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Synergistic Impact of Polyherbal Formulations on Metabolic Syndrome: A Comprehensive Review of Mechanisms and Therapeutic Potential

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ABSTRACT:

Obesity, dyslipidemia, hypertension, and insulin resistance are all components of metabolic syndrome, which significantly increases the risk of cardiovascular diseases and type 2 diabetes. Current conventional pharmacological therapies typically have limited efficacy and might induce side effects, highlighting the need for innovative therapeutic strategies. This mini-review looks at polyherbal formulations' potential as an effective multi-target therapy for metabolic syndrome, which may offer a more suitable alternative to the current monotherapy agents. Drawing from current Research, our team investigates how these formulations provide anti-obesity, antihyperglycemic, and hypolipidemic effects. Bioactive compounds in herbs such as Citrus reticulata, Momordica Charantia, and Glycine max collaborate to enhance lipid metabolism, reduce adipogenesis, and strengthen antioxidant defense. This Research also checks the safety profiles and therapeutic potential of these formulations to relieve the complicated symptoms resulting from metabolic syndrome. This study reinforces the opportunity of using herbal medications as a comprehensive approach to manage metabolic syndrome, paving the way for further clinical studies creating standardized herbal medications.

KEYWORDS:

"Polyherbal Formulation"; "Metabolic Syndrome"; "Anti-Hyperglycemia"; "Anti-Obesity"; "Herbal Medicine"; "Hypolipidemic"; "Antihypertensive" .

1. INTRODUCTION

1.1 Metabolic Syndrome Definition and Diagnosis Criteria:

Metabolic syndrome (MetS) is identified as a group of interdependent metabolic conditions. The most important five components are: insulin resistance, visceral obesity, hypertension, increased LDL, and decreased HDL (Figure 1).

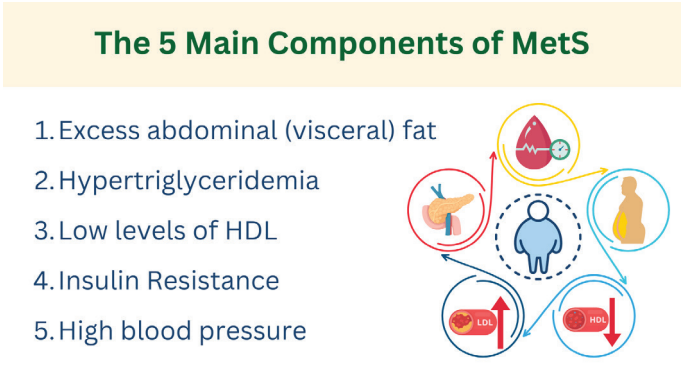

Figure 1: The Five Main Components of Metabolic Syndrome

significantly increase the incidence of cardiovascular diseases (CVDs) and type 2 diabetes mellitus (T2DM) (1)

The new approaches and Research focus on holistic therapeutic strategies to target several, dependent, and complicated metabolic pathways in order to reach better outcomes than conventional therapies targeting single pathways.

During the last years, diagnostic criteria of metabolic syndrome have been subjected to variation. In 2001, the National Cholesterol Education Program's (NCEP) Adult Treatment Panel III (ATP III) stated standard criteria for metabolic syndrome diagnosis, which are based on

These criteria were based on standard clinical measurements such as blood pressure, HDL-C, triglycerides, waist circumference, and fasting glucose level, where these criteria have been widely used by epidemiological researchers and in clinical practice.

To be diagnosed with metabolic syndrome, abnormalities in 3 of 5 clinical parameters should be determined. The criteria paved the way for focusing on more than one cause. In The AHA and NHLBI are going forward to use and clarify these criteria with new adjustment to meet the scientific variability where according to guidelines for insulin resistance, the threshold for counting elevated fasting glucose is lowered from ≥110 mg/dL to ≥100 mg/dL; permitting blood pressure, HDL-C, and triglycerides to be counted as abnormal when an individual is taking medication for these conditions; and permitting waist circumference to be adjusted to lower thresholds when individuals or ethnic groups are predisposed to insulin resistance. (2–4).

