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A STUDY ON DEVELOPMENT AND EVALUATION OF ANTIDIABETIC POLYHERBAL FORMULATION

Narendra Patel, Research Scholar, Dept of Pharmacy, Monad University, Hapur

Dr Anuj Kumar Sharma, Professor, Dept of Pharmacy, Monad University, Hapur

ABSTRACT

Plant crude powders are standardised using pharmacognostical and physicochemical factors, such as powder microscopy and organoleptic properties. The results of the microbiological limit test, ash value, extractive value, fluorescence analysis, and drying loss were all confirmed to be within standardisation bounds.The people have trusted nature for his or her primary desires along with meals, safe haven, garb, fertilizers, flavours, fragrances, and medicines from prehistoric time. This practice, the great civilizations of the ancient Indians, Chinese, Arabians and North Africans supplied written proof of man's ingenuity in making use of flora for the treatment of a huge style of diseases. Thus, flora have fashioned the basis of state-of-the-art conventional medication systems which have been in life for lots of years and retain to provide humankind with new treatments. Through durations of trial, errors and fulfilment, the ancient guy and their followers have collected a huge know-how approximately medicinal plant life. The first records, written on clay pills in cuneiform, are from Mesopotamia and date from approximately 2600 BC. Among the substances that used had been oils of Cedrus species (Cedar) and Cupressus sempervirens (Cypress), Glycyrrhiza glabra (Liquorices), Commiphora species (Myrrh) and Papaver somniferum (poppy juice), all of which are nevertheless in used for the treatment of illnesses ranging from coughs and colds to parasitic infections and infection.

KEY WORDS: Polyphenols, Nature's Bioactive Compounds, Antidiabetic Polyherbal Formulation

INTRODUCTION

Background and Significance of Polyphenols: Nature's Bioactive Compounds

Due to their capacity health advantages and bioactive qualities, polyphenols, an extensive series of evidently occurring secondary metabolites located in plants, have attracted a whole lot of research. These substances are generally present in a whole lot of plant-primarily based ingredients, such as result, veggies, whole grains, nuts,

seeds, and alcoholic liquids like tea and purple wine. They are distinguished by using their several phenolic earrings and hydroxyl businesses. As studies have shown polyphenols' wonderful organic activities, together with their antioxidative, anti-inflammatory, antibacterial, and anticancer effects, interest in polyphenols among scientists has grown through the years.

The significance of polyphenols inside the context of antidiabetic movement arises from their potential to alter vital pathways linked to insulin sensitivity and glucose homeostasis. Chronic hyperglycemia is an indicator of diabetes mellitus, which develops because of inadequate insulin synthesis, reduced insulin motion, or each. Alternative and complementary procedures to standard treatment plans have grown essential as the prevalence of diabetes continues rising.

Polyphenols present a viable choice due to the fact mounting research suggests that they may be capable of enhancing many components of diabetic pathogenesis. Enhancing insulin sensitivity is one of the number one methods that polyphenols exert their anti-diabetic benefits. It has been demonstrated that they have got an effect on the insulin signaling pathways, promoting glucose absorption into cells and lowering insulin resistance.

Additionally, polyphenols can influence the expression and release of adipokines, cytokines, and different mediators which are critical for controlling infection and the metabolism in diabetes. By focusing on these complicated interactions, polyphenols have the strength to reduce oxidative strain and continual low-grade infection, two elements that are without delay related to the onset and development of diabetes. Polyphenols' importance in antidiabetic motion is similarly complicated by using their bioavailability and metabolism.

The body's ability to take in and distribute polyphenols is motivated by the aid of factors such as chemical composition, food matrix, intestine plants, and interactions with different dietary components. Understanding these dynamics is important for effectively utilizing their healing capability. Research has lately targeted pinpointing certain polyphenols that show off sturdy anti-diabetic results. The capability of flavonoids, an enormous subclass of polyphenols, to modify glucose transporters, insulin receptors, and enzymes concerned with glucose metabolism, has drawn several interest. Aside from that, phenolic acids, along with hydroxycinnamic and hydroxybenzoic acids, display promise for improving insulin signaling and decreasing postprandial hyperglycemia reactions.

