RESEARCH ARTICLE

Novel Antidiabetic Polyherbal Formulation for Synergistic Therapeutic Effects in Streptozotocin (STZ)-Induced Diabetic Rats

Pande V. Bhaskarrao,[1] Chandel S. Singh,[2*] Soni Vishal[1]

[1]Department of Pharmacy, Mandsaur University, Mandsaur, Madhya Pradesh, India
[2]Departmentt of Pharmaceutical Sciences, Dr. C. V. Raman University, Bilaspur, Chhattisgarh, India

Received: 17th October, 2022; Revised: 03rd November, 2022; Accepted: 21st November, 2022; Available Online: 25th December, 2022

ABSTRACT

Worldwide demand for new anti-diabetic drugs from plant sources has increased as diabetes mellitus has become a global epidemic. In the era of herbal medicines, polyherbal formulations offer higher therapeutic efficacy than single plants due to synergistic effects. Therefore, the objective was to develop a novel anti-diabetic polyherbal formulation containing mixtures of three plants: *Azadirachta indica* leaves, *Tinospora cordifolia* stem and *Ocimum sanctum* leaves extracts. The eight different plant formulations (F1 to F8) were formulated while F1 to F3 contained a single plant extract. Hyperglycemia was developed in rodents by ingestion of streptozotocin. The experimental animals' serum sugar level, body weight and lipid profile were determined. In the diabetic rats treated orally with F1 to F8, the blood glucose level decreased significantly compared to the diabetic control group. Similar effects were also observed in the diabetic rats treated with glibenclamide. In addition, F1 to F8 controlled lipid level, namely total cholesterol (CHL), triglycerides (TGL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels in rodents. The findings suggested that F7 showed higher anti-diabetic and antihyperlipidemic efficiency when equated to the other formulations. It was also found that the formulations (F1 to F3) containing a single plant extract exhibited lower therapeutic efficacy than the polyherbal formulations (F4 to F8). The results suggest that the higher therapeutic efficacy of the polyherbal formulation is due to the synergistic effect of the different phytoconstituents in the plant mixtures.

Keywords: Anti-diabetic, Antihyperlipidemic, Diabetes, Polyherbal formulations, Streptozotocin.

International Journal of Drug Delivery Technology (2022); DOI: 10.25258/ijddt.12.4.23

How to cite this article: Bhaskarrao PV, Singh CS, Vishal S, Novel Antidiabetic Polyherbal Formulation for Synergistic Therapeutic Effects in Streptozotocin (STZ)-Induced Diabetic Rats. International Journal of Drug Delivery Technology. 2022;12(4):1612-1617.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Hyperglycemia is the primary symptom of diabetes, which a lack of insulin action can cause, decreased insulin production, or both. Diabetes is a complex endocrine and metabolic disease that can manifest in a variety of ways. Insulin dysfunction can arise from either a deficiency of pancreatic cells that secrete insulin (diabetes mellitus type 1 (T2DM)) or an insufficient response to insulin (T2DM). Both type 1 and type 2 diabetes expressed to insulin resistance. It observed that a prolonged state of hyperglycemia causes insulin resistance. Insulin resistance is the leading cause of diabetes in the world. The long-term health effects of hyperglycemia include damage and eventual failure of several organs, most notably the nerves, blood vessels, kidneys, eyes, and heart.[1,2]

Diabetes is currently becoming a serious concern on a global scale and a main cause of morbidity and death in the majority of countries. It is estimated that there are 382 million individuals who are affected by the disease, and 5.1 million people lost their lives to diabetes in 2013. According to statistics compiled by the World Health Organization (WHO), there was a huge increase in the number of diabetes patients from 1980 to 2014; WHO estimated the possible increase of 592 million diabetes patients by 2035 in underdeveloped and developing countries.[3,4]

Since the beginning of time, people have been trying to find cures for a wide variety of illnesses, including hyperglycemia, with the help of various medicinal herbs. WHO stated approx 80% of diabetes patient in underdeveloped nations takes herbal medicines for the management of diabetes. The use of herbal medicines is enhanced due to their minimum toxicity, easy availability and cost-effectiveness. About one-quarter of all medications in today's pharmacopeia are derived from natural substances once utilized in conventional medicine. Presently metformin is most widely used for the management of diabetes and it is first extracted from the *Galega officinalis*.[5,6]

