Effect of a Novel Phytopharmaceutical Formulation with an Innovative Potential in Patients with Treated Uncontrolled Type 2 Diabetes Mellitus

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Abstract

Background and Aims: Diabetes mellitus is a major health problem in India. The development of a new drug of natural origin that assures safety with moderate but definite efficacy is the need of the time. Authors have developed formulation containing phytoactives from Pterocarpus marsupium Roxb and Andrographis paniculata Nees in specific proportion for the first time, as an anti-diabetic supplement which improves the glycemic control. We aim to study the effect of Ptyrone™ in patients with treated uncontrolled T2DM and its safety and tolerability.

Study Design: In an open labelled trial, 115 patients with T2DM were divided in three groups: Metformin, Metformin + Gliptins and Metformin + Sulphonylurea. Ptyrone™ capsules were given to all the patients along with their OHA's, orally twice a day for 12 weeks. Laboratory investigations were studied at the baseline and at fixed intervals till the end of the study.

Results: There was a statistically significant decrease (p value< 0.0001) in fasting and post prandial blood sugar along with triglycerides in all groups. There was reduction in levels of glycosylated haemoglobin also in all the groups. All other biochemical investigations were within normal limits. Ptyrone™ capsules were well tolerated clinically and no serious adverse events were reported during the period of therapy.

Conclusion: The authors have shown, for the first time, the therapeutic potential of Ptyrone™ at a dose of 450 mg twice a day supplemented along with anti-diabetic medications. This therapeutic efficacy needs to be evaluated further in a larger sample size, with a placebo/active controlled randomized double blind multicentric trial.

Clinical Trial Registration No.: CTRI/2019/05/019446

Key Words: Treated uncontrolled type 2 diabetes mellitus, andrographolide, Pterostilbene, blood sugar, lipids.

Conflict of Interest: Dr. Yogesh Dound is Proprietor of Shreepad Shree Vallabh, SSV Phytopharmaceuticals

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Abbreviations

ESR- Erythrocyte Sdimentation Rate
FBS- Fasting Blood Sugar
GLUT4- Glucose transporter type 4
HbA1c- Glycosylated haemoglobin
mRNA- Messenger RNA
PPAR- Peroxisome Proliferator Activated Receptor
PPBS- Post Prandial Blood sugar
PT-INR- Prothrombin Time-International Normalised Ratio
SGLT2- Sodium Glucose Transport Protein 2
SSV- Shreepad Shree Vallabh SSV Phytopharmaceuticals, Mumbai
STZ- Streptozotocin
T2DM- Type 2 Diabetes Mellitus
TG- Triglyceride

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Introduction

Type 2 Diabetes Mellitus is a metabolic disorder characterized by hyperglycemia with inadequate insulin secretion and/or insulin resistance. Currently 537 million people worldwide have diabetes and 74.2million people in India have diabetes as per an International Diabetes Federation (IDF) report.[1] India, after China, has the largest number of type 2 diabetic patients. The number is expected to be 109 million by 2025 in India.[2] With increased prevalence globally or in India; Diabetes Mellitus has become a huge economic and health burden to our nation.

About 80% of India's population relies on the use of traditional medicines, which is predominantly based on plant materials.[3] Several clinical and preclinical studies on the Ayurvedic medicinal plants have shown their antidiabetic potential.[4] There have also been placebo-controlled clinical studies with plants and polyherbal formulations. During the seventies, thirty medicinal plants/formulations were studied in diabetic patients with placebo control for their antihyperglycemic activity.[5]

The development of a new drug of natural origin that assures safety with moderate but definite efficacy is the need of the time. A safe and effective plant- based antidiabetic drug, hence, offers an opportunity as an adjuvant. Various attempts are being made to prepare formulations with optimized contents of phytoactives of the plant. Their combined activity against multiple targets can be pooled together in a phytopharmaceutical by a novel approach with an innovative potential as a complementary agent with specific actions for the management of diabetes. Ptyrone™ is one such candidate that has potential in the management of diabetes and can emerge as a promising alternative to currently used modalities.

