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Evaluation of hypoglycaemic activity of polyherbal formulation developed with bioenhancer

Archana Gorle and Chhaya Gadgoli

Abstract
Present study focuses on the hypoglycemic activity of poly herbal formulation (PF) with and without piperine in STZ induced diabetic rat model. Poly herbal formulation contain the dried 70% aqueous ethanolic extract of herbs *Pterocarpus marsupium, Gymnema sylvestre, Trigonella foenumgrecum, Momordica charantia* and piperine from *Piper nigrum as bioenhancer*. Diabetes was induced by streptozotocin (60 mg/kg, i.p.) and poly herbal formulation was given with and without piperine (250 and 500 mg/kg) for 14 days in the separated groups. The effect of the polyherbal formulation on blood glucose levels was studied at regular intervals. At the end of the study, the blood samples were collected from all the animals for biochemical estimation. Result of the study suggested that there was significant decrease in the blood glucose level in STZ+PF (250 and 500 mg/kg) with piperine than negative control group and STZ+PF (250 and 500 mg/kg) without piperine. Moreover treatment with PF with piperine significantly decreases BUN, creatinine and triglyceride level than negative control group. Present study concludes that polyherbal formulation developed with bienhancer (piperine) showed more potent antidiabetic activity in same dose compare to without piperine formulation.

Keywords: Diabetes; Piperine; Polyherbal formulation; *Pterocarpus marsupium; Gymnema sylvestre; Trigonella foenumgrecum; Momordica charantia*

Introduction
Diabetes mellitus is one of the most common disorders affecting almost 6% of the world population and the dynamics of the diabetes are changing rapidly in low- to middle-income countries [1]. According to International Diabetes Federation's (IDF) estimates, 80% of the world diabetic population will be from low- and middle-income countries in 2030 [2]. Globally, diabetes is one of the six major causes of death and also causing various systemic complications. Development of an adverse event is one of the complications in the treatment of any systemic disorder; hence, many of the research institutes and pharmaceutical companies are involved in drug development to find the molecules with good therapeutic potential and less adverse events.[3] In the USA, 10-25% of patients experience an adverse drug reaction and these adverse drug reactions are responsible for 3.4-7.0% of hospital admissions [4].
In traditional systems of medicine, many plants have been documented to be useful for the treatment of various systemic disorders. The concept of polyherbal formulation is well documented in the ancient literature. Compared to the single herb, the polyherbal formulation has better and extended therapeutic potential. *Gymnema sylvestre, Trigonella foenumgrecum and Momordica charantia, Pterocarpus marsupium* are very common plant drugs utilized in controlling blood glucose levels. Many polyherbal formulations containing these drugs are marketed; however the labels do not reveal the content of active constituents or marker compounds. Herbal drugs being prone to content variations in each harvest need serious efforts to be put in standardizing with respect to marker and bioavailability study of formulations. The great interests for the improvement of bioavailability of a large number of drugs are (1) poorly available, (2) administered for long periods, (3) toxic, and (4) expensive. Maximizing bioavailability is therapeutically important because the extent of bioavailability directly influences plasma concentrations and consequently therapeutic efficacy. Bioavailability enhancement can make the expensive drugs affordable and reduce the toxic effects by reducing the required dose of drugs [5, 6] Hence, the present study was planned to formulate and standardize a polyherbal formulation using a plant having known antidiabetic activity and evaluate its therapeutic effects in rodents.

Materials and Methods

Animals

Healthy Wistar rats of either sex, weighing 180-220 g were procured from registered breeder Bharat Serum Pvt. Ltd., Mumbai. India. Experimental animals were maintained on standard pelleted laboratory animal feed and water *ad libitum*. Animals were maintained at 22 ± 2 ºC and 55 ± 5% relative humidity in a light controlled (12 h light/12 h dark) room. Animals that are described as fasting were deprived of food for at least 16 h but were allowed free access to drinking water. The rats were housed and treated according to the rules and regulations of CPCSEA and IAEC. The protocols for all the animal studies were approved by the Institutional Animal Ethics Committee (IAEC). CPCSEA registration no: SVBCP/IAEC/PhD/16-17/59.