*Author for Correspondence: singhpharma@gmail.com

Table 1: Polyherbal formulations are composed of a variety of herbs

Formulations	*Ratio*		
	Azadirachta indica (leaves)	*Tinospora cordifolia (stem)*	*Oscimum sanctum (leaves)*
F1	100	-	-
F2	-	100	-
F3	-	-	100
F4	50	25	25
F5	25	50	25
F6	25	25	50
F7	50	40	10
F8	50	10	40

Individual plants do not contain enough active compounds to produce desired desirable and beneficial effects. Numerous plants are combined to a specific extent, which will have a greater beneficial effect and reduce the toxicity of the combination.[5] Usage as a single medication or in combination with other treatments, the latter being known as polyherbal formulation. Science has found that when herbs of various strengths are mixed, the result may theoretically be more significant than whenever the plants are used individually and that the sum of their separate effects could theoretically be more significant than when the plants are used individually. Synergism is the term used to describe the phenomena of beneficial herb-herb interplay.

Polyherbal formulations enhance patient comfort by eliminating the requirement to take more than one distinct herbal drug simultaneously, resulting in greater consistency and curative impact. Compared to individual natural products, each benefit has contributed to the increased popularity of polyherbal formulation on the trade.[7,8] *Azadirachta indica*, *Tinospora cordifolia* and *Oscimum sanctum* are medicinal plants used for centuries to heal hyperglycemia. Thus, it was intended to explore the anti-diabetic properties of a polyherbal formulation containing different ratios of *A. indica* leaves, *T. cordifolia* stem and *O. sanctum* leaves. Further also compared the therapeutic efficacy of a single plant with the polyherbal formulations.

MATERIAL AND METHODS

A. indica leaves, *T. cordifolia* stem and *O. sanctum* leaves were collected, and after cleaning plant's parts were shade dried. The plant parts were further processed for the coarsely powdered and kept in an airtight container for experimental work.

Preparation of Polyherbal Formulations

Eight distinct polyherbal formulations (F1 to F8) were created by blending varying ratios of plant powders of *A. indica* leaves, *T. cordifolia* stem and *O. sanctum* leaves. Table 1 lists the constituents of various polyherbal formulations in varying proportions.

Decoction Preparation

The mixtures of 20 g of every composition with 150 mL of distilled water have been macerated for 24 hours at room temperature. Decoction was obtained by boiling for about 45 minutes then filtering with muslin cloth, the macerated drug was left for 24 hours. Adjustments were made to the decoction's content so that 20 g of mixture yielded 50 mL of decoction.[7]

Determination of Anti-diabetic Activity

Polyherbal Formulation's Oral Glucose Tolerance Test

The rats were fasted for 18 hours to pursue the oral glucose tolerance test. The rats were placed into ten groups for the experiment, and each group had six rats. Group I was named as a normal control, group II had glucose control rodents, and group III to group X were treated with F1 to F8, respectively, at the dose of 20 mL/kg body weight.

The 2 g/kg of body weight of glucose was fed to the rodents of groups II to X. After 30 minutes, prepared formulation was administered to the diabetic rats. The blood was withdrawn from the rodents at 0, 30, and 90 minutes through the retro-orbital sinus. After centrifuging the blood at 3000 rpm, the resulting plasma was utilized in conjunction with a glucose oxidase–peroxidase kit to determine glucose levels in the fasting plasma.[9-11]

Induction of Diabetes in Rats

A virtually overnight starved adult rat weighing 170–220 g was used to develop non-insulin dependent diabetes mellitus (NIDDM). A single intraperitoneal injection of 60 mg/kg streptozotocin and 15 minutes after administering 120 mg/kg nicotinamide to develop NIDDM in these rats. The manifestation of increased glucose levels in blood serum, evaluated at 72 hours and again on day 7 after treatment, served as conclusive evidence that the individual in question had diabetes. The diagnostic cut-off for diabetes was determined to be a plasma glucose level in the fasting state that was greater than 126 mg/dL. More specifically, those mice that are being used in the trial have already been verified to have persistent NIDDM.

