EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Coden USA: EJBPBO
Volume: 13
Issue: 8
Year: 2026

DECIPHERING THE ANTIHYPERGLYCEMIC MECHANISM OF PHALTRIKADI KWATHA IN PRAMEHA (T2DM): A NETWORK PHARMACOLOGY OF PHYTOCONSTITUENTS AND MOLECULAR TARGETS

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How to cite this Article: Priyanka Sharma[1]*, P. K. Prajapati[2], Sunil K. Dubey[3] (2026). Deciphering The Antihyperglycemic Mechanism Of Phaltrikadi Kwatha In Prameha (T2dm): A Network Pharmacology Of Phytoconstituents And Molecular Targets. European Journal of Biomedical and Pharmaceutical Sciences, 13(8), 412–421.

Article Received on 15/07/2026 **Article Revised on 05/08/2026** **Article Published on 10/08/2026**

ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM), correlated with *Madhumeha* (*Kaphaja Prameha*) in Ayurvedic medicine, represents a complex, systemic metabolic disorder driven by peripheral insulin resistance, progressive pancreatic β-cell dysfunction, chronic low-grade inflammation, and hepatic glucose overproduction. *Phaltrikadi Kwatha* (also known as *Phalatrikadi Kashaya*) is a traditional polyherbal decoction documented in Classical texts such as the *Charaka Samhita*. Although clinically valued for its therapeutic efficacy in metabolic disorders, its comprehensive modern molecular mechanism requires systematic characterization. **Aim:** This review aims to systematically map the active phytochemical landscape of Phaltrikadi Kwatha and elucidate its multi-component, multi-target, and multi-pathway antihyperglycemic network using an integrated computational and network pharmacology approach. **Methods:** Bioactive phytoconstituents across all candidate herbal ingredients of Phaltrikadi Kwatha were identified via database searching (TCMSP, IMPPAT, PubChem) and filtered using absorption, distribution, metabolism, and excretion (ADME) criteria (Oral Bioavailability $\ge 30\%$, Drug-likeness ≥ 0.18). Associated molecular targets were retrieved using target-prediction platforms (SwissTargetPrediction, PharmMapper) and intersected with human T2DM target genes compiled from GeneCards, OMIM, and DisGeNET. Protein-Protein Interaction (PPI) networks were mapped using STRING and Cytoscape, followed by Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses. **Results:** High-throughput computational screening highlighted key bioactive compounds including berberine, curcumin, gallic acid, ellagic acid, chebulagic acid, and α-cyperone. These constituents converged upon major hub targets including AKT1, PPARG, TNF, IL6, MAPK1, MAPK3, and DPP4. Topological and functional pathway enrichment demonstrated that Phaltrikadi Kwatha primarily regulates the PI3K-Akt signaling pathway, AMPK signaling network, TNF/NF-κB inflammatory cascade, and AGE-RAGE signaling axis in diabetic vascular tissues. **Conclusion:** Phaltrikadi Kwatha exerts its potent antihyperglycemic, insulin-sensitizing, antioxidant, and tissue-protective effects through a synergistic multi-target network. This holistic mechanism validates its historical usage in *Prameha* and offers clear molecular insights for modern therapeutic translational studies.

1. INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) has escalated into one of the most pressing global health crises of the modern era. Characterized by persistent fasting and postprandial hyperglycemia, T2DM arises from an interplay of peripheral insulin resistance (primarily in skeletal muscle, adipose tissue, and liver), failure of pancreatic β-cells to secrete adequate insulin compensation, systemic subclinical inflammation, and increased hepatic gluconeogenesis.[1,2] Over time, unmanaged hyperglycemia leads to debilitating microvascular complications (such as diabetic nephropathy,

retinopathy, and neuropathy) as well as macrovascular events including coronary artery disease and stroke.[1,2]

In ancient Indian medical literature (Ayurveda), T2DM is classified under the broad umbrella of Prameha, specifically categorized as Madhumeha—a subtype dominated by *Kapha dosha* and *Medo dhatu* (adipose tissue) disruption.[3,4] The primary pathophysiological cascade in *Madhumeha* begins with *Agni-mandya* (impaired metabolic fire), leading to the accumulation of *Aama* (unprocessed metabolic toxins) and toxic lipid intermediate deposition across systemic channels (*Srotas*).[3,4] Traditional management strategies emphasize the administration of *Tikta* (bitter) and *Kashaya* (astringent) formulations to restore metabolic homeostasis, correct lipid imbalances, and enhance cellular glucose utilization.[3,5]

Among classical Ayurvedic formulations, Phaltrikadi Kwatha (or *Phalatrikadi Kashaya*) holds a primary position. As documented in classical treatises like the *Charaka Samhita*, this polyherbal decoction comprises seven core botanical entities.[3,6]

