Review Paper:

Advances and prospects of medicinal herbs and their natural bioactive components for effective control of diabetics

Dey Pinaki*, Sowmya Ashok, Jain Atishya Mahesh, Sreenath Amritha and Saji Gladys Sara
Karunya Institute of Technology and Sciences, Department of Biotechnology, Coimbatore- 641114, Tamil Nadu, INDIA
***saspinaki@gmail.com, pinakidey@karunya.edu**

Abstract

Diabetes is considered one of the common and serious metabolic disorders throughout the world. As the incidence of diabetics, allied mortality is increasing rapidly and it has become a big threat to the global population. It is mainly identified as deficiency in insulin release by the pancreas and hence inability of the body to metabolize sugar. Such chronic hyperglycemia can lead to longer duration damage, abnormality and organs failure. Conventional expensive synthetic drugs failed to reduce the overall complications of this disease and also demonstrate several side effects. Such limitations necessitate the development of alternative therapies using antidiabetic agents originated from commonly available medicinal plants.

Presently herbal medicines have received enough attention for the successful management of diabetics due to added advantages like better access, affordability and lower side effects. The present review provides enlightenment about the ability of herbal plants, mainly from Indian origin to regulate diabetics and their mechanisms involving bioactive compounds.

Keywords: *Diabetes mellitus*, Health impact, Medicinal herbs, Bioactive compounds, Hypoglycemic activity.

Introduction

Diabetes mellitus (DM) which is known as a serious metabolic disorder is highly prevalent among the citizen of both developed and underdeveloped countries. It is also considered as a metabolic abnormality mainly characterized by inadequate secretion and action of insulin followed by alteration in lipid, carbohydrate and protein metabolism[39]. Mainly two types of diabetics are well-known based on insulin dependency (i.e. type I and type II diabetes). People are mostly suffering from elevated levels of glucose in the blood caused by insulin deficiency in the first type.

The second type is known as insulin-independent and mostly affects people with abnormalities in lipid metabolism through chronic hyperglycemia [41]. For a diabetic person, blood sugar level remains high after taking meal due to the inefficient production of insulin from β-Langerhans islet cells of pancreas or as a result of imperfect insulin uptake mechanism through peripheral tissues[4]. People above the age of 40 are mostly affected by the disease and disease is also responsible for developing other disorders including retinopathy, cardiovascular disorder, polyuria, polyphagia, damage and failure of various organ systems[41]. Presently 25% of the citizens of the world are suffering from this crippling disease and in India, more than 61 million patients are affected with diabetics[18,74]. International Diabetes Federation (IDF) predicted that worldwide around 642 million people will be affected by the end of 2040[49] and in India, the affected number is likely to be 69.9 million by the end of 2025[47].

The management of diabetes is still considered a big challenge and a fully successful treatment procedure for this disease is yet to be discovered. Conventional diabetes treatment mainly includes application of insulin and several synthetic drugs. Most of such drugs have serious undesirable side effects upon administration like gastrointestinal abnormalities, gain in body weight, changes in blood glucose level and chances of cardiovascular disease.[2,19,75] Therefore, there has been a demand for the development of more reliable and efficient hypoglycemic agents. On the other side, due to the expensive nature of such conventional anti-diabetic medicines, they are not affordable for common people in developing countries.

Such overall drawbacks of the conventional system mainly attributed the need for inventing an alternative way for the management of diabetics through cost-effective indigenous plant and herbal formulations. Considering the large accessibility of medicinal plants compared to synthetic drugs and its minimal side effects, herbal therapy has been widely validated and implemented for the treatment of diabetes [32]. Plants are always considered as a genuine source for drugs and bioactive compounds like carotenoids, flavonoids, terpenoids, alkaloids, glycosides in the form of several drugs which have been successfully formulated and implemented against diabetes[1].

The performance of pancreatic tissue can be largely enhanced in terms of regulated insulin secretions upon the administration of such traditional herbal medicine or related fruits or vegetables[21,55]. Already 700 recipes containing more than 400 plants were successfully investigated for their antidiabetic activity[62].

A number of review articles have been published in the direction of revealing antidiabetic properties of medicinal

plants with their bioactive compounds[10,18,28,56] for treatment of diabetes. The present review clearly explains about the characteristics of such important medicinal plants which are specifically available in India and subcontinent regions in terms of their bioactive compounds and their pharmaceutical formulations for prospective management of diabetes. The review also elucidates with some case studies that represents how different animal models were successfully implemented to prove the effectiveness of such plant extract against diabetic associated disorders.

Diabetics and its impact

Diabetes mellitus is considered as a metabolic disorder in the form of chronic hyperglycemia which is developed due to improper insulin release and/or its activity and comes up with elevated level of sugar level in bloodstream [22,34]. The particular disorder is responsible for altering lipids, carbohydrates, hindering common protein metabolism mechanism and increases the risk for getting affected by cardiovascular diseases [14]. Even untreated cases of diabetes for a long term can develop complications like cardiovascular disease, nerve damage, kidney damage, eye damage and skin conditions which are schematically represented in fig. 1.

The occurrence of diabetes and its impact is very large throughout the world. People who are having poor control of their life style are likely to be more affected by diabetes complications. Considering the facts of several associated health complications, early mortality and continuous involvement of treatment and prevention cost, *Diabetes Mellitus* (DM) is regarded as one of the main public health disorders[6]. Due to the rapid expansion of such chronic disorder, it is also comparable with the diseases which are responsible for pandemic conditions. In view of the facts like number of affected people with diabetes in 2011 and prediction about doubling the death rates between 2005 and 2030, The World Health Organization already warned about the effect of diabetics on economic conditions of patients, their families and in national health systems[6].

