetes.

References

- [1] Sonal, Narhe, Sandip, Kshirsagar S, and Vishal, Patil S. (2018) Review on Medicinal Herbs Used for Diabetes. *International Journal of Pharmaceutical and Clinical Research*. 10(8): 224-228 ISSN- 0975 1556.
- [2] Lorenzati, B.; Zucco, C.; Miglietta, S.; Lamberti, F.; Bruno, G. (2010). Oral hypoglycemic drugs: pathophysiological basis of their mechanism of action. *Pharmaceuticals*, v.3, p.3005-3020, 2010.
- [3] Tzoulaki, I., Molokhia, M., Curcin, V. et al. (2009) Risk of cardiovascular disease and all-cause mortality among patients with type 2 diabetes prescribed oral antidiabetic drugs: retrospective cohort study using UK general practice research database. *BMJ*, v.339, p.b4731, 2009. .
- [4] Roglic, G. and Norris, S.L. 2018. Medicines for treatment intensification in type 2 diabetes and type of insulin in type 1 and type 2 diabetes in low-resource settings: synopsis of the world health organization guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in nonpregnant adults with diabetes mellitus *Ann. Intern.Med.*, 169 (2018), pp. 394-397
- [5] Ghosh R.K., Gupta I.: *Indian J. Anim. Health*19, 145 (1980).
- [6] Bertilsson G., Heidrich J., Svensson K., Asman M., Jendeberg L., Sydow-Backman M., Ohlsson R., Postlind H., Blomquist P., Berkenstam A. Identification of a human nuclear receptor defines a new signaling pathway for CYP3A induction. *Proc. Natl. Acad. Sci. USA*. 1998;95:12208–12213.
- [7] Blumberg B., Sabbagh W., Jr., Juguilon H., Bolado J., Jr., van Meter C.M., Ong E.S., Evans R.M. SXR, a novel steroid and xenobiotic-sensing nuclear receptor. *Genes Dev*. 1998; 12:3195–3205.
- [8] Lehmann J.M., McKee D.D., Watson M.A., Willson T.M., Moore J.T., Kliewer S.A. The human orphan nuclear receptor PXR is activated by compounds that regulate CYP3A4 gene expression and cause drug interactions. *J. Clin. Investig*. 1998;102:1016–1023.

- [9] Moore D.D., Kato S., Xie W., Mangelsdorf D.J., Schmidt D.R., Xiao R., Kliewer S.A. International Union of Pharmacology. LXII. The NR1H and NR1I receptors: Constitutive androstane receptor, pregnane X receptor, farnesoid X receptor alpha, farnesoid X receptor beta, liver X receptor alpha, liver X receptor beta, and vitamin D receptor. *Pharm. Rev.* 2006;58:742–759.
- [10] Nicolussi S., Drewe J., Butterweck V., Meyer Zu Schwabedissen H.E. Clinical relevance of St. John's wort drug interactions revisited. *Br. J. Pharmacol.* 2020;177:1212–1226.
- [11] Huang W., Zhang J., Wei P., Schrader W.T., Moore D.D. Meclizine is an agonist ligand for mouse constitutive androstane receptor (CAR) and an inverse agonist for human CAR. *Mol. Endocrinol.* 2004;18:2402–2408.
- [12] Xie W., Barwick J.L., Downes M., Blumberg B., Simon C.M., Nelson M.C., Neuschwander-Tetri B.A., Brunt E.M., Guzelian P.S., Evans R.M. Humanized xenobiotic response in mice expressing nuclear receptor SXR. *Nature.* 2000;406:435–439.
- [13] Zhang J., Huang W., Chua S.S., Wei P., Moore D.D. Modulation of acetaminophen-induced hepatotoxicity by the xenobiotic receptor CAR. *Science.* 2002;298:422–424.