To study the effect of Ptyrone™ in patients with treated, uncontrolled T2DM and its safety and tolerability.

Materials and Methods

Study Method

This study was an open-labelled study for the evaluation of activity and tolerability of Ptyrone™ in patients of treated, uncontrolled type 2 diabetes mellitus. The study was conducted at Kokan Hospital, Jogeshwari, Mumbai.

Subjects

Prior to the study, permission from the Independent Ethics Committee was obtained. Total of 139 patients suffering from type 2 diabetes mellitus without any major micro and macro vascular complications, as reported by medical and biochemical history, of age 18-65 years were screened. A written informed consent (approved by the ethics committee) was taken from all the patients prior to the enrollment. Out of 139 patients, 115 patients completed the study. The patients were divided in three groups depending upon the type of OHSA's medication they were taking for diabetes. So, they were randomly divided in to three groups, viz., patients who were only on Metformin (Group A), patients who were taking Metformin + Sulphonylurea (Group B) and patients who were on Metformin + Gliptins (Group C) groups.

Table 1 shows the number of patients in each group along with other demographic data.

The Study Procedure and Assessments

One hundred and fifteen patients after signing the Informed Consent Documents and after taking a proper history, examination and investigations were enrolled as per the selection criteria mentioned in the protocol (approved by Ethics Committee). Blood investigations viz. complete blood counts with ESR, homocysteine, glycosylated haemoglobin, fasting and post prandial plasma glucose, PT-INR, triglyceride, liver function tests and renal function tests were done at base line, at second week, at fourth week and at the end of the study (12th week). The patients were serially followed up at 2nd week, 4th week, 8th week and 12th week. A detailed physical (general and systemic) examination was

Table 1

	Group A		Group B		Group C	
	Male	Female	Male	Female	Male	Female
N	17	19	24	17	21	17
Age (yrs)	46.59 ± 8.2	42.42 ± 8.0	41.08 ±7.6	43.71 ± 9.9	46.33 ± 8.2	46.0 ± 7.3
FBS (gm/dL)	133.56 ± 7.3	133.47 ± 9.5	142.79 ± 6.0	142.65 ± 5.9	149.62 ± 8.4	150.69 ± 7.8
PPBS (gm/dL)	259.00 ± 11.3	259.00 ± 11.3	278.17 ± 11.3	278.17 ± 11.3	291.19 ± 5.1	291.19 ± 5.1

Values expressed in Mean ± SD; SD- Standard Deviation

done at the baseline and at every follow up visits. A predesigned case record form (approved by Ethics Committee), which included a page of adverse events, was used. Each patient received Ptyrone™ 450 mg capsules manufactured by SSV for 12 weeks. The patients were advised to consume 2 capsules a day of Ptyrone™ for 12 weeks, just after or along with the breakfast and dinner. The patients continued to take their regular prescribed oral anti-diabetic medications throughout the study. The safety was assessed by clinical tolerability, adverse events and by any change in the organ function tests. The therapeutic activity was assessed by noting the reduction in the blood sugar levels fasting and post-prandial, glycosylated haemoglobin and triglycerides levels as compared to the baseline.

Statistical Analysis

Data of 115 patients was analyzed by using unpaired t-test method. This method has been used to determine the significance of two sets of data for blood sugar levels fasting and post prandial, glycosylated haemoglobin and triglycerides levels in comparison to the baseline.

Table 2: The Fasting Blood Sugar (FBS), Post Prandial Blood sugar (PPBS), Glycosylated haemoglobin (HbA1c) and Triglyceride (TG) levels in Group A (Ptyrone™ + Metformin), Group B (Ptyrone™ + Metformin + Sulphonylurea Group) and Group C (Ptyrone™ + Metformin + Gliptin Group) from Baseline to 12th week.

Parameters	Sex	Baseline	2nd Week	4th Week	8th Week	12th Week
Group A						
HbA1c (%)	M	7.8 ± 0.5	7.8 ± 0.5	7.7 ± 0.5	7.6 ± 0.5	7.4 ± 0.5
	F	7.7 ± 0.4	7.7 ± 0.4	7.6 ± 0.4	7.5 ± 0.4	7.3 ± 0.4
FBS* (mg/dL)	M	133.56 ± 7.3	120.20 ± 6.6	109.52 ± 6.0	100.17 ± 5.5	93.49 ± 5.1
	F	133.47 ± 9.5	120.12 ± 8.6	109.45 ± 7.8	100.10 ± 7.2	93.43 ± 6.7
PPBS* (mg/dL)	M	259.00 ± 11.3	227.92 ± 9.9	207.20 ± 9.0	189.07 ± 8.2	170.94 ± 7.4
	F	262.21 ± 7.5	230.75 ± 6.6	209.77 ± 6.0	191.41 ± 5.4	173.06 ± 4.9
TG* (mg/dL)	M	239.09 ± 24.4	219.96 ± 22.4	200.84 ± 20.5	191.27 ± 19.5	181.71 ± 18.5
	F	242.10 ± 24.3	222.73 ± 22.4	203.36 ± 20.4	193.68 ± 19.5	184.00 ± 18.5
Group B						
HbA1c (%)	M	8.3 ± 0.8	8.3 ± 0.8	8.2 ± 0.8	8.1 ± 0.8	7.9 ± 0.8
	F	8.0 ± 0.5	8.0 ± 0.5	7.9 ± 0.5	7.8 ± 0.5	7.6 ± 0.5
FBS* (mg/dL)	M	142.79 ± 6.0	128.51 ± 5.4	117.09 ± 5.0	107.09 ± 4.5	99.95 ± 4.2
	F	142.65 ± 5.9	128.38 ± 5.3	116.97 ± 4.9	106.99 ± 4.4	99.85 ± 4.1
PPBS* (mg/dL)	M	278.17 ± 11.3	244.79 ± 9.9	222.53 ± 9.0	203.06 ± 8.2	183.59 ± 7.4
	F	271.65 ± 10.3	239.05 ± 9.1	217.32 ± 8.3	198.30 ± 7.5	179.29 ± 6.8
TG* (mg/dL)	M	239.83 ± 29.8	220.65 ± 27.4	201.46 ± 25.0	191.87 ± 23.8	182.27 ± 22.6
	F	243.23 ± 32.3	223.77 ± 29.7	204.31 ± 27.1	194.59 ± 25.8	184.86 ± 24.5
Group C						
HbA1c (%)	M	8.8 ± 0.6	8.8 ± 0.6	8.7 ± 0.6	8.6 ± 0.6	8.4 ± 0.6
	F	8.9 ± 0.6	8.9 ± 0.6	8.8 ± 0.6	8.7 ± 0.6	8.5 ± 0.6
FBS* (mg/dL)	M	149.62 ± 8.4	134.66 ± 7.6	122.69 ± 6.9	112.21 ± 6.3	104.73 ± 5.9
	F	150.69 ± 7.8	135.62 ± 7.0	123.56 ± 6.4	113.02 ± 5.8	105.48 ± 5.5
PPBS* (mg/dL)	M	291.19 ± 5.1	256.25 ± 4.5	232.95 ± 4.1	212.57 ± 3.7	192.19 ± 3.4
	F	288.00 ± 5.8	253.44 ± 5.1	230.40 ± 4.6	210.24 ± 4.2	190.08 ± 3.8
TG* (mg/dL)	M	248.84 ± 21.9	228.93 ± 20.1	209.03 ± 18.4	199.07 ± 17.5	189.12 ± 16.6
	F	252.10 ± 27.4	231.93 ± 25.2	211.77 ± 23.0	201.68 ± 21.9	191.60 ± 20.8

Values expressed in Mean ± SD; SD- Standard Deviation.

* Denotes decrease is statistically significant (p value< 0.0001) from baseline to 12th week.