Chemicals

Streptozotocin was procured from Mylabs Solutions, India. Metformin was procured from Sun Pharmaceutical Industries Ltd, Mumbai, India; The diagnostic kits used for biochemical estimation were blood glucose (GOD/POD Method), blood urea nitrogen (BUN) (Berthelot method), albumin (BCG method), triglyceride (GPO/POD method), creatinine (modified Jaffes method), and total protein (BCA method) kits. All of these were purchased from Ambika Diagnostics, Aurangabad, India.

Preparation of polyherbal formulation

Formulation content 70% aqueous ethanolic extract of herbs *Pterocarpus marsupium, Gymnema sylvestre, Trigonella foenumgrecum, Momordica charantia* and piperine from *Piper nigrum* (5mg and 10mg in 250mg, 500mg dose capsule respectively)

Preparation of Dose

Standard Substance

Metformin (0.25 mg/kg/day) solution was prepared by accurately measuring 0.25 mg of Metformin and suspending it in 10 mL of 2% w/v, tween 80.

Test substances:

1. Polyherbal preparation (250 mg/kg and 500mg/kg without piperine.)
2. Polyherbal preparation (250 mg/kg and 500mg/kg with piperine.) solutions were prepared by Suspending these capsule content in 10 mL of 2% w/v, tween 80.

Induction of Diabetes

Rats were fasted overnight before being injected with STZ at a dose of 60 mg/kg of body weight (BW) via intraperitoneal (i.p.) route. The induction of diabetes was confirmed by determination of high fasting blood glucose level with polydipsia and polyuria on the third day of STZ administration. Rats with fasting blood glucose level >200 mg/dl were selected for experimentation. All the diabetic rats were divided into seven different groups of six animals each as such as normal control, negative control which receives STZ, Diabetic rats treated with Metformin (0.25 mg/kg), Diabetic rats treated with polyherbal preparation (250 mg/kg without piperine), Diabetic rats treated with polyherbal preparation (500 mg/kg without piperine), Diabetic rats treated with polyherbal preparation (250 mg/kg with piperine), Diabetic rats treated with polyherbal preparation (500 mg/kg with piperine).

The standard (metformin) and herbal formulation were suspended in water with 2% w/v, tween 80. and administered once daily through oral gavage for 14 consecutive days. At the end of the experiment, the blood sample was withdrawn from all the experimental animals through retro-orbital plexus puncture/posterior vena cava in plain and sodium ethylene diaminetetra acetic acid (EDTA) tubes for biochemical analysis.[7] Finally the animals were sacrificed by thiopental sodium anesthesia, and liver and pancreatic tissues were excised and used for biochemical analysis.

Biochemical Estimations

Blood glucose was estimated by glucose oxidase-peroxidase (GOD/POD) method using commercially available diagnostic kits [8]. Serum cholesterol and triglycerides were measured by enzymatic colorimetric method [9, 10] using commercially available diagnostic kits. Serum HDL was measured by precipitating reagent method [11] Serum urea and creatinine were estimated by the modified Berthelot reaction method and without deproteinisation method [12, 13] respectively using commercially available diagnostic kits.

Statistical Analysis

All the values of these experiments were articulated as mean ± SD and the data was statistically analyzed by one-way ANOVA and thereafter applied to Dunnett post hoc test. $p<0.05$ was considered significant statistically.

Results and Discussion

Treatment with streptozotocin resulted into induction of hyperglycemia and this was found to be sustained till the end of the study. Treatment with the polyherbal formulations could significantly ($P<0.05$) reduce the elevated glucose levels. There was significant ($P<0.05$) reduction in the blood glucose levels due to administration of formulation containing the piperine as compared to the administration of formulation without piperine. The results of the study are presented in the Tables 1and 2 and Figure 1.