It was indicated that 69% adult populations will be more infected by the disease in 2030 in developing countries whereas 20% increase will be prevalent in developed countries[69]. It was estimated that more than 30 million adults in the U.S which is 9.4 % of the overall population was affected with type 2 diabetes[78]. According to Murphy et al[52], around 84.1 million population which is more than one out of three adults in the age of 65 in United States are affected with diabetics. Based on the estimation of American Diabetes Association, overall financial cost involvement for treatment of diabetics, associated complications and premature death was $327 billion in 2017 [48].

According to the Government report of Japan, 16.2 million populations were affected by such deadly disease and there was rapid increase in this number by 3 million in the last 5 years[65]. Among the available ways to trickle diabetics, treatment through the application of medicinal plants or herbal medicines is considered as low-cost promising method with less side effects.

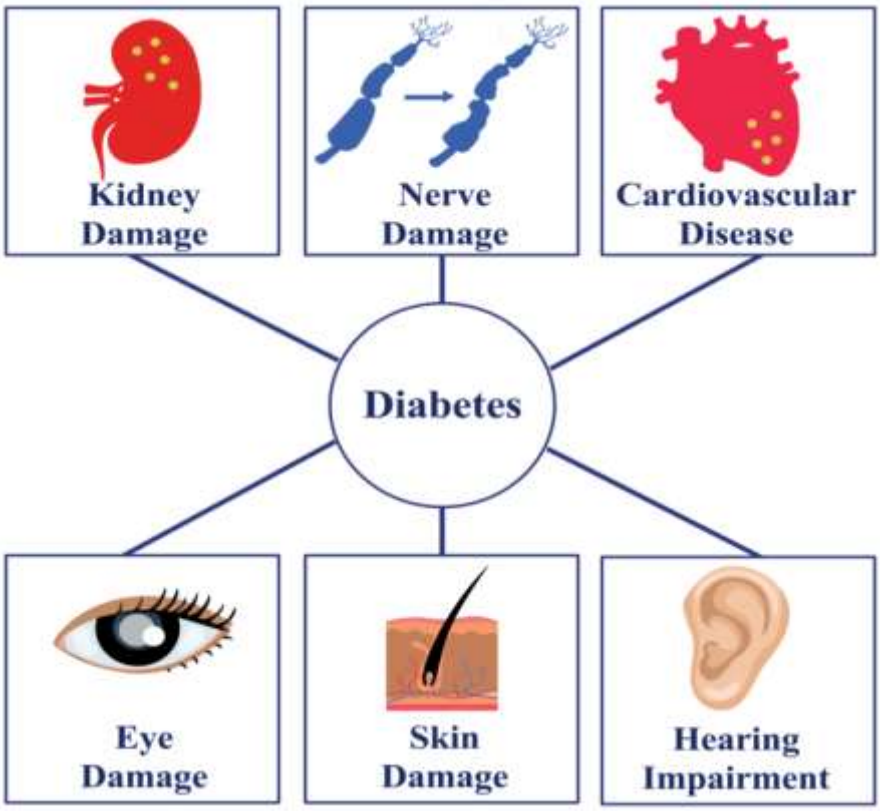

Fig. 1: Health complications of Diabetics

Importance of medicinal plants to treat diabetics

To control diabetes, traditional therapies originating from medicinal plants got enough attention and importance. Many plant species including several from indigenous Indian origin have been identified for better management of diabetics. Accessibility, cost-effective nature and insignificant side effects are the most important features of such plant species [68]. The existence of different bioactive, pharmacologically active compounds like phenolics, alkaloids, flavonoids, terpenoids, coumarins and glycosides made those plants highly demanding for multinational drug companies. Some of such medicinal plants are considered as a regular part of our diet, vegetables and fruits. WHO already identified around 21000 plants across the world that can be used for therapeutic purposes and among them, 2500 plants are of Indian origin[46].

Specifically, 400 traditional plants got special attention by the scientists to cure diabetics and among that few were experimentally evaluated for management of diabetics [11]. It was observed that significant number of studies were conducted using animal models till now. Hence emphasis should be given more on human cell lines during experimental investigations. There has been a practice of using numerous plants as a dietary supplement for the treatment of different diseases by common people without knowing their active constituents or their functions. So, it is important to spread detail information about the effectiveness of such individual medicinal plants in terms of their active ingredients to common people.

On the other hand, due to huge therapeutic applications, requirement of such type of medicinal herb has been largely enhanced in both national and international market which comes up with rapid depletion of such wild plant populations [38]. At the same time, performing over-exploitation with such precious herbal species caused extensive reduction of their natural habitat. As a result, Government from different nations developed some regulations for conservation of critically endangered medical herbs. Descriptions of some important medicinal plants which have been actively utilized for the treatment of diabetes and experimental investigations carried out with such plants is presented here.

***Allium cepa* - Onion:** Onion is considered a cardinal constituent of the diet. From ancient days, it has been traditionally used for the treatment of various diseases. Among different therapeutic activities, *Allium cepa* is mostly regarded for its hypoglycemic activity. The secondary metabolites and bioactive compounds present in onions such as quercetin and organosulfur were reported to have anti-obesity, antidiabetic and hyperlipidemia activities[43]. Sulphur containing compounds like S-methyl cysteine and flavonoids like quercetin present in onions mainly helps to reduce blood glucose levels, serum lipids, oxidative stress and lipid peroxidation[3]. Administration of S-methyl cysteine sulphoxide (SMCS) from *Allium cepa* with dosages of 200 mg/kg for 45 days to diabetic rats induced by alloxan was found to have regulated glucose and lipids levels in blood and serum respectively[46].

In a separate case study, it was observed that *Allium cepa* in boiled conditions could effectively reduce its hypoglycemic potential and it is comparative effectiveness with conventional drugs like insulin or metformin in improving hyperglycemia was also proved[54].

***Aloe barbadensis* - Aloe vera:** *Aloe vera*, an evergreen perennial ayurvedic plant is usually well known for multipurpose folk remedies including anti-diabetic effects. Throughout the world, Aloe plants have been traditionally used as therapeutic medicine and specifically recognized for its antidiabetic properties. Along with that, the plant extract is also well known for other biological effects including anti-tumor activity, antimicrobial activity, anti-inflammatory activity, antioxidant activity and for wound-healing properties[37]. Methanolic extract of the plant was dragonized with significant effects in eliminating carbonyls bound to proteins by inhibiting the formation of AGEs group of compounds[51]. The plant leaves possess different groups of bioactive compounds like anthraquinones, anthrones, chromones, flavonoids, amino acids, lipids, carbohydrates, vitamins and minerals[7].

***Allium sativum* - Garlic:** *Allium sativum* is a perennial herb, generally available as raw vegetable and well-known to people as garlic. Due to its most effective therapeutic and medicinal properties, the herb is largely used in both traditional and modern medicine. In a case study, antidiabetic potential of garlic was evaluated against diabetic rats where the effects of garlic in depression and anxiety-related behaviors were checked and the oxidative reaction of the brain in diabetics induced rats was found to be normalized[58]. Sulfur consisting of non-volatile amino acids like alliin or S-allyl-cysteine sulfoxide (ACSO), present in the plant extract is mainly responsible for flavor and anticancer, antidiabetic, anti-inflammatory, antimicrobial, antioxidant, cardioprotective and immunomodulatory activities[44].

***Azadirachta indica* - Neem:** This fast-growing evergreen tree is available throughout India, more specifically in deciduous forests. The plant has been traditionally used for therapeutic purposes in different forms and its preparations have been consumed through various generations of people. Gedunin, a limonoid present in the plant extract was reported with anti-hyperglycaemic activities[45]. Other bioactive compounds like nimbins (triterpene), catechins which are present in the plant extract are having antipyretic, antifungal, antihistamine and antiseptic properties[30].

***Aegle marmelose* - Bael:** *Aegle marmelos* is mainly cultivated in dry forests and it was successfully implemented in ethno medicinal system. The tree is well-known for its therapeutic property for the management of *Diabetes mellitus* while lowering blood glucose level[5]. Different parts

of the plant like leaves, fruits, stem and roots have been investigated for several medicinal properties including astringent, antidiarrheal, antidysenteric, demulcent, antipyretic, antiscourbutic, haemostatic, aphrodisiac and as an antidote to snake venom[35].

Pharmacological properties of the plant were examined by using Streptozotocin-induced rats and positive results like restoration of plasma glucose level to normal level, lipid-lowering activity, α- glucosidase inhibition, improved hepatic function enzymes were observed [42]**.** In another case study, effect of *Aegle marmelos* seed extract was examined on normal, abnormal and mild (FBG 120–250 mg/dl) diabetic rats with varying doses like 100-500 mg/kg [35]. A dose of 250 mg/kg was highly effective for lowering blood glucose level by 60.84% and urine sugar by 75% from 14 days treatment.

***Biophytum sensitivum* - Lajjalu:** *Biophytum sensitivum* belongs to the family of Oxalidaceae and is normally observed in tropical parts of India. This annual herb also grows in the foothills of the Himalayas, surrounding the inner Tarai region of the Eastern Nepal[8]. It is a well-known folk medicine for the treatment of diabetes as dry leaves powder developed from the plant are having a traditional application against Madhumeha or diabetes[8]. Presence of bioactive phytochemicals like two biflavones, (cupressuflavone and amentoflavone) three flavonoids, (luteolin 7-Methyl ether, isoorinentin and 3-methoxyluteolin 7-O-glucoside) was proved in the plant extract. In the same report, effect of aqueous extract of *Biophytum sensitivum* leaf was studied against streptozotocin (STZ)-nicotinamide-induced diabetic rats and as a result, blood glucose and glycosylated haemoglobin level were significantly reduced after 28 days.

***Citrullus colocynthis* - Bitter apple (English):** The plant fruit is recognized for its anti-diabetic properties [25]. Along with diabetes, the plant extract is also useful for the management of infectious diseases, inflammation, haemorrhoids and cancer[15,16,57]. In an experimental investigation, when alloxan-induced diabetic rats were orally administrated with plant pulp extract with doses of 300 mg/kg, it shows reduction in plasma glucose and improves insulin level after 1 to 6 hours. Secondary metabolites content, essentially cucurbitacins, saponins, polyphenols, flavonoids, alkaloids and terpenoids which are present in the plant extract are mainly responsible for its pharmacological activity[29,53,61].

***Coccinia indica* - Ivy Guard (English) or Kanturi (Hindi):** This perennial tendril climber is well known in Ayurveda and Unani system for treatment of diabetics, skin eruptions, tongue sore, earache etc.[20] The plant is well recognized in Ayurveda as it has been successfully used for effective treatment of *Diabetes mellitus* from ancient times. Additionally, the treatment through the plant extract is comparatively known for negligible side effects or toxic contribution[12]. Oral doses of the plant leaves extract were proved for hypoglycemic activities in alloxan-diabetic dogs and 18 hrs fasted STZ diabetic rats when they were treated with ethanolic extract of the same plant[70]. Ethanolic plant extract from its aerial parts was evaluated in terms of antihyperglycemic and hypolipidemic effects while doing experiments with STZ induced diabetic rats[12]. Treatment with the dosages of plant extract (100 to 200 mg/kg) for continuously 14 days was effective to develop efficient antihyperglycemic and hypolipidemic effects.

***Eugenia jambolana* - Indian Gooseberry:** Since ancient times, the plant fruit has been traditionally implemented for remedial purposes for diabetes. The plant is also well known in Indian traditional medicine for the remedy of various other health complications. Significant antihyperglycemic potential was already established from different parts of the plant like kernel, leaves and septum[31]. The plant was reported to contain bioactive compounds like alkaloids, glycosides, terpenoids, flavonoids with anti-diabetic property[59].

***Eucalyptus globulus* - Safeda (Hindi):** This lofty tree is normally find out in different places of India, Australia, South Africa, Southern Europe and it is around 90 m in height. Along with diabetics, the plant is well recognized for antibacterial, antioxidative, antiplaque, antiviral and antifungal activities[67]. The compounds isolated from *Eucalyptus globulus* leaves like quercetin, d-limonene, dipentene, citronellal, caffeic, gentisic and protoca techuic acids were reported with anti-inflammatory, antianxiety and other medicinal properties[67].

***Ficus bengalensis* - Moraceae or Indian Banyan tree (Hindi):** This holy tree is available throughout India and it is traditionally well reputed for its antidiabetic properties including diabetics. The plant is also known to cure various other diseases in Indian traditional medicinal system [72]. Different parts of the plant extract were evaluated to have anti-tumor and anti-bacterial activities and it was implemented as folk medicine to cure respiratory problems and certain skin disorders[50]. The promising hyperglycemic effect of the plant extract was successfully observed in STZ diabetic rats, normal and moderately alloxanized diabetic dogs when they were administrated with bark extract of the plant[25]. In another study, the plant root extract was examined for antidiabetic potential using normal, sub and mild diabetic model rats and the extract with dosages of 300 mg/ kg was effective to reduce 43.8 and 40.7% in BGL during FBG and glucose tolerance test. Existence of glycemic elements in high concentration was proved in the plant extract.

***Gymnema Sylvestre* - Periploca of the woods:** *Gymnema Sylvestre* is popularly well-known as Gudmar or Merasingi in India and along with India, such woody perennial vine is also available in tropical areas of Africa, Australia and India. Such therapeutically potential plant has been largely used in folk, ayurvedic, homeopathic and in modern medicine. Oral

use of such plant extract was diagnosed with diverse range of remedial properties for diabetes, obesity, pancreatic malfunction and other chronic disorders[33]. It is medicinal properties are mainly recognized due to the presence of the classes of triterpene saponins, gymnemic acids (I - XVIII and gymnemosaponins I - V)[33].

Antidiabetic properties of the plant extract due to the presence of bioactive compounds and the relationship between such antidiabetic compounds with antioxidants present in plant extract was identified in the reduction of blood sugar[40]. In an experimental observation, effect of ethanolic extracts of the wild plant leaves and *in vitro* grown suspension cells of the plant was observed on alloxan induced diabetic rats[33]. It was significantly effective to reduce glucose level from blood and urine and sugar and lipids levels from serum.

***Momordica charantia* - Bitter Gourd (English):** Bitter Gourd is widely cultivated in India and Africa as an edible vegetable. The plant has been successfully used for the medicinal purposes in different Asian countries and it is having a long therapeutic history. It is well recognized for its several therapeutic activities which includes anti-tumor, anti-inflammation, anti-oxidation, improving immunity, lowering cholesterol and anti-AIDS[60,63,77]. Presence of an important compound charantin, an α-glucosidase inhibitor in the plant extract is responsible for developing antidiabetic properties[27].

***Ocimum sanctum* - Holi basil or Tulsi (Hindi):** This traditional herbal plant is normally available all over India and is specifically cultivated in gardens or surrounding of temples. From the ancient times, the plant has been effectively used for the treatment of cough, respiratory disorders, poisoning, impotence and arthritis and due the nontoxic nature, application of the herb is considered fully safe for human[13,23]. It was already reported that the plant contains bioactive components with antihyperglycemic potentials. Additionally, the plant is known for its wound healing, antioxidant, radiation protective, immunomodulatory, antifertility, anti-inflammatory, antimicrobial, antistress and anticancer activities[71]. The leaves of the plant are enriched with volatile oil (0.7%), phenolics, flavonoids, neolignans, terpenoids and fatty acid derivatives[9]. Blood glucose levels were significantly reduced for both normal and alloxan-induced diabetic rats when they were administrated with aqueous leaves extract of the plant[76].

***Swertia chirayita*:** *Swertia chirayita* which is the most popular Ayurvedic plant indigenous to the climate of Himalaya has been successfully used for the treatment of numerous diseases including diabetics. Due to the presence of multiple bioactive compounds like amarogentin, swertiamarin, mangiferin, swechirin, gentianine, sweroside, gentiopicrin, the plant contributes for several medicinal purposes[38]. Traditionally, this herb has been effectively used to reduce blood pressure and blood sugar[38]. Substantial antihyperglycemic activity with improved glucose tolerance, increased glycogenesis, decreased insulin resistance was noticed in neonatal-streptozotocin induced type 2 diabetic model (nSTZ-T2DM) rats when they were treated with the stem-bark extract of the plant[17]. Similarly, methanolic extract of the plant leaf was also diagnosed with anti-diabetic potential[64]. Therapeutically active phytochemicals which are normally available in *S. chirayita* plant extract are amarogentin, mangiferin, swertiamarin[22].

***Tinospora cordifolia* - Guduci (Hindi):** This medicinal plant is well known in Ayurveda to cure diabetics and other metabolic disorders[20]. The plant is normally available in some places in India, Myanmar, Sri Lanka and China [24]. Due to the presence of enormous therapeutic properties, the plant has been traditionally used for the treatment of jaundice, rheumatism, urinary disorder, skin diseases, diabetes, anaemia, inflammation, allergic condition and to develop strong immune system[73]. Chemical constituents which are mainly responsible for the pharmacological potential of the plant are terpenoids, alkaloids, lignans diterpenoid lactones, glycosides, steroids, sesquiterpenoid, phenolics, aliphatic compounds, essential oils, fatty acids and polysaccharides[36]. Even it was also evident that regular administration of alcoholic or aqueous plant extract was effective to bring down blood glucose level as well as to increase glucose tolerance in rodents[26].

Conclusion

The review concludes that medicinal plants are able to show potential antidiabetic properties similar to or even more efficiently than conventional synthetic drugs. Plant extracts in different forms are quite capable in the management of insulin secretion, regulation of blood glucose level as well as serum lipids. Different animal models including normal fasted rats, alloxan-induced diabetic rats, diabetic dogs, normal fasting guinea pigs and rabbits were successfully investigated for standardization of such plant extract dosages.

Still there is a lack of belief in such derived medicines over commercially known medicines. More significant research studies are needed to be conducted for the development of trust on such plant-based remedies of diabetics.

Acknowledgement

Authors are thankful to University research grant to conduct the research work.

References

1. Afrisham R., Aberomand M., Ghaffari M.A., Siahpoosh A. and Jamalan M., Inhibitory Effect of Heracleum persicum and Ziziphus jujuba on Activity of Alpha-Amylase, *J. Bot*, **2015**, 824683 **(2015)**

2. Ahmadian M., Suh J.M., Hah N., Liddle C., Atkins A.R., Downes M. and Evans R.M., Pparγ signaling and metabolism: The good, the bad and the future, *Nat. Med*, **19**, 557–566 **(2013)**

3. Akash M.S.H., Rehman K. and Chen S., Spice plant Allium cepa: Dietary supplement for treatment of type 2 diabetes mellitus, *Nutr*, **30**, 1128–1137 **(2014)**

4. Al-Goblan A.S., Al-Alfi M.A. and Khan M.Z., Mechanism linking diabetes mellitus and obesity, *Diabetes, Metab. Syndr. Obes. Targets Ther*, **7**, 587–591 **(2014)**

5. Alam, M.M., Siddiqui M.B. and Husain W., Treatment of diabetes through herbal drugs in rural India, *Fitoter*, **61**, 240–242 **(1990)**

6. Albuquerque C., Correia C. and Ferreira M., Adherence to the Therapeutic Regime in Person with Type 2 Diabetes, *Procedia - Soc. Behav. Sci*, **171**, 350–358 **(2015)**

7. Aldayel T.S., Grace M.H., Lila M.A., Yahya M.A., Omar U.M. and Alshammary G., LC-MS characterization of bioactive metabolites from two Yemeni Aloe spp. with antioxidant and antidiabetic properties, *Arab. J. Chem*, **13**, 5040–5049 **(2020)**

8. Ananda Prabu K., Kumarappan C.T., Christudas S. and Kalaichelvan V.K., Effect of Biophytum sensitivum on streptozotocin and nicotinamide-induced diabetic rats, *Asian Pac. J. Trop. Biomed*, **2**, 31–35 **(2012)**

9. Antora R.A. and Salleh R.M., Antihyperglycemic effect of Ocimum plants: A short review, *Asian Pac. J. Trop. Biomed*, **7**, 755–759 **(2017)**

10. Arumugam G., Manjula P. and Paari N., A review: Anti diabetic medicinal plants used for diabetes mellitus, *J. Acute Dis*, **2**, 196–200 **(2013)**

11. Aruna A., Nandhini R., Karthikeyan V., Bose P. and Vijayalakshmi K., Comparative anti-diabetic effect of methanolic extract of insulin plant (Costus pictus) leaves and its silver nanoparticle, *Indo Am. J. Pharm. Res*, **4**, 3217–3230 **(2014)**

12. Balaraman A.K., Singh J., Dash S. and Maity T.K., Antihyperglycemic and hypolipidemic effects of Melothria maderaspatana and Coccinia indica in Streptozotocin induced diabetes in rats, *Saudi Pharm. J*, **18**, 173–178 **(2010)**

13. Bano N., Ahmed A., Tanveer M., Khan G. and Ansari M., Pharmacological Evaluation of Ocimum sanctum, *J. Bioequiv. Availab*, **9**, 387–392 **(2017)**