Results

Ptyrone™ + Metformin Group (Group A): The FBS levels decreased from 133.58 ± 8.38 mg/dL to 93.42 ± 6.02 mg/dL. The PPBS levels decreased from 260.69 ± 9.45 mg/dL to 172.08 ± 6.26 mg/dL. HbA1c levels decreased from 7.75 ± 0.42% to 7.35 ± 0.43%. The TG levels decreased from 240.68 ± 24.06 mg/dLto 182.92 ± 18.28 mg/dL (Table 2). The decrease in the FBS, PPBS and TG levels was found to be extremely statistically significant (p value< 0.0001).

Ptyrone™ + Metformin + Sulphonylurea Group

(Group B): The FBS levels decreased from 142.73 ± 5.92 mg/dL to 99.98 ± 4.20 mg/dL. The PPBS levels decreased from 275.46 ± 11.24 mg/dL to 172.08 ± 6.26 mg/dL. HbA1c levels decreased from 8.17 ± 0.67% to 7.77 ± 0.67%. The TG levels decreased from 241.24 ± 30.47 mg/dL to 183.34 ± 23.16 mg/dL (Table 2). The decrease in the FBS, PPBS and TG levels was found to be extremely statistically significant (p value< 0.0001).

Ptyrone™ + Metformin + Gliptin Group (Group C): The FBS levels decreased from 150.11 ± 8.08 mg/dL to 105.16 ± 5.63 mg/dL. The PPBS levels decreased from 289.76 ± 5.57 mg/dL to 191.13 ± 3.69 mg/dL. HbA1c levels decreased from 8.88 ± 0.59 % to 8.48 ± 0.59%. The TG levels decreased from 250.32 ± 24.20 mg/dL to 190.23 ± 18.39 mg/dL (Table 2). The decrease in the FBS, PPBS and TG levels was found to be extremely statistically significant (p value< 0.0001).

Figure 1 shows decrease in HbA1c levels of Group A, Group B and Group C. Figure 2, 3 and 4 shows decrease in FBS, PPBS and TG levels of Group A, Group B and Group C, respectively.

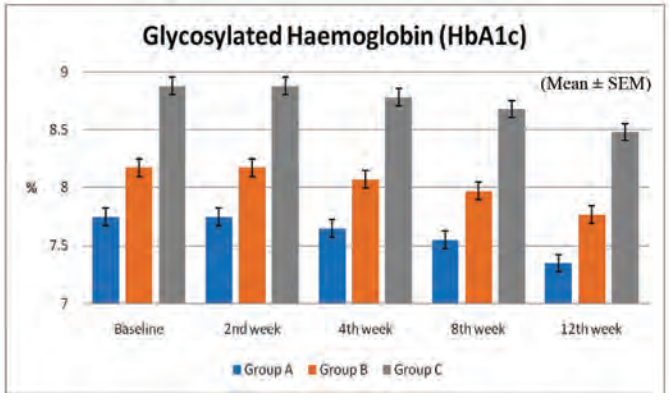

Figure 1: Glycosylated haemoglobin (HbA1c) levels of Group A (Ptyrone™ + Metformin); Group B (Ptyrone™ + Metformin + Sulphonylurea Group) and Group C (Ptyrone™ + Metformin + Gliptin Group) from baseline to Week 12.

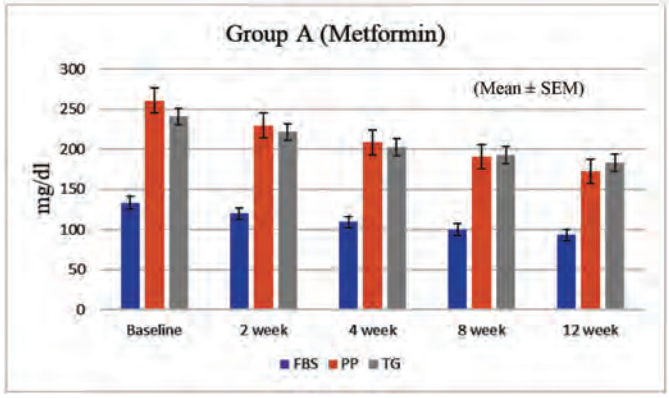

Figure 2: Fasting Blood Sugar (FBS), Post Prandial Blood sugar (PPBS) and Triglyceride (TG) levels of Group A (Ptyrone™ + Metformin) from baseline to Week 12.