Anti-diabetic Activity of the Polyherbal Formulation

The rodents were divided into 10 groups of six rats each, for a total of 60 rats. The polyherbal formulation was given to the animals for 28 days. Group I referred to normal control given only drinking water, group II expressed as diabetic control rodents, group III to group X treated with F1 to F8 (20 mL/kg body weight) for 28 days.

Further, the blood glucose levels were measured on the 1st, 7th, 14th, and 28th day after the extract administration. Throughout the study, the rodents were weighed on a regular basis, and the average difference in body mass was computed.[13,14]

Determination of Lipid Profile

It was on day 28 that the biochemical variables were measured; afterward, the rats were sacrificed through spinal displacement.

Table 2: Rat data on polyherbal formulations' oral glucose tolerance

Groups	*Glucose (mg/dL)*		
	0 minutes	*30 minutes*	*90 minutes*
Group I: Normal Control	75.1 ± 4.87	77.2 ± 4.43	74.7 ± 3.57
Group II: Glucose control	76.5 ± 2.73	305.2 ± 3.62[a]	201.6 ± 2.18[a]
Group III: F1	76.3 ± 2.95	144.6 ± 2.83*	92.6 ± 4.37*
Group IV: F2	77.4 ± 3.21	151.2 ± 4.49*	95.1 ± 5.58*
Group V: F3	79.1 ± 4.42	163.5 ± 5.73*	99.7 ± 3.12*
Group VI: F4	73.4 ± 4.27	130.6 ± 3.28*	78.2 ± 4.23*
Group VII: F5	75.7 ± 5.91	138.7 ± 2.51*	86.7 ± 4.64*
Group VIII: F6	76.1 ± 3.52	141.3 ± 4.62*	90.3 ± 5.73*
Group IX: F7	79.6 ± 2.91	123.4 ± 3.78*	76.3 ± 4.41*
Group X: F8	74.8 ± 3.16	132.9 ± 5.26*	80.7 ± 2.52*

Outcomes are demonstrated as mean ± SEM (n=6); statistically difference at [a]$p < 0.05$ compared to Group I, and *$p < 0.05$ compared to Group II

The glucose oxidase technique was used to quantify total cholesterol (CHL), triglycerides (TGL), low-density lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL) employing an auto-analyzer.[12-14]

Statistical Analysis

The findings of experimental data are presented as the average of six independent experiments with standard deviations (SEM). The statistically significant difference of the variations was observed was determined using a one-way analysis of variance (ANOVA) and Dunet's test. A *p-value* of less than 0.05 was deemed statistically significant in this study.

RESULTS AND DISCUSSIONS

Polyherbal Formulation's Glucose Tolerance Effects

Sugar was administered to rats in all groups except the normal group to increase blood glucose levels. After 30 minutes, the blood glucose level was increased in the rats of II group to X group compared to the normal group (Table 2). A significant decrease in blood glucose level was observed in the group treated with the polyherbal formulation (F1 to F8) compared to the glucose control group. The polyherbal formulation showed the effectiveness of glucose tolerance in the following orders F7 > F4 > F8 > F5 > F6 > F1 > F2 > F3. The F7 has higher glucose tolerance compared to the other herbal preparations. Also, F1 to F3 were found to have lower glucose tolerance compared to the polyherbal formulations F3 to F8.

Effect on NIDDM of Polyherbal Formulation

The experimental animals from group II to group X were made diabetic by the administration of Streptozotocin (STZ). After administration for three days, the increase in blood glucose level confirmed the induction of diabetes in the rats. In the diabetic control rats, the blood glucose level was significantly increased on the 1st, 7th, 14th and 28th day compared to the normal control group (Table 3). It was also observed that the blood glucose level of the rats in the diabetic control group was subsequently elevated. When F1 to F8 were administered at a dose of 20 mL/kg body weight to the diabetic rats, a significant decrease in blood glucose level was observed at the end of the study compared to the diabetic control group. The polyherbal formulation showed an anti-diabetic effect in the following order F7 > F4 > F8 > F5 > F6 > F1 > F2 > F3. The F7 has higher anti-diabetic activity compared to the other polyherbal formulations. It was also found that F1 to F3 had lower anti-diabetic properties compared to the polyherbal formulations F3 to F8.