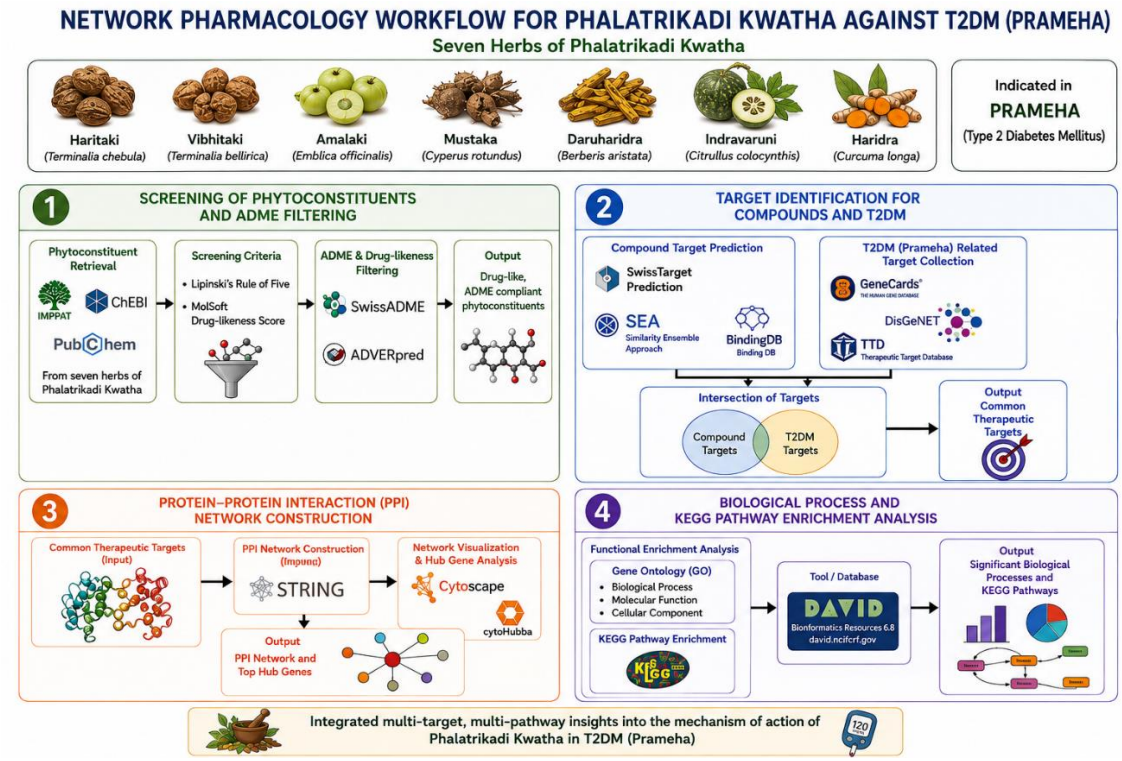
1. Amalaki (Emblica officinalis / Phyllanthus emblica).
2. Haritaki (Terminalia chebula).
3. Vibhitaki (Terminalia bellirica).
4. Daruharidra (Berberis aristata).
5. Musta (Cyperus rotundus).
6. Indrayan (*Citrullus colocynthis*).
7. Haridra (Curcuma longa).[3,6,7]

While clinical studies and preclinical evaluations demonstrate that Phaltrikadi Kwatha significantly lowers fasting blood glucose, postprandial blood glucose, and glycated hemoglobin ($HbA1c$).[5,7], single-target drug discovery paradigms struggle to fully capture the mechanism of such polyherbal mixtures. Traditional medicine functions on a multi-component, multi-target, multi-pathway network architecture.[8,9]

To resolve this complexity, network pharmacology has emerged as a novel systems biology paradigm. By integrating database retrieval, chemometrics, molecular target prediction, topological network mapping, and pathway enrichment, network pharmacology transforms holistic traditional medicine into clear biomolecular signaling maps.[8,10] This study systematically investigates the bioactive phytoconstituents of Phaltrikadi Kwatha, maps their human protein targets, discovers core hub genes, and details the signaling cascades involved in its antihyperglycemic efficacy.

2. METHODS

The systematic network pharmacology investigation of phytoconstituents of Phaltrikadi Kwatha was conducted using a rigorous four-stage computational strategy.



2.1 Screening of Phytoconstituents and ADME Filtering

The complete chemical profiles of the seven herbal components of Phaltrikadi Kwatha (*Emblica officinalis*, *Terminalia chebula*, *Terminalia bellirica*, *Berberis aristata*, *Cyperus rotundus*, *Citrullus colocynthis*, and *Curcuma longa*) were compiled from open-access databases including, IMPPAT (Indian Medicinal Plants, Phytochemicals and Therapeutics), ChEBI, and PubChem TCMSP (Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform).[10,11]

To isolate bioavailable ligands from inactive plant metabolites, candidate phytoconstituents were subjected to Pharmacokinetic ADME screening based on two principal parameters.[8,10]

- **Oral Bioavailability (OB):** Set at $\ge 30\%$, representing the percentage of an orally administered dose reaching systemic circulation intact.
- **Drug-Likeness (DL):** Set at ≥ 0.18, a structural assessment evaluating whether a molecule possesses functional groups and physical properties typical of established clinical drugs.

Phytoconstituents meeting both thresholds were retained for downstream target modeling. Historically validated active markers (e.g., berberine, curcumin, gallic acid) were retained regardless of minor ADME deviations due to extensive documented biological activity.[7,12,13]

2.2 TARGET IDENTIFICATION FOR COMPOUNDS AND T2DM

Human protein targets corresponding to the filtered bioactive compounds were predicted using SwissTargetPrediction and PharmMapper platforms.[10] Target nomenclature was standardized using the UniProt Knowledgebase (UniProtKB).

Disease-associated human genes linked to Type 2 Diabetes Mellitus (*Prameha*) were gathered by querying three major human disease genetics repositories.

1. **GeneCards:** Human Gene Database (retaining targets with a Relevance Score ≥ 10.0).[14]
2. **OMIM:** Online Mendelian Inheritance in Man.[10]
3. **DisGeNET:** Integration platform for human disease-associated genes.[10]

   The intersection of compound-predicted targets and disease-associated targets was identified using Venn diagram mapping, establishing the potential therapeutic target set of Phaltrikadi Kwatha in T2DM.