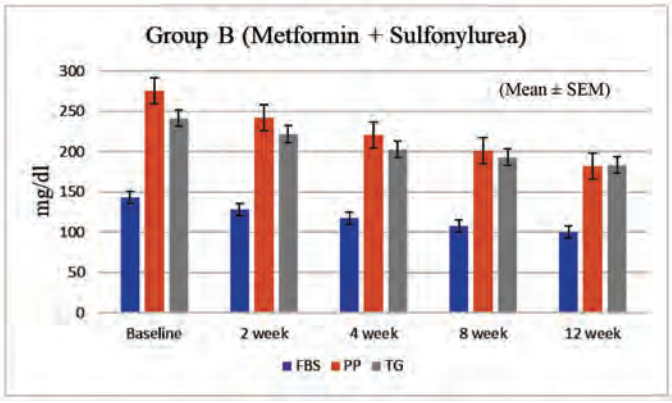

Figure 3: Fasting Blood Sugar (FBS), Post Prandial Blood sugar (PPBS) and Triglyceride (TG) levels of Group B (Ptyrone™ + Metformin + Sulphonylurea Group) from baseline to Week 12.

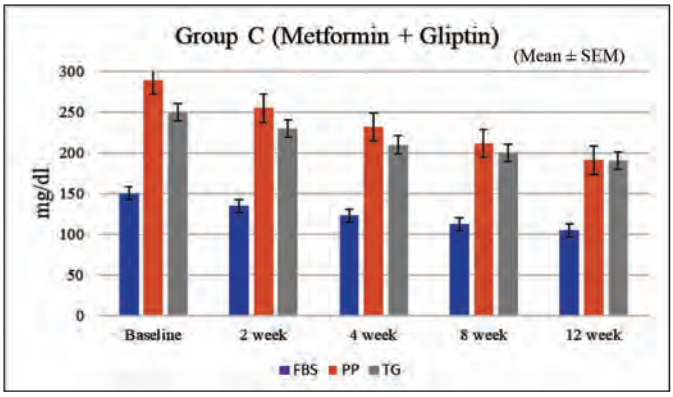

Figure 4: Fasting Blood Sugar (FBS), Post Prandial Blood sugar (PPBS) and Triglyceride (TG) levels of Group C (Ptyrone™ + Metformin + Gliptin Group) from baseline to Week 12.

Discussion

Diabetes mellitus is a major health problem leading to increased morbidity and mortality due to the microvascular and macrovascular complications. It is rapidly growing worldwide with a huge economic and social burden. Confirmed timely diagnosis, appropriate treatment, and effective follow-up are essential in any health care system to prevent complications of diabetes and ensure patients' well-being.

Currently available and prescribed drugs are metformin, sulfonylureas, glitazones, gliptins, glinides, canagliflozin, liraglutide and insulin. They are effective for glycemic control. However, the spectrum of side effects demand the discovery and development of new safer, effective drugs.[6-8] Even a new drug like muraglitazar (a dual alpha/gamma-peroxisome proliferator-activated receptor activator) that promised to control both glycemia and hyperlipidemia has side effects like weight gain and edema and cardiac failure.[9]

Metformin is widely used and considered first line treatment of type 2 diabetes mellitus. It has been shown to prevent diabetes in people who are at high risk and decrease most of the diabetic complications. Metformin reduces serum glucose level by several different mechanisms, notably through nonpancreatic mechanisms without increasing insulin secretion, suppresses the endogenous glucose production by the liver, which is mainly due to a reduction in the rate of gluconeogenesis and a small effect on glycogenolysis. It also activates the enzyme adenosine monophosphate kinase resulting in the inhibition of key enzymes involved in gluconeogenesis and glycogen synthesis in the liver while stimulating insulin signaling and glucose transport in muscles. Sulphonylureas control the blood glucose levels in patients with type 2 diabetes mellitus by stimulating the production of insulin in the pancreas and increasing the effectiveness of insulin in the body. Gliptins improve beta cell health and suppress glucagon, resulting in improved post-prandial and fasting hyperglycemia. They function by augmenting the incretin system (GLP-1 and GIP) preventing their metabolism by dipeptidyl peptidase-4 (DPP-4).