1.2. Prevalence and global burden

MetS affects about 25% of the global population, with a prevalence rate of 35% in the Middle East and North Africa (MENA). Dietary choices, genetic predispositions, financial issues, and sedentary lifestyles are all factors contributing to metabolic syndrome. These high prevalence rates increase the risk of premature mortality, reduce quality of life, and significantly increase the burden of noncommunicable illnesses. (5,6)

1.3. Recent Treatment Challenges

Traditional pharmacological therapies—such as antihypertensives, statins, and antidiabetic medications manage specific MetS components separately, but they are limited by side effects, high prices, and poor patient non-adherence. In addition, the interrelated mechanisms of MetS components impair the effectiveness of monotherapies, where addressing hyperglycemia doesn't mean that they target the inflammatory or dyslipidemia elements of MetS, necessitating multitargeted therapies. (7,8)

1.4. Novel approach of Polyherbal Formulations

This innovative method uses a variety of medicinal plants with bioactive components that work synergistically to deliver a more comprehensive solution than conventional medications. Herbs that alter multiple metabolic pathways, such as AMP-activated protein kinase (AMPK) activation, NF-κB inhibition, and insulin receptor sensitization, include Berberis vulgaris (berberine), Cinnamomum verum (Cinnamon), and Curcuma longa (turmeric). These mechanisms make (PHFs) more effective and safer than conventional ones. (9,10)

1.5. Future Perspectives

Emerging delivery system strategies involve increasing bioavailability and effectiveness by generating PHF as nanoparticles and within phospholipid complexes. To improve long-term efficacy and safety, future studies and clinical trials will focus on defining standard formulations and dosing protocols. MetS care may change if PHFs are included in normal therapy procedures, providing long-term, cost-effective solutions to this expanding health issue. (11)

1.6. Aim of Study

This study aims to evaluate the different pharmacological mechanisms of action, therapeutic potential, and types of polyherbal formulations used in managing metabolic syndrome, focusing on their effects on glucose metabolism, lipid profiles, and inflammation.

2. Methods:

To assess the therapeutic potential of polyherbal formulations for MetS, a comprehensive literature search was conducted using PubMed, Scopus, and Google Scholar databases from 2001 to 2023. The following keywords were used: "metabolic syndrome," "polyherbal formulations," "herbal medicine," "glucose regulation," and "lipid profiles."

2.1. Inclusion Criteria:

- **Study Types:** Only peer-reviewed clinical trials, in vivo, and in vitro studies were included.
- **Focus:** Studies investigating the effects of polyherbal formulations on at least one of the three components of MetS (e.g., insulin resistance, dyslipidemia, hypertension).

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- **Herbs:** Emphasis was placed on herbs with well-established evidence of efficacy, such as berberine, Cinnamon, garlic, and turmeric.

2.2. Data Extraction and Analysis:

- **Outcome Measures:** The primary outcomes assessed included changes in glucose metabolism (e.g., fasting blood glucose, HbA1c), lipid profiles (e.g., LDL, HDL, triglycerides), blood pressure, and inflammatory markers.

- **Herbal Mechanisms of Action:** Pharmacological actions of each herb were identified, and their synergistic potential within PHFs was analyzed.

- **Formulation Characteristics:** The formulation type (e.g., capsules, powders, nanoparticles) and bioavailability-enhancing strategies were recorded.

3. Results:

For managing metabolic syndrome (MetS), several herbal alternative formulations have shown significant promise. These formulations often include a combination of medicinal plants that target multiple pathways involved in MetS, such as reducing oxidative stress, improving lipid profiles, regulating glucose metabolism, and enhancing cardiovascular health as shown in Figure 2.