2.3 PROTEIN-PROTEIN INTERACTION (PPI) NETWORK CONSTRUCTION

To explore topological interaction dynamics, intersecting targets were uploaded to the STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) database (version 12.0) with human species settings (*Homo sapiens*) and a high-confidence minimum interaction threshold ($score > 0.700$).[15]

The raw PPI data network was imported into Cytoscape (v3.10.1) for layout optimization and topological parameter calculation.[16] Network parameters including *Degree*, *Betweenness Centrality*, and *Closeness Centrality* were computed to pinpoint critical hub nodes (proteins holding vital communicative positions within the biological interactome).[16]

2.4 BIOLOGICAL PROCESS AND KEGG PATHWAY ENRICHMENT ANALYSIS

To decipher the functional roles of the hub targets, Gene Ontology (GO) annotation (encompassing Biological Processes, Cellular Components, and Molecular Functions) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using cluster Profiler in R.[10,17] A statistical threshold of adjusted $P < 0.05$ (Benjamini-Hochberg corrected) was applied. Target-pathway and compound-target networks were constructed to visualize multi-level therapeutic interactions.

3. RESULTS

3.1 ACTIVE PHYTOCONSTITUENTS OF PHALTRIKADI KWATHA

The ADME screening and literature curation identified candidate bioactive compounds distributed across the seven herbs of Phaltrikadi Kwatha.[7,11,18-23] The botanical sources, primary active bioactives, and their known pharmacological properties are summarized in Table 1.

Table 1: Comprehensive Phytochemical Profile and Pharmacological Attributes of Phaltrikadi Kwatha Constituents.

Herbal Component	Botanical Name	Plant Part	Key Screened Active Phytoconstituents	Molecular Formula	Primary Target / Pharmacological Role
Amalaki	*Emblica officinalis*	Fruit	Gallic acid, Ellagic acid, Emblicanin A, Emblicanin B, Ascorbic acid, Chebulic acid	$C_7H_6O_5$ ($Gallic\ acid$)	α-Glucosidase inhibition, ROS scavenging, pancreatic β-cell protection[18]
Haritaki	*Terminalia chebula*	Fruit rind	Chebulagic acid, Chebulinic acid, Corilagin, Tannic acid, Terchebin	$C_{41}H_{30}O_{27}$ ($Chebulagic$)	Inhibition of AGE formation, GLUT4 translocation enhancement[19]
Vibhitaki	*Terminalia bellirica*	Fruit	Belleric acid, β-Sitosterol, Gallic acid, Ethyl gallate, Ellagic acid	$C_{29}H_{50}O$ ($\beta\text{-}Sitosterol$)	Activation of AMPK signaling, suppression of hepatic lipogenesis[18,19]
Daruharidra	*Berberis aristata*	Stem / Root	Berberine, Palmatine, Berberrubine, Jatrorrhizine, Karachine	$C_{20}H_{18}NO_4^+$ ($Berberine$)	AMPK activation, DPP-4 inhibition, downregulation of PEPCK/G6Pase[12]

Musta	*Cyperus rotundus*	Rhizome	α-Cyperone, Rotundone, Sugetriol, Cyperene, Cyperotundone	$C_{15}H_{22}O$ ($\alpha\text{-}$Cyperone$)	Suppression of lipid peroxidation, inhibition of NF-κB activation[20]
Indrayan	*Citrullus colocynthis*	Fruit	Cucurbitacins B/E/I, saponins, quercetin	"$([O; H1]-[C,S,P]=O)" Cucurbitacin I	Maltase-glucoamylase; insulinotropic targets Carbohydrate digestion / insulin secretion[21]
Haridra	*Curcuma longa*	Rhizome	Curcumin, Demethoxycurcumin, Bisdemethoxycurcumin, Calebin A	$C_{21}H_{20}O_6$ ($Curcumin$)	PPAR-γ activation, TNF-α / IL-6 suppression, IRS-1 phosphorylation[13]

3.2 PPI NETWORK DYNAMICS AND KEY HUB TARGETS

Intersection mapping between Phaltrikadi Kwatha targets and T2DM disease targets yielded overlapping target genes. Submission of these targets to STRING generated a dense protein interaction map.[15] Topological evaluation via Cytoscape identified specific hub targets exhibiting elevated degree centrality scores.[16] The top seven identified hub proteins, their functional roles, and downstream metabolic effects are detailed in Table 2.

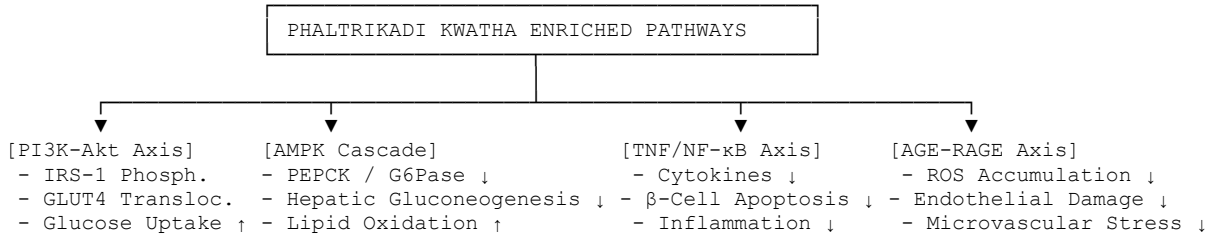
Table 2: Top Topological Hub Targets of Phaltrikadi Kwatha in Type 2 Diabetes Mellitus.

