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Development and Evaluation of Polyherbal Formulation for the Management of Chronic Disorder (Diabetes)

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Abstract: Polyherbal formulation having more than one plant in the particular dosage form. These formulation shows greater therapeutic efficacy compared to single plant. In the present study it was intended to formulate antidiabetic polyherbal formulation incorporating different ratio of the Annona squamosa (leaves), Withania somnifera (roots), Tinospora cordifolia (stems)and Azadirachta indica (leaves). The seven different polyherbal formulation (HF1 to HF4) were prepared and administered orally to the streptozotocin induced diabetic rats. The experimental rats treated with the HF1 to HF4 and reference drug Glibenclamide significantly reduced the blood glucose level compared to the diabetic control group. Further, the HF1 to HF4 showed antihyperlipidemic activity by lowering the total cholesterol, triglycerides and low-density lipoprotein level as well asenhanced the high-density lipoprotein. The polyherbal formulations and reference drug improve the body wights of the rats.

Keywords: Polyherbal formulation, antidiabetic.

I. Introduction

The astronomic increment in the commonness of diabetes has made diabetes a noteworthy general wellbeing challenge for India and is turned out to be significant human disease harassing numerous from different backgrounds in various nations and indeed the entire world being viewed ayurvedic the most established recuperating arrangement of medication for the treatment of diabetes. In spite of the fact that there are numerous synthetic medicines developed for patients, yet the reality it has never been accounted for that somebody had recouped absolutely from diabetes. The latest oral hypoglycemic medications are associated with a number of unwanted and adverse consequences. So much effort has been put into considering the antidiabetic properties of medicinal plants and herbal formulations in the treatment of disease in recent years that it is now a major focus of research.

When it comes to Ayurvedic medication details, two things must be considered: Usage as a single medication or in combination with other treatments, the latter being known as Polyherbal formulation. In this fundamental traditional curative herbal technique, which is also known as polypharmacy or polyherbalism, the combining of a handful medicinal herbs in order to obtain more beneficial effectiveness is exploited to create greater beneficial viability.

According to the Ayurvedic text Sarangdhar Samhita, polyherbalism can be used to create increasingly evident therapeutic sufficiency over time. Individual plants do not contain enough active compounds to produce the desirable and beneficial effects that are desired. Whenever the numerous plants are combined to a specific extent, this will have a greater beneficial effect and will reduce the toxicity of the combination5. Science has found the fact that when herbs of various strength 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. A number of the pharmacological actions of botanical active compounds are notable primarily when they are potentiated by the effects of different herbs, but are not noticeable if they're used alone. For example, combining ginger with dark pepper and long pepper enhances therapeutic efficacy. Black pepper, Cuminand asafoetida are historically combined to reduce edoema caused by poor digestion, while guduchi and turmeric enhance immunity.

II. Related Work

The exploration of polyherbal formulations as therapeutic agents for chronic disorders such as diabetes mellitus has garnered considerable attention due to their multifaceted pharmacological potential and synergistic effects. Recent studies emphasize that polyherbal combinations often target multiple pathophysiological pathways involved in diabetes, including insulin resistance, oxidative stress, inflammation, and pancreatic β-cell dysfunction (Kumar et al., 2023; Singh et al., 2022; Patel & Shah, 2023). The complex etiology of diabetes, particularly type 2 diabetes mellitus, necessitates interventions capable of modulating various metabolic and cellular mechanisms simultaneously, which polyherbal formulations can address through their diverse bioactive phytochemicals (Gupta et al., 2021; Roy & Banerjee, 2022). Investigations have reported that formulations integrating herbs such as *Gymnema sylvestre*, *Momordica charantia*, *Trigonella foenum-graecum*, and *Azadirachta indica* exhibit enhanced hypoglycemic effects compared to individual extracts, attributed to the synergism among flavonoids, alkaloids, and saponins that improve glucose uptake, insulin secretion, and hepatic glucose metabolism (Chauhan et al., 2022; Das et al., 2023; Ahmed & Khan, 2022).

Mechanistically, the antioxidant capacity of polyherbal mixtures plays a pivotal role in mitigating oxidative stress-induced β-cell damage, as supported by in vitro and in vivo models demonstrating significant reductions in reactive oxygen species and lipid peroxidation markers (Khan et al., 2022; Singh & Prasad, 2023). Moreover, anti-inflammatory constituents within these formulations inhibit pro-inflammatory cytokines such as TNF-α and IL-6, which are

implicated in insulin resistance and pancreatic inflammation (Reddy et al., 2023; Suresh & Rao, 2022). Clinical evaluations of standardized polyherbal preparations, including those based on Ayurvedic and Traditional Chinese Medicine principles, report improved glycemic control evidenced by lowered fasting blood glucose and HbA1c levels, alongside favorable effects on lipid profiles and body mass index (Verma et al., 2022; Chen et al., 2023; Zhang & Li, 2023). These outcomes are further corroborated by meta-analyses indicating that polyherbal therapies can serve as adjunctive treatments, potentially reducing dependence on conventional antidiabetic drugs and their associated adverse effects (Patel et al., 2023; Kumar & Singh, 2022).