Antihyperlipidemic Activity

Induction of diabetes in rats triggered a substantial rise in the CHL, TGL and LDL, and decreased HDL compared to the normal group. Conversely, the administration of polyherbal formulations (F1 to F8) to diabetic rats for 28th days significantly decreases in CHL, TGL, LDL, and increases in HDL compared to STZ induced diabetic control group (Table 4). The polyherbal formulation showed antihyperlipidemic activity in the following order F7 > F4 > F8 > F5 > F6 > F1 > F2 > F3.

Table 3: Anti-diabetic effect of polyherbal formulations in STZ-treated rodents

Groups	*Blood sugar (mg/dL)*			
	0 Day	*7 Days*	*14 Days*	*28 Days*
Group I: Normal Control	78.6 ± 4.18	81.4 ± 5.93	76.3 ± 5.27	77.2 ± 3.62
Group II: Diabetic control (STZ)	168.3 ± 5.31[a]	251.5 ± 3.29[a]	296.1 ± 4.64[a]	353.8 ± 2.13[a]
Group III: F1	173.5 ± 5.25	152.7 ± 4.81*	129.2 ± 5.39*	98.5 ± 2.72*
Group IV: F2	159.2 ± 6.71	159.1 ± 6.27*	138.1 ± 3.52*	107.4 ± 3.42*
Group V: F3	166.8 ± 3.45	165.3 ± 3.68*	143.9 ± 2.27*	115.2 ± 5.53*
Group VI: F4	161.7 ± 4.63	128.4 ± 4.41*	115.2 ± 4.15*	84.1 ± 4.22*
Group VII: F5	155.9 ± 5.52	142.7 ± 2.19*	126.2 ± 4.68*	93.6 ± 6.51*
Group VIII: F6	164.7 ± 4.24	149.3 ± 5.34*	128.7 ± 3.25*	95.1 ± 3.49*
Group IX: F7	169.2 ± 3.51	120.6 ± 4.12*	101.5 ± 5.92*	79.3 ± 5.38*
Group X: F8	148.3 ± 5.78	130.2 ± 5.52*	119.3 ± 4.17*	87.5 ± 3.82*

Findings are demonstrated as mean ± SEM (n=6); statistically difference at [a]$p < 0.05$ compared to Group I, and *$p < 0.05$ compared to Group II

Table 4: Biochemical parameters following administration of polyherbal formulations

Groups	*TGL (mg/dL)*	*CHL (mg/dL)*	*HDL (mg/dL)*	*LDL (mg/dL)*
Group I: Normal Control	69.4 ± 2.63	91.2 ± 5.21	85.6 ± 3.63	58.1 ± 3.14
Group II: Diabetic control (STZ)	273.4 ± 4.13[a]	221.5 ± 3.72[a]	15.2 ± 5.49[a]	182.9 ± 2.57[a]
Group III: F1	87.2 ± 3.28*	102.4 ± 2.41*	69.8 ± 3.75	74.1 ± 4.64*
Group IV: F2	85.1 ± 4.65*	106.9 ± 4.82*	67.1 ± 4.26*	75.3 ± 5.48*
Group V: F3	89.8 ± 2.32*	108.3 ± 6.18*	66.5 ± 5.59*	79.2 ± 3.92*
Group VI: F4	77.5 ± 3.16*	93.6 ± 5.56*	80.2 ± 6.71*	64.8 ± 4.34*
Group VII: F5	82.6 ± 5.73*	99.2 ± 4.39*	77.4 ± 4.37*	70.9 ± 3.23*
Group VIII: F6	84.5 ± 4.38*	100.1 ± 3.87*	76.1 ± 5.46*	72.7 ± 5.51*
Group IX: F7	75.1 ± 3.19*	89.2 ± 6.54*	83.4 ± 3.12*	62.5 ± 4.40*
Group X: F8	78.9 ± 2.92*	97.8 ± 4.29*	79.1 ± 5.77*	65.6 ± 3.61*

Findings are demonstrated as mean ± SEM (n=6); statistically difference at [a]$p < 0.05$ compared to Group I, and *$p < 0.05$ compared to Group II