These findings highlight how polyphenols are various and can be turned into specific antidiabetic capsules or nutraceutical dietary supplements. The research of polyphenols as nature's bioactive substances is of maximum significance in the look for new anti-diabetic treatments. Their complicated consequences on oxidative stress, infection, and insulin sensitivity offer a robust justification for greater research.

DIABETIC MELLITUS

The main effect of this is an increase in blood glucose levels. Hyperglycemia arises as a result of this variation and unbalanced state, and if it persists for an extended length of time, it eventually results in the syndrome known as diabetes mellitus.Diabetes, which means to pass through intense thirst and frequent urination, is derived from the Greek term "Diab," which was first used in 230 BCE. The Latin word "mellitus" means "sweetened with honey," and it denotes the presence of sugar in the urine. The mention of diabetes mellitus is explained in 1874 by renowned Egyptologist Georg Ebers, along with a number of other illnesses and their treatments.

Around the same time, Indian doctors created the first clinical test for diabetes. They noticed that ants and flies, among other insects, were drawn to the urine of diabetic patients. They refer to the illness as "madhumeha" or "honey urine." Indian doctors conducted research that suggested individuals suffering from "madhumeha," or severe thirst and foul-smelling breath, might be in ketosis. The two most famous Indian doctors, Sushruta and Charaka, were the first to distinguish between the two different forms of diabetes mellitus. The discovery of insulin by Frederick Banting and Charles Best served as the gold standard for determining the chemical, the lack of which was thought to be the cause of diabetes. Wikipedia and Ahmed A.M. (2002) both note that although numerous approaches, tests, and procedures were attempted, no successful, secure, and efficient treatment for diabetes was identified until the 20th century, when two Canadian scientists, Frederick Banting and Charles Herbert Best, created insulin in 1921 and 1922. In the 1940s, long-acting insulin NPH was developed as a result.

PREVALENCE AND INCIDENTS OF DIABETES

Diabetes mellitus is a chronic metabolic disease characterised by a decrease in insulin activity and an absolute, partial, or relative shortage of insulin. This leads to hyperglycemia and abnormalities in the metabolism of fat, carbohydrates, and proteins. First and foremost, it is the most prevalent endocrine condition, affecting 16 million people in the US and as many as 200 million globally. With an estimated 171 million cases worldwide in 2000 and a projected 366 million cases by 2030, diabetes is a serious and expanding public health concern globally. Currently, 40.9 million people in India are estimated to have diabetes, and by 2030, that number is predicted to reach 69.9 million.

INDIAN PERSPECTIVE OF DIABETIC MELLITUS

Rapid urbanisation and socioeconomic development are currently occurring in many developing nations, such as India. This has resulted in a shift in dietary habits and a sedentary lifestyle, which has given rise to metabolic illnesses. Based on available data, it has been seen that urbanisation leads to a notable decrease in physical activity, along with a rise in obesity and body mass index. These findings suggest that Indian communities are more vulnerable to the problems of diabetes mellitus than Western cultures. The management of this illness has several obstacles in India, including limited knowledge, a shortage of skilled medical and paramedical personnel, and the high cost of treatments and medications.

Diabetes mellitus is becoming more widespread in India, maybe reaching epidemic proportions. Diabetes complications have a significant healthcare cost in terms of morbidity and mortality for families as well as society at large. Given how prevalent the disease is today in India's population at large, innovative, readily available, and reasonably priced treatments must be developed.

According to the World Diabetes Atlas published by the International Diabetes Federation (IDF) during the 20th World Diabetes Congress in Montreal, Canada, India would likely continue to be the "diabetes capital" of the world by 2030, with about 9% of the population expected to be affected. The Atlas estimates that of the entire amount spent globally on diabetes, the United States spends $198 billion, or 52.7%, while India spends close to $2.8 billion, or 1%. In India, the poorest people with diabetes spend an average of 25% of their income on private healthcare, which helps them stay alive by preventing dangerously high blood glucose levels.

Nonetheless, individuals from Indian tribes with reduced threshold limits for environmental risk variables demonstrated a higher ancestry and genetic vulnerability to diabetes. The fact that Indians experience mild weight gain and Type 2 Diabetes Mellitus at a younger age than Western cultures is a serious concern.