Pharmacokinetic studies reveal that polyherbal formulations may enhance the bioavailability and stability of active compounds through mutual interactions, influencing absorption and metabolic pathways, which necessitates rigorous standardization and quality control for clinical translation (Jain et al., 2023; Wang et al., 2023). However, challenges remain regarding the heterogeneity of formulations, variability in constituent herb quality, and the need for large-scale, randomized controlled trials to validate efficacy and safety comprehensively (Sharma & Mehta, 2022; Li et al., 2023). Emerging research is also focused on integrating nanotechnology with polyherbal formulations to improve targeted delivery and therapeutic indices, potentially revolutionizing diabetes management (Singh et al., 2023; Kumar & Das, 2024). Overall, the collective evidence underscores the promise of polyherbal formulations as multifactorial agents in diabetes therapy, warranting continued investigation to optimize their clinical utility and mechanistic understanding.

III. Material and Method

The leaves of Annona squamosa and Azadirachta indica, roots of Withania somnifera and stems of Tinospora cordifolia were collected, after cleaning plants parts were shade dried. The plant parts were further processed for the coarsely powdered and kept in air tight container for experimental work.

Preparation of Polyherbal Formulations

There were a total of seven distinct polyherbal formulations (HF1, HF2, HF3, HF4, HF5, HF6 and HF7) by blending varying ratios squamosa (leaves), Withaniasomnifera (roots), Tinospora of plant powders of Annona cordifolia (stems)and Azadirachta indica (leaves).

Table 1 lists the constituents of various polyherbal formulations in varying proportions.

Formulations	**Ratio**			
	Annona squamosa	***Withania somnifera***	***Tinospora cordifolia***	***Azadirachta indica***
HF1	1	1	1	1
HF2	1	2	1	1
HF3	1	2	2	1
HF4	1	2	2	2

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 were obtained by boiling about 45 minutes then filtering with muslin cloth the drug macerate that had been left for 24 hours. Adjustments were made to the decoction's content so that 20 g of mixture yielded 50 ml of decoction.

Antidiabetic Activities are as follows:

Polyherbal Formulation's Oral Glucose Tolerance Test

The oral glucose tolerance test was carried out in the experimental rats that had been fasted for18 hours. The rats were placed into ten groups for the experiment, and each group have six rats. Group I named as a normal control, group II have glucose control rodents, group III treated with reference drug Glibenclamide(0.5 mg/kg), while group IV to Group X treated with HF1 to HF10, respectively at the dose of 20 ml/kg body weight.

Thirty minutes before the administration of the extracts and the reference medication, rats in Groups II to X were given glucose (2 g/kg). Blood being taken from the retro-orbital sinus at 0, 30, and 90 minutes following introduction of the extract and reference medication. The plasma obtained after centrifugation of blood at 3000 rpm, was used to assess fasting plasma glucose levels using a glucose oxidase–peroxidase kit.

Non-Insulin-Dependent Diabetes Mellitus Onset

A virtually overnight starved adult rat weighing 170–220 g were used to develop non-insulin dependent diabetes mellitus (NIDDM). A single intraperitoneal injection of 60 mg/kg Streptozotocin 15 minutes after administering 120 mg/kg nicotinamide to develop NIDDM in these rats. The presence of diabetes was verified by the appearance of raised glucose levels in plasma, that were measured at 72 hours and again on day 7 after administration. The fasting plasma glucose level of > 126 mg/dl was established as the diagnostic threshold for diabetes. Specifically, those rodents being employed in the experiment who were confirmed to be have persistent NIDDM.

Antidiabetic Activity of Polyherbal Formulation

The rodents have been divided into 10 groups of six rats each, for a total of 120 rats. The polyherbal formulation and reference drug was given to the animals for a total of 28 days. Group I named as a normal control administered only drinking water, group II have diabetic control rodents, group III treated with reference drug Glibenclamide (0.5 mg/kg), while group IV to Group X treated with HF1 to HF10, respectively at the dose of 20 ml/kg body weight for 28 days.

The blood glucose levels were measured on the first, seventh, fourteenth, and twenty-eighth days after the extract administration. Over the course of the study, the rodents have been weighed on a regular basis, and the average difference in body mass was computed.

Estimation of Biochemical Parameters

It was on day 28 that the biochemical variables was measured afterwards the rats were sacrificed through spinal displacement. The glucose oxidase technique was used to quantify total cholesterol, triglycerides (TGL), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) employing an auto-analyzer.

Statistical Analysis

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

IV. Results and Discussions

Effects of polyherbal formulation on oral glucose tolerance

Table 2 illustrates the impact of polyherbal formulations on the amount of glucose in the blood plasma of animals. Following the ingestion of sugar, an increase in blood glucose was detected in the glucose control, polyherbal formulation (HF1 to HF7) medicated, and reference group animals. When comparing the animals treated with polyherbal formulation to the control group, a substantial drop in hyperglycaemia was noted. The glibenclamide-treated group also experienced a substantial reduction in plasma glucose levels, according to the findings. The polyherbal

formulation showed glucose tolerance efficacy in following orders HF6 > HF3 > HF2 > HF4 > HF7 > HF5 > HF1. The HF6 has greatest glucose tolerance properties compared to other polyherbal formulation.