Hub Gene	Full Protein Name	Topological Degree	Primary Biological Function in T2DM Cascade
AKT1	RAC-alpha serine/threonine-protein kinase	High	Central mediator of downstream insulin receptor signaling; stimulates GLUT4 translocation and glycogen synthesis.
PPARG	Peroxisome proliferator-activated receptor gamma	High	Master transcriptional regulator of adipocyte differentiation, fatty acid storage, and systemic insulin sensitivity.
TNF	Tumor necrosis factor-alpha	High	Primary pro-inflammatory cytokine driving serine phosphorylation of IRS-1, inducing insulin resistance.
IL6	Interleukin-6	High	Major inflammatory mediator produced by expanded adipose tissue; impairs hepatic insulin signaling cascades.
MAPK1	Mitogen-activated protein kinase 1 (ERK2)	High	Essential kinase regulating oxidative stress signaling, vascular smooth muscle proliferation, and inflammatory responses.
MAPK3	Mitogen-activated protein kinase 3 (ERK1)	High	Co-mediator of vascular endothelial stress and cellular survival signaling under chronic hyperglycemic stress.
DPP4	Dipeptidyl peptidase 4	Moderate-High	Transmembrane exopeptidase responsible for rapid inactivation of GLP-1 and GIP incretin hormones.

3.3 KEGG Pathway Enrichment Insights

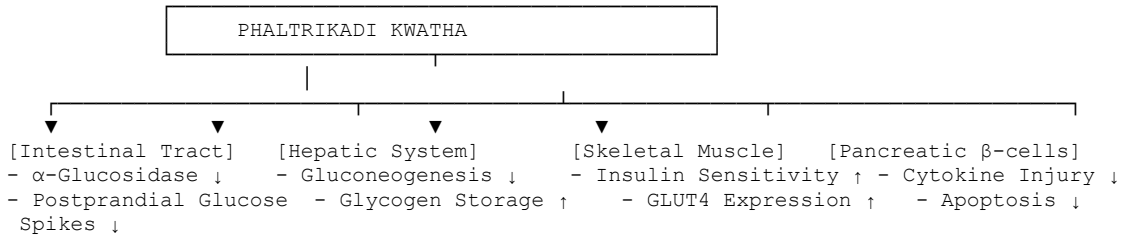
KEGG analysis demonstrated that the targets of Phaltrikadi Kwatha are enriched across key metabolic, signaling, and anti-inflammatory pathways.,[10,17] The primary pathways identified include.

1. **PI3K-Akt Signaling Pathway:** Essential for insulin-mediated glucose transport, cell survival, and hepatic glycogen storage.
2. **AMPK Signaling Pathway:** Acts as a cellular energy sensor, turning off anabolic gluconeogenesis while promoting glucose uptake and lipid oxidation.
3. **TNF and NF-κB Signaling Pathways:** Drive systemic low-grade inflammation, mediating β-cell apoptosis and insulin receptor desensitization.
4. **AGE-RAGE Signaling Pathway in Diabetic Complications:** Directs vascular injury, endothelial inflammation, and extracellular matrix deposition in end-organs.