RESEARCH METHODOLOGY

Collection plant material

The chosen plant material, which was needed for the current study, was gathered from the Satpuda Mountains' hills, particularly those of Toranmal and Boradi Forest. Plant material such as Evolvulus alsinoide, Gymnema sylvestre (Retz.) R. Br. Ex Roem and schut, (Asclepidaceae) (Bedki Pal), Tinospora cordifolia (Gulvel), and Caesalpinia bonduc L. Roxb. are obtained with the assistance of traditional healers in Tranmal.paneer, Withania coagulance Dunal (Solanaceae), (Caesalpiniaceae) (Sagargota), bought from the neighbourhood market.Curcuma

caesia Roxb (Zingiberaceae) acquired from Mr. Ashish Behuria Bhuvneshawar, Asam, and Mr. Ruuvilie Kotsu Medziphema. Purchased from the neighbourhood market, watermelon (Citrullus lanatus (Thumb) Matsumura and Nakai; Family: Cucurbitaceae).

Procurement of Drug and chemical

For this study, A.R. grade chemicals, solvents, and conventional pharmaceuticals were all employed. Purchased alloxan monohydrate from S.D. Fine Chemicals in Mumbai. Commercially available kits (ERBA diagnostics) were purchased for biochemical observation.

Development and Evaluation of Antidiabetic Polyherbal Formulation

Development of Polyherbal Formulation : The most effective way to deliver medication to body organs is through formulations. In order to get the desired outcome in an efficient manner, it is also proven and customary to formulate the medication into the formulation. Therefore, it was deemed valuable to investigate the impact of the extracts demonstrating noteworthy anti-diabetic activity in the formulation.

Depending on how soluble the extract was, the ones that had the strongest anti-diabetic effects were selected for the polyherbal formulation in the form of suspension rather than solution using 2% Tween-80 / water. The ayurvedic antidiabetic formulation suggested by Pandey served as the foundation for the preparation of the herbal and polyherbal formulation.

The doses of the other chosen plants are determined based on a thorough assessment of the literature, taking into account their reported toxicities and antidiabetic potential, with formulation developed according to a 1:1:1 ratio, respectively.

General procedure

A variety of bioactive extracts of particular plant materials were used to make the suspension, which was then made in a mortar and pestle using the appropriate suspending agent (Tween 80) and sodium CMC (Sodium carboxy methyl cellulose).

together with other excipients listed in the general formula in Table No. 1.

Table 1: General formula for the development of herbal formulation

Ingredient	Quantity in % w/w
Bio-active extract	10gm
Tween 80	0.1 %
Sodium CMC	2 gm
Methyl paraben	0.20 %W/V
Lemon oil	0.01 %V/V
Purified water	100 ml

Table 2: Composition of Alcoholic extracts for Formulation

Sr. No.	Name of Ingredient	Quantity
1.	*Curcuma Caesia* Alcohol (ethanolic) extract	0.72g
2.	*Evolvulus Alsinoide* Alcohol (ethanolic) extract	0.72g
3	*Citrullus lanatus*. Alcohol (ethanolic) extract	0.72g
4	*Gymnema sylvestre* Alcohol (etanolic) extract	0.72g
5	*Tinospora Cordifolia*. Alcoholic (ethanolic) extract	0.72g
6	*Withania .Coagulance*. Alcoholic (ethanolic) extract	0.72g
7	*Caesalpinia.bounduc*. Alcoholic (ethanolic) extract	0.72g
8	Tween-80	0.1%
9	Sodium CMC	2.0g
11	Methyl Paraben	0.20%W/V
12	Lemon oil	0.01%V/V
13	Distilled water	Up to 100ml

RESULTS AND DISCUSSION

The doses of the other chosen plants are determined based on a thorough assessment of the literature, taking into account their reported toxicities and antidiabetic potential, with formulation developed according to a 1:1:1 ratio, respectively.

The formula used to make the polyherbal suspension of different extracts. The lyophilized ethanolic extracts of the following herbs are included in the polyherbal formulation: Citrullus lanatus (seeds), Gymnema sylvestre (leaf), Tinospora cordifolia (stem), Caesalpinia bonduc (seed), Evolvulus alsinoide whole plants, Gymnema sylvestre (leaf), and Withania coagulance (fruit). These extracts were properly mixed in a portion of 1:1:1 by trituration with sodium CMC and tween 80 suspending agent. Following that, the other excipients, like methyl paraben and lemon oil, were combined by continuous trituration, and distilled water was added to make up the remaining volume.

All of the medication extracts contain primarily glycosides, triterpenoid, flavonoids and alkaloids, steroids, and phenolic compounds, according to the preliminary phytochemical analysis. There was no death noted in the acute oral toxicity trials for polyherbal formulations up to 5000 mg/kg.

Table 3: Dose selection and finalizing LD50 Cut off value PHF

Sr. No.	Polyherbal formulation	LD_{50} Cut-Off mg/ kg, b.w
1	PHF Formulation	5000mg/kg

The effective dose, or therapeutic dose, for the ensuing anti-diabetic action was 1/10th of the deadly amount.

Different dosages (100, 200, and 400 mg/kg) of the polyherbal formulation were tested to see how it affected the hypoglycemic effect on glucose tolerance in normal rats. It was discovered that PHF 1 and PHF 2 did not significantly lower their blood glucose levels over a 90-minute interval. When compared to glucose loaded (109.8±5.2) at 90 and 150 minutes after glucose injection, the blood glucose level at 400 mg/kg of a polyherbal formulation significantly drops.

Table 4: Effect of Polyherbal formulations on blood glucose level in OGTTInduced diabetes

Groups	Blood Glucose Level (mg/dl) At Various Timepoints			
	0 min	30 min	90 min	150 min
Glucoseloaded	55.1±3.7	132.5±3.24	124±4.2	109.8±5.2
Test 1	60.5±5.2	125.3±5.24	115±4.7	96.3±5.3
Test 2	57.6±4.2	107.6±2.57	111±3.5	84±3.6***
Test 3	58.4±2.6	110.4±3.18	87.2±2.68**	81.4±3.4***

Data were expressed as mean ± SEM (n =6). Statistical significances were determined using one-way analysis of variance (ANOVA) followed by Dunnet post hoc test. ###p<0.001 as compared to normal, **p<0.01, ***p<0.001 as compared to loaded

Table 5: Effect of Polyherbal formulations on Body weight

Group		Normal	Standard	Alloxan	Test 1	Test 2	Test 3
Body Wt.	**Initial**	194.7± 5.27	197.6± 6.66	204.0± 5.62	201.86± 6.38	188.8± 2.39	190.5±2 .37
	14th day	198.9± 5.24	205.5± 5.56	188.0± 4.47	198.25± 4.34	194.8±2 .25***	197± 4.15***

Data were expressed as mean ± SEM (n =8). Statistical significances were determined using one-way analysis of variance (ANOVA) followed by Dunnet post hoc test. ###p<0.001 as compared to normal, **p<0.01, ***p<0.001 as compared to Alloxan

The body weight of the rats in the diabetic control group decreased on day 14 (188.0±4.47). Rat weight did not significantly decrease (as seen in PHF 1 (100 mg/kg).It was discovered that rats treated with PHF 3 (400 mg/kg) had a significantly higher body weight (195±4.15) than those treated with Alloxan (188.0±4.47).

On the ninth day, the blood glucose level in PHF-1, the diabetic animal, does not significantly decrease in comparison to PHF 2 and PHF 3, which were treated with alloxan. After administering the polyherbal formulation continuously for 14 days, it was shown that PHF3 (100.4±2.997) had a significantly lower blood glucose level

than Normal (96.44±6.149) and Alloxan-treated (330.4±4.137). Consequently, it was determined that the anti-diabetic activity of the polyherbal formulation in suspension form is almost as effective when administered at a dose of 400 mg/kg body weight (100.4±2.997) as it is when administered with Alloxan treated (330.4±4.137).

In comparison to the normal control group of rats, the diabetic control group's blood total cholesterol (189.1±13.96), triglycerides (258.9±16.15), SGPT (179.7±12.88), SGOT (182.6±5.58), and lowered HDL (28.9±1.823) increased statistically significantly ($P < 0.001$) on the fourteenth day.

When compared to diabetic control rats, the repeated dosage treatment of PHF (200 and 400 mg/kg/day) and Glibenclamide (10 mg/kg/day) for 14 days dramatically ($P < 0.001$) reversed these changes in plasma lipid profile. Compared to the diabetic control group, treatment with Glibenclamide, PHF 2, and PHF 3 for 14 days resulted in significant reductions in total cholesterol (132.3±10.05), triglyceride (155.9±3.17), SGPT (92.60±8.37), SGOT (85.54±19.53), and HDL levels (52.31±1.192). PHF 2 and PHF 3 formulations shown more or comparable action to Glibenclamide in terms of relative efficacy, and they also demonstrated diabetes control on all biochemical parameters. However, PHF 400 mg/kg is the most effective formulation overall across all parameters.

When comparing PHF 400 mg/kg to the standard, it was discovered on the fourteenth day following insulin determination that there is insulin stimulation.

According to other biochemical indicators and hypoglycemic activity, the current study's results are consistent with those of earlier investigations. PHF-3 demonstrated optimal efficacy in reducing blood glucose levels in the diabetic rats and demonstrated superior plasma glucose lowering capabilities. Diabetes typically results in higher serum lipid levels, which is a high-risk factor for coronary heart disease. Triglycerides are hydrolyzed by the enzyme lipoprotein lipase, which is normally activated by insulin. However, in a diabetic state, insufficient insulin causes lipoprotein lipase to be insufficiently active, which leads to hypertriglyceridemia. The administration of Polyherbal (PHF-3) resulted in a noteworthy reduction in triglycerides and total cholesterol, suggesting that these formulations may mitigate the difficulties related to lipid metabolism and related cardiovascular risk factors in individuals with diabetes. In the current investigation, the formulation known as Polyherbal (PHF-3) outperformed Glibenclamide in terms of enhancing lipid metabolism. Another potential hazard for long-term oral hypoglycemia usage is hepatotoxicity. By lowering the dosage of oral hypoglycemic medications and taking them in conjunction with herbal remedies, this risk factor can be reduced. For SGOT and SGPT levels, the Polyherbal (PHF-3) performed better than Glibenclamide.

While the formulation Polyherbal (PHF-3) had the highest efficacy for several biochemical parameters, a comprehensive analysis of the data for all parameters suggests that Polyherbal (PHF-3) was superior than Polyherbal (PHF-2), Glibenclamide, and diabetes control. During the fourteenth day of the trial, there were no harmful effects in terms of hepatotoxicity.

CONCLUSION

Herbs are not a novel treatment for diabetes. In Ayurvedic and Chinese medicine, herb-herb mixes, also known as polyherbal remedies, have been used for many years. Since ancient times, plants and plant extracts have been used to cure or prevent diabetes, which appears to be the most successful and non-toxic method.

Globalisation, industrialization, and fast urbanisation have all contributed to India's economic and social growth, but they have also drastically changed people's lifestyles and increased the risk of lifestyle-related illnesses. The primary causes of India's diabetes epidemic in urban areas are sedentarism, or the lack of exercise, and the fast-food culture. Despite advancements in modern medicine, patients and their families in rural areas face significant financial challenges. As a result, health care is often neglected, leading to severe morbidities and early mortality from metabolic illnesses including diabetes and heart disease, particularly type II. There is no extensive diabetic healthcare programme in India. Patients visit various healthcare providers in search of medical attention. While conventional treatment concentrates on the quick fix of lowering blood glucose levels, Ayurveda and polyherbal formulations aim to address the underlying chronic problems that cause the condition and treat its complications on its own. Since type 2 diabetes mellitus (T2DM) is a multigenic chronic illness, treating it requires a multitargeted strategy. Since developing a medicine using a multi-targeted method is challenging, polyherbal therapy—which has the potential to be safe, cost-effective, and multi-targeted—might be a viable option for creating more potent diabetes formulations. Treatment for diabetes is lifelong, and the main benefit of using an alternative conventional medical system that includes herbal formulations is the use of medications with no known adverse effects.

Herbal formulation based on two principles: polyherbalism, or the use of many drugs in place of a single medicine. There are two ways that synergism operates, depending on how the herbs interact. Two polyherbal formulations, pharmacodynamics and pharmacokinetics (the ability of a herb to aid in the absorption, distribution, metabolism, and elimination of other herbs), have a broad therapeutic range, are safe at high doses and effective even at low doses. They also remove potential poisonous effects that may also arise from high doses of plant extracts.

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