- [14] Prakash C., Zuniga B., Song C.S., Jiang S., Cropper J., Park S., Chatterjee B. Nuclear Receptors in Drug Metabolism, Drug Response and Drug Interactions. *Nucl. Recept. Res.* 2015;2.
- [15] Jeuken A., Keser B.J., Khan E., Brouwer A., Koeman J., Denison M.S. Activation of the Ah receptor by extracts of dietary herbal supplements, vegetables, and fruits. *J. Agric. Food Chem.* 2003;51:5478–5487.
- [16] Wei Y., Tang C., Sant V., Li S., Poloyac S.M., Xie W. A Molecular Aspect in the Regulation of Drug Metabolism: Does PXR-Induced Enzyme Expression Always Lead to Functional Changes in Drug Metabolism? *Curr. Pharmacol. Rep.* 2016;2:187–192.
- [17] Ponnusamy S, Ravindran R, Zinjarde S, Bhargava S, Kumar AR. Evaluation of traditional Indian antidiabetic medicinal plants for human pancreatic amylase inhibitory effect *in vitro*. *Evid Based Complement Alternat Med.* 2011;2011:515647.
- [18] Jung M, Park M, Lee HC, Kang YH, Kang ES, Kim SK. Antidiabetic agents from medicinal plants. *Curr Med Chem.* 2006;13(10):1203–1218.
- [19] Grover JK, Yadav S, Vats V. Medicinal plants of India with anti-diabetic potential. *J Ethnopharmacol.* 2002;81(1):81–100.
- [20] Al-Awadi F, Fatania H, Shamte U. The effect of a plants mixture extract on liver gluconeogenesis in streptozotocin induced diabetic rats. *Diabet Res.* 1991;18(4):163.
- [21] Yagi A, Hegazy S, Kabbash A, Wahab EA-E. Possible hypoglycemic effect of Aloe Vera L. high molecular weight fractions on type 2 diabetic patients. *Saudi Pharm J.* 2009;17(3):209–15.
- [22] Sharrif Moghaddasi M, Sandeep KV. Aloe Vera their chemicals composition and applications: a review. *Int J Biol Med Res.* 2011;2(1):466–71.
- [23] Rajasekaran S, Aathishsekar D. Therapeutic evaluation of Aloe Vera leaf gel extract on glycoprotein components in rats with streptozotocin diabetes. *J Pharmacol Toxicol.* 2007;2(4):380–5.
- [24] Can a, Akev N, Ozsoy N, Bolkent S, Arda BP, Yanardag R, et al. Effect of Aloe Vera leaf gel and pulp extracts on the liver in type-II diabetic rat models. *Biol Pharm Bull.* 2004; 27(5):694–8.
- [25] Parihar M, Chaudhary M, Shetty R, Hemnani T. Susceptibility of hippocampus and cerebral cortex to oxidative damage in streptozotocin treated mice: prevention by extracts of *Withania somnifera* and *Aloe vera*. *J Clin Neurosci.* 2004;11(4):397–402.
- [26] Agarwal O. Prevention of atheromatous heart disease. *Angiology.* 1985;36(8):485–92
- [27] Bunyaphatsara N, Yongchaiyudha S, Rungpitarangsi V, Chokechajaroenporn O. Antidiabetic activity of Aloe vera L. juice II. Clinical trial in diabetes mellitus patients in combination with glibenclamide. *Phytomedicine.* 1996;3(3):245–8.

- [28] Devaraj S, Yimam M, Brownell LA, Jialal I, Singh S, Jia Q. Effects of Aloe vera supplementation in subjects with prediabetes/metabolic syndrome. *Metab Syndr Relat Disord*. 2013;11(1):35–40.
- [29] Fallah HH, Kianbakht S, Hajiaghaee R, Afkhami AM, Bonakdaran A, Hashem DF. Aloe vera leaf gel in treatment of advanced type 2 diabetes mellitus needing insulin therapy: a randomized double-blind placebo-controlled clinical trial. *J Med Plants*. 2012;11(43):19–27.
- [30] Hogan P, Dall T, Nikolov P. Economic costs of diabetes in the US in 2002. *Diabetes Care*. 2003;26:917–932.
- [31] Pandey A, Tripathi P, Pandey R, Srivatava R, Goswami S. Alternative therapies useful in the management of diabetes: a systematic review. *J Pharm Bioallied Sci*. 2011;3:504–512.
- [32] Ansari R, Ansari S. Effectiveness of fenugreek for lowering hemoglobin (HbA1c) in patients with self-management of type 2 diabetes: a randomized, controlled trial. In: Croniger C, editor. *Medical Complications of Type 2 Diabetes*. Croatia: InTech; 2011. pp. 393–412.
- [33] Neelakantan N, Narayanan M, de Souza RJ, van Dam RM. Effect of fenugreek (*Trigonella foenum-graecum* L.) intake on glycemia: a meta-analysis of clinical trials. *Nutr J*. 2014;13:7.
- [34] Roberts KT. The potential of fenugreek (*Trigonella foenum-graecum*) as a functional food and nutraceutical and its effects on glycemia and lipidemia. *J Med Food*. 2011;14:1485–1489.
- [35] Aroda VR, Ratner R. Approach to the patient with prediabetes. *J Clin Endocrinol Metab*. 2008;93:3259–3265.
- [36] Li Y, Tran VH, Duke CC, Roufogalis BD. Gingerols of *Zingiber officinale* enhance glucose uptake by increasing cell surface GLUT4 in cultured L6 myotubes. *Planta Medica*. 2012;78:1549–1555.
- [37] Elshater A-EA, Muhammad MA Salman, Mahrous MA Moussa. Effect of ginger extract consumption on levels of blood glucose, lipid profile and kidney functions in Alloxan induced-diabetic rats. *Egypt. Acad. J. Biology. Sci*. 2009;2:153–162.
- [38] Al-Azhary DB. Ginger enhances antioxidant activity and attenuates atherogenesis in diabetic cholesterol-fed rats. *Aust. J. Basic. Appl. Sci*. 2011;5:2150–2158.
- [39] Al-Amin ZM, Thomson M, Al-Qattan KK, Peltonen-Shalaby R, Ali M. Anti-diabetic and hypolipidemic properties of ginger (*Zingiber officinale*) in streptozotocin-induced diabetic rats. *Br J. Nutr*. 2006;96:660–666.
- [40] Akhiani SP, Vishwakarma SL, Goyal RK. Anti-diabetic activity of *Zingiber officinale* in Streptozotocin-induced type I diabetic rats. *J. Pharm. Pharmacol*. 2004;6:101–105.
- [41] Sharma I, Gusain D, Dixit VP. Hypolipidemic and antiatherosclerotic effects of *Zingiber officinale* in cholesterol-fed rabbits. *Phyto. Res*. 1996;10:517–518.
- [42] Ghayur M, Gilani A, Afridi M, Houghton P. Cardiovascular effects of ginger aqueous extract and its phenolic constituents are mediated through multiple pathways. *Vasc. Pharmacol*. 2005;43:234–241.
- [43] Siddaraju M, Dharmesh S. Inhibition of gastric H⁺, K⁺-ATPase and *Helicobacter pylori* growth by phenolic antioxidants of *Zingiber officinale*. *Mol. Nutr. Food Res*. 2007;51:324–332.
- [44] Corzo-Martínez MCN. Biological properties of onions and garlic. *Trends Food Sci Technol*. 2007;18(12):609–625.
- [45] Santhosha SG, Jamuna P, Prabhavathi SN. Bioactive components of garlic and their physiological role in health maintenance: A review. *Food Biosci*. 2013;3(2013):59–74.
- [46] Tejani A. Garlic for the prevention of cardiovascular morbidity and mortality in hypertensive patients: summaries of nursing care-related systematic reviews from the cochrane library. *Cochrane Database Syst Rev*. 2013;11(1):CD007653.