14. Bastaki S., Review Diabetes mellitus and its treatment, *Int J Diabetes Metab*, **13**, 111–134 **(2005)**

15. Benarba B., Meddah B. and Aoues A., Bryonia dioica aqueous extract induces apoptosis through mitochondrial intrinsic pathway in BL41 Burkitt's lymphoma cells, *J. Ethnopharmacol*, **141**, 510–516 **(2012)**

16. Benariba N., Djaziri R., Bellakhdar W., Belkacem N., Kadiata M., Malaisse W.J. and Sener A., Phytochemical screening and free radical scavenging activity of Citrullus colocynthis seeds extracts, *Asian Pac. J. Trop. Biomed*, **3**, 35–40 **(2013)**

17. Bhowmik A., Mosihuzzaman M., Kabir Y. and Rokeya B., Antihyperglycemic Activity of Swertia chirata on nSTZ-T2DM Rats: A Chronic Study, *J. Pharm. Res. Int*, **22**, 1–11 **(2018)**

18. Bindu J. and Narendhirakannan R.T., Role of medicinal plants in the management of diabetes mellitus: a review, *3 Biotech*, **9(1)**, 4 **(2019)**

19. Bischoff H., The mechanism of α-glucosidase inhibition in the management of diabetes, *Clin. Investig. Med*, **18**, 303–311 **(1995)**

20. Chopra R.N., Nayar S.L. and Chopra I.C., Glossary of Indian medicinal plants, CSIR, New Delhi **(1956)**

21. Dattatraya S.K., Dattatray S.K., Sunil K.G. and Suryakant M.S., Formulation and Evaluation of Herbal Antidiabetic Tablet, *Asian J. Res. Pharm. Sci*, **10**, 145–148 **(2020)**

22. Dey P., Singh J., Suluvoy J.K., Dilip K.J. and Nayak J., Utilization of Swertia chirayita Plant Extracts for Management of Diabetes and Associated Disorders: Present Status, Future Prospects and Limitations, *Nat. Products Bioprospect*, **10**, 431–443 **(2020)**

23. Gautam, M.K. and Goel R.K., Toxicological study of Ocimum sanctum Linn leaves: Hematological, biochemical and histopathological studies, *J. Toxicol*, **2014**, 1-10 **(2014)**

24. Ghosh S. and Saha S., Tinospora cordifolia: One plant, many roles, *Anc. Sci. Life*, **31**, 151 **(2012)**

25. Grover J.K., Yadav S. and Vats V., Medicinal plants of India with anti-diabetic potential, *J. Ethnopharmacol*, **81**, 81–100 **(2002)**

26. Gupta S.S., Verma S.C., Garg V.P. and Rai M., Anti-diabetic effects of Tinospora cardifolia. I. Effect on fasting blood sugar level, glucose tolerance and adrenaline induced hyperglycaemia, *Indian J. Med. Res*, **55**, 733–45 **(1967)**

27. Hartajanie L., Fatimah-Muis S., Heri-Nugroho Hs K., Riwanto I. and Sulchan M., Probiotics Fermented Bitter Melon Juice as Promising Complementary Agent for Diabetes Type 2: Study on Animal Model, *J. Nutr. Metab*, **2020**,1-7 **(2020)**

28. Hasanpour M., Iranshahy M. and Iranshahi M., The application of metabolomics in investigating anti-diabetic activity of medicinal plants, *Biomed. Pharmacother*, **128**, 110263 **(2020)**

29. Hussain A.I., Rathore H.A., Sattar M.Z.A., Chatha S.A.S., Ahmad F. ud din, Ahmad A. and Johns E.J., Phenolic profile and antioxidant activity of various extracts from Citrullus colocynthis (L.) from the Pakistani flora, *Ind. Crops Prod*, **45**, 416–422 **(2013)**

30. Islas J.F, Acosta E., G-Buentello Z., Delgado-Gallegos J.L., Moreno-Treviño M.G., Escalante B. and Moreno-Cuevas J.E., An overview of Neem (Azadirachta indica) and its potential impact on health, *J. Funct. Foods*, **74**, 104171 **(2020)**

31. Jana K., Bera T.K. and Ghosh D., Antidiabetic effects of Eugenia jambolana in the streptozotocin-induced diabetic male albino rat, *Biomarkers Genomic Med*, **7**, 116–124 **(2015)**

32. Karimi A., Majlesi M. and Rafieian-Kopaei M., Herbal versus synthetic drugs; beliefs and facts, *J. Nephropharmacology*, **4**, 27–30 **(2015)**

33. Karthic R., Nagaraj S., Arulmurugan P., Seshadri S., Rengasamy R. and Kathiravan K., Gymnema sylvestre R. Br. suspension cell extract show antidiabetic potential in Alloxan

induced diabetic albino male rats, *Asian Pac. J. Trop. Biomed*, **2**, S930–S933 **(2012)**

34. Kerner W. and Brückel J., Definition, classification and diagnosis of diabetes mellitus, *Exp. Clin. Endocrinol. Diabetes*, **122**, 384–386 **(2014)**

35. Kesari A.N., Gupta R.K., Singh S.K., Diwakar S. and Watal G., Hypoglycemic and antihyperglycemic activity of Aegle marmelos seed extract in normal and diabetic rats, *J. Ethnopharmacol*, **107**, 374–379 **(2006)**