Table 2: Effect of oral glucose tolerance test of polyherbal formulationson rats

Group	Blood glucose (mg/dl)		
	0 min	30 min	90 min
Normal Control	73.1±5.3	76.7±6.5	75.5±3.8
Glucose control	79.4±3.2	214.3±2.1a	153.4±2.2a
Glucose + Glibenclamide	77.3±5.6	109.7±2.5*	77.2±5.2*
HF1	78.2±4.1	159.1±5.3*	90.6±1.4*
HF2	74.8±6.4	118.1±4.1*	77.2±5.4*
HF3	77.6±1.8	112.3±7.1*	75.9±7.2*
HF4	73.1±5.1	122.4±3.6*	79.5±3.3*

Effect on Niddm of Polyherbal Formulation

The observation of elevated plasma glucose levels in glucose treated rats validated the establishment of hyperglycemia in these animals. On the other hand, the efficacy of a HF1 to HF7 on serum glucose levels in normal and STZ-induced diabetic rodents is demonstrated in Table 3.

When comparing the STZ treated diabetic control rodents to the normal control rodents, a substantial increased serum glucose levels was seen on the first, seventh, fourteenth, and twenty-eighth days after treatment with streptozotocin. A considerable reduction in serum glucose levels was observed in the rodents administered with theHF1 to HF7 and reference drug glibenclamide (0.5 mg/kg p.o.) as compared to STZ induced diabetic rats. When HF6 is compared to other polyherbal formulations, the findings show that HF6 has more significant antidiabetic effects.

Table 3: Antidiabetic effect of polyherbal formulationsin STZ treated rodents

Groups	**Blood glucose (mg/dl)**			
	0Day	**7thDay**	**14thDay**	**28thDay**
Normal Control	80.3±7.2	77.1±4.2	79.6±4.7	80.7±4.5
Diabetic control (Streptozotocin)	153.8±2.5^{a}	198.2±6.7^{a}	254.7±6.3^{a}	291.3±5.3^{a}
Glibenclamide	152.1±4.2	104.7±5.7*	87.2±3.8*	72.8±5.1*
HF1	163.4±5.7	149.8±5.3*	121.7±4.5*	96.9±4.3*
HF2	154.7±5.3	119.1±5.1*	92.5±4.3*	78.7±5.9*
HF3	149.7±1.8	108.6±6.2*	90.3±5.2*	78.2±4.3*
HF4	160.2±3.5	121.7±2.8*	98.4±6.8*	79.6±7.5*

Anti-Hyperlipidaemic Activity of Polyherbal Formulation

As shown in Table 4, the results of the blood lipids of control and experimental rodents were comparable. As comparison to normal rodents, diabetic control animals had a large rise in total serum cholesterol, LDL cholesterol, and HDL cholesterol, despite having a substantial decrease in HDL cholesterol. When comparing to the diabetic control group, the rodents administered with glibenclamide and polyherbal formulations had lower TGL, lower total cholesterol, lower LDL, and higher HDL. All of such impacts were found on the 28th day of the experiment. When HF6 was contrasted to other polyherbal formulations, the results of the blood lipids revealed that HF6 has the greatest antihyperlipidemic effect.

Table 4: Biochemical parameters following administration of polyherbal formulations

Group	Biochemical Lipid Profile			
	TGL (mg/dl)	TCL (mg/dl)	LDL (mg/dl)	HDL (mg/dl)
Normal control	71.3± 3.9	79.5± 7.1	61.4± 1.9	82.7± 6.6
Diabetic control (Streptozotocin)	225.1 ±6.1[a]	196.6 ±5.9[a]	176.8 ±7.5[a]	22.9± 7.5[a]
Glibenclamide	72.8± 5.6*	73.9± 3.2*	65.4± 4.7*	84.1± 2.6*
HF1	93.7± 4.9*	90.1± 4.6*	88.3± 2.6*	60.3± 5.8
HF2	74.6± 5.3*	79.4± 2.5*	65.3± 4.9*	80.6± 6.5*
HF3	73.7± 5.3*	75.8± 7.3*	64.2± 5.8*	83.6± 2.1*
HF4	74.2± 4.6*	80.1± 7.2*	68.1± 5.5*	77.9± 4.9*

V. Conclusion

In the present study, the polyherbal formulation namely HF1 to HF4 incorporating different ratio of the Annona squamosa (leaves), Withania somnifera (roots), Tinospora cordifolia (stems)and Azadirachta indica (leaves) were prepared for the evaluation of the antidiabetic activity. The HF1 to HF4 significantly reduced the blood glucose level in the diabetic rats and also monitor the lipid profile. The findings suggested, HF6 having higher antidiabetic and antihyperlipidemic activity compared to other formulation. Looking on antidiabetic efficacy of the polyherbal formulation, planned to carry out the safety profile study in the future. Also this study has scope to illustrate the possible mechanism of antidiabetic activity of this polyherbal formulation.

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