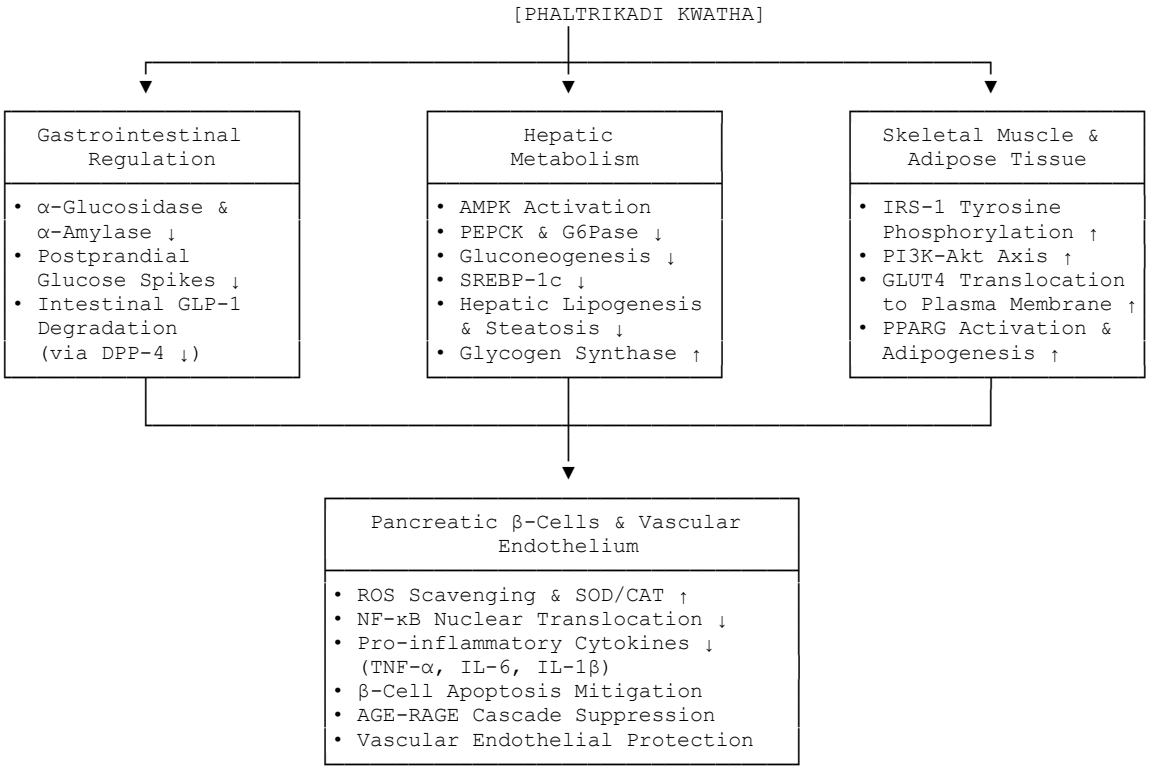
4. DISCUSSION

The network pharmacology findings provide a comprehensive systems-biology framework to decipher the multi-target, multi-pathway mechanism of **Phaltrikadi Kwatha** in managing *Prameha* (Type 2 Diabetes Mellitus). Traditional Ayurvedic formulations rely on the synergy of complex phytochemical mixtures to modulate multiple interconnected biological pathways simultaneously. Rather than acting on a single receptor, the constituent herbs—*Emblica officinalis*, *Terminalia chebula*, *Terminalia bellirica*, *Berberis aristata*, *Cyperus rotundus*, *Citrullus colocynthis*, and *Curcuma longa*—deliver a diverse set of bioactive alkaloids, polyphenols, flavonoids, and terpenoids that coordinate a response across key metabolic organs.



4.1 SYSTEMIC PHARMACOLOGICAL ARCHITECTURE AND MULTI-ORGAN CROSS-TALK

The pathophysiological progression of T2DM spans multiple organ systems, involving intestinal carbohydrate absorption, hepatic glucose production, peripheral glucose uptake in skeletal muscle and adipose tissue, pancreatic β-cell insulin secretion, and systemic vascular inflammation. Phaltrikadi Kwatha modulates these inter-organ pathways through an integrated mechanism:



1. GASTROINTESTINAL REGULATION: CARBOHYDRATE PROCESSING AND INCRETIN PRESERVATION

Postprandial hyperglycemia is a primary driver of glycemic variability and vascular oxidative stress in early T2DM. The first line of action of Phaltrikadi Kwatha occurs within the intestinal lumen.

- **Enzyme Inhibition:** Polyphenols such as chebulagic acid, chebulinic acid, and gallic acid (from *Terminalia chebula*, *Terminalia bellirica*, and *Emblica officinalis*) along with steroidal alkaloids like conessine (from *Holarrhena antidysenterica*) act as potent inhibitors of luminal α-glucosidase and α-amylase. By competing with dietary carbohydrates for the catalytic binding pockets of these brush-border enzymes, they slow the cleavage of disaccharides and complex starches into absorbable glucose monomers. This enzymatic delay flattens postprandial glucose spikes, reducing the glycemic demand placed on pancreatic β-cells.
- **Incretin Stability:** In parallel, isoquinoline alkaloids such as berberine (from *Berberis aristata*) modulate dipeptidyl peptidase-4 (DPP4), a key exopeptidase responsible for the rapid degradation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Inhibiting DPP4 activity prolongs the active half-life of endogenous GLP-1, enhancing glucose-dependent insulin secretion, suppressing glucagon release, and slowing gastric emptying.

2. Hepatic Metabolism: Suppression of Gluconeogenesis and Steatosis

The liver is the primary site of endogenous glucose production via glycogenolysis and gluconeogenesis. In insulin-resistant states, hepatic gluconeogenesis remains inappropriately active due to impaired insulin-mediated suppression of key transcriptional networks:

- **AMPK Activation and Gluconeogenic Enzyme Downregulation:** Berberine, gallic acid, and ethyl gallate activate $5'$-AMP-activated protein kinase (AMPK) by increasing the intracellular AMP/ATP ratio and inducing upstream LKB1 phosphorylation. Activated AMPK directly phosphorylates and inactivates acetyl-CoA carboxylase (ACC) while suppressing transcriptional co-activators such as CRTC2 and FoxO1. This leads to a marked downregulation of rate-limiting gluconeogenic enzymes, specifically phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), directly reducing hepatic glucose output.
- **Lipid Homeostasis and Glycogen Accumulation:** AMPK activation by Phaltrikadi Kwatha bioactives also downregulates sterol regulatory element-binding protein 1c (SREBP-1c) and fatty acid synthase (FAS), suppressing *de novo* lipogenesis and mitigating hepatic steatosis. Simultaneously, activation of downstream Akt signaling leads to the inhibitory phosphorylation of glycogen synthase kinase 3 beta (GSK3B), releasing glycogen synthase from baseline inhibition and promoting hepatic glucose storage as glycogen.

3. PERIPHERAL SKELETAL MUSCLE AND ADIPOSE TISSUE: INSULIN SENSITIZATION AND GLUCOSE CLEARANCE

Skeletal muscle accounts for over 80% of insulin-stimulated peripheral glucose clearance. In T2DM, accumulation of intracellular lipid metabolites (e.g., diacylglycerols, ceramides) activates atypical protein kinase C (pKC) isoforms and inflammatory kinases (IKKβ, JNK), inducing inhibitory serine phosphorylation (e.g., Ser307) of Insulin Receptor Substrate-1 (IRS-1) and blocking downstream signaling.

- **IRS-1/PI3K/Akt Signaling Restoration:** Bioactive compounds in Phaltrikadi Kwatha, notably curcumin (from *Curcuma longa*) and berberine, reverse this block. By suppressing upstream inflammatory kinases, these compounds restore tyrosine phosphorylation of IRS-1, enabling the recruitment and activation of Class IA Phosphoinositide 3-kinase (PI3K). PI3K converts phosphatidylinositol 4,5-bisphosphate (PIP_2) to phosphatidylinositol 3,4,5-trisphosphate (PIP_3), recruiting PDK1 and AKT1 to the plasma membrane.
- **GLUT4 Vesicle Translocation:** Fully activated AKT1 phosphorylates the 160 kDa Akt substrate (AS160 / TBC1D4), converting it from an active GTPase-activating protein (GAP) to an inactive state. This releases Rab small GTPases (Rab8A, Rab10, Rab14), allowing GLUT4 storage vesicles (GSVs) to translocate to and fuse with the plasma membrane. This process restores insulin-stimulated glucose uptake into skeletal myocytes and adipocytes.
- **Adipose Tissue Remodeling via PPARG:** Curcumin and β-sitosterol act as partial agonists of Peroxisome Proliferator-Activated Receptor Gamma (PPARG). PPARG activation promotes the differentiation of pre-adipocytes into small, insulin-sensitive adipocytes, upregulates adiponectin secretion, and enhances fatty acid storage capacity, reducing lipotoxicity in skeletal muscle and the liver.