36. Khan M.M., Haque M.S. and Chowdhury M.S.I., Medicinal use of the unique plant Tinospora Cordifolia: evidence from the traditional medicine and recent research, *Asian J. Med. Biol. Res*, **2**, 508–512 **(2017)**

37. Kumar R., Singh A.K., Gupta A., Bishayee A. and Pandey A.K., Therapeutic potential of Aloe vera—A miracle gift of nature, *Phytomedicine*, **60**, 1-11 **(2019)**

38. Kumar V. and Van Staden J., A Review of Swertia chirayita (Gentianaceae) as a Traditional Medicinal Plant, *Front. Pharmacol*, **6**, 308 **(2015)**

39. Naveen K.L., Veigas G.J. and Bhattacharjee A., Patient with Diabetes Mellitus and Ocular Complications: A Brief review, *Asian J. Pharm. Technol.*, **11**, 141–145 **(2021)**

40. Laha S. and Paul S., Gymnema sylvestre (Gurmar): A potent herb with anti-diabetic and antioxidant potential, *Pharmacogn. J*, **11**, 201–206 **(2019)**

41. Mamun-or-Rashid A., Hossain M.S., Hassan N., Dash B.K., Sapon M.A. and Sen M.K., A review on medicinal plants with antidiabetic activity, *J. Pharmacogn. Phytochem*, **3**, 149–159 **(2014)**

42. Manandhar B., Paudel K.R., Sharma B. and Karki R., Phytochemical profile and pharmacological activity of Aegle marmelos Linn, *J. Integr. Med*, **16(3)**, 153-163 **(2018)**

43. Marrelli M., Amodeo V., Statti G. and Conforti F., Biological properties and bioactive components of allium cepa L.: Focus on potential benefits in the treatment of obesity and related comorbidities, *Molecules*, **24(1)**, 119 **(2019)**

44. Martins N., Petropoulos S. and Ferreira I.C.F.R., Chemical composition and bioactive compounds of garlic (Allium sativum L.) as affected by pre- and post-harvest conditions: A review, *Food Chem*, **211**, 41–50 **(2016)**

45. Mazumdar S., Marar T., Patki J., Devarajan S., Zambare V. and Swami D., *In silico* and *in vitro* analysis reveal multi-target anti-hyperglycaemic properties of gedunin, a limonoid from neem (Azadirachta indica), *Clin. Phytoscience*, **6**, 1–11 **(2020)**

46. Modak M., Dixit P., Londhe J., Ghaskadbi S. and Devasagayam T.P.A., Indian herbs and herbal drugs used for the treatment of diabetes, *J. Clin. Biochem. Nutr*, **40**, 163–73 **(2007)**

47. Mohan V., Sandeep S., Deepa R., Shah B. and Varghese C., Epidemiology of type 2 diabetes: Indian scenario, *Indian J Med Res*, **125**, 217–230 **(2007)**

48. Moini J., The Health Impact of Diabetes, In Epidemiology of Diabetes, 115–145 **(2019)**

49. Moukette B.M., Ama Moor V.J., Biapa Nya C.P., Nanfack P., Nzufo F.T., Kenfack M.A., Ngogang J.Y. and Pieme C.A., Antioxidant and Synergistic Antidiabetic Activities of a Three-Plant Preparation Used in Cameroon Folk Medicine, *Int. Sch. Res. Not*, **2017**, 1–7 **(2017)**

50. Mousa O., Vuorela P., Kiviranta J., Wahab S.A., Hiltunen R. and Vuorela H., Bioactivity of certain Egyptian Ficus species, *J. Ethnopharmacol*, **41**, 71–76 **(1994)**

51. Muñiz-Ramirez A., Perez R.M., Garcia E. and Garcia F.E., Antidiabetic Activity of Aloe vera Leaves, *J Evid. based Complementary Altern. Med*, **2020**, 1-9 **(2020)**

52. Murphy W.J., Hand R.K., Abram J.K. and Papoutsakis C., Impact of Diabetes Prevention Guideline Adoption on Health Outcomes: A Pragmatic Implementation Trial, *J. Acad. Nutr. Diet*, **21(10)**, 2090-2100 **(2020)**

53. Najafi S., Sanadgol N., Sadeghi Nejad B., Beiragi M.A. and Sanadgol E., Phytochemical screening and antibacterial activity of Citrullus colocynthis (Linn.) Schrad against Staphylococcus aureus, *J. Med. Plants Res*, **4**, 2321–2325 **(2010)**

54. Ojieh A.E., Ugorji A.E., Ovuakporaye I.S., Ewhre O.L. and Ossai N.R., Comparative Evaluation of Hypoglycemic Properties of Raw and Boiled Allium cepa in Alloxan-Induced Diabetes Mellitus Rats, *UK J. Pharm. Biosci*, **4**, 38 **(2016)**

55. Ota A. and Ulrih N.P., An overview of herbal products and secondary metabolites used for management of type two diabetes, *Front. Pharmacol*, **8**,436 **(2017)**

56. Patel D., Prasad S., Kumar R. and Hemalatha S., An overview on antidiabetic medicinal plants having insulin mimetic property, *Asian Pac. J. Trop. Biomed*, **2**, 320–330 **(2012)**

57. Rachid A., Rabah D., Farid L., Zohra S.F., Houcine B. and Nacéra B., Ethnopharmacological survey of medicinal plants used in the traditional treatment of diabetes mellitus in the North Western and South Western Algeria, *J. Med. Plants Res*, **6**, 2041–2050 **(2012)**