Management of type 2 diabetes mellitus has changed in current years with the introduction of newer antidiabetic agents used as monotherapy or in combination. Various studies have been conducted for standalone anti-diabetic medications and also in combinations, and it has been observed that the newer anti-diabetic medications in combination have proven to be effective in comparison to stand-alone therapies. The treating physicians, depending upon the severity of the disease and its complications, prescribe either stand-alone or more commonly combination therapy. Literature cites decrease in the blood sugar levels and triglycerides with the use of Metformin alone or in combination with Sulphonylureas and Gliptins. In a study conducted by Raghvan Vijay *et al*. (2019), it was shown that Metformin decreased glycosylated haemoglobin by 7%, fasting blood sugar by 10% and post prandial blood glucose by 15% as compared to baseline with 12 weeks.[10]

In another study by Nishant T *et al.* in 2018,[11] Metformin in combination with Sulphonylureas reduced glycosylated haemoglobin by 10%, fasting blood sugar by 20%, post-prandial blood sugar by 30% and no change in Triglyceride level as compared to baseline by 6 months.

Devrajan TV *et al*. in 2017 studied effect of Metformin in combination with Gliptins and it was observed that Metformin in combination with Gliptins reduced glycosylated haemoglobin by 4%, fasting blood sugar by 5% and post-prandial blood sugar by 5% when compared with baseline within 12 weeks.[12]

Ptyrone™ is an oral anti-hyperglycemic formulation derived from the combination of phytoactives in specific proportions for the first time ever from standardized plants extracts viz. Pterostilbene from Pterocarpus marsupium Roxb and Andrographolide from Andrographis paniculata Nees, which have been mentioned in Ayurvedic texts and have been used individually since centuries for various ailments primarily being for type 2 diabetes mellitus. But reference for combination use of these plants is nowhere found in literature.

Pterocarpus marsupium Roxb. more commonly called Vijaysar, is extensively used to treat type 2 diabetes mellitus for thousands of years.[13,14] Andrographis paniculata Nees with common name green chireta has been traditionally also used as an anti-diabetic agent, along with its other activities such as analgetic, antioxidants,[15] and hepatoprotector.[16] These plants and their major phytoactives, viz Pterostilbene and Andrographolide, have been studied as anti-diabetics alone or in combination with various other plants or phytoactives for anti-diabetic activity.[17-19] They have also been evaluated for their interactions with GLUT4, PPARα and PPARγ.[20-27]

Dound YA *et al*.[28] recently conducted a series of studies which included in-silico studies for the various anti-diabetic targets followed by in vivo studies for STZ model and mRNA expression studies for Ptyrone™. For the first time ever, it has been shown that Ptyrone™ is an SGLT2 inhibitor and selective PPARγ agonist, as seen in the in-silico studies and later confirmed in the in vivo STZ model and mRNA expression studies. These have for the first time shown to overcome the common knowledge of only c–glycoside based molecules inhibiting SGLT2. The possible mechanism for Ptyrone™ in the management of diabetes could be a selective PPARγ agonist, GLUT4 translocation and SGLT2 inhibition.

In the current study, when Ptyrone™ is supplemented with Metformin, Metformin in combination with Sulphonylureas and Metformin with Gliptins in combination it was observed that there was a decrease in glycosylated haemoglobin approximatelyby 0.04%, fasting blood sugar decreased approximately by 30%, post prandial blood sugar decreased approximately by

34% and triglyceride levels decreased approximately by 24% compared to baseline.

