The Science of Formulation: Developing Standardized and Effective Herbal Tablets

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***Abstract*—Diabetes mellitus is a chronic metabolic disorder affecting millions of individuals worldwide and represents an emerging challenge in global health [1]. The rise in the prevalence of diabetes has increased interest in complementary and alternative therapy approaches, mainly the herbal medicines traditionally used for glycaemic control [2]. The current study explores the formulation and evaluation of a polyherbal tablet that involves Azadirachta indica neem, Cinnamomum verum cinnamon, Gymnema sylvestre gurmar, Momordica charantia bitter melon, and Trigonella foenum graecum fenugreek all are of known traditional use in diabetes management [3].**

Although all of these plants demonstrate different antidiabetic mechanisms, like insulin sensitisation, inhibition of α-glucosidase, and pancreatic β-cell regeneration, their use in combination is expected to show synergistic actions by attacking a number of pathogenic pathways simultaneously [4]. The formulated tablets were subjected to various physicochemical studies, like flowability, compressibility, and disintegration behavior, which ensured that all the pharmacopeial requirements were met [5]. In-vitro antidiabetic activity was determined by performing an α-glucosidase inhibition assay using p-nitrophenyl-α-D-glucopyranoside and acarbose as a reference standard [6].

The polyherbal formulation showed α-glucosidase inhibitory activity comparable to that of the standard drug and complied with established pharmacopoeial quality specifications for tablets [7]. These findings underline the potential of integrative herbal formulations as safer and more sustainable therapeutic options for diabetes management, emphasizing the need for further in-vivo and clinical validation to confirm efficacy and long-term safety [8].

***Index Terms*—Diabetes mellitus, Herbal Remedies, Azadirachta indica, Cinnamomum verum, Gymnema sylvestre, Momordica charantia, Trigonella foenum graecum.**

I. INTRODUCTION

Diabetes mellitus is a chronic, polygenic metabolic disorder characterized by persistent hyperglycaemia resulting from defects in insulin secretion, impaired insulin action, or both [9]. It presents one of the most serious global public health challenges because of its increasing prevalence and association with devastating long-term complications. According to the IDF Diabetes Atlas (2023), an estimated 537 million adults-roughly 10.5% of the adult population-were living with diabetes in 2021, and this number is expected to rise to almost 785 million by 2045 [10].

Diabetes also imposes a very high economic burden beyond its clinical impact, with estimated direct healthcare expenditure of approximately USD 966 billion worldwide [11]. Classic pharmacological therapies including metformin, sulfonylureas, sodium–glucose cotransporter-2 inhibitors, and glucagon-like peptide-1 receptor agonist have greatly enhanced glycemic control and decreased the rates of diabetes-related complications. However, their long-term use is usually compromised by adverse effects, potential drug–drug interactions, and high treatment costs. These constraints are much more severe in low and middle-income countries, where access to continuous therapy is a major limitation [12].

1.1 The Growing Interest in Complementary and Alternative Medicines (CAM)

The ever-increasing load of diabetes has evinced renewed interest in the use of CAMs, especially herbal therapeutics that are widely perceived as natural, culturally acceptable, and economically accessible [13]. Medicinal plants have traditionally been used in various systems of healthcare in the management of metabolic disorders including diabetes. A critical review of ethnobotanical studies has cataloged over

800 plant species traditionally used for glycaemic control, out of which nearly 150 plants have been reported to exhibit antidiabetic activity in in-vitro or in-vivo experimental models [14].

Despite this enormous botanical diversity, the majority of modern scientific research has focused on single-herb extracts. In contrast, Ayurvedic, Traditional Chinese Medicine, and Unani traditional medical systems largely employ polyherbal formulations. The rationale behind the polyherbal formulation is that numerous phytoconstituents may sometimes result in synergistic action on multiple pathological targets, increasing therapeutic efficacy but potentially decreasing toxicity and adverse effects [15].

1.2 Rationale for a Polyherbal Tablet

Given the multifactorial nature of the pathogenesis of diabetes mellitus and the limitations of single-target therapies, polyherbal formulations represent a rational and holistic therapeutic strategy. In this regard, the current study was designed to formulate a polyherbal tablet that combines five medicinal plants with a well-documented traditional use and experimental evidence supporting antidiabetic activity.

Plant (Scientific name)	Common name	Principal bioactive constituents	Reported antidiabetic mechanisms
Azadirachta indica	Neem	Azadirachtin, nimbidin, flavonoids	↑ Insulin secretion, antioxidant, anti-inflammatory
Cinnamomum verum	Ceylon cinnamon	Cinnamaldehyde, eugenol, procyanidins	↑ Insulin receptor phosphorylation, α-glucosidase inhibition
Gymnema sylvestre	Gurmar	Gymnemic acids, saponins	↓ glucose absorption (taste receptor antagonism), β-cell regeneration
Momordica charantia	Bitter melon	Charantin, momordicosides, lectins	↑ GLUT4 translocation, AMPK activation
Trigonella foenum-graecum	Fenugreek	4-Hydroxy-isoleucine, diosgenin, saponins	↑ GLP-1 secretion, α-amylase inhibition

Table 1

These herbs target different pathogenic mechanisms involved in the development of diabetes mellitus, such as enhancing insulin sensitivity, preserving pancreatic β-cell function, inhibiting carbohydrate digestion enzymes, and facilitating peripheral glucose uptake. This formulation is based on the hypothesis that the simultaneous presentation of these phytoconstituents through a single oral dosage form will result in additive or synergistic therapeutic effects. This approach should enhance glycaemic control as a whole while allowing for the use of lower doses of each individual agent, reducing the risk of adverse effects and enhancing treatment tolerability.

II. OBJECTIVES

• Development of Formulations:

The objective is to formulate and optimize a direct-compression tablet containing standardized extracts of the five chosen medicinal plants.

• Physico-chemical evaluation:

The properties to be evaluated are flow properties, compressibility, hardness, friability, disintegration time, and assay of the tablet, according to IP 2023 and USP 45.

• Antidiabetic activity - In vitro:

Assay for α-glucosidase inhibitory activity using p-nitrophenyl-α-D-glucopyranoside (pNPG) as substrate, using acarbose as the reference standard.

• The Comparative Efficacy Assessment:

This will determine whether the polyherbal tablet developed will exhibit an inhibitory potency comparable or higher compared to the standard anti-diabetic drug.

• Safety and Quality Assurance:

Evaluation of microbial load, heavy metal contents, and pesticide residues to ensure compliance with the pharmaco-technical safety and quality standards.

Fig. 1 *Cinnamomum verum*

Fig. 3 *Azadirachta indica*

Fig. 2 *Gymnema sylvestre*

Fig. 5 *Momordica charantia*

Fig. 4 Trigonella foenum-graecum

III. MATERIALS AND METHODS

3.1. Collection of Plant Material and Authentication

Neem (leaf), Cinnamon (bark), Gymnema (leaf), Bitter melon (fruit), and Fenugreek (seed) were procured from certified organic farms in Kerala, India, between May–July 2024.

Authentication was done by the Department of Pharmacognosy, University of Kerala, using both macroscopic and microscopic characters; voucher specimens were deposited as NIM 2024 01 to FEN 2024 05.

3.2. Extraction and Standardisation

- Each plant part was air-dried at 40 °C below 10 % RH and then milled to ≤ 250 µm.
- Extraction was carried out using 90 % ethanol (solid to solvent ratio 1:10 w/v) for 48 h under continuous stirring at 30 °C followed by filtration and rotary evaporation at 45 °C.
- Freeze-dried extracts were kept at –20 °C.

❖ Standardisation:

- ➢ Neem– Azadirachtin quantified by HPLC (C18 column, 280 nm, reference ≥ 0.5 % w/w).
- ➢ Cinnamon – Cinnamaldehyde by GC MS (≥ 1.2 % w/w).
- ➢ Gymnema oGymnemic acids (≥ 0.8 % w/w) by LC MS.
- ➢ Bitter melon – Charantin by HPTLC (≥ 2.0 % w/w).
- ➢ fenugreek – 4-Hydroxy isoleucine by UPLC–MS (≥ 0.5% w/w).

3.3. Tablet Formulation - Direct Compression

Component	Quantity per tablet (mg)	Function
Polyherbal extract (combined)	300	Active botanical blend
Microcrystalline cellulose (MCC, PH 101)	150	Diluent
Croscarmellose sodium	15	Super-disintegrant
Sodium starch glycolate	10	Disintegrant
Magnesium stearate	5	Lubricant
Talc (pharmaceutical grade)	2	Glidant

Table 2

• Blend uniformity: extracts mixed with MCC for 10 min; disintegrants added and mixed for 5 min; lubricants added last with gentle mixing (2 min).

• Compression: 10 mm flat face punches, target tablet weight 482 ± 5 mg, compression force 10–12 kN using a Korsch EK 0 tablet press.

Test	Method	Acceptance criteria
Angle of repose	Fixed funnel method	≤ 30°
Bulk density / Tapped density	USP 41	Carr's index ≤ 15 %
Compressibility index	USP 41	Hausner's ratio ≤ 1.25
Hardness	Monsanto hardness tester	5–8 kgf
Friability	Roche friabilator (100 rpm, 4 min)	≤ 1 % weight loss
Disintegration time	USP 41 (6 min)	≤ 15 min
Uniformity of content	USP 41 (Assay by HPLC)	90–110 % of label claim
Dissolution	USP II paddle, 50 rpm, pH 6.8 (phosphate buffer)	Q ≥ 80 % in 30 min
Microbial limit	USP 61	≤ 10^3 CFU/g bacteria, ≤ 10^2 CFU/g fungi
Heavy metals	ICP-MS (Pb, Cd, As, Hg)	< 10 ppm (Pb), < 0.5 ppm (Cd) etc.

Table 3

3.4. In Vitro A Glucosidase Inhibition Assay

- Enzyme source: Saccharomyces cerevisiae α-glucosidase (EC 3.2.1.20) (1 U/mL)
- Substrate: p-nitrophenyl-α-d-glucopyranoside (pNPG) 5 mM in 0.1 M phosphate buffer, at pH 6.8
- Procedure: 50 µL test sample, (extract or powder of tablets dissolved in 10 % DMSO), added to 100 µL buffer and 50 µL enzyme; preincubation for 10 min at 37 °C. The reaction is initiated by adding 50 µL pNPG. Absorbance was recorded at 405 nm after 30 min.
- Controls: i) Blank, without inhibitor; ii) Positive control – Acarbose (0.5–10 µg/mL).
- Calculations: % inhibition = [(A_blank – A_sample)/A_blank] × 100. IC_{50} values derived from non-linear regression (GraphPad Prism 9).

3.5. Statistical Analysis

Data are presented as mean ± SD (n = 3). One way ANOVA followed by Tukey's post hoc test was used for multiple comparisons ($p < 0.05$ considered significant).

IV. RESULTS

4.1. Extraction Yields & Phytochemical Standardisation

Plant	Yield (% w/w)	Marker content (w/w)
Neem leaf	12.5	Azadirachtin 0.68 %
Ceylon cinnamon bark	15.2	Cinnamaldehyde 1.48 %
Gymnema leaf	10.8	Gymnemic acids 0.94 %

Bitter melon fruit	9.6	Charantin 2.3 %
Fenugreek seed	13.4	4-Hydroxy-isoleucine 0.62 %

Table 4

All extracts met the set standardisation thresholds, thus ensuring uniformity from batch to batch.

4.2. Tablet Physicochemical Properties

Parameter	Result	Specification
Angle of repose	27.4°	≤ 30°
Bulk density	0.49 g/mL	–
Tapped density	0.55 g/mL	–
Carr's index	10.9 %	≤ 15 %
Hausner's ratio	1.12	≤ 1.25
Hardness	6.2 kgf	5–8 kgf
Friability	0.62 %	≤ 1 %
Disintegration time	8 min	≤ 15 min
Uniformity of content	102.3 % (± 2.1)	90–110 %
Dissolution (Q_{80})	85 % (pH 6.8)	≥ 80 %
Microbial load	< 10^2 CFU/g (bacteria), < 10 CFU/g (fungi)	USP limits
Heavy metals (Pb, Cd, As, Hg)	< 5 ppm (Pb), < 0.2 ppm (Cd) etc.	< 10 ppm (Pb) etc.

Table 5

The tablets passed all the pharmaco-technical requirements, showing strong processing and acceptable quality attributes for oral dosage forms.

4.3. α Glucosidase Inhibitory Activity

cc	IC_{50} (µg/mL)	% Inhibition at 10 µg/mL
Polyherbal tablet powder	4.7 ± 0.3	71.2 ± 2.1
Individual extracts (average)	12.5 ± 1.1	38.6 ± 3.4
Acarbose (reference)	3.9 ± 0.2	78.5 ± 1.8
Blank (0.1 % DMSO)	—	2.1 ± 0.5

Table 6

Statistical analysis showed that there was no significant difference ($p > 0.05$) between the polyherbal tablet and acarbose in terms of IC_{50} but the tablet was significantly more potent than any single herb extract at $p < 0.001$.

4.4. Comparative Potency Index

A Potency Ratio (PR) was calculated as: IC_{50} of acarbose / IC_{50} of test.

- PR_polyherbal = 3.9 / 4.7 ≈ 0.83 (≈ 83 % of acarbose potency).
- PR_individual = 3.9 / 12.5 ≈ 0.31 (≈ 31 % of acarbose potency).

These data support the hypothesis that synergistic interaction among the five botanicals greatly enhances α glucosidase inhibition beyond the capacity of isolated extracts.

V. DISCUSSION

5.1 Rationale for Polyherbal Synergy

Diabetes mellitus is a multi-factorial, complex disorder involving insulin resistance, progressive pancreatic β-cell dysfunction, excessive hepatic glucose production, and exaggerated postprandial hyperglycemia. In view of this multi-targeted pathophysiology, the effective management often

requires therapeutic interventions capable of modulating more than one biochemical pathway simultaneously rather than acting on a single molecular target [16].

The herbs chosen for the current polyherbal formulation have been individually documented to affect complementary mechanisms related to glucose homeostasis. Azadirachta indica, or neem, enhances insulin signalling by activating the phosphatidylinositol-3-kinase (PI3K) pathway and confers antioxidant protection that helps maintain pancreatic β-cell integrity [17]. Cinnamomum verum, or cinnamon, enhances insulin receptor autophosphorylation and retards carbohydrate digestion by inhibiting key intestinal enzymes, including α-glucosidase and α-amylase [18]. Gymnema sylvestre acts to reduce intestinal glucose absorption through the antagonism of sweet-taste receptors and has been reported to regenerate β-cells through its saponin constituents [19]. Momordica charantia, or bitter melon, activates AMP-activated protein kinase (AMPK), which in turn upregulates the translocation of GLUT4 into skeletal muscle, while its bioactive constituent, charantin, possesses insulin-mimetic properties [20]. Trigonella foenum-graecum, or fenugreek, lowers blood glucose by increasing incretin hormones, including GLP-1, inhibiting hepatic gluconeogenesis, and delaying glucose absorption due to its soluble fibre content [21].

These botanicals are incorporated into a single dosage form with the expectation of a resultant synergistic antidiabetic effect: intestinal glucose absorption inhibition, enhancement of peripheral insulin sensitivity, protection, and regeneration of pancreatic β-cells, and modulation of incretin hormone secretion. Such a multi-pathway modulation fits well with current therapeutic strategies pursuing comprehensive glycaemic control.

The in-vitro α-glucosidase inhibition assay used in this study gives an early indication that the formulation may have the potential to reduce post-prandial glucose excursions, which are still a key target in the management of diabetes according to recent ADA recommendations [22]. The finding that the formulation has an IC_{50} value comparable to acarbose emphasizes its potential as a natural product α-glucosidase inhibitor. Significantly, the ethnopharmacological use of the plant does not report severe gastrointestinal adverse effects, a fact that may imply its safety profile could be better than that of the conventional enzyme inhibitors [23].

5.2 Tablet Quality and Patient Compliance

The findings showed that the employment of a direct compression technique with microcrystalline cellulose along with suitable super-disintegrants yielded tablets exhibiting excellent flow, reflected in low Carr's index values. Moreover, rapid disintegration was achieved, necessary for swift drug release in the upper small intestine where the primary location of α-glucosidase activity is.

The evaluated hardness and friability values remained within pharmacopeial specifications, ensuring adequate mechanical strength during manufacturing, packaging, transportation, and routine handling. Besides, the low moisture content (less than 5%) as well as the absence of microbial contamination remarkably minimize the product degradation and microbial growth. These quality attributes collectively enhance formulation stability and patient acceptability while aligning with WHO GMP guidelines for herbal medicinal products [24].

5.3 Safety Considerations

Safety assessment showed that the levels of heavy metals in the formulation were within the permissible limits set by FAO/WHO guidelines. In addition, pesticide residues were found to be below the limit of quantification, which could be credited to the fact that plant materials were organically cultivated. These data are crucial, given that chronic exposure to heavy metals may be associated with enhancement of oxidative stress and worsening of diabetic complications [25]. The observed compliance with international safety standards supports the suitability of the formulation for further preclinical and clinical investigation.

5.4 Limitations And Future Directions

Despite such encouraging findings, the present study has several limitations. For instance, the antidiabetic activity assessment was restricted to in-vitro α-glucosidase inhibition, a surrogate marker of value but certainly not enlightening about the in-vivo pharmacokinetic and pharmacodynamic behaviour of the formulation. Another limitation is that standardization was restricted to a single marker compound per herb; more comprehensive

metabolomic profiling may further strengthen batch-to-batch consistency. Above all, translation of these findings into clinical use requires comprehensive evaluation of safety, optimal dosing, and therapeutic efficacy in human subjects.

Therefore, future research will be targeted at in-vivo studies in streptozotocin-induced diabetic rat models assessing their fasting blood glucose, HbA1c, insulin levels, and pancreatic histopathology following a 12-week treatment regimen. Pharmacokinetic interaction studies will also be carried out in order to rule out the possibility of potential cytochrome P450 enzyme inhibition-especially CYP3A4-which may interfere with co-administered conventional antidiabetic medications. QbD-based optimisation will also be undertaken to further refine formulation and granulation parameters, including investigation of alternative excipients for further enhancement of dissolution and therapeutic performance.

VI. CONCLUSIONS

The present study successfully designed and characterized a uniform polyherbal tablet containing Azadirachta indica, Cinnamomum verum, Gymnema sylvestre, Momordica charantia, and Trigonella foenum-graecum. The developed tablets met all the pharmaceutical requirements according to the Indian and United States Pharmacopeias and exhibited significant α-glucosidase inhibitory activity with results comparable to the standard drug acarbose.

These observations reveal that the integrative herbal formulation, besides being safe and economical, may work through a synergistic interaction among multiple phyto-constituents to provide multi-targeted therapeutic options in the management of diabetes mellitus. However, in-depth in-vivo studies and clinical trials will be required to support therapeutic efficacy, optimize dosing schedules, and determine long-term safety profiles.

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