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Original Research Paper

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HERBAL INTEGRATIVE TREATMENT APPROACH FOR DIABETES MELLITUS TYPE-2 IN INDIAN CONTEXT

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ABSTRACT

Objective: This study aimed to assess the efficacy and safety of the compound herbal drug *Guduchyadhi Choornam* in managing Type-2 Diabetes Mellitus (T2DM). With a focus on blending traditional Ayurvedic wisdom with modern clinical trial design, the research sought to provide evidence-based alternatives to conventional oral hypoglycemic agents. **Material and Methods:** The methodology combined ancient Ayurvedic knowledge retrieval with contemporary clinical trial principles. Medicinal herbs identified from Ayurvedic Sanskrit treatises underwent standardization based on Indian pharmacopeia criteria. The clinical trial included polyherbal compound standardization, patient selection, treatment protocols, education, followup, and robust statistical analyses using SPSS. **Results:** Among 200 participants, the compound herbal drug demonstrated significant efficacy. Post-treatment, there was a 21.29% reduction in fasting blood sugar levels and a 29.66% decrease in post-lunch blood sugar levels. Fasting blood insulin levels increased by 51.33%, and post-lunch blood insulin levels rose by 85.5%. HbA1c levels showed an average reduction of 19.11%, while blood cholesterol exhibited a substantial average reduction of 27.73%. Statistical tools, including paired t-tests, correlation analyses, and case distribution assessments, underscored the robustness of the findings. **Conclusion:** This research, bridging ancient wisdom and modern evidence, showcased the potential of *Guduchyadhi Choornam* in T2DM management. The recommendation for future studies emphasized exploring nano-sized particles for enhanced therapeutic action, holding promise for a paradigm shift in diabetes care. Beyond contributing to medical literature, this study exemplifies the harmonious integration of traditional and modern knowledge for improved healthcare outcomes in the realm of T2DM.

KEYWORDS : Ayurveda, Guduchyadhi Choornam, Type-2 Diabetes Mellitus, Polyherbal Compounds.

INTRODUCTION

In the realm of T2DM research, India grapples with a staggering diabetic population, currently standing at approximately 33 million individuals, predominantly concentrated in urban areas. T2DM, a prevalent endocrine disorder affecting about 10% of the global population, has emerged as a significant public health concern due to its severe impact on multiple organ systems [1,2]. Conventional oral hypoglycemic agents, such as sulphonyl-ureas and bi-guanines, are commonly used for T2DM treatment, but their effectiveness is hampered by adverse side effects, underscoring a critical limitation in current therapeutic options [3,4].

Responding to the challenges posed by conventional drugs, herbal medicines have gained momentum for their perceived efficacy and safety compared to mainstream pharmaceuticals in T2DM management [5]. Plants harboring anti-diabetic properties have become a focal point for the ethno-botanical community, offering potential medicinal compounds across various plant parts. These plant-derived compounds exhibit varying degrees of hypoglycemic and antihyperglycemic activities, presenting promising avenues for further investigation. Traditional approaches, focused on isolating bioactive constituents for use as drugs or pharmacological agents, hold promise for addressing T2DM complications [6].

The evolving socio-economic landscape, particularly in rural areas, has heightened susceptibility to T2DM [7]. Factors such as improved transportation, reduced physical activity, dietary changes, and genetic predispositions have created an environment conducive to the expression of diabetes. Notably, Indians exhibit a genetic phenotype characterized by low body mass index and high upper body adiposity, body fat percentage, and insulin resistance [8,9]. Against this backdrop, exploring natural remedies rooted in Phyto-therapy becomes imperative, with a particular emphasis on plant-based compounds and their synergistic effects [10].

Throughout history, plants have played a pivotal role in the treatment and management of various diseases, including T2DM. Phytotherapy, involving the use of plants, plant extracts, or isolated pure chemicals from natural sources, has been employed to address T2DM and associated complications [11]. Despite the prevalence of synthetic drugs today, many pharmaceutical agents trace their origins back to plants and animals. Recognizing the value of plants as a source of bioactive compounds, there is a pressing need for systematic studies on medicinal plants for the development of novel and effective therapeutics tailored specifically for T2DM [12].

Table 1: Table Of Herbal Drugs Used In Formulation For Treatment Of Diabetes Mellitus Type-2.

S. No.	Plant Name	Part Used in Medicinal Herb	Reference
1.	*Tinospora cordifolia* (Guduchi)	Stem, root	[15]
2.	*Gymnema sylvestre* (Madhunashini)	Leaves	[16]
3.	*Curcuma longa* (Haridra)	Rhizome	[17]
4.	*Azadiracta indica* (Nimba)	Leaves, bark	[18]

5.	*Syzygium jambu* (Jambu)	Seeds, leaves	[19]
6.	*Momordica charantia* (Kerela)	Fruits, leaves	[20]
7.	*Withania somnifera* (Ashwagandha)	Root, leaves	[21]
8.	*Phyllanthus emblica* (Amalaki)	Fruits	[22]
9.	*Terminalia belerica* (Vibhithaki)	Fruits	[23]
10.	*Terminalia chebula* (Haritaki)	Fruits	[24]

The compound herbal drug *Guduchyadhi Choornam*, tailored for treating T2DM, emerges as a promising candidate, representing a crucial step toward the development of a side-effect-free therapeutic approach in the context of T2DM [13,14] (**Table 1**).

METHODOLOGY

The methodology employed in this study combines rigorous traditional knowledge retrieval with contemporary clinical trial design to investigate the potential efficacy of herbal compounds in managing T2DM. Drawing inspiration from ancient Ayurvedic Sanskrit treatises, a meticulous review was conducted to identify medicinal herbs associated with hypoglycemic properties, followed by a selection process and subsequent standardization based on Indian pharmacopeia criteria.

A. Medicinal Herb Identification And Standardization

• Ayurvedic Sanskrit Treatise Review:

A thorough review of ancient Ayurvedic Sanskrit treatises to identify medicinal herbs for T2DM or *Prameha* diseases was conducted [25].

• Herb Selection And Standardization:

Compilation of a selected list of herbs based on potential hypoglycemic properties. Identification of common plants with similar properties and standardization, based on Indian pharmacopeia standards [26, 27].

B. Clinical Trial Design and Patient Management

• Polyherbal Compound Standardization:

Standardization of polyherbal compounds with suitable hypoglycemic and hypolipidemic activity [28].

• Patient Selection and Treatment Protocol:

Selection of T2DM patients based on inclusion/exclusion criteria. Administeration of *Guduchyadi Churna* (GC) for 30 days and collected blood samples for glucose, insulin, cholesterol, and HbA1C [29].

• Ethical Considerations:

This study was perofrmed according to the declaration of Helsinki for ethical treatment of participants [30]. This study was approved by Institutional Ethical Committee and registered on CTRI (reg. REF/2014/09/007681). A signed informed consent was obtained from all participants before enrolment.

Education And Follow-up:

A comprehensive training was given to patients on T2DM and the study's objectives were explained to them along with potential benefits and side-effects of the treatment plan. Educated patients about hypoglycemia and preventive measures. Follow-up was taken in a Pre-post design [31].

Statistical Analysis:

The study will employ a range of statistical tools to analyze the data and assess the efficacy of the polyherbal compound in managing T2DM. These tools include:

Descriptive Statistics:

Mean, standard deviation, and frequency distributions will be calculated to summarize and describe the baseline characteristics of the study participants.

Paired T-tests:

Paired t-tests will be utilized to compare pre- and post-treatment levels of glucose, insulin, blood cholesterol, and HbA1C within individual subjects, providing insights into the effectiveness of the herbal intervention.

Analysis of Variance (ANOVA):

ANOVA or its non-parametric equivalent will be employed to assess significant variations in the measured parameters across different time points during the 30day treatment period, providing an overall understanding of treatment effects.

Correlation Analyses:

Correlation analyses will explore potential associations between changes in glucose levels and insulin sensitivity, providing insights into the interplay between these variables.

Regression Analyses:

Regression analyses will be conducted to assess the predictive value of the polyherbal compound on glucose levels, insulin sensitivity, and other parameters, while considering potential confounding variables.

Significance Level:

All statistical tests will be performed with a predetermined significance level ($p < 0.05$) to determine the statistical significance and reliability of the observed effects.

Inclusion Criteria:

Considering the different definitions put forth by various scientists for Diabetic condition, the inclusion criteria for the present study will keep as under:

1. Individuals with only Type-2 Diabetes on treatment with other herbal drugs.
2. Duration of diabetes more than 1 year.
3. Patients of above 25 years of age and below 65 years of both genders.
4. Patients whose blood sugar dose ranges from FBS 70mg to 250mg was monitored on a weekly basis for one month done on OPD base before planning to admit him in in-patient department for the study.

Exclusion Criteria:

Patients with Hepatitis-B, individuals with AIDS, and those suffering from Tuberculosis were excluded from the clinical study, as were individuals undergoing alternative therapies, drug abusers, and those with major psychiatric illnesses. Exclusion criteria also extended to patients with heart disease, gestational diabetes mellitus, and pregnant individuals. This exclusion was essential to ensure the accuracy of the compound drug's action.

Investigations Required:

A series of investigations were conducted before and after the study period to assess the impact of the compound drug. The required investigations included ECG, complete blood count (CBP), erythrocyte sedimentation rate (ESR), HBSAg, Lipid Profile, HIV 1&II, complete urine examination (CUE), fasting blood sugar (FBS), post-lunch blood sugar (PLBS), serum insulin estimation, HbA1C before and after the study, thyroid profile, renal function tests, and liver function tests. Not all investigations were performed for every individual; rather, only the necessary tests were conducted based on individual requirements deemed reasonable for the study trial. Routine investigations such as CBP, ESR, CUE, HbA1C, FBS, PLBS, blood cholesterol, and fasting blood insulin levels were carried out for all study participants. The collected results were meticulously tabulated, and various appropriate statistical tests, including paired t-tests and correlation analyses, were conducted to arrive at logical inferences.

RESULTS

The study analyzed the distribution of cases based on gender and family history. In **Table 2**, it was observed that out of the total 200 cases, 64.5% were male, while 35.5% were female. Regarding family history, 48.0% of cases had a positive family history, while 52.0% had no family history.

Table 3 further delves into the distribution of cases based on age group and gender. In the age group of 20-39, 66.7% of cases were male, and 33.3% were female. For the age group of 40-64, 64.9% were male, and 35.1% were female. Among individuals aged 65 and above, 42.9% were male, and 57.1% were female. These findings provide a detailed insight into the demographic patterns of the studied cases, highlighting variations in both gender and age group distributions.

The percentage of decrease in Fasting blood sugar levels after the treatment is 21.29%, and post lunch blood sugar level percentage is 29.66 % (**Figure 1**). The percentage of increase in Fasting blood insulin levels after the treatment is 51.33%, and post lunch blood insulin level percentage is 85.5% (**Figure 2**). The percentage of reduction in average HbA1C levels is 19.11% (**Figure 3**). The percentage of average reduction in blood cholesterol level is 27.73% (**Figure 4**). Two hundred patients completed the study. Mean baseline FBS was 157 (SD 49) and decreased to 122 (SD 23) after the intervention process [mean (SEM) decrease 34.89 (2.52)]. A paired-samples *t*-test showed this change to be significant ($p<0.001$) (**Table 4**). Statistical significance was defined as $p<0.001$ (**Table 5**).

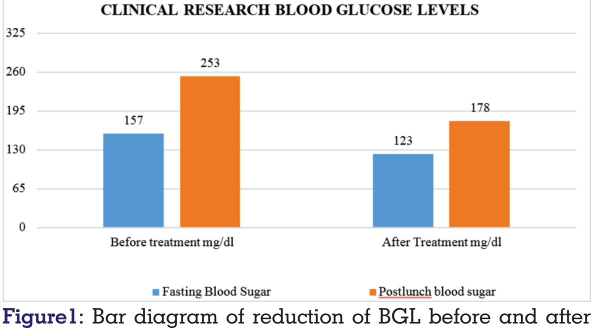

Figure1: Bar diagram of reduction of BGL before and after treatment.

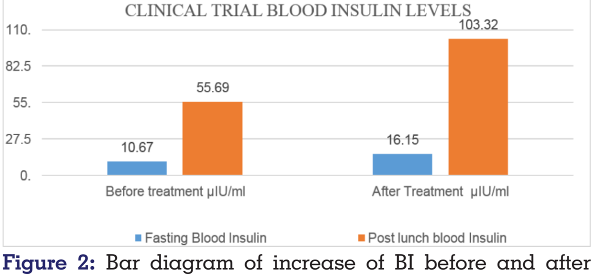

Figure 2: Bar diagram of increase of BI before and after treatment.

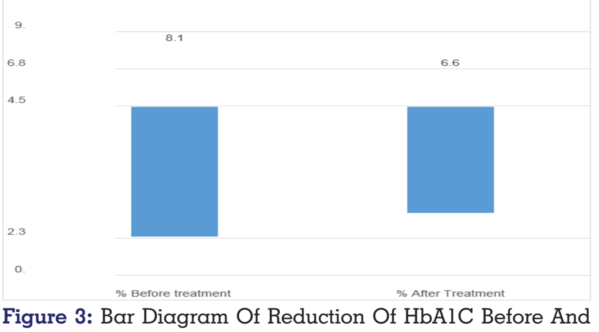

Figure 3: Bar Diagram Of Reduction Of HbA1C Before And After Treatment.

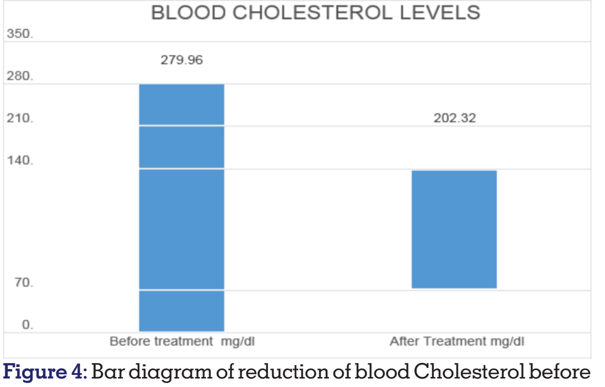

Figure 4: Bar diagram of reduction of blood Cholesterol before and after treatment.

Table 2: Case Distribution Gender Wise.

		n	%
Gender	Female	71	35.5
	Male	129	64.5
	Total	200	100
Family history	Yes	86	48.0
	No	93	52.0
	Total	179	100

Table 3: Case Distribution Age Group And Gender Wise.

Gender					
		Male		**Female**	
		n	%	n	%
Age	20-39	16	66.7	8	33.3
	40 - 64	109	64.9	59	35.1
	65+	3	42.9	4	57.1

Table 4: Clinical Objective Parameters, SEM, T Value And P values

Parameter	**Before**		**After**		**Mean Change**	**SEM**	**t Value**	**P-Value**
	Mean	**SD**	**Mean**	**SD**				
FBS	157	49	122	23	34.8	2.52	13.85	0.001
PLBS	253	77	176	27	76.1	0.38	-14.37	0.001
Fasting insulin	10.68	6.73	16.1	4.2	-5.4	0.06	27.73	0.001
Post lunch blood insulin	55.68	33.78	103.3	47.5	-47.6	2.52	13.85	0.001
HbA1C	8.2	1.5	6.6	.9	1.5	0.38	-14.37	0.001
Total cholesterol	280	56	202	38	77.6	0.06	27.73	0.001

Table 5: Paired Sample Correlation Before And After Treatment.

Paired Samples Correlations			
		Correlation	Sig.
Pair 1	Before treatment FBS & After treatment FBS	.734	.0001
Pair 2	Before treatment PLBS & After Treatment PLBS	.588	.0001
Pair 3	Before treatment fasting insulin & After treatment fasting insulin	.615	.0001
Pair 4	Before treatmen post lunch blood insulin & After treatment post lunch insulin	.554	.0001
Pair 5	Before treatment HbA1C & After treatment HbA1C	.887	.0001
Pair 6	Before treatment total cholesterol & After treatment total cholesterol	.771	.0001

DISCUSSION:

In this comprehensive study involving 200 participants, that holds immense promise in the management of Type-2 Diabetes Mellitus. The research focused on evaluating the efficacy and safety of a polyherbal drug [32], presenting a meticulous analysis of various physiological parameters before and after treatment. The mean baseline fasting blood sugar (FBS) level of 157mg/dl (SD 49) among the participants marked the starting point of the investigation. Following the intervention process, which will be explored in detail shortly, this baseline FBS level showed a remarkable reduction to 122mg/dl (SD 23). The mean (SEM) decrease of 34.89mg/dl (2.52) was statistically significant, as confirmed by a paired-samples t-test with a $p < 0.001$. Post-treatment, there was a notable 21.29% reduction in fasting blood sugar levels and an even more substantial 29.66% decrease in post-lunch blood sugar levels. These percentages underscore the drug's ability not only to address fasting glucose but also to impact postprandial sugar levels, a critical aspect of diabetes management [33, 34].

Beyond glycemic control, the study explored the drug's influence on insulin levels. Fasting blood insulin levels exhibited a robust 51.33% increase, while post-lunch blood insulin levels rose significantly by 85.5%. These findings suggest a multifaceted impact of the intervention, indicating a potential role in enhancing insulin production and secretion, crucial for glucose metabolism [35]. HbA1C levels, a widely accepted marker of long-term glucose control, witnessed an average reduction of 19.11%. This reduction is particularly promising, as it signifies the drug's effectiveness in maintaining sustained glycemic control over an extended period [36]. Additionally, the study unveiled a substantial average reduction of 27.73% in blood cholesterol levels, hinting at the drug's potential in mitigating cardiovascular risk associated with T2DM.

Critical to any medical intervention is an assessment of safety, and in this case, drug toxicity studies provided reassuring results. The findings indicated that the drug is safe for human use, a pivotal aspect in its potential integration into routine clinical practice. The significance of this cannot be overstated, as patient safety is paramount in any therapeutic approach [37]. The statistical significance of the results, coupled with the positive impact on multiple diabetes-related parameters, positions this polyherbal drug as an excellent candidate for T2DM. It not only controls blood sugar levels but also addresses the often-neglected aspect of dyslipidemia, which is intricately linked to diabetes complications [38]. The study then delved into the intricacies of the drug's mechanism of action, aiming to decipher how it exerts its hypoglycemic effects.

The investigation explored three distinct scenarios, each offering valuable insights into the drug's interaction with glucose and insulin metabolism [39, 40]. The first scenario, where insulin levels increased while blood sugar levels decreased, implies that the drug acts on the beta cells of the islets of Langerhans and the peripheral receptors of muscle cells. This dual action enhances insulin production and facilitates glucose uptake by muscle cells, contributing to improved glycemic control. The second scenario, where insulin levels did not respond to the treatment but blood sugar levels reduced, suggests that the drug primarily acts on the peripheral receptors of muscle cells. This finding implies a direct impact on glucose uptake by muscle cells independent of insulin, showcasing a unique mechanism of action. The third scenario, where blood sugar levels did not reduce after treatment, suggests that the drug may not directly influence glucose metabolism. This scenario, fortunately not observed in this study, would prompt further investigation into alternative mechanisms or potential limitations of the drug.

The actual findings aligned with the first scenario, indicating that the drug increases insulin levels and decreases blood sugar levels. This suggests a nuanced action on insulin GLUT-2 receptors of the islets of Langerhans and GLUT-4 receptors of adipose tissue and striated muscle fibers [41]. By enhancing insulin production and promoting glucose entry into designated cells, the drug orchestrates a comprehensive response to diabetes management. The interpretation of these findings extends beyond conventional medical terminology, delving into the realm of ancient Ayurvedic principles [42]. The study contextualizes the results by framing diabetes, or *madhumeha*, as a manifestation of vitiated *vata* and a *Kapha*-predominant disease. In this framework, the polyherbal drug is seen as indirectly increasing cellular *agni*, reducing *Kapha* (represented by blood sugar and cholesterol levels), and normalizing *vata* by streamlining insulin production [43]. This intricate interplay aligns with the holistic philosophy of Ayurveda, aiming not just at symptom management but also at restoring balance across various aspects of the body. The drug's ability to achieve equilibrium of *dosha*, *dhatu*, *mala*, and *kriya* resonates with the broader goal of promoting overall well-being, providing not just relief from symptoms but fostering a state of *prasanna atma* and *indriya* – a tranquil mind and harmonious senses [44].

In the modern context, these findings mark a significant step forward in diabetes research, offering a multifaceted approach to disease management. The integration of traditional wisdom with contemporary scientific methodologies presents a unique synergy, potentially paving the way for more personalized and holistic approaches to diabetes care. As the study concludes, the polyherbal drug emerges as a beacon of hope in the realm of T2DM. Its positive impact on glycemic control, insulin levels, and cholesterol profiles, coupled with its safety profile, positions it as a compelling option for individuals grappling with the complexities of diabetes. This research not only contributes valuable insights to medical literature but also exemplifies the potential of bridging ancient wisdom with modern science for the betterment of healthcare.

CONCLUSION

In conclusion, the assessment of the anti-diabetic activity of selected medicinal plants in human beings has yielded promising results, as evidenced by the substantial reduction in blood sugar levels, increased insulin levels, and a significant decrease in cholesterol levels. The meticulous examination of the herbal drugs' impact on T2DM, particularly through the measurement of blood glucose, insulin, and cholesterol levels before and after treatment, has revealed statistically significant changes with a *p*-value of 0.001. The utilization of the statistical tool, specifically the SPSS paired t-test, underscores the robustness of the findings, providing a rigorous scientific basis for the evaluation. One of the notable aspects of this study is the revalidation of ancient drugs as described in Ayurvedic texts, aligning them with modern evidencebased parameters, tools, and methodologies. The integration of traditional herbal wisdom with contemporary scientific approaches contributes to a comprehensive understanding of the antidiabetic potential of these medicinal plants. This synthesis of ancient and modern knowledge not only enhances the credibility of traditional practices but also opens avenues for novel therapeutic interventions grounded in historical wisdom. Looking ahead, the findings of this study pave the way for future research endeavors. A noteworthy recommendation is the exploration of nano-sized particles of the identified drug. This avenue holds the potential to amplify its therapeutic action, presenting a promising alternative to synthetic drugs. By harnessing the benefits of nanotechnology, the drug's efficacy could be further optimized, potentially obviating or delaying the need for synthetic medications. This prospect is particularly significant in the context of insulin-dependent diabetes, as postponing its onset could contribute to a healthier population and an increase in both healthy life years and life expectancy. The potential impact of this recommendation extends beyond the realm of academia and research, reaching into the broader landscape of public health. If successful, the development of Nano-sized particles of the identified drug could translate into practical applications, providing a tangible solution for diabetes management. The reduction or delay in the dependence on synthetic drugs could not only alleviate the economic burden on healthcare systems but also contribute to a paradigm shift in diabetes care, emphasizing sustainable, natural alternatives.

The combine effect of herbal drug appears to be : Reduces the free radicle formation , Reduce the microvascular complications of Diabetes Melittus type 2 , Reduces the platelet dysfunction hypofibrinolysis and endothelial dysfunction.

Ultimately, this study bridges the gap between traditional herbal knowledge and contemporary scientific scrutiny, reinforcing the relevance of Ayurvedic principles in the context of modern healthcare. The pursuit of knowledge in this field not only enriches our understanding of diabetes management but also propels us towards innovative and sustainable solutions. As we navigate the intersection of ancient wisdom and cutting-edge research, the potential for transformative impact on human health becomes increasingly evident, holding promise for a healthier and more resilient future.

Competing Interests:

There are no financial or personal conflicts of interest to report.

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Authors' Contributions:

CBD conceptualized and conducted the study, SRR and CDK helped in the pre-clinical and clinical analysis, CBD wrote the original manuscript, GB and RV provided critical comments and improved the manuscript, CBD finalized the manuscript.

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