Ptyrone™ capsules were clinically tolerated well by all the patients. Constipation was reported as an adverse event in 7 patients receiving Ptyrone™ + Metformin and Ptyrone™ + Metformin + Sulphonylurea; two patients in Ptyrone™ + Metformin + Gliptin complained of fever, which were said to be unrelated to the test substance as decided by the Principal Investigator. No serious adverse events were reported during the period of therapy. The other biochemical investigations and the organ function tests were within the normal limits at the baseline, at fourth week, at eighth week and at the end of twelfth week. The patients continued to take other oral anti-diabetic medications along with Ptyrone™ without any side effects in all the three groups.

This observational effect of Ptyrone™ in supplementation with oral anti-diabetic medications with a large sample size of treated, uncontrolled type 2 diabetes mellitus has indicated a therapeutic potential in terms of reduction in the levels of Glycosylated hemoglobin along with statistically significant decrease in the levels of fasting and post prandial blood sugar along with triglycerides.

Conclusion

This study has shown that Ptyrone™ at a dose of 450 mg twice a day supplemented along with oral anti-diabetic medications for 12 weeks was well tolerated and had no serious side effects with a therapeutic activity as an anti-diabetic supplement, which can improve the glycemic control with better understanding of a mechanism (vide supra) without causing hypoglycaemia. However, the therapeutic efficacy needs to be evaluated further in a larger sample size, with a placebo/active controlled, randomized, double-blind multicentric trial.

References

1. International Diabetes Federation. IDF Diabetes Atlas, 10th edn. Brussels, Belgium: International Diabetes Federatio; 2021.
2. Pradeepa R, Deepa R, Mohan V.Epidemiology of diabetes in India- current perspective and future projections. *J Indian Med Assoc. 2002* Mar;100(3):144-8.
3. Vaidya ADB, Devasagayam TPA. Current status of herbal drugs in India: An overview. *J Clin Biochem Nutr. 2007*;41:1-11.
4. Vaidya AB, Vaidya R A, Shah SJ, Nabar N S, Subrato Sarkar. Current Status of Indigenous Drugs and Alternative Medicine in Management of Diabetes mellitus. *In: RSSDI Text book of Diabetes Mellitus*. Hyderabad; 2008.
5. Vaidya AB, Antarkar DS, Joshi BS. Traditional Remedies for diabetes Mellitus: Trails, Trials and Trilateral Quest. *Diabetes Bulletin 1989*;186-191.
6. Ertek S, Cetinkalp S. Is There U Turn From Insulin Back to Pills in Diabetes? *Curr Vasc Pharmacol. 2014*;12(4):617-626
7. Panicker GK, Karnad DR, Salvi V, Kothari S. Cardiovascular risk of oral antidiabetic drugs: current evidence and regulatory requirements for new drugs. *J Assoc Physicians India. 2012*;60:56-61.
8. Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, *et al.* Systematic Review: Comparative Effectiveness and Safety of Oral Medications for Type 2 Diabetes Mellitus. *Annals of Internal Medicine. 2007*;147:386.
9. Muraglitazar Briefing Document, Safety Endocrine and Metabolic Drugs Advisory Committee Meeting. In FDA report of September 9, 2005.
10. Raghavan V, Lahiri A, SK A, Goswami U, Gupta CN, Sen S. Effect of teneligliptin vs metformin on glycemic control in Indian patients with newly-diagnosed, drug-naïve type 2 diabetes mellitus: a 12-week randomized comparative clinical study. *Int J Adv Med. 2019* Apr;6(2):481-488.
11. Nishanth T,Maheswari CU, Lakshmi RS, Sri D, Goud P, Tabassum K. A Study to compare efficacy of metformin-glimepiride versus metformin-teneligliptin in type ii diabetic patients. *IJPSR, 2018*;9(12):5258-5264.
12. Devarajan TV, Venkataraman S, Kandasamy N, Oomman A, Boorugu HK, Karuppiah S, *et al*. Comparative evaluation of safety and efficacy of glimepiride and sitagliptin in combination with metformin in patients with type 2 diabetes mellitus: Indian multicentric randomized trial - START Study. *Indian J Endocr Metab. 2017*;21:745-50.
13. Jung M, Park M, Lee HC, Kang YH, Kang ES, Kim SK. Antidiabetic agents from medicinal plants. *Current Medicinal Chemistry. 2006*;13(10):1203-1218.
14. Joshi MC, Dorababu M, Prabha T, Kumar MM, Goel RK. Effects of Pterocarpus marsupium on NIDDM-induced rat gastric ulceration and mucosal offensive and defensive factors. *Indian Journal of Pharmacology. 2004*;36(5):296.
15. Karto. Tingkat manfaat, keamanan, dan efektivitas tanaman obat dan obat tradisional. Karanganyar, Balai Besar Penelitian dan Pengembangan Tanaman Obat dan Obat Tradisional (B2P2TO-OT). Badan Penelitian dan Pengembangan Kesehatan Departemen Kesehatan RI; 2008. pp. 5-13.
16. Ahmad I, Aqil F, Owais M. Modern phytomedicine: Turning medicinal plants into drugs. Weinheim: WILEY-VCH Verlag GmbH & Co. KGaA; 2006p.273.
17. Komalasari T, Harimurti S. A Review on the Anti-diabetic Activity of Andrographis paniculata (Burm. f.) Nees based in-vivo study. *IJPHS 2015*;4(4):256-263.
18. Perera HKI. Antidiabetic Effects of Pterocarpus marsupium (Gammalu). *EJMP.2016*;13(4):1-14.
19. ModakM, DixitP, LondheJ, GhaskadbiS, Thomas Paul A. Devasagayam. Indian Herbs and Herbal Drugs Used for the Treatment of Diabetes. *J. Clin. Biochem. Nutr.2007*; 40:163–