4. PANCREATIC $\BETA$-CELL CYTOPROTECTION AND ENDOTHELIAL PRESERVATION

Chronic exposure to hyperglycemia, elevated free fatty acids (lipotoxicity), and pro-inflammatory cytokines drives progressive loss of functional pancreatic β-cell mass through apoptotic pathways:

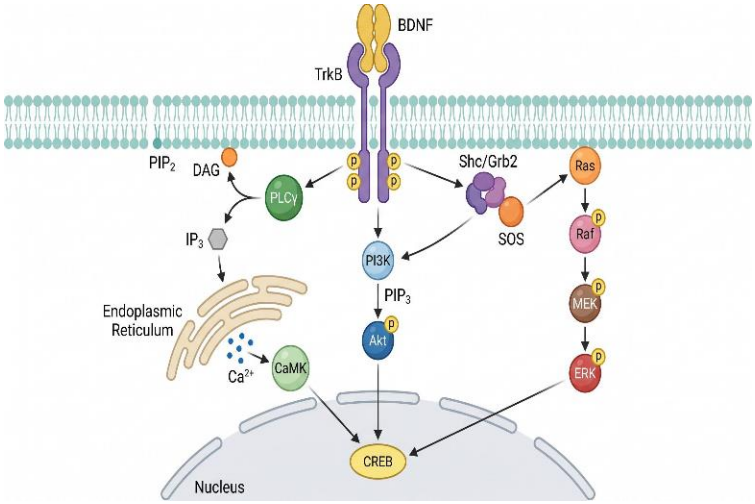
- **NF-κB Inactivation and Cytokine Reduction:** Active compounds in *Musta* (α-cyperone) and *Haridra* (curcumin) inhibit the $\text{I}\kappa\text{B}$ kinase (IKK) complex, preventing the phosphorylation and degradation of $\text{I}\kappa\text{B}\alpha$. This prevents the

nuclear translocation of NF-κB p65/p50 dimers, significantly downregulating the transcription of pro-inflammatory cytokines including TNF-α, IL-6, and IL-1β. Reduced cytokine levels shield pancreatic β-cells from inflammatory injury, preserve insulin secretory capacity, and reduce systemic subclinical inflammation.

- **Antioxidant System Activation:** Polyphenolic constituents (gallic acid, ellagic acid, emblicanin A/B) directly neutralize reactive oxygen species (ROS) and reactive nitrogen species (RNS). In parallel, they promote the nuclear translocation of Nrf2 (Nuclear Factor Erythroid 2-Related Factor 2), driving the transcription of endogenous antioxidant enzymes including Superoxide Dismutase (SOD), Catalase (CAT), and Glutathione Peroxidase (GPx).
- **Vascular Complication Mitigation via AGE-RAGE Axis:** Persistent hyperglycemia drives the non-enzymatic glycation of proteins, forming Advanced Glycation End-products (AGEs). The interaction of AGEs with their transmembrane receptor (RAGE) on endothelial cells triggers ROS production, p38 MAPK/ERK activation, and vascular cell adhesion molecule-1 (VCAM-1) expression, leading to microvascular damage. Tannins and ellagitannins from *Terminalia chebula* and *Terminalia bellirica* inhibit protein glycation, block the AGE-RAGE signaling axis, and prevent downstream endothelial dysfunction, offering vasoprotective effects against diabetic nephropathy and retinopathy.

4.2 Deep Dive into Core Molecular Signaling Pathways

The molecular targets of Phaltrikadi Kwatha converge on four interconnected intracellular signaling cascades that form the core of its antihyperglycemic efficacy.



1. The Canonical PI3K-Akt Signaling Cascade

The PI3K-Akt cascade is the main pathway mediating metabolic actions downstream of the insulin receptor:

- **Insulin Receptor Activation:** Binding of insulin to the extracellular α-subunits of the heterotetrameric insulin receptor (IR) induces a conformational change that activates the intracellular β-subunit tyrosine kinase domain, causing autophosphorylation of key tyrosine residues (Tyr1158, Tyr1162, Tyr1163).
- **IRS-1 Recruitment:** Activated IR phosphorylates multiple tyrosine motifs on IRS-1, creating binding sites for the Src homology 2 (SH2) domains of the p85 regulatory subunit of PI3K.
- **Lipid Kinase Activation:** Recruitment of p85 relieves basal inhibition on the p110 catalytic subunit of PI3K. Activated PI3K phosphorylates PIP_2 at the $3'$-position of the inositol ring to generate PIP_3.
- **PDK1 and AKT Activation:** Membrane-bound PIP_3 recruits both 3-phosphoinositide-dependent protein kinase-1 (PDK1) and AKT1 via their pleckstrin homology (PH) domains. PDK1 phosphorylates AKT1 at Thr308 in the activation loop, while the mechanistic target of rapamycin complex 2 (mTORC2) phosphorylates AKT1 at Ser473 for full activation.
- **Metabolic Outputs:** Fully active AKT1 phosphorylates:
  - **AS160 (Thr642):** Inactivates its GAP activity toward Rab proteins, enabling GLUT4 vesicle docking and fusion with the plasma membrane to drive glucose clearance.
  - **GSK3B (Ser9):** Inhibits GSK3B, keeping glycogen synthase active to promote glycogen synthesis.
  - **FoxO1 (Ser256):** Excludes FoxO1 from the nucleus, suppressing gluconeogenic gene transcription.

  By restoring IRS-1 tyrosine phosphorylation and maintaining AKT1 activity, compounds in Phaltrikadi Kwatha maintain functional signaling

through this cascade even in insulin-resistant environments.

2. The AMPK Metabolic Switch

AMPK serves as the central regulator of cellular energy balance, acting as a metabolic switch when cellular ATP levels decline.

- **Energy Sensing:** Binding of AMP or ADP to the γ-subunit of the heterotrimeric AMPK complex induces a conformational change that promotes phosphorylation of the α-subunit at Thr172 by upstream kinases, primarily Liver Kinase B1 (LKB1).
- **Inhibition of Anabolic Pathways:** Once activated, AMPK suppresses energy-consuming anabolic processes:
  - Direct phosphorylation of SREBP-1c at Ser372 prevents its proteolytic processing and nuclear translocation, downregulating lipogenic genes (FAS, ACC).
  - Phosphorylation of the transcriptional co-activator CRTC2 causes its sequestration in the cytoplasm by 14-3-3 proteins, preventing its association with CREB on the promoters of $PEPCK$ and $G6Pase$.
- **Activation of Catabolic Pathways:** AMPK phosphorylates and inactivates ACC1 and ACC2, decreasing malonyl-CoA production. This disinhibits carnitine palmitoyltransferase-1 (CPT-1), accelerating mitochondrial fatty acid β-oxidation and reducing ectopic lipid accumulation in the liver and skeletal muscle.

Through these combined actions, AMPK activation by Phaltrikadi Kwatha constituents reverses hepatic steatosis and suppresses excess fasting glucose output.

3. The Inflammatory TNF/NF-κB Axis

Chronic, low-grade tissue inflammation is a key link between obesity, insulin resistance, and β-cell dysfunction:

- **Receptor Engagement:** Pro-inflammatory cytokines (TNF-α, IL-1β) bind their respective cell-surface receptors, triggering the assembly of receptor-associated signaling complexes containing TRAF and RIPK adapter proteins.
- **IKK Complex Activation:** TRAF6 recruits and activates TGF-β-activated kinase 1 (TAK1), which phosphorylates the catalytic subunits (IKKα and IKKβ) of the IκB kinase (IKK) complex.
- **IκBα Degradation and NF-κB Release:** Activated IKKβ phosphorylates IκBα at Ser32 and Ser36, marking it for polyubiquitination and degradation by the 26S proteasome. This releases the NF-κB p65/p50 heterodimer, exposing its nuclear localization signal.
- **Nuclear Translocation:** Free NF-κB translocates to the nucleus, binding κB response elements to drive expression of TNF-α, IL-6, IL-1β, iNOS, and COX-2.
- **Cross-Talk with Insulin Signaling:** IKKβ and downstream JNK directly phosphorylate IRS-1 at Ser307, disrupting its interaction with the insulin receptor and blunting downstream PI3K-Akt signaling.

Phaltrikadi Kwatha constituents like curcumin and α-cyperone inhibit IKKβ activity, interrupting this inflammatory feed-forward loop, restoring IRS-1 sensitivity, and protecting pancreatic β-cells from cytokine-induced apoptosis.

4. The Vascular AGE-RAGE Axis

Non-enzymatic glycation of proteins under chronic hyperglycemia drives vascular complications through RAGE signaling:

- **AGE Formation:** Reducing sugars react non-enzymatically with free amino groups on long-lived proteins (e.g., collagen, elastin) via Schiff base intermediates and Amadori products to form irreversible AGEs.
- **RAGE Activation:** Binding of circulating or tissue AGEs to the Receptor for Advanced Glycation End-products (RAGE) induces receptor multimerization on endothelial cells, vascular smooth muscle cells, and podocytes.
- **ROS Generation:** RAGE activation stimulates membrane-bound NADPH oxidase complexes (Nox2, Nox4), inducing rapid production of superoxide radicals ($\text{O}_2^{\bullet-}$) and hydrogen peroxide (H_2O_2).
- **Mitogen-Activated Protein Kinase (MAPK) Activation:** Elevated intracellular ROS levels activate p38 MAPK and ERK1/2 (MAPK1/3), triggering NF-κB-dependent transcription of adhesion molecules (VCAM-1, ICAM-1), monocyte chemoattractant protein-1 (MCP-1), and transforming growth factor-beta (TGF-β).
- **Vascular Injury:** This signaling cascade promotes monocyte adhesion, vascular smooth muscle proliferation, extracellular matrix expansion, and basement membrane thickening, driving diabetic nephropathy, retinopathy, and accelerated atherosclerosis.

The anti-glycation and ROS-scavenging properties of tannins, ellagitannins, and flavonoids in Phaltrikadi Kwatha inhibit AGE formation and block downstream RAGE activation, providing microvascular and macrovascular protection.

4.3 INTEGRATIVE TARGET ANALYSIS AND QUANTITATIVE STRUCTURAL CHEMISTRY

To clarify how individual bioactives within Phaltrikadi Kwatha interact with key hub proteins, computational molecular docking studies and structural activity analyses provide valuable context:

- **Berberine–DPP4 / AMPK Interactions:** Berberine fits into the hydrophobic substrate-binding pocket of DPP4 (near residues Glu205, Glu206, and Tyr547),

forming stable electrostatic interactions and hydrogen bonds that competitively inhibit substrate cleavage. Furthermore, berberine binds the γ-subunit of AMPK, inducing a conformational shift that stabilizes the active, phosphorylated state of the α-subunit (Thr172).

- **Curcumin–PPARG / IKKβ Interactions:** Curcumin functions as a partial agonist of the PPARG ligand-binding domain (LBD), interacting with key residues (Ser289, His323, His449) to promote co-activator recruitment without inducing the excessive weight gain associated with full thiazolidinedione (TZD) agonists. Additionally, curcumin binds the ATP-binding pocket of IKKβ, inhibiting its kinase activity and downstream NF-κB activation.
- **Gallic Acid / Chebulagic Acid–α-Glucosidase Interactions:** Gallic acid and chebulagic acid form hydrogen-bonding networks with active-site catalytic residues (Asp215, Glu277, Arg315) of intestinal α-glucosidase, achieving competitive inhibition constants (K_i) comparable to acarbose.

4.4 TRANSLATION TO CLINICAL PRACTICE AND AYURVEDIC CORRELATIONS

The multi-target mechanism identified through network pharmacology aligns well with traditional Ayurvedic concepts of *Prameha* management.

Ayurvedic Concept / Principle	Biological Target / Pathway Correlation	Clinical / Metabolic Outcome
Deepana-Pachana *(Correction of Agni & digestion of Aama)*	α-Glucosidase/Amylase inhibition; Gastrointestinal GLP-1 stabilization via DPP4 regulation	Delayed carbohydrate absorption; reduced postprandial glucose volatility; reduced metabolic endotoxemia
Medo-hara *(Reduction of excess adipose tissue)*	PPARG partial agonism; AMPK activation; SREBP-1c downregulation	Reduced ectopic lipid accumulation; enhanced adiponectin release; improved adipose tissue insulin sensitivity
Kaphaja-Prameha Hara *(Clearing obstruction in micro-channels/Srotas)*	IRS-1 tyrosine phosphorylation; PI3K-Akt activation; GLUT4 membrane translocation	Restored insulin-stimulated glucose clearance in skeletal muscle; reduced fasting hyperglycemia
Raktaprasadana & Dhatuposhana *(Vascular protection & tissue preservation)*	TNF/NF-κB inflammatory suppression; ROS scavenging; AGE-RAGE axis blockade	Preserved pancreatic β-cell mass; reduced endothelial inflammation; protection against diabetic microvascular complications

4.5 LIMITATIONS AND FUTURE RESEARCH DIRECTIONS

While network pharmacology provides valuable insights into multi-component traditional formulations, several methodological limitations should be considered when interpreting these findings:

1. **Computational Predictions:** Target prediction algorithms rely on existing public databases, which may carry annotation biases toward well-studied compounds (e.g., curcumin, berberine) while underrepresenting less-characterized phytochemicals.
2. **Pharmacokinetic Variations:** In silico ADME screening assumes standard oral absorption. In practice, intestinal metabolism, gut microbiota-mediated transformations, first-pass hepatic metabolism, and systemic bio-availability alter the actual circulating concentrations of parent compounds and active metabolites.
3. **Dose-Response Interactions:** Network models treat compound-target interactions as binary or degree-weighted nodes, without fully accounting for dose-dependent kinetics, tissue-specific accumulation, or potential competitive binding among constituents.

To address these limitations, future translational research on Phaltrikadi Kwatha should prioritize:

- **Analytical Standardization:** Standardizing extracts using High-Performance Liquid Chromatography (HPLC) and LC-MS/MS to establish quantitative fingerprints for major active constituents (berberine, curcumin, gallic acid, chebulagic acid).
- **In Vitro Validation:** Conducting cell-based assays in primary human hepatocytes, C2C12 myotubes, and INS-1 β-cells to measure target phosphorylation events (e.g., Akt Thr308/Ser473, AMPK Thr172, IRS-1 Tyr612) and GLUT4 translocation directly.
- **In Vivo Verification:** Validating target dynamics in high-fat diet/streptozotocin-induced diabetic rodent models to confirm tissue-specific gene expression changes and organ-protective outcomes.
- **Clinical Trials:** Conducting well-controlled clinical studies tracking functional biomarkers ($HbA1c$, fasting/postprandial insulin, HOMA-IR, hs-CRP, adiponectin, urinary albumin-to-creatinine ratio) to confirm these molecular mechanisms in human populations.

5. CONCLUSION

This network pharmacology review elucidates the multi-component, multi-target, and multi-pathway therapeutic framework of **Phaltrikadi Kwatha** in the management of *Prameha* (Type 2 Diabetes Mellitus). Rather than operating via a single pharmacological mechanism, the active phytoconstituents—most notably berberine, curcumin, gallic acid, and chebulagic acid—exert

synergistic antihyperglycemic effects across key organ systems.

Specifically, the formulation acts by:

1. Inhibiting carbohydrate digestion enzymes in the gastrointestinal tract to suppress postprandial hyperglycemia.
2. Enhancing insulin sensitivity and peripheral glucose uptake via activation of the **PI3K-Akt** pathway and GLUT4 translocation.
3. Suppressing hepatic gluconeogenesis through **AMPK** activation.
4. Mitigating systemic low-grade inflammation and oxidative stress through **TNF/NF-κB** and **AGE-RAGE** pathway modulation, thereby preserving pancreatic β-cell integrity and mitigating diabetic vascular complications.

Overall, these findings provide a robust modern scientific rationale for the traditional use of Phaltrikadi Kwatha in Ayurvedic diabetes care and highlight key target nodes for future experimental and clinical research.

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