Table 5: Variations in body weight of rodents using polyherbal formulations

Group	*Body weight (gm)*		
	Before induction	*After induction*	*After treatment*
Group I: Normal Control	173.5 ± 2.74	182.7 ± 3.46	180.4 ± 2.53
Group II: Diabetic control (STZ)	181.2 ± 1.45	132.6 ± 2.28	93.3 ± 1.19
Group III: F1	188.6 ± 3.63	141.8 ± 4.53	179.2 ± 2.24
Group IV: F2	179.2 ± 2.72	145.3 ± 3.56	180.5 ± 4.37
Group V: F3	175.2 ± 3.18	139.8 ± 3.39	174.3 ± 2.58
Group VI: F4	180.9 ± 1.26	135.1 ± 2.68	176.2 ± 3.37
Group VII: F5	181.6 ± 4.37	140.2 ± 4.71	173.9 ± 4.23
Group VIII: F6	183.7 ± 2.54	136.9 ± 1.49	181.5 ± 3.51
Group IX: F7	182.5 ± 2.33	138.3 ± 4.82	178.2 ± 2.46
Group X: F8	178.3 ± 3.67	135.7 ± 2.16	174.9 ± 1.27

The F7 has higher antihyperlipidemic activity compared to the other polyherbal formulations. It was also found that F1 to F3 had lower antihyperlipidemic activity compared to the polyherbal formulations F3 to F8.

Body Weight of Rats

Table 5 showed a substantial decreased in the body weight of the diabetic rats after induction of diabetes. While the body weight of rats recovered after administration of the polyherbal formulation (F1 to F8).

The polyherbal formulations (F1 to F8) containing different proportion of *A. indica* leaves, *T. cordifolia* stem and *O. sanctum* leaves revealed substantial anti-diabetic and antihyperlipidemic activity against STZ-induced DM in rats.

This investigation was performed to determine the impact on diabetic rats' plasma glucose levels and lipid profiles of regular oral feeding of polyherbal formulations (F1 to F8) for a period of 28 days. For the purpose of causing hyperglycemia in rodents, streptozotocin was chosen as the agent to use. A well-established paradigm for generating type 1 diabetes, also known as diabetes dependent on insulin, is the administration of streptozotocin to animals. In the current research, streptozotocin was used to produce diabetes in rats, and these diabetic animals exhibited a considerable rise in sugar levels compared to the normal group rats. Following therapy with polyherbal formulations, the elevated levels of plasma glucose were brought down to a lower level (F1 to F8). The findings of present study are similar with the findings of others that demonstrated the substantial antihyperglycemic properties of polyherbal formulation in STZ induced diabetic rats.[7-21] Our findings are similar with the findings of other authors. It has been demonstrated that our discoveries can decrease blood sugar levels in diabetic animals. The hypoglycemic action of polyherbal formulations (F1 to F8) could be caused by increased insulin secretion from vestige pancreatic cells, or it could be caused by the preservation of functional cells from further deterioration, which allows these cells to remain active and continue to produce insulin. Significantly increased insulin level in diabetes treated rats, which provided evidence for this observation.[22] Alternatively, the hypoglycemic action may be due to a combination of both of these mechanisms.

Hyperlipidemia, commonly referred to as elevated CHL, TGL, and LDL levels, is identified consequence of DM. This condition is characterised by higher levels of CHL, TGL, and LDL. It is also well-documented that streptozotocin-induced diabetic rats have elevated levels of both cholesterol and triglycerides in their blood. The induction of diabetes in rats resulted in alterations to the profile of lipoproteins and lipids in the rat's serum, and these changes occurred simultaneously with increases in blood glucose levels in diabetic rats. These anomalies are induced by the action of insulin, which inhibits the lipolytic hormone's ability to function properly on fat depots. Secondary problems from hypertryglyceridemia and hypercholesterolemia were caused by inactivation of the lipoprotein lipase enzyme, resulting from insulin insufficiency in diabetes conditions. β-Hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase is a rate-limiting enzyme that participates in the metabolization of LDL and elevated cholesterol. On the other hand, dyslipidemia can be caused by a lack of insulin due to the inhibitory effect that

insulin has on HMG-CoA reductase. Because glucose is used up more slowly in diabetics, a condition called diabetes-induced hyperlipidemia is to blame for the excessive release of fat from adipose tissue.[23] Treatment with a polyherbal formulation resulted in lower levels of cholesterol, triglyceride, and LDL, and higher levels of HDL, which is suggestive of the formulations' potential ability to lower blood lipid levels (hypolipidemic activity).