173.

20. Jin L, Fang W, Li B, Shi G, Li X, Yang Y *et al*. Inhibitory effect of andrographolide in 3T3-L1 adipocytes differentiation through the PPARγ pathway. *Mol Cell Endocrinol. 2012*;358:81-7.
21. Chen CC, Chuang WT, Lin AH, Tsai CW, Huang CS, Chen YT, *et al*. Andrographolide inhibits adipogenesis of 3T3-L1 cells by suppressing C/EBPβ expression and activation. *Toxicol Appl Pharmacol 2016*;307:115-22.
22. Yang Y, Yan H, Jing M, Zhang Z, Zhang G, Sun Y, et al. Andrographolide derivative AL-1 ameliorates TNBS-induced colitis in mice: involvement of NF-κB and PPAR-γ signaling pathways. *Sci Rep. 2016*;6:29716.
23. Yu BC, Hung CR, Chen WC, Cheng JT. Antihyperglycemic effect of andrographolide in streptozotocin-induced diabetic rats. Planta Med. 2003;69(12): 1075-9.
24. Zhang Z1, Jiang J, Yu P, Zeng X, Larrick JW, Wang Y. Hypoglycemic and beta cell protective effects of andrographolide analogue for diabetes treatment. *J Transl Med.2009*;7:62.
25. Aguirre L, Milton-Laskibar I, Hijona E, Bujanda L, Rimando AM, Portillo MP. Effects of pterostilbene in brown adipose tissue from obese rats. *J Physiol Biochem. 2016*; 73:457-64.
26. Gomez-Zorita S, Fernández-Quintela A, Aguirre L, Macarulla MT, Rimando AM, Portillo MP. Pterostilbene improves glycaemic control in rats fed an obesogenic diet: involvement of skeletal muscle and liver. *Food Funct. 2015*;6:1968-76.
27. Rimando AM, Nagmani R, Feller DR, Yokoyama W. Pterostilbene, a new agonist for the peroxisome proliferator-activated receptor alpha-isoform, lowers plasma lipoproteins and cholesterol in hypercholesterolemic hamsters. *J Agric Food Chem. 2005*;53:3403-7.
28. Dound YA, Chaudhary S, Rawat S, Alqarni MG, Ahmad MM, Geesi MH and Alam P. Novel Mechanistic Understanding of PtyroneTM: A Plant based Natural Anti-Diabetic Product. *Journal of King Saud University - Science 2021*;33(5):101454.