58. Rahmani G., Farajdokht F., Mohaddes G., Babri S., Ebrahimi V. and Ebrahimi H., Garlic (Allium sativum) improves anxiety- and depressive-related behaviors and brain oxidative stress in diabetic rats, *Arch. Physiol. Biochem*, **126**, 95–100 **(2020)**

59. Rai M.K., A review on some antidiabetic plants of India, *Anc. Sci. Life*, **14**, 168–80 **(1995)**

60. Raina K., Kumar D. and Agarwal R., Promise of bitter melon (Momordica charantia) bioactives in cancer prevention and therapy, *Semin. Cancer Biol*, **40-41**,116-129 **(2016)**

61. Ramanathan T., Gurudeeban S. and Satyavani K., Characterization of Volatile Compounds from Bitter Apple (Citrullus colocynthis) Using GC-MS, *Int. J. Chem. Anal. Sci*, **2**, 108–110 **(2011)**

62. Ranjan V. and Vats M., A Comprehensive Review on Antidiabetic Potential of Medicinal Plants, *Int J Ayu Pharm Chem*,

7, 233–285 **(2017)**

63. Rao C.V., Immunomodulatory effects of momordica charantia extract in the prevention of oral cancer, *Cancer Prev. Res*, **11**, 185–186 **(2018)**

64. Roy P., Abdulsalam F.I., Pandey D.K., Bhattacharjee A., Eruvaram N.R. and Malik T., Evaluation of antioxidant, antibacterial and antidiabetic potential of two traditional medicinal plants of India: Swertia cordata and Swertia chirayita, *Pharmacognosy Res*, **7**, S57–S62 **(2015)**

65. Saito I., Inami F., Ikebe T., Moriwaki C., Tsubakimoto A., Yonemasu K. and Ozawa H., Impact of diabetes on health-related quality of life in a population study in Japan, *Diabetes Res. Clin. Pract*, **73**, 51–57 **(2006)**

66. Shabab S., Gholamnezhad Z. and Mahmoudabady M., Protective effects of medicinal plant against diabetes induced cardiac disorder: A review, *J. Ethnopharmacol*, **265**, 113328 **(2021)**

67. Shah G., Kaur M., Singh P.S., Rahar S., Dhabliya F., Arya Y. and Shri R., Pharmacognostic Parameters of Eucalyptus globulus Leaves, *Pharmacogn. J*, **4**, 38–43 **(2012)**

68. Sharma R. and Arya V., A Review on Fruits Having Anti-Diabetic Potential, *J. Chem. Pharm. Res*, **3**, 204–212 **(2011)**

69. Shaw J.E., Sicree R.A. and Zimmet P.Z., Global estimates of the prevalence of diabetes for 2010 and 2030, *Diabetes Res. Clin. Pract*, **87**, 4–14 **(2010)**

70. Shibib B.A., Khan L.A. and Rahman R., Hypoglycaemic activity of *Coccinia indica* and *Momordica charantia* in diabetic rats: depression of the hepatic gluconeogenic enzymes glucose-6-phosphatase and fructose-1,6-bisphosphatase and elevation of both liver and red-cell shunt enzyme glucose-6-phosphate dehydrogenase, *Biochem. J*, **292**, 267–270 **(1993)**

71. Singh D. and Chaudhuri P.K., A review on phytochemical and pharmacological properties of Holy basil (Ocimum sanctum L.), *Ind. Crops Prod*, **118**, 367–382 **(2018)**

72. Singh R.K., Mehta S., Jaiswal D., Rai P.K. and Watal G., Antidiabetic effect of Ficus bengalensis aerial roots in experimental animals, *J. Ethnopharmacol*, **123**, 110–114 **(2009)**

73. Sonkamble V.V. and Kamble L.H., Antidiabetic Potential and Identification of Phytochemicals from Tinospora cordifolia, *Am. J. Phytomedicine Clin. Ther*, **3(1)**, 97–110 **(2015)**

74. Suryavanshi A. and Saxena A.M., The Antidiabetic Activity Of Bioactive Compounds Of Indian Medicinal Plants: A Meta Data Review, *Biosci. Biotechnol. Res. Commun*, **12**, 397–407 **(2019)**

75. Thulé P.M. and Umpierrez G., Sulfonylureas: A new look atold therapy topical collection on pharmacologic treatment of type 2 diabetes, *Curr. Diab. Rep*, **14 (4)**, 473 **(2014)**

76. Vats V., Grover J.K. and Rathi S.S., Evaluation of anti-hyperglycemic and hypoglycemic effect of Trigonella foenum-graecum Linn, Ocimum sanctum Linn and Pterocarpus marsupium Linn in normal and alloxanized diabetic rats, *J. Ethnopharmacol*, **79**, 95–100 **(2002)**

77. Yang W.S., Yang E., Kim M.J., Jeon D., Yoon D.H., Sun G.H., Lee S., Yoo B.C., Yeo S.G. and Cho J.Y., Momordica charantia Inhibits Inflammatory Responses in Murine Macrophages via Suppression of TAK1, *Am. J. Chin. Med*, **46**, 435–452 **(2018)**

78. Zylla D.M., Gilmore G., Eklund J., Richter S. and Carlson A., Impact of diabetes and hyperglycemia on health care utilization, infection risk and survival in patients with cancer receiving glucocorticoids with chemotherapy, *J. Clin. Oncol*, **36**, 19–19 **(2018)**.

(Received 08th January 2022, accepted 05th March 2022)