- [47] Schwingshackl L, Missbach B, Hoffmann G. An umbrella review of garlic intake and risk of cardiovascular disease. *Phytomedicine*. 2015.
- [48] Chiavarini M, Minelli L, Fabiani R. Garlic consumption and colorectal cancer risk in man: a systematic review and meta-analysis. *Public Health Nutr*. 2015;19(2):308–317.

- [49] Ashraf R, Aamir K, Shaikh AR, et al. Effects of garlic on dyslipidemia in patients with type 2 diabetes mellitus. *J Ayub Med Coll Abbottabad*. 2005;17(3):60–64.
- [50] Sobenin IA, Nedosugova LV, Filatova LV, et al. Metabolic effects of time-released garlic powder tablets in type 2 diabetes mellitus: the results of double-blinded placebo-controlled study. *Acta Diabetol*. 2008;45(1):1–6.
- [51] Sukandar EY, Permana H, Adnyana IK, et al. Clinical study of turmeric (*Curcuma longa* L.) and garlic (*Allium sativum* L.) extracts as antihyperglycemic and antihyperlipidemic agent in type-2 diabetes-dyslipidemia patients. *Int J Pharmacol*. 2010;6(4):456–463.
- [52] Ashraf R, Khan RA, Ashraf I. Garlic (*Allium sativum*) supplementation with standard antidiabetic agent provides better diabetic control in type 2 diabetes patients. *Pak J Pharm Sci*. 2011;24(4):565–570.
- [53] Ashraf R, Khan RA, Ashraf I. Effects of garlic on blood glucose levels and HbA1c in patients with type 2 diabetes mellitus. *J Med Plants Res*. 2011;5(13):2922–2928.
- [54] Song AL, Song HF, Xiao YH, et al. Changes of plasma hs-CRP and C-peptide In T2DM patients after garlic and insulin combination therapy. *Chin J Clin Rehabil*. 2006;10(9):122.
- [55] Chhatwal S, Sharma RK, Sharma G, et al. To study the antihyperglycaemic and lipid lowering effect of garlic as an adjunct to metformin in patients of type 2 diabetes mellitus with obesity. *Int J Basic Clin Pharmacol*. 2012;1(1):22–26.
- [56] Kumar R, Chhatwal S, Arora S, et al. Antihyperglycemic, antihyperlipidemic, anti-inflammatory and adenosine deaminase-lowering effects of garlic in patients with type 2 diabetes mellitus with obesity. *Diabetes Metab Syndr Obes*. 2013;6:49.
- [57] Manafikhi R, Kalie L, Lahdo R. Effects of garlic supplementation on fasting blood sugar, HbA1c and lipid profile in type 2 diabetics receiving metformin and glyburide. *Int J Acad Scientific Res*. 2015;3(5):11–18.
- [58] Atkin M, Laight D, Cummings MH. The effects of garlic extract upon endothelial function, vascular inflammation, oxidative stress and insulin resistance in adults with type 2 diabetes at high cardiovascular risk. A pilot double blind randomized placebo controlled trial. *J Diabetes Complications*. 2016;30:723–727.
- [59] Cefalu WT, Ye J, Wang ZQ. Efficacy of dietary supplementation with botanicals on carbohydrate metabolism in humans. *Endocr Metab Immune Disord Drug Targets*. 2008;8:78–81.
- [60] Cousens G. *There is a cure for diabetes: the tree of life 21 day program*. California: North Atlantic Books; 2008. pp. 191–192.
- [61] Joseph B, Raj SJ. Pharmacognostic and phytochemical properties of *Aleo vera* Linn - An overview. *Int J Pharm Sci Rev Res*. 2010a;4(2):106–110.
- [62] Joseph B, Jini D. A medicinal potency of *Capparis decidua* - A harsh terrain plant. *Res J Phytochem*. 2011b;5(1):1–13.