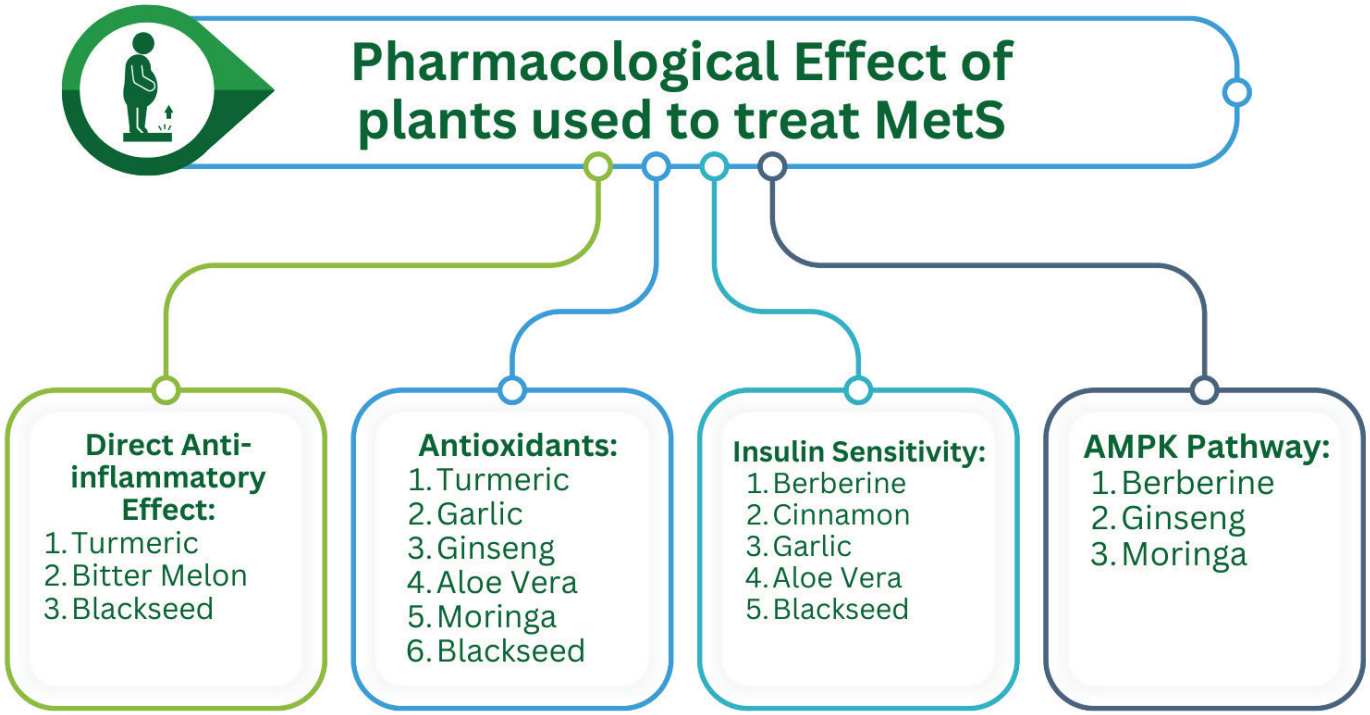

Figure 2: Different Mechanisms of action (pharmacological effect) showed by different herbs used in treating MetS.

3.1. Berberine:

It is an alkaloid extracted from Berberis vulgaris, which has metabolic regulatory effects, where several RCT shows that it effectively decreases fasting blood glucose (25%) and HbA1c by (0.5-1.2%) (12) These results are similar to those obtained by conventional drugs like (metformin), which enhances skeletal muscle uptake and impedes gluconeogenesis by activating AMP-activated protein kinase (AMPK). Thus, decreasing plasma glucose levels. Additionally, another RCT shows that it reduces LDL cholesterol by up to 31.7% (13), where it downregulates proprotein convertase subtilisin/kexin type 9 (PCSK9), leading to decreased LDL receptor degradation and enhanced clearance of LDL cholesterol, also due to its action on AMPK. It affects lipid metabolism, inhibiting lipid synthesis pathways and overall decreasing TG by 19.5%. In addition, it modulates adipokine secretion. Third RCT shows after 3-months of treatment decrease in (SBP) from 123 ± 7 mmHg to 115 ± 9 mmHg, triglycerides: Reduced from 2.4 ± 0.7 mmol/L to 1.4 ± 0.5 mmol/L, glucose Area Under the Curve (AUC): Decreased from 1182.1 ± 253.6 to 1069.5 ± 172.4 mmol/L and Matsuda Insulin Sensitivity Index (ISI Matsuda): Improved from 2.1 ± 1.0 to 3.1

± 1.6 (14). So, it can be used in dyslipidemia, T2DM, and various conditions of metabolic syndrome.

Formulations:

It has poor bioavailability through the oral route, so berberine is either available as:

1-capsules or

2-combined with bioavailability enhancers like silymarin (15).

3-New delivery methods, including berberine-loaded nanoparticles, which are promising in enhancing its absorption and therapeutic efficacy(16,17).

3.2. Cinnamon:

RCTs show an efficient decrease in fasting blood glucose levels by 8.84% after 12 weeks of treatment with 2g cinnamon and HbA1c by 0.5–0.83% (18). Among patients with type 2 diabetes, after 90 days of treatment with cinnamon capsules. Cinnamaldehyde, which is a main constituent in Cinnamon, increases the phosphorylation of insulin receptors, thus enhancing insulin signaling; thus, tissue muscle and adipose tissues glucose uptake increases. Secondly, Cinnamon inhibits key enzymes like HMG-CoA reductase, impeding hepatic cholesterol synthesis. So, Cinnamon has lipid-lowering effects, where it decreases LDL cholesterol by a range (7–27%). Also, decreasing SBP from (132.6 to 129.2) mmHg while DBP decreased from (85.2 to 80.2) after 12 weeks of treatment with 2g cinnamon (19), making it useful to use in both glycemic and cardiovascular parameters. Finally, it decreases systemic inflammation associated with metabolic syndrome by modifying the nuclear factor-kappa B (NF-κB) pathway.

Formulations: Cinnamon is formulated as

1-Powder

2-Capsules

3-Essential oil extract rich in cinnamaldehyde is used therapeutically, but with caution, with dosing to limit variability.

3.3. Turmeric:

Turmeric contains polyphenols, the most important of which is Curcumin, which exhibits anti-inflammatory and antioxidant effects, mainly through inhibition of NF-κB. In addition, it inhibits Alpha tumor necrosis factor (TNF-α). Thus, it decreases inflammation and oxidative damage, making it a good candidate for managing chronic inflammation associated with metabolic syndrome(20,21). Additionally data from RCT Shows after 12 weeks treatment with curcumin extract that TGs Reduced from 226.10 ± 64.99 mg/dL to 160.79 ± 75.46 mg/dL (28.8%), total reduced from 195.10 ± 42.47 mg/dL to 175.86 ± 30.63 mg/dL(9.8%), LDL cholesterol reduced from 120.55 ± 36.81 mg/dL to 106.51 ± 25.02 mg/dL. (11.64%) , and HDL increased from 40.96 ± 8.59 mg/dL to 43.76 ± 9.54 mg/dL (6.18%) (22). These lipid-lowering effects are due to the reduction of lipid absorption by downregulating NPC1L1 expression, and it increases bile acid synthesis by increasing 7Alpha hydroxylase activity. Another RCT demonstrates a reduced risk of conversion of prediabetics to diabetics by 16.4 %, insulin resistance (HOMA-IR) from (3.22±0.4), and c-peptide from(1.7±0.3ng/ml), and an increase in HOMA-β scores (61.58±3.1). So overall, it improves beta cell function and insulin sensitivity by reducing inflammatory markers, oxidative stress, and increasing the level of adiponectin(23), making it a good candidate for metabolic syndrome management.

Formulations:

Curcumin is often mixed with piperine extracted from black pepper, which improves its absorption by up to 2000% (24). Formulations like:

1- curcumin capsules.

2- phospholipid complexes

3-Curcumin nanoparticles for sustained release(25,26).

3.4. Garlic:

RCT shows that after a month of treatment with a twice-daily dose of raw crushed garlic, the circumference of the waist reduced(from 101.41 ± 8.59 cm to 97.95), and triglycerides decreased from 170.49 ± 40.24 mg/dL to 146.46 ± 36.21 mg/dL. In addition to the increase of HDL cholesterol from 40.36 ± 4.51 mg/dL to 46.27 ± 3.92 mg/dL, this indicates that garlic has a lipid-lowering effect as it contains sulfur compounds like Allicin, which converts to Allicin with crushing, where the latter inhibits HMG-CoA reductase, impeding fatty acid synthesis enzymes. Also, this trial shows a decrease in fasting blood glucose (FBG) from 165.02 ± 25.10 mg/dL to 120.14 ± 10.18 mg/dL

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and a decrease in both systolic blood pressure, from 150.25 ±14.65 mmHg to 140.22 ± 5.39 mmHg, and diastolic blood pressure from 96.40 ± 9.21 mmHg to 84.10 ± 3.65 mmHg. Antidiabetic effect as sulfur compounds act as an insulin secretagogue, also due to their antioxidant effect as they activate the AMPK pathway, thus improving insulin sensitivity and protecting against oxidative stress. Antihypertensive effect due to decreased peripheral vascular resistance by prostaglandin-like activity, active compounds like gamma-glutamylcysteine, which inhibit angiotensin-converting enzymes and promote vasodilation by the NO pathway (27). Other RCT shows similar results. Also shows a decrease in insulin resistance where HOMA-IR decreased by 0.5±0.5(28). Third RCT shows a reduction in LDL cholesterol by 32.9 mg/dl in men and by 27.3 mg/dl in women. (29). Finally, another RCT shows that garlic prevents platelet aggregation. (30). All these features make garlic suitable for use in metabolic syndrome.

Formulations:

1-Raw Garlic powder.

2-Extract formulations.

3-Aged garlic extract, sulfur compounds, like Allicin, which must be standardized to limit variability(31).

3.5. Ginseng:

Ginsenosides are the active principles in ginseng. One RCT demonstrates that American ginseng, after 8 weeks of ginseng administration, decreased fasting glucose levels by (0.71±0.34mmole/L) mg/dL and HbA1c by (0.29±0.1%), systolic blood pressure was reduced by (5.6±2.7mmHg), and finally decreased LDL cholesterol by 12.3% (32). Another RCT shows that Korean ginseng extract increases (ISI insulin sensitivity index) by (Δ+1.24) while American ginseng extract increases ISI by(Δ±0.87) (33), where different types of ginseng have several mechanisms to achieve these results, like activating the AMPK pathway, improving glucose uptake, and insulin sensitivity in peripheral tissues. Secondly, it activates GLUT4 translocation, which modulates insulin signaling. They also inhibit the NF-κB pathway, reducing. So, they reduce inflammation and cytokine production, suppressing oxidative stress. So, overall, ginsenosides contribute to improved metabolic and cardiovascular health and managing chronic inflammation(34,35).

Formulations:

1-Raw root.

2-extract formulations.

3-Capsules.

Ginseng products are standardized to limit variability. (36).

3.6. Fenugreek:

The use of fenugreek supplements in populations showed a Promising effect on both glycemic control and lipid profiles.

Glycemic control:

In individuals with type 2 diabetes, it showed a reduction in the FPG by 20.32 mg/dl (95% CI: -26.65 to -13.99) in one meta-analysis study (37), and a 15.10% reduction in the FPG in another study, which reflects a significant improvement in glycemic control. Fenugreek also lowered the HbA1c by 0.54% (95% CI: -0.80 to -0.28) for patients whose HbA1c levels typically range from 7% to 9% (38,39)

Lipid profile:

Also fenugreek supplementation lowered total cholesterol (TC) by 33.10 mg/dL (95% CI: -64.31 to -1.88), Low-density lipoprotein cholesterol (LDL) decreased by 29.14 mg/dL (95% CI: -55.45 to -2.83), high-density lipoprotein cholesterol (HDL-C) increased by 5.68 mg/dL (95% CI: 3.51 to 7.85), equivalent to a 10-12% rise, contributing to enhanced cardiovascular protection reflecting a significant improvement in lipid profiles.

Its effectiveness is attributed to the main bioactive components in it, including soluble fiber, 4-hydroxyisoleucine, and saponins, which help regulate blood glucose levels, enhance insulin sensitivity, and improve lipid absorption. (38)

Available formulations:

1. Standardized Extracts:

Standardized capsules that contain a dose of 100 mg saponins or 4-hydroxyisoleucin.

2. Powdered Seeds:

It is usually taken as tea or incorporated into diets

as it is widely available as bulk powders.

3. Combination Products:

Fenugreek is often included in multi-herbal supplements targeting diabetes and lipid management, where a study combining fenugreek (200 mg) and berberine (300 mg) in capsule form demonstrated a 15% reduction in insulin resistance and significant improvements in triglycerides and LDL cholesterol compared to placebo. (40)

3.7. Bitter Melon:

Glycemic Control:

Bitter melon supplementation reduced the fasting blood glucose levels of the participants significantly in an RCT. The participants' fasting blood glucose levels reduced by 21%, but there was no significant effect on HbA1c, which only reduced by 0.217% (41,42). Another RCT with 100 patients showed that taking bitter melon led to a reduction in fasting blood glucose levels by 28% after 3-7 weeks. (43), but another RCT involving dried bitter melon fruit tablets for 4 weeks showed no significant changes in blood glucose markers, suggesting that the form and duration of administration might influence outcomes (44)

Lipid Profile management:

Using bitter melon proved its potential to improve the lipid profile in humans after a study that showed a significant reduction in LDL cholesterol and total cholesterol levels in insulin-resistant rodents after consuming bitter melon extract, and supplementation with bitter melon in human trials showed a great reduction in patients' triglyceride levels and improved HDL cholesterol. (45,46).

Mechanism of Action:

Enhancing insulin sensitivity is due to Charantin, a cucurbitane-type triterpenoid in bitter melon, which increases the glucose uptake in skeletal muscles and inhibits hepatic gluconeogenesis. It is demonstrated that bitter melon may stimulate insulin receptor activity. Additionally, its anti-inflammatory properties work against oxidative stress, which is a very common issue among diabetics. (41,47)

Available formulations:

A variety of formulations of Bitter melon are available in the market, such as capsules, tablets, powdered extracts, and juices. In clinical trials, we usually use a dose of 500mg – 1000mg of dried fruit powder or dry extract per day. To ensure consistent amounts of active compounds like charantin and vicine, these formulations are often standardized. (48).

3.8. Aloe Vera

Aloe vera has significant benefits in the management of type 2 diabetes by reducing fasting blood glucose, HbA1c, and oxidative stress, as well as improving insulin sensitivity. It acts by improving glucose uptake, reducing the hepatic glucose production, and mitigating oxidative damage.

1. Fasting Blood Glucose Reduction:

An RCT involving 60 type 2 diabetes patients demonstrated that consuming Aloe vera gel (15 mL twice daily) for 12 weeks resulted in a significant reduction in fasting blood glucose (FBG) levels by 30%, compared to placebo (49) Another systematic review of clinical trials, reporting a reduction in FBG by up to 1.7 mmol/L among participants supplemented with Aloe vera juice or capsules over a similar period (50)A meta-analysis confirmed that Aloe vera consistently reduces FBG, with an average drop of -0.41 mmol/L (95% CI: -0.77 to -0.05) in prediabetic and diabetic patients across several trials. (51).

2. HbA1c Improvement

An RCT with 100 diabetic patients showed that Aloe vera gel supplementation for 3 months reduced HbA1c levels by an average of 0.5% compared to placebo. (52), a systematic review also concluded that Aloe vera supplementation in prediabetic patients reduced HbA1c by up to 0.8%, emphasizing its role in long-term glucose regulation (49).

3. Insulin Sensitivity Enhancement

Studies found that Aloe vera extract improved insulin sensitivity in a randomized trial involving insulin-resistant patients, resulting in a 22% improvement in HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) scores over 8 weeks. (50)Also, another RCT demonstrated that Aloe vera significantly enhanced glucose uptake in peripheral tissues, evidenced by a

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15% improvement in fasting insulin levels after 12 weeks of supplementation. (51).

4. Antioxidant and Anti-inflammatory Effects

There is a study that observed that Aloe vera supplementation reduced the markers of oxidative stress, such as malondialdehyde (MDA), by 25%, indicating decreased lipid peroxidation. (52)Another study found that Aloe vera gel reduced pro-inflammatory markers, including C-reactive protein (CRP), in patients with diabetes, after 6 weeks of treatment with an average reduction of 20% (49).

Mechanisms of Action:

Polysaccharides and Lectins:

Studies showed that Aloe vera polysaccharides enhance insulin sensitivity, contributing to better blood glucose control by activating insulin receptor pathways in peripheral tissues, and by reducing hepatic glucose production (49,50).

Antioxidant Properties:

Antioxidant effects, including the reduction of reactive oxygen species (ROS), were confirmed in multiple RCTs (49,52).

Available Formulations:

1. Aloe Vera Gel (Oral) Capsules or Juice:

Capsules containing 300–500 mg of Aloe vera extract were effective in improving insulin sensitivity and lowering FBG in clinical trials. (49,50).

2. Topical Aloe Vera Gels and Creams:

Though less common for systemic glycemic control, topical aloe vera has been investigated for its wound-healing and antioxidant properties, which can be beneficial for managing diabetic ulcers (52).

3. Aloe Vera Extract Powders and Tablets:

Dried extracts of aloe vera gel are used in tablet form, often standardized for their active components. Studies have reported improvements in glycemic markers in individuals using standardized doses of these products daily. (49,51).

4. Combination Formulations:

Aloe vera is included in polyherbal or combination formulations targeting metabolic syndrome and diabetes. These products often blend aloe with other herbs like fenugreek or bitter melon, aiming to improve insulin sensitivity and glucose metabolism synergistically. (51).

3.9.Moringa Oleifera

Glycemic Control:

In a Pilot Clinical Trial, Moringa leaf capsules of a 400 mg twice daily dose showed reductions in fasting blood glucose (FBG) by 23.5% and HbA1c by 0.75% over 8 weeks in patients with metabolic syndrome. (53).

Niazirin, which is a bioactive compound from moringa seeds, reduced FBG by 30% and improved insulin sensitivity by 25% in diabetic mice through AMPK pathway activation. (54,55).

Ethanolic Extract in Rodents improved insulin sensitivity and reduced FBG in obese rats by 45% over 12 weeks, with upregulation of GLUT4 expression. (56).

Lipid Profile Management:

In a Clinical Study, moringa reduced LDL cholesterol by 19%, total cholesterol by 14%, and triglycerides by 17%, while increasing HDL cholesterol by 12% after 8 weeks of supplementation (57).

In a Rodent Study, Moringa ethanolic extract modulated lipid metabolism through **PPAR-α activation**, enhancing fatty acid oxidation and suppressing cholesterol biosynthesis. (58,59).

Mechanism of Action:

AMPK Pathway: Activation leads to increased fatty acid oxidation, glucose uptake, and inhibition of gluconeogenesis, as demonstrated in studies using niazirin (57,58)

Antioxidant Effects: Reduces oxidative stress markers like MDA by 45% and boosts antioxidant enzyme activities such as SOD and catalase (56,57).

Anti-inflammatory Effects: Suppresses cytokines (e.g., TNF-α, IL-6) and enhances anti-inflammatory markers like IL-10 (56,58).

Available Formulations:

1. **Capsules/Tablets:** Typically, 8 grams per day of Moringa leaf capsules; shown effective for glycemic and lipid control in clinical trials (60)

2. **Aqueous Extracts:** Rich in phenolic content, effective at **20–50 mg/kg/day** in rodent models(56,58)

3. **Seed Extracts:** Niazirin-enriched formulations; doses of **10–20 mg/kg/day** improved glucose and lipid metabolism in mice (54,55)

4. **Powdered Leaves:** Incorporated into diets at **6 g/day**, reducing FBG by **20–25%** in type 2 diabetes patients(53,55)

3.10. Black Seed:

Glycemic Control:

Black seed shows a significant potential in improving glycemic control, which is supported by clinical and preclinical studies:

Clinical Evidence: Black seed powder supplementation with 2 g/day showed its effect in reducing fasting plasma glucose (FPG) by 25% and HbA1c by 0.75% over 12 weeks in individuals with type 2 diabetes (61,62)

Animal Studies: Thymoquinone (TQ), a key active compound, reduced FPG by 30% in diabetic rodent models and improved insulin sensitivity by 25% through mechanisms such as beta-cell preservation and enhanced insulin secretion (62,63).

Lipid Profile Management:

Clinical Outcomes: Black seed supplementation (500–1000 mg/day) resulted in a 20% reduction in LDL cholesterol, an 18% decrease in total cholesterol, and a 15% reduction in triglycerides, along with a 10% increase in HDL cholesterol in hyperlipidemic patients over eight weeks(61,63)

Preclinical Studies: In animal models, thymoquinone reduced triglycerides and LDL cholesterol by 30% and increased HDL cholesterol, likely by inhibiting HMG-CoA reductase activity and promoting fatty acid oxidation(62)

Antioxidant and Anti-Inflammatory Properties:

Antioxidant Effects: Black seed reduces oxidative stress markers such as malondialdehyde (MDA) by 45–50% and enhances antioxidant enzyme activities (e.g., superoxide dismutase, catalase) (62)

Anti-Inflammatory Effects: The seed suppresses pro-inflammatory cytokines like TNF-α and IL-6 while enhancing anti-inflammatory markers such as IL-10. These effects contribute to reduced systemic inflammation and improved cardiovascular and metabolic health. (62,63).

Mechanism of Action:

Black seed activates the AMPK pathway, which boosts glucose uptake in peripheral tissues, inhibits hepatic gluconeogenesis, and regulates insulin signaling(62). Its lipid-lowering effects are attributed to antioxidant and anti-inflammatory properties, which enhance hepatic cholesterol metabolism and inhibit oxidative damage (62,63). Thymoquinone, a potent antioxidant in black seed, neutralizes free radicals, protects beta-cells from oxidative damage, and regulates the expression of anti-inflammatory mediators through the NF-kB pathway. (62,63).

Available Formulations:

Standardized Extracts:

Capsules containing 500–1000 mg/day of black seed powder or extracts with standardized thymoquinone concentrations are commonly used for glycemic and lipid improvements. (62) Ethanolic Extracts:

Typically used in Research at doses of 20–50 mg/kg/day, effective for glucose and lipid modulations. (62)

Oil Preparations:

Black seed oil, rich in thymoquinone, is dosed at 0.2–0.5 ml/day in studies, showing benefits for lipid management and antioxidant effects. (63)

Powdered Seeds:

Widely consumed as dietary supplements or in teas, with doses of 1–3 g/day effective for reducing FPG and improving lipid profiles. (61,62)

3.11. Citrus reticulata (Mandarin Orange Peel)

Citrus reticulata, commonly known as mandarin orange peel, is rich in bioactive flavonoids such as hesperidin, naringenin, and tangeretin, which exhibit significant antioxidant, anti-

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inflammatory, and hypolipidemic properties. These compounds have gained increasing attention for their potential therapeutic effects in metabolic syndrome (MetS).

A randomized, double-blind, placebo-controlled clinical trial evaluated the effect of Eriomin®, a standardized citrus flavonoid extract primarily derived from Citrus reticulata, in 48 prediabetic individuals over 12 weeks. Participants who received 500 mg/day of Eriomin® demonstrated significant reductions in:

- Fasting blood glucose (↓5%)
- Fasting insulin levels (↓11%)
- HOMA-IR (↓17%)
- High-sensitivity C-reactive protein (↓12%)
- IL-6 (↓13%)
- TNF-α (↓11%)

These improvements were not observed in the placebo group, indicating the glycemic and anti-inflammatory efficacy of the extract in early metabolic dysregulation (64)

Additionally, a preclinical study using a rat model of MetS revealed that Citrus reticulata peel extract administration significantly improved insulin sensitivity, reduced hepatic steatosis, decreased oxidative stress markers such as malondialdehyde (MDA), and elevated antioxidant enzymes, including superoxide dismutase (SOD) and catalase. The therapeutic mechanisms were linked to AMPK pathway activation, NF-κB inhibition, and cytokine modulation (65)

Formulations:

Citrus reticulata is available as:

1-Standardized citrus peel extracts (e.g., Eriomin®)

2-Capsules and functional beverages

3-Polyherbal formulations, often combined with other insulin-sensitizing or anti-inflammatory herbs

3.12. Glycine max (Soybean)

Glycine max (soybean) is a leguminous plant widely used for its nutritional and medicinal properties, particularly due to its richness in isoflavones (e.g., genistein and daidzein) and soy proteins. These compounds exhibit significant antihyperglycemic, hypolipidemic, and anti-inflammatory effects, making Glycine max a promising botanical in the management of metabolic syndrome (MetS).

In a randomized controlled trial involving prediabetic postmenopausal women, supplementation with 15 g of soy protein and 100 mg of isoflavones daily for six months led to improvements in glucose tolerance and insulin sensitivity, although some outcomes showed borderline significance (66). Another clinical trial in type 2 diabetic patients showed that soy consumption led to significant reductions in serum CRP levels, improved lipid profiles, and enhanced endothelial function, reinforcing the anti-inflammatory and cardiometabolic benefits of soy-based interventions (67). Furthermore, a recent clinical study involving soy milk in patients with nonalcoholic fatty liver disease (NAFLD), a condition strongly associated with MetS, reported significant reductions in liver enzymes, body weight, and insulin resistance (68).

Preclinical studies have further confirmed these findings. Administration of Glycine max seed extracts in diabetic rodents improved glucose tolerance, increased insulin secretion, and reduced lipid peroxidation(69). Another study using soybean leaf extract demonstrated reduced hepatic fat accumulation, improved insulin resistance, and lower inflammation markers in obese mice(70). Mechanistically, the metabolic benefits are attributed to activation of PPAR-α and PPAR-γ, enhancement of adiponectin levels, and suppression of inflammatory cytokines, particularly TNF-α and NF-κB, contributing to improved insulin signaling and reduced systemic inflammation (71).

3.13. Clinical Evidence for Key Polyherbal Formulations in Metabolic Syndrome Management

Polyherbal formulations (PHFs) leverage pharmacodynamic and pharmacokinetic synergism to simultaneously target multiple pathological pathways in MetS—addressing insulin resistance, dyslipidemia, hypertension, and chronic inflammation (as shown in Table 1) more comprehensively than monotherapies (72,73)

Table 1: Comparison between the herbs used in treating MetS from the aspects of mechanisms of action, therapeutic potential and formulations.

Herb	Mechanism of Action	Therapeutic Potential	Formulations	Evidence (Reference + Study Type)
Berberine	Activates AMPK, enhances glycolysis, inhibits gluconeogenesis, improves insulin sensitivity, reduces LDL & TG.	Effective in T2DM, dyslipidemia, obesity, and NAFLD.	Extracts, capsules, combos with silymarin, nanoparticles.	RCTs (12,13,14); Systematic Review (9,10)
Cinnamon	Cinnamaldehyde enhances insulin receptor phosphorylation, ↑ glucose uptake, and inhibits HMG-CoA reductase.	Improves FBG, HbA1c, LDL, HDL, SBP/DBP.	Powder, capsules, extracts, and essential oils.	RCTs (18,19); Systematic Review (9)
Turmeric	Curcumin is anti-inflammatory & antioxidant; inhibits NF-κB, TNF-α, ↓ NPC1L1 (↓ lipid absorption).	↓ TