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NETWORK PHARMACOLOGY OF PRAMEHNIL TABLET IN THE MANAGEMENT OF KAPHAJ PRAMEHA (TYPE 2 DIABETES MELLITUS): A COMPREHENSIVE DRUG REVIEW

***Dr. Kirti Sachdeva¹, Dr Avinash Kumar Jain², Dr Divya singh charan³**

¹Associate Professor Kayachikitsa Department, MJF Ayurved Mahavidyalaya, Chomu, Jaipur

²Research Officer, MSRARI, Jaipur

³Assistant Professor Kayachikitsa Department, MJF Ayurved Mahavidyalaya, Chomu, Jaipur

*Corresponding Author: Dr. Kirti Sachdeva, Associate Professor Kayachikitsa Department, MJF Ayurved Mahavidyalaya, Chomu, Jaipur, kirtiayurveda2012@gmail.com

ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) is a rapidly growing metabolic disorder characterized by insulin resistance, impaired insulin secretion, and chronic inflammation. In Ayurveda, its clinical features closely resemble Kaphaj Prameha. Since conventional antidiabetic drugs often target a single pathway and may produce adverse effects or reduced long-term efficacy, there is increasing interest in evidence-based polyherbal formulations with multitarget therapeutic potential. Pramehnil Tablet is a polyherbal formulation containing eight medicinal plants processed with Guduchi (*Tinospora cordifolia*) decoction through the classical Bhavana technique. **Objective:** To critically review the Ayurvedic properties, phytochemical constituents, and molecular pharmacological mechanisms of Pramehnil Tablet and establish a scientific basis for its clinical evaluation in Kaphaj Prameha (T2DM). **Methods:** Relevant evidence was collected from PubMed, Scopus, Web of Science, Embase, Cochrane Library, and classical Ayurvedic texts. Experimental and clinical studies evaluating the pharmacological activities of the constituent herbs were reviewed and correlated with modern molecular pathways and Ayurvedic principles. **Results:** The formulation integrates the classical Nisha-Amalaki concept with herbs possessing complementary antihyperglycemic, anti-inflammatory, antioxidant, and lipid-lowering activities. Key phytoconstituents, including berberine, gymnemic acids, curcuminoids, and embelin, modulate multiple therapeutic targets by improving insulin sensitivity, activating AMPK signaling, reducing hepatic gluconeogenesis, preserving pancreatic β -cell function, inhibiting intestinal glucose absorption, and suppressing oxidative stress and inflammatory pathways. The Guduchi Bhavana process may further enhance the bioavailability and therapeutic efficacy of the formulation. **Conclusion:** Available evidence suggests that Pramehnil Tablet acts through multiple interconnected mechanisms consistent with both Ayurvedic

principles and modern network pharmacology. Its multitarget therapeutic profile provides a strong scientific rationale for further validation through randomized controlled clinical trials in patients with Kaphaj Prameha (Type 2 Diabetes Mellitus).

Keywords: Pramehnil Tablet, Kaphaj Prameha, Type 2 Diabetes Mellitus, Network Pharmacology, Guduchi Bhavana, Insulin Resistance.

1. INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia caused by a combination of insulin resistance and progressive dysfunction of pancreatic β -cells, resulting in inadequate insulin secretion. The disease gradually progresses over time and is associated with serious long-term complications affecting multiple organ systems. Persistent hyperglycemia damages small blood vessels, leading to diabetic retinopathy, nephropathy, and neuropathy, while also increasing the risk of macrovascular complications such as coronary artery disease, cerebrovascular disease, and peripheral arterial disease [1].

From the Ayurvedic perspective, T2DM closely resembles Prameha, particularly Kaphaj Prameha. Classical Ayurvedic texts describe Prameha as a metabolic disorder characterized by excessive (Prabhoota) and turbid (Avila) urination resulting from disturbances in Kapha Dosha, Meda, Mamsa, Kleda, and Mutra. These pathological changes reflect impaired metabolism of carbohydrates, fats, and body fluids, making Kaphaj Prameha conceptually comparable to the early stages of Type 2 Diabetes Mellitus [2].

The history of diabetes extends back several thousand years. One of the earliest descriptions appears in the Egyptian Ebers Papyrus (approximately 1550 BCE), where excessive urination was documented as a characteristic symptom. Later, the Greek physician Aretaeus of Cappadocia introduced the term "diabetes," meaning "to pass through," to describe the excessive flow of urine associated with the disease. Around the same period, classical Ayurvedic scholars provided detailed descriptions of Prameha. Charaka Samhita classifies Prameha into twenty subtypes based on the predominance of the three Doshas, comprising ten Kaphaja, six Pittaja, and four Vataja varieties. Among these, Madhumeha is considered the advanced stage of the disease and closely resembles uncontrolled diabetes mellitus. Sushruta Samhita further categorized Prameha into Sahaja (hereditary or congenital) and Apathya Nimittaja (acquired due to unhealthy diet and lifestyle), a classification that closely parallels the modern distinction between inherited susceptibility and lifestyle-related Type 2 Diabetes Mellitus [2,3].

Today, T2DM has emerged as one of the most significant public health challenges worldwide. According to the International Diabetes Federation (IDF), the number of individuals living with diabetes continues to rise, placing an enormous clinical and economic burden on healthcare systems. The increasing prevalence of obesity, sedentary lifestyles, unhealthy dietary habits, and population ageing has accelerated the global incidence of T2DM. India, in particular, bears a substantial share of this burden and is recognized as one of the countries with the largest diabetic population. Findings from the Indian Council of Medical Research–India Diabetes (ICMR-INDIAB) study demonstrate a high prevalence of both diabetes and prediabetes across the country [4].

The Indian population also exhibits a unique metabolic susceptibility, commonly referred to as the "Asian Indian Phenotype." Individuals with this phenotype tend to develop diabetes at a lower body mass index than many other ethnic groups because of increased visceral fat accumulation, greater central obesity, higher insulin resistance, and an elevated risk of premature cardiovascular disease. These characteristics contribute to the early onset and rapid progression of T2DM among Indians [4].

Modern medicine primarily explains T2DM through abnormalities in glucose metabolism, insulin signaling, and lipid metabolism. Current therapeutic strategies include lifestyle modification along with pharmacological agents such as metformin, sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists. Although these medications effectively reduce blood glucose levels, they mainly target specific molecular pathways and may be associated with adverse effects, reduced long-term efficacy, hypoglycemia, gastrointestinal disturbances, weight changes, and other limitations [1].

In contrast, Ayurveda adopts a holistic approach that focuses on correcting the underlying metabolic imbalance rather than merely lowering blood glucose. Restoration of Agni, elimination of Ama, correction of Dosha imbalance, and normalization of tissue metabolism form the basis of treatment. Polyherbal formulations are considered particularly valuable because they contain multiple bioactive compounds capable of acting on different biological pathways simultaneously. This multidimensional therapeutic approach corresponds closely with the modern concept of network pharmacology, which emphasizes multitarget interventions for complex disorders such as T2DM.

With the growing recognition that Type 2 Diabetes Mellitus is a multifactorial disease involving interconnected metabolic and inflammatory pathways, there is increasing scientific interest in standardized polyherbal formulations. Pramehnil Tablet, a classical Ayurvedic polyherbal formulation processed with Guduchi Bhavana, has been developed to target multiple pathogenic mechanisms associated with Kaphaj Prameha. Before evaluating its efficacy in human subjects, it is essential to establish a strong scientific foundation by critically reviewing the available Ayurvedic literature, phytochemical evidence, and pharmacological studies. Therefore, the present review aims to compile and analyze the existing evidence supporting the therapeutic potential of Pramehnil Tablet and to provide a scientific rationale for its evaluation in randomized controlled clinical trials for the management of Kaphaj Prameha (Type 2 Diabetes Mellitus).

This review aims to systematically dissect the phytochemical, molecular pharmacological, and traditional Ayurvedic properties of the ingredients of Pramehnil Tablet. It establishes the scientific rationale, synergetic mechanics, and safety profile supporting its evaluation in a Randomized Controlled Clinical Trial for Kaphaj Prameha w.s.r. to Type 2 Diabetes Mellitus.

2. REVIEW OBJECTIVES

Primary Objective

- To evaluate the scientific rationale and molecular mechanism of action of the individual ingredients and the combined polyherbal matrix of Pramehnil Tablet in modulating the pathogenesis of *Kaphaj Prameha* (Type 2 Diabetes Mellitus).

Secondary Objectives

1. To map the classical Ayurvedic pharmacodynamics (*Rasa, Guna, Virya, Vipaka, Prabhava*) of the individual herbs to understand their collective ability to achieve *Samprapti Vighatana* (disruption of disease pathogenesis).
2. To investigate the precise role of the pharmaceutical bio-amplification process (*Bhavana*) utilizing *Guduchi Kwath* on particle physics, solubility, and bioavailability of the final compound.
3. To analyze the toxicological safety profiles, organoprotective mechanisms (especially cardiac and pancreatic), and potential herb-drug interactions of the constituents based on peer-reviewed preclinical and clinical trial data.

3. SEARCH STRATEGY

Methodology and Search Parameters

A systematic literature search was carried out across major biomedical databases up to the present date (2026). The primary electronic databases included:

- PubMed / MEDLINE
- Scopus
- Web of Science
- Embase
- The Cochrane Central Register of Controlled Trials (CENTRAL)
- Google Scholar (restricted to verifying grey literature and classical commentary access)

Keywords and Boolean Operators

The search strings were constructed using MeSH terms and text words as follows: ("Prameha" OR "Kaphaj Prameha" OR "Diabetes Mellitus, Type 2" OR "Insulin Resistance" OR "Hyperglycemia") AND ("Emblica officinalis" OR "Amalaki" OR "Curcuma longa" OR "Haridra" OR "Berberis aristata" OR "Daruharidra" OR "Gymnema sylvestre" OR "Meshashringi" OR "Embelia ribes" OR "Vidanga" OR "Terminalia arjuna" OR "Arjuna" OR "Valeriana wallichii" OR "Tagara" OR "Cyperus rotundus" OR "Nagarmotha" OR "Tinospora cordifolia" OR "Guduchi") AND ("pharmacology" OR "phytochemistry" OR "mechanism" OR "toxicity" OR "clinical trial").

Inclusion Criteria

1. Peer-reviewed, published research articles including *in vitro*, *in vivo* (animal models of diabetes), and human clinical trials.
2. Studies detailing the isolated phytoconstituents, crude extracts, or standardized formulations of the specified nine herbs.
3. Classic Ayurvedic texts recognized by the Drugs and Cosmetics Act, 1940 (First Schedule), providing authentic formulations or therapeutic mandates for the individual herbs.
4. Studies published in the English language or possessing official English translations.

Exclusion Criteria

1. Non-peer-reviewed preprints, brief conference abstracts lacking methodology, editorials, and popular media articles.
2. Studies using unauthenticated plant species or heavily adulterated commercial extracts.
3. Literature focusing exclusively on unrelated clinical conditions (e.g., infectious diseases, oncology) without reference to metabolic, inflammatory, or stress-response pathways.

4. MAIN REVIEW

Formulation Composition and Quality Standardization

Pramehnil Tablet is a specialized polyherbal formulation containing eight solid botanical components processed in a liquid decoction medium of a ninth herb (Guduchi). To ensure therapeutic reproducibility, the formulation must be prepared in a Good Manufacturing Practice (GMP) certified facility utilizing authenticated raw herbs that comply with the standards set by the Ayurvedic Pharmacopoeia of India (API).

Table 1: Standardized Quantitative Formula of Pramehnil Tablet

S.No.	Common Name	Botanical Name	Family	Part Used	Physical Nature in Input	Quantitative Proportion
1	Amalaki	<i>Emblica officinalis</i> L.	Phyllanthaceae	Fruit pulp	Fine Powder (Churna)	2 Parts
2	Haridra	<i>Curcuma longa</i> L.	Zingiberaceae	Rhizome	Fine Powder (Churna)	2 Parts
3	Daruharidra	<i>Berberis aristata</i> DC.	Berberidaceae	Fruit and Stem	Fine Powder (Churna)	1 Part
4	Meshshringi	<i>Gymnema sylvestre</i> (Retz.) R.Br.	Apocynaceae	Leaves	Fine Powder (Churna)	1 Part
5	Vidang	<i>Embelia ribes</i> Burm.f.	Primulaceae	Fruit / Seed	Ethanollic Extract	1 Part
6	Arjun	<i>Terminalia arjuna</i> Roxb.	Combretaceae	Bark	Fine Powder (Churna)	1 Part
7	Tagar	<i>Valeriana wallichii</i> DC.	Caprifoliaceae	Rhizome / Roots	Fine Powder (Churna)	1 Part
8	Nagarmotha	<i>Cyperus rotundus</i> L.	Cyperaceae	Bulb / Tuber	Fine Powder (Churna)	1 Part
Media	Guduchi	<i>Tinospora cordifolia</i> Miers	Menispermaceae	Stem	Aqueous Decoction (Kwath)	Quantum satis (for Bhavana)

Ayurvedic Pathogenesis: Kaphaj Prameha Samprapti- In Ayurvedic pathophysiology, Prameha is categorized as a Santarpana-nimittaja vyadhi (a disease caused by over-nutrition and metabolic excess) and a Bahudosha-vyadhi (a complex condition involving multiple systemic toxins) [2]. The ingestion of Kapha-aggravating foods—such as Nava-anna (freshly harvested grains), Asyasukha (sedentary habits), Swapnasukha (excessive sleeping), and heavy dairy products—leads to the primary vitiation of Kapha Dosha (specifically Kledaka Kapha).

The Cascade of Dushya Vitiatiion: Vitiated Kapha dampens the gastrointestinal and tissue-level metabolic fires (Mandaragni), leading to the formation of Ama (toxic, semi-digested metabolic by-products). Because of its structural similarity to Kapha, the primary tissue affected (Dushya)

is Meda (adipose tissue/lipids). The text notes that the Meda involved is Abaddha (unbound, poorly structured, fluid-like fat).

This morbid combination of Kapha, Ama, and Abaddha Meda spreads throughout the body, overwhelming the Medovaha Srotas (fat channels) and entering the Mutravaha Srotas (urinary tracts). The excess Kleda (morbid body fluids) is then drawn toward the kidneys and bladder, resulting in the core symptom: Prabhoota-avila-mutrata [2,5].

Samprapti Ghataka (Pathological Matrix)

- **Dosha:** *Kapha (Pradhana)*, *Pitta* and *Vata (Anubandha)*
 - **Dushya:** *Meda* (Adipose tissue), *Kleda* (Metabolic fluids), *Mamsa* (Muscle tissue), *Rasa* (Plasma), *Rakta* (Blood), *Ojas* (Vital immune essence)
 - **Srotas:** *Mutravaha Srotas*, *Medovaha Srotas*, *Rasavaha Srotas*
 - **Sroto-Dushti Lakshana:** *Sanga* (Micro-vascular and cellular channel blockade) and *Atipravritti* (Polyuria at the macro-level)
 - **Adhithana:** *Vrikka* (Kidneys), *Basti* (Bladder), and *Sarva Shareera* (Systemic tissues)
1. **Insulin Resistance:** The process begins with long-term calorie overload, which leads to visceral obesity and high levels of circulating Free Fatty Acids (FFAs). These FFAs, along with inflammatory cytokines like TNF- α , IL-6, and MCP-1 released from hypertrophied adipocytes, activate intracellular stress kinases such as c-Jun N-terminal kinase (JNK) and Inhibitor of κ B kinase (IKK β). These kinases cause inhibitory serine phosphorylation of Insulin Receptor Substrate-1 (IRS-1), blocking downstream PI3K/Akt signaling. As a result, GLUT4 vesicles fail to translocate to the plasma membrane in skeletal muscles and adipose tissues, leading to insulin resistance [6].
 2. **Hepatic Glucose Output:** In the liver, insulin resistance prevents the suppression of gluconeogenesis and glycogenolysis, causing unregulated hepatic glucose output via the upregulation of key enzymes like Phosphoenolpyruvate carboxykinase (PEPCK) and Glucose-6-phosphatase (G6Pase) [6].
 3. **Pancreatic β -cell Dysfunction:** Initially, the pancreatic islets compensate by increasing insulin secretion (hyperinsulinemia). However, sustained metabolic stress triggers endoplasmic reticulum (ER) stress, mitochondrial ROS production, and the accumulation of islet amyloid polypeptide (IAPP). This combined stress leads to progressive β -cell exhaustion, structural dedifferentiation, and apoptosis, resulting in a steady decline in insulin secretory capacity [7].

5. PHYTOCHEMICAL & PHARMACOLOGICAL PROFILING OF COMPONENTS

Understanding the therapeutic potential of Pramehnil Tablet requires analyzing the specific molecular pathways targeted by its individual ingredients.

1. Amalaki (*Emblica officinalis*)

- **Key Phytoconstituents:** Hydrolyzable tannins (emblicanin A and B, punigluconin, pedunculagin), gallic acid, ellagic acid, corilagin, and high concentrations of ascorbic acid stabilized by the tannin matrix.
- **Molecular Targets and Mechanisms:** *Amalaki* acts as a powerful antioxidant and cytoprotectant. Its hydrolyzable tannins protect pancreatic β -cells from oxidative stress by restoring endogenous catalase, superoxide dismutase (SOD), and glutathione peroxidase (GPx) levels.

Gallic acid and ellagic acid competitively inhibit aldose reductase, the rate-limiting enzyme in the polyol pathway. Under hyperglycemic conditions, this pathway converts excess glucose to sorbitol, leading to osmotic stress and cellular damage. By blocking this conversion, *Amalaki* helps prevent microvascular complications like diabetic cataract, neuropathy, and nephropathy [8].

2. Haridra (*Curcuma longa*)

- **Key Phytoconstituents:** Curcuminoids (curcumin, demethoxycurcumin, bisdemethoxycurcumin) and volatile oils (turmerones, atlantones).
- **Molecular Targets and Mechanisms:** Curcumin is a natural ligand and agonist for **Peroxisome Proliferator-Activated Receptor gamma (PPAR- γ)**. Similar to the thiazolidinedione class of drugs, it enhances the transcription of genes involved in lipid and glucose uptake, such as adiponectin and GLUT4.

Additionally, curcumin suppresses the nuclear factor-kappa B (NF- κ B) signaling cascade. By inhibiting the activation of the upstream inhibitor of κ B kinase (IKK) and preventing the downstream phosphorylation and degradation of I κ B α , curcumin downregulates the transcription of pro-inflammatory cytokines—such as interleukin-1 beta (IL-1 β) and interleukin-6 (IL-6)—that drive peripheral insulin resistance [9].

3. Daruharidra (*Berberis aristata*)

- **Key Phytoconstituents:** Isoquinoline alkaloids, primarily **Berberine**, along with oxyberberine, berbamine, and palmatine.
- **Molecular Targets and Mechanisms:** Berberine is an effective plant-derived activator of **Adenosine Monophosphate-Activated Protein Kinase (AMPK)**. It works by transiently inhibiting Complex I of the mitochondrial respiratory chain, which increases the intracellular AMP/ATP ratio.

Activated AMPK triggers an insulin-independent signaling pathway that promotes GLUT4 translocation to the cell membrane in skeletal muscle, enhancing glucose clearance from the bloodstream. Simultaneously, AMPK activation in the liver downregulates the expression of PEPCK and G6Pase, suppressing hepatic gluconeogenesis and reducing fasting plasma glucose levels [10].

4. Meshshringi (*Gymnema sylvestre*)

- **Key Phytoconstituents:** Gymnemic acids (a complex mixture of triterpene saponins), gymnemasides, and the peptide gurmarin.
- **Molecular Targets and Mechanisms:** Gymnemic acids possess a molecular structure that structurally resembles glucose molecules. When present in the intestinal lumen, they competitively bind to **Sodium-Glucose Cotransporter 1 (SGLT1)** and **Glucose Transporter 2 (GLUT2)** on enterocytes, reducing the absorption of dietary carbohydrates [11].

At the pancreatic level, *Gymnema* extracts have been shown to support the regeneration of insulin-secreting β -cells in the islets of Langerhans and increase cell membrane permeability to stimulate insulin release [11].

5. Vidanga (*Embelia ribes*)

- **Key Phytoconstituents:** **Embelin** (2,5-dihydroxy-3-undecyl-1,4-benzoquinone), homoembelin, and vilangin.
- **Molecular Targets and Mechanisms:** Standardized ethanolic extracts of *Vidanga* containing embelin target lipotoxicity and insulin resistance associated with obesity. Embelin modulates the expression of **PPAR- α** and **SREBP-1c**, helping restore lipid balance.

It lowers circulating plasma Free Fatty Acids (FFAs), Triglycerides (TG), and Low-Density Lipoprotein Cholesterol (LDL-C). By reducing lipid accumulation in non-adipose tissues like skeletal muscle and the liver, it helps mitigate lipotoxicity-induced insulin resistance [12].

6. Arjun (*Terminalia arjuna*)

- **Key Phytoconstituents:** Triterpenoid saponins (arjungenin, arjunolic acid), flavonoids (arjunone, luteolin), and oligomeric proanthocyanidins (OPCs).
- **Molecular Targets and Mechanisms:** *Arjuna* provides essential macrovascular and myocardial protection. Chronic hyperglycemia accelerates the formation of **Advanced Glycation End-products (AGEs)**, which form cross-links with cardiovascular collagen, increasing arterial stiffness and contributing to diabetic cardiomyopathy.

Arjunolic acid and OPCs inhibit the non-enzymatic glycation of proteins, preventing AGE formation. Furthermore, *Arjuna* upregulates endothelial nitric oxide synthase (eNOS), increasing nitric oxide (NO) production to help restore endothelial function and reduce cardiovascular strain [13].

7. Tagar (*Valeriana wallichii*)

- **Key Phytoconstituents:** Valepotriates (valtrate, didrovaltrate), valerenic acid, valeranone, and specific iridoid glucosides.
- **Molecular Targets and Mechanisms:** *Tagara* addresses a frequently overlooked factor in metabolic syndrome: chronic stress and sleep disruption. Chronic psychological stress or poor sleep activates the **Hypothalamic-Pituitary-Adrenal (HPA) axis**, resulting in sustained cortisol secretion. Cortisol acts as a functional antagonist to insulin, increasing hepatic glucose production and worsening insulin resistance.

Valerenic acid acts as a positive allosteric modulator of GABA-A receptors, enhancing GABAergic inhibitory pathways in the central nervous system. This helps stabilize HPA axis hyperactivity, reduce circulating cortisol levels, and lower stress-induced morning glucose spikes [14].

8. Nagarmotha (*Cyperus rotundus*)

- **Key Phytoconstituents:** Volatile sesquiterpenes (cyperene, α -copaene, cyperotundone, patchoulene) and polyphenols.
- **Molecular Targets and Mechanisms:** In Ayurveda, *Nagarmotha* is recognized for its *Deepana-Pachana* (metabolic stimulant and carminative) properties, helping clear metabolic *Ama*.

Biochemically, it acts as an inhibitor of pancreatic lipase, reducing the breakdown and subsequent absorption of dietary fats in the intestinal lumen. It also dampens metabolic endotoxemia by reducing the systemic absorption of Lipopolysaccharides (LPS) from the gut flora, helping lower the low-grade systemic inflammation that drives metabolic syndrome [15].

9. Guduchi (*Tinospora cordifolia*) — The *Bhavana* Medium

- **Key Phytoconstituents:** Clerodane diterpene glucosides (tinosporaside, cordifolioside A), alkaloids (magnoflorine, berberine, choline), and immunomodulatory arabinogalactan polysaccharides.
- **Molecular Targets and Mechanisms:** *Guduchi* serves as the processing medium (*Bhavana Kwath*), contributing its own therapeutic benefits. Its arabinogalactan polysaccharides activate macrophages via toll-like receptor 4 (TLR4), helping redirect the immune response away from chronic inflammation toward metabolic repair.

Its diterpene compounds show protective effects on insulinotropic pathways, supporting β -cell viability and defending these cells against cytokine-induced apoptosis [16].

Part Used and Standardized Visual Archetypes of Components

To ensure proper pharmaceutical quality control, understanding the specific plant parts used and their classical visual characteristics is essential.

Botanical Parts & Pharmacognostic Findings

1. Amalaki (Fruit Pulp) Dried, wrinkled pericarp, dark blackish-grey segments.	2. Haridra (Rhizome Core) Deep bright orange-yellow fractured interior matrix.	3. Daruharidra (Stem) Characteristic bright yellowish woody xylem.
4. Meshashringi (Leaves) Oval-elliptic, smooth entire margins, distinct venation.	5. Vidanga (Dry Berries) Globular, warty surface, five-lobed persistent calyx.	6. Arjuna (Bark Plate) Thick, smooth, pinkish-grey exfoliating bark.
7. Tagara (Root/Rhizome) Twisted, aromatic brownish roots with nodal ridges.	8. Nagarmotha (Tuberous Bulb) Ovoid, dark brown, covered with hairy fibrous remnants.	9. Guduchi (Stem Core) Succulent, wheel-like star-shaped cross section.

6. THE SCIENCE OF BHAVANA (BIO-AMPLIFICATION) VIA GUDUCHI KWATH

The inclusion of Bhavana (the process of wet levigation or continuous trituration of a dry powder matrix with a liquid plant decoction until dry) represents an advanced method of drug processing in traditional Ayurvedic pharmacy [17]. In the production of Pramehnil Tablet, the combined powders of the eight primary herbs undergo systematic levigation with a concentrated aqueous decoction (Kwath) of Guduchi. This process induces several physical and chemical modifications:

Physicochemical Basis of Bhavana

The classical Bhavana process produces several physicochemical modifications that may improve the pharmaceutical and therapeutic performance of herbal formulations.

Particle Size Reduction: During prolonged trituration, continuous mechanical grinding exerts shear forces that progressively break down coarse plant tissues into finer particles. This transformation reduces particle size from the macro range to micro- and submicron levels, thereby substantially increasing the effective surface area available for dissolution and absorption.

Improved Dissolution Characteristics: Reduction in particle size accelerates drug dissolution by increasing the exposed surface area. According to the Noyes-Whitney equation, the dissolution rate is directly proportional to the surface area of the drug particles:

$$dW/dt = D \cdot A \cdot (C_s - C_b) / h$$

where D is the diffusion coefficient, A is the surface area, C_s is the saturation solubility, C_b is the bulk concentration, and h represents the thickness of the diffusion layer. Therefore, the increased surface area generated during Bhavana facilitates faster dissolution of phytoconstituents in gastrointestinal fluids.

Formation of a Natural Phytosomal Delivery System: Guduchi Kwatha, used as the levigating medium, contains naturally occurring mucilage, saponins, and arabinogalactan polysaccharides. During repeated wet grinding and gradual evaporation of moisture, these amphiphilic constituents surround lipophilic bioactive compounds such as curcumin, valerenic acid, and embelin, forming a protective phytosomal or micelle-like matrix. This natural encapsulation may shield sensitive phytochemicals from premature degradation within the gastrointestinal tract while improving their stability [17,18].

Enhanced Bioavailability of Lipophilic Constituents: The surfactant properties of Guduchi saponins reduce the interfacial tension between aqueous gastrointestinal fluids and hydrophobic phytochemicals. Consequently, micellar transport of poorly water-soluble compounds across the intestinal lumen is facilitated, leading to improved absorption and greater systemic availability of bioactive molecules such as curcumin, berberine, and other lipophilic constituents [18].

7. COMPARATIVE ANALYSIS & SYNERGY MATRIX

Table 2: Ayurvedic Pharmacodynamic Coding (Rasa-Virya-Vipaka) & Molecular Mapping

Herb Name	Rasa (Taste)	Guna (Attributes)	Virya (Potency)	Vipaka (Post-Digestive)	Karma (Ayurvedic Action)	Modern Biomarkers Targeted
<i>Amalaki</i>	Amla, Madhura, Tikta, Katu, Kashaya	Guru, Sheeta, Ruksha	Sheeta	Madhura	<i>Rasayana, Pramehahara, Tridosahara</i>	Aldose Reductase, SOD, Catalase, HbA1c
<i>Haridra</i>	Tikta, Katu	Ruksha, Laghu	Ushna	Katu	<i>Lekhana</i> (Scraping), <i>Vishaghna, Meahara</i>	PPAR- γ , NF- κ B, TNF- α , IL-6
<i>Daruharidra</i>	Tikta, Kashaya	Laghu, Ruksha	Ushna	Katu	<i>Kapha-Pitta Shamaka, Srotas-Shodhaka</i>	AMPK, GLUT4, G6Pase, PEPCK
<i>Meshshringi</i>	Tikta, Kashaya	Laghu, Ruksha	Ushna	Katu	<i>Madahunashini, Chakshushya</i>	SGLT1, GLUT2, Beta-cell count, Insulin
<i>Vidang</i>	Katu, Tikta	Laghu, Ruksha, Tikshna	Ushna	Katu	<i>Krimighna, Medohara, Vata-Anulomana</i>	PPAR- α , Total Cholesterol, TG, LDL-C
<i>Arjun</i>	Kashaya	Laghu, Ruksha	Sheeta	Katu	<i>Hridya, Rakta-Prasadana, Sandhaniya</i>	eNOS, AGE cross-links, CK-MB, BNP
<i>Tagar</i>	Tikta, Katu, Kashaya	Laghu, Snigdha	Ushna	Katu	<i>Akshepa-shamaka, Manovaha-Prasadana</i>	GABA-A receptor, Cortisol, HPA axis
<i>Nagarmotha</i>	Tikta, Katu, Kashaya	Laghu, Ruksha	Sheeta	Katu	<i>Deepana, Pachana, Grahi, Ama-hara</i>	Pancreatic Lipase, LPS endotoxins
<i>Guduchi</i> (Media)	Tikta, Kashaya	Guru, Snigdha	Ushna	Madhura	<i>Rasayana, Triptighna, Jvarahara</i>	TLR4, Macrophages, Islet protection

8. DISCUSSION

Integrating Multi-Target Network Pharmacology: The therapeutic value of polyherbal formulations such as Pramehnil Tablet lies in their ability to influence multiple biological targets simultaneously, making them particularly suitable for complex, multifactorial disorders like Type 2 Diabetes Mellitus (T2DM). Unlike conventional pharmacotherapy, which generally focuses on a single molecular target, polyherbal interventions can modulate interconnected metabolic pathways and thereby reduce the likelihood of compensatory mechanisms that often limit long-term therapeutic success. For example, inhibition of a single gluconeogenic enzyme may be bypassed through activation of alternative metabolic pathways, reducing treatment efficacy.

Pramehnil Tablet is formulated to exert a coordinated pharmacological effect through multiple phytoconstituents acting at different stages of glucose metabolism. Meshashringi (*Gymnema sylvestre*) decreases intestinal glucose absorption by interfering with glucose transport mechanisms. Daruharidra (*Berberis aristata*) facilitates peripheral glucose utilization by activating AMP-activated protein kinase (AMPK), an insulin-independent metabolic pathway. Haridra (*Curcuma longa*) enhances insulin signaling by suppressing inflammatory mediators that contribute to insulin resistance, while Amalaki (*Emblica officinalis*) provides antioxidant protection, minimizing oxidative injury to pancreatic and peripheral tissues. Together, these complementary actions form a comprehensive multi-target therapeutic network.

Step-by-Step Pathological Breakdown and Formulation Strategy

Neuroendocrine Regulation in Glycemic Homeostasis: An important distinguishing component of the formulation is Tagara (*Valeriana wallichii*), which introduces a neuroendocrine dimension to diabetes management. Chronic psychological stress, sleep disturbances, and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis are increasingly recognized as significant contributors to poor glycemic control, although they are often underemphasized in conventional treatment strategies.

Experimental evidence suggests that Tagara modulates central GABAergic neurotransmission, thereby reducing excessive HPA-axis activation. This neuroendocrine regulation may decrease cortisol-mediated hepatic gluconeogenesis and attenuate fasting or early-morning hyperglycemia. Consequently, the formulation addresses both peripheral metabolic abnormalities and central neuroendocrine disturbances, providing a broader therapeutic approach for T2DM management.

Chronopharmacological Basis of Drug Administration: The prescribed regimen of two 500 mg tablets twice daily, administered 30 minutes before major meals with lukewarm water for 90 days, is consistent with the Ayurvedic concept of Aushadha Sevana Kala. Specifically, preprandial administration (Pragbhakta Kala) is traditionally recommended to influence Apana Vayu, which governs metabolic processing, gastrointestinal functions, and elimination [19].

From a contemporary pharmacological perspective, administering the formulation before food intake allows bioactive constituents, particularly gymnemic acids, to interact with intestinal glucose transporters such as SGLT1 and GLUT2 before dietary carbohydrate absorption begins, thereby reducing postprandial glucose excursions. Furthermore, lukewarm water, used as the Anupana, may enhance tablet disintegration and facilitate the dissolution of phytoconstituents, potentially improving gastrointestinal absorption following the Bhavana processing technique.

Key Findings

The present review highlights several important therapeutic characteristics of Pramehnil Tablet:

- **Integrated Pathophysiological Approach:** The Ayurvedic concept of *Kaphaja Prameha* provides a multidimensional framework that closely parallels the complex pathophysiology of T2DM.
- **Network Pharmacology:** The formulation demonstrates a multi-target mode of action by simultaneously modulating several metabolic pathways involved in glucose homeostasis.
- **Synergistic Core Combination:** The classical *Nisha-Amalaki* combination (*Haridra* and *Amalaki*) reduces oxidative stress and inflammatory responses, thereby improving insulin sensitivity.
- **Insulin-Independent Glucose Utilization:** Berberine from *Daruharidra* activates AMPK signaling, enhancing skeletal muscle glucose uptake even under insulin-resistant conditions.

- **Reduction of Intestinal Glucose Absorption:** Gymnemic acids present in *Meshashringi* inhibit intestinal glucose transporters, contributing to lower postprandial blood glucose levels.
- **Cardiovascular Protection:** *Arjuna* (*Terminalia arjuna*) may reduce macrovascular complications by limiting advanced glycation end-product (AGE)-mediated collagen cross-linking within cardiovascular tissues.
- **Neuroendocrine Modulation:** *Tagara* supports glycemic regulation by reducing stress-related activation of the HPA axis and subsequent cortisol release.
- **Enhanced Pharmaceutical Processing:** Bhavana using *Guduchi Kwatha* improves particle size reduction and enhances the bioavailability of relatively hydrophobic phytochemicals.
- **Scientific Basis for Administration Timing:** Pre-meal administration optimizes therapeutic interaction with intestinal glucose transport mechanisms before nutrient absorption.
- **Clinical Translation:** Existing experimental evidence, traditional documentation, and pharmaceutical standardization collectively support progression toward randomized controlled clinical evaluation.

Regulatory and Safety Considerations

Ensuring safety and quality is essential before introducing any polyherbal formulation into clinical research. Accordingly, Pramehnil Tablet should undergo comprehensive quality assessment to confirm that concentrations of heavy metals (lead, cadmium, arsenic, and mercury), pesticide residues, aflatoxins, and microbial contaminants remain within permissible limits prescribed by the Ministry of AYUSH and international regulatory standards. Available toxicological studies on the principal herbal ingredients indicate a favorable safety profile. Experimental investigations involving *Tinospora cordifolia*, *Emblica officinalis*, and *Curcuma longa* have reported relatively high median lethal dose (LD₅₀) values and an absence of significant organ toxicity within therapeutic dosage ranges. Nevertheless, clinical monitoring should include surveillance for uncommon hypersensitivity reactions and transient gastrointestinal discomfort during the initial treatment period.

CONCLUSION

Pramehnil Tablet represents a scientifically rational integration of classical Ayurvedic therapeutics with contemporary concepts of systems pharmacology. Rather than acting through a single molecular target, the formulation utilizes multiple botanicals that collectively influence insulin resistance, chronic inflammation, oxidative stress, dyslipidemia, impaired glucose transport, and neuroendocrine dysfunction—key mechanisms underlying Kaphaja Prameha and T2DM.

Future Research Directions

Future investigations should focus on expanding the mechanistic and clinical understanding of Pramehnil Tablet through multidisciplinary research approaches:

- **Network Pharmacology:** Develop comprehensive interactome models to identify relationships between phytoconstituents and molecular targets involved in T2DM.
- **Gut Microbiome Research:** Evaluate the influence of *Nagarmotha* and *Vidanga* on gut microbial composition, particularly their effects on metabolic endotoxemia, lipopolysaccharide (LPS) production, and short-chain fatty acid (SCFA)-producing bacterial populations.
- **Pharmacokinetic Evaluation:** Conduct comparative pharmacokinetic studies to determine whether the Bhavana process enhances systemic bioavailability of marker compounds such as berberine and curcumin.
- **Metabolomic Investigations:** Employ serum metabolomics during clinical trials to characterize treatment-induced alterations in carbohydrate, lipid, amino acid, and energy metabolism throughout the 90-day intervention period.

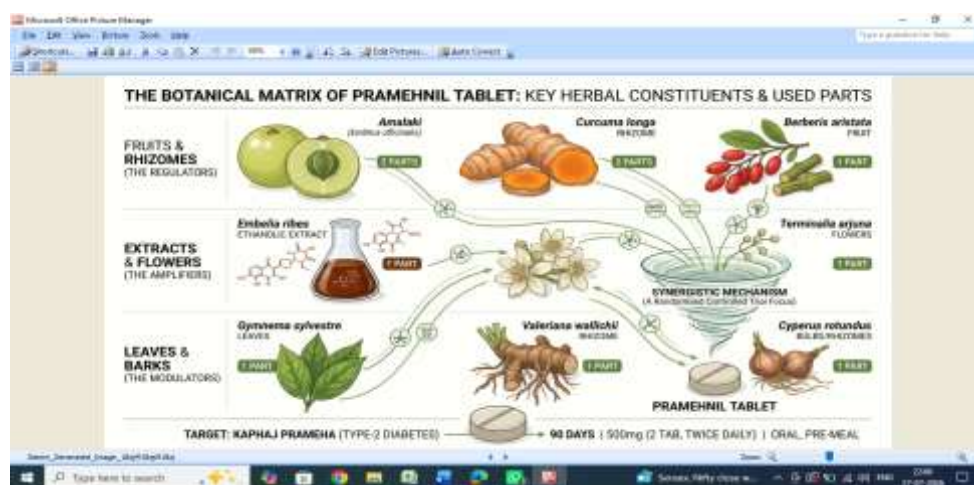


Figure 1: The Botanical Matrix of Pramehnil Tablet: Key Herbal Constituents & Used Parts

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