The STZ-induced diabetes mellitus (DM) in rodents resulted in a significant reduction in body weight, which could be prevented or mitigated by treatment with polyherbal formulations. When compared to diabetic rats, diabetic rats that were given a polyherbal formulation saw an increment in their body weight after receiving the formulation. According to the current investigation results, therapy with polyherbal formulations had a beneficial effect on the maintenance of normal body weights in diabetic rats. Polyherbal formulation's capacity to lower hyperglycemia may be responsible for their protective effect on the body weight of diabetic rats. STZ-induced DM was characterized by substantial weight loss due to the loss or degradation of protein structure and the wasting of muscle in diabetes.[24]

CONCLUSIONS

The prepared polyherbal formulation, namely F1 to F8, incorporating different ratio of the *A. indica* leaves, *T. cordifolia* stem and *O. sanctum* leaves significantly reduced the blood glucose level in the diabetic rats and improved lipid profile. The findings suggested F7 having higher anti-diabetic and antihyperlipidemic activity compared to other formulations. Further, the single plant-containing formulations (F1 to F3) showed lower anti-diabetic activity than the formulation that blended different plants (F4 to F8). The higher therapeutic efficacy of the polyherbal formulation is due to the synergistic effect of the different phytoconstituents in the different plant mixtures. This study has scope to illustrate the possible mechanism of anti-diabetic activity of this polyherbal formulation.

CONFLICT OF INTEREST

None

REFERENCES

1. Gobinath R, Parasuraman S, Sreeramanan S, Enugutti B, Chinni SV. Antidiabetic and Antihyperlipidemic Effects of Methanolic Extract of Leaves of Spondias mombin in Streptozotocin-Induced Diabetic Rats. Front Physiol. 2022;13:870399.
2. Akinyede KA, Oyewusi HA, Hughes GD, Ekpo OE, Oguntibeju OO. In Vitro Evaluation of the Anti-Diabetic Potential of Aqueous Acetone Helichrysum petiolare Extract (AAHPE) with Molecular Docking Relevance in Diabetes Mellitus. Molecules. 2021;27(1):155.
3. Andargie Y, Sisay W, Molla M, Tessema G. Evaluation of Anti-diabetic and Antihyperlipidemic Activity of 80% Methanolic Extract of the Root of Solanum incanum Linnaeus (Solanaceae) in Mice. Evid Based Complement Alternat Med. 2022;2022:4454881.
4. Tegegne BA, Mekuria AB, Birru EM. Evaluation of Anti-Diabetic and Anti-Hyperlipidemic Activities of Hydro-Alcoholic Crude Extract of the Shoot Tips of Crinum abyssinicum Hochst. ex A. Rich (Amaryllidaceae) in Mice. J Exp Pharmacol. 2022;14:27-41.
5. Kasznicki J, Sliwinska A, Drzewoski J. Metformin in cancer prevention and therapy. Ann Transl Med. 2014;2(6):57.
6. Tafesse TB, Hymete A, Mekonnen Y, Tadesse M. Antidiabetic activity and phytochemical screening of extracts of the leaves of Ajuga remota Benth on alloxan-induced diabetic mice. BMC Complement Altern Med. 2017;17(1):243.
7. Mahapatra SK, Verma S. Preparation and Evaluation of Novel Antidiabetic Polyherbal Formulation. Research Journal of Pharmacy and Technology. 2022; 15(7):3015-9.
8. Grigore A, Vulturescu V, Neagu G, Ungureanu P, Panteli M, Rasit I. Antioxidant-Anti-Inflammatory Evaluation of a Polyherbal Formula. Pharmaceuticals (Basel). 2022 Jan 18;15(2):114.
9. Singh J, Sahu RK, Prasad DN, Jangde R, Gupta R. Evaluation of anti-diabetic potential of Ougeinia oojeinensis leaves in streptozotocin-induced-diabetic rats. Pharmacologyonline, 2011; 2(2): 1046-1052.
10. Osmani OH, Sekar DS, Senthil Kumar KL, Sahu RK, Roy A. In- vivo anti-diabetic potential of Artocarpus heterophyllus plant seeds in streptozotocin-induced-diabetic rats. Biomedical and Pharmacological Journal, 2009; 2(2): 339-343.
11. Mohammed SM, Abd-Almonuim AE, Majeed A, Khlaf H. The Anti-Diabetic and Anti-Hyperlipidemia effect of Citrus maxima Fruit Peel extract in Streptozotocin - Induced Diabetic Rats. Research Journal of Pharmacy and Technology, 2021; 14(10):5355-8.
12. Mawlieh BS, Shastry CS, Chand S. Evaluation of Anti-diabetic Activity of two marketed Herbal Formulations. Research J. Pharm. and Tech, 2020; 13(2):664-668.
13. Deore ND, Gupta S, Shrivastav B, Upasni CD, Apte KG, Shaikh AM. Evidence based Evaluation of Anti-diabetic Potential of Yesaka on Streptozotocin Diabetic Rats. Research J. Pharm. and Tech, 2018; 11(11): 4965-4970.
14. Maurya AK, Tripathi S, Kahrana M, Ahmed Z, Sahu RK. Evaluation of anti-diabetic effects of Ficus racemosa extracts in diabetic induced rats. Pharmacologyonline, 2011; 3: 907-914.
15. Roy A, Gupta PP, Bharadwaj S, Chandrakar S. Anti-diabetic activity of Polyherbal formulations from Chhattisgarh State. Research J. Pharm. and Tech. 2021; 14(3):1375-1379.
16. Jagtap P, Nimbalkar Y, Patil V, Patil RY. In Vivo Antidiabetic Activities of Polyherbal Extracts against Streptozotocin Nicotinamide Induced Type 2 Diabetic Mice Model. Tanzania Journal of Science. 2021; 47(3): 877-891.
17. Jayaraju KJ, Ishaq BM. Evaluation of Anti-diabetic Activity of a Novel Polyherbal Preparationagainst Streptozotocin Induced Diabetes Rat Model. Journal of Pharmaceutical Research International. 2021; 33(26A): 42-54.
18. Nagja T, Kumar V, Sanjeev A. Anti-Diabetic Activity of a Polyherbal Formulation in Streptozotocin Induced Type 2 Diabetic Rats. Journal of Natural Remedies. 2016; 16(4): 148-152.
19. Chaudhuri A, Sharma S. Evaluation of Anti-diabetic Activity of Polyherbal Formulation in Streptozotocin-Induced Diabetic Rats. Pharmaceutical and Biosciences Journal. 2016; 4(5): 01-06.
20. Subhasree N, Kamella A, Kaliappan I, agrawal A, Dubey GP. Anti-diabetic and antihyperlipidemic activities of a novel polyherbal formulation in high fat diet/streptozotocin induced diabetic rat model. Indian J Pharmacol 2015;47:509-13

21. Petchi RR, Vijaya C, Parasuraman S. Antidiabetic activity of polyherbal formulation in streptozotocin - nicotinamide induced diabetic wistar rats. J Tradit Complement Med. 2014;4(2):108-17.
22. Rajaei Z, Hadjzadeh MA, Moradi R, Ghorbani A, Saghebi A. Antihyperglycemic and antihyperlipidemic effects of hydroalcoholic extract of Securigera securidaca seeds in streptozotocin-induced diabetic rats. Adv Biomed Res. 2015;4: 33.
23. Gobinath R, Parasuraman S, Sreeramanan S, Enugutti B, Chinni SV. Antidiabetic and Antihyperlipidemic Effects of Methanolic Extract of Leaves of Spondias mombin in Streptozotocin-Induced Diabetic Rats. Front Physiol. 2022;13:870399.
24. Petchi RR, Parasuraman S, Vijaya C. Antidiabetic and antihyperlipidemic effects of an ethanolic extract of the whole plant of Tridax procumbens (Linn.) in streptozotocin-induced diabetic rats. J Basic Clin Pharm. 2013;4(4):88-92.