Table 1: Effect of poly herbal formulations on the blood glucose level of animals

S. No	Group	Blood Glucose (mg/dL)		
		3rd day	10th day	15th day
01	Control Group	94.68±3.96	92.82±5.05	95.1±4.21
02	Negative Control	293.78±8.03**	243.02±9.21**	285.7±8.4**
03	STZ+MET	290.06±13.07**	93.47±6.7@@	88.57±4.8**
04	STZ+PF 250 mg/kg (without piperine)	302.52±16.81**	187.66±10.68@	144.9±9.7@
05	STZ+PF 500 mg/kg (without piperine)	299.4±10.89**	114.86±8.91@@	101.62±6.4@@
06	STZ+PF 250 mg/kg (with piperine)	293.7±10.3**	125.35±11.78@@	105.7±9.6@@
07	STZ+PF 500 mg/kg (with piperine)	291.7±11.6**	107.63±7.38@@	93.7±6.4@@

The results were expressed as Mean ± SD (n = 8),

** $p<0.01$ when compared to control group of rats, @ $p<0.05$, @@ $p<0.01$ when compared to negative control group

Effect of polyherbal formulation on blood glucose level

Effect of poly herbal formulations with and without piperine was observed on the blood glucose level of STZ induced diabetic rats. There was significant increase ($p<0.01$) in the blood glucose level of all the STZ treated group up to 302.52 mg/dl on 3rd day of STZ administration. This increased blood glucose level confirmed the diabetes. The confirmation of diabetes was done after observing the increase in the blood glucose level in STZ treated animal. STZ enhances the level of oxidative stress which results in destruction of pancreatic β- cells & increase in blood glucose level. Treatment with poly herbal formulation with and without piperine was significantly ($p<0.05$, $p<0.01$) decreases blood glucose level in diabetic rats compared to negative control group of rats on 10th and 14th day of protocol.

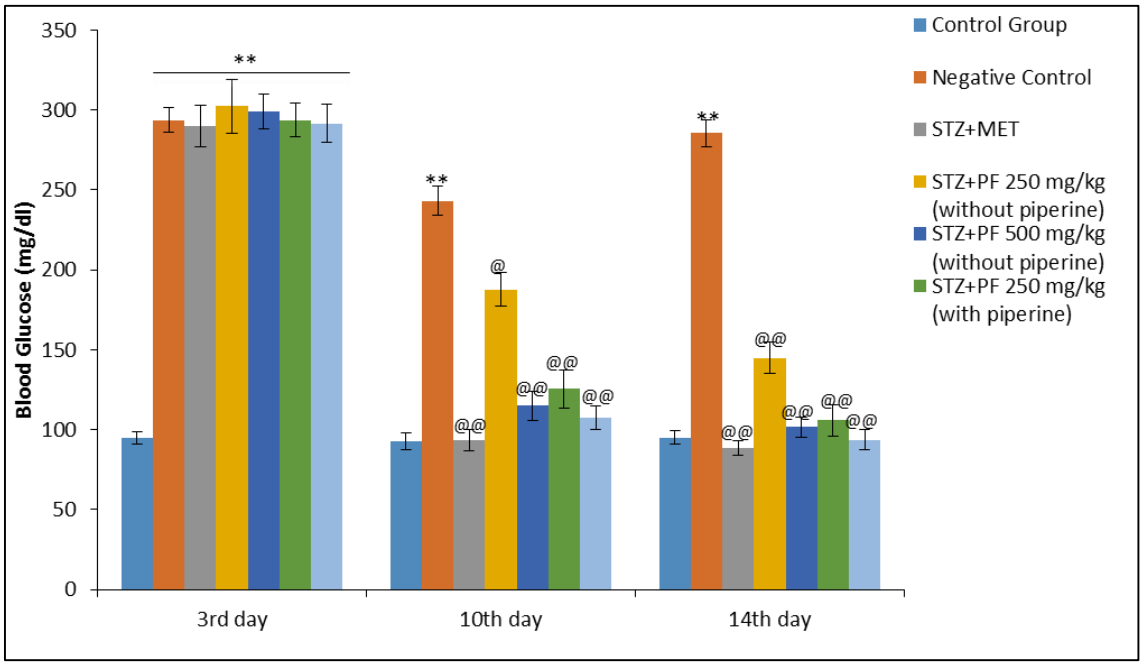

Fig 1: Effect of polyherbal formulation with and without piperine on blood glucose level in STZ induced diabetic rats the results were expressed as Mean ± SD (n = 8), ** $p<0.01$ when compared to control group of rats, @ $p<0.05$, @@$p<0.01$ when compared to negative control group

Effect of polyherbal formulation on biochemical parameters

Effect of poly herbal formulations on the serum concentration of creatinine, BUN, serum albumin and triglyceride in STZ induced diabetic rats as shown in Table 2. There was significant ($p<0.05$, $p<0.01$) increase in concentration of creatinine, BUN, albumin and triglyceride level in the serum of STZ induced diabetic rats than control group of rats. However treatment with herbal formulations with and without piperine significantly ($p<0.05$, $p<0.01$) decreases the serum concentration of creatinine, BUN, serum albumin and triglyceride in STZ induced diabetic rats than negative control group of rats on 10th and 17th d ay of protocol.

Table 2: Effect of poly herbal formulations on the serum creatinine, BUN, serum albumin and triglyceride level in diabetic animals

S. No	Group	10th day				17th day			
		Serum Creatinine (mg/dL)	BUN (mg/dL)	Serum Albumin (mg/dL)	Triglyceride (mg/dL)	Serum Creatinine (mg/dL)	BUN (mg/dL)	Serum Albumin (mg/dL)	Triglyceride (mg/dL)
01	Control Group	0.48±0.056	12.06±0.64	3.22±0.10	81.04±8.69	0.43±0.07	12.82±0.72	3.31±0.21	82.32±5.9
02	Negative Control	0.69±0.13*	16.17±1.81*	3.7±0.09	95.1±6.98*	0.86±0.15**	21.29±1.36**	4.5±0.52**	102.1±6.98**
03	STZ+MET	0.46±0.02@	14.65±1.37@	2.96±0.11@@	83.03±3.03@	0.42±0.04@@	13.23±1.12@@	3.16±0.08@@	82.3±2.5@@
04	STZ+PF 350 mg/kg (without piperine)	0.53±0.12	15.49±1.43	3.46±0.10	91.67±6.68	0.79±0.21	17.92±1.32@	3.92±0.36	95.74±4.8@
05	STZ+PF 700 mg/kg (without piperine)	0.47±0.08@	14.24±1.21@	3.24±0.14@	87.96±7.2@	0.58±0.13@@	15.11±0.81@@	3.42±0.38@@	86.47±4.2@@
06	STZ+PF 350 mg/kg (with piperine)	0.45±0.06@	13.47±0.9@	3.26±0.09@	84.82±5.9@	0.55±0.07@@	14.26±0.97@@	3.47±0.41@@	85.25±3.6@@
07	STZ+PF 700 mg/kg (with piperine)	0.41±0.04@	11.84±0.85@	2.56±0.08@@	82.60±7.5@	0.44±0.02@@	11.54±0.52@@	3.13±0.39@@	81.50±5.2@@

The results were expressed as Mean ± SD (n = 8),

**$p<0.01$ when compared to control group of animals, @$p<0.05$, @@$p<0.01$ when compared to negative control group

Conclusion

Present study concludes that poly herbal formulation with piperine effectively manages diabetes in compare to poly herbal formulation without piperine. So it proves piperine lower dosage level, which in combination with a drug or nutrient provides more availability of the drug by reducing the consumption of the drug or nutrient resulting in enhanced efficacy of the drugs.

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Conflict of interest

Authors declare that there is no conflict of interests regarding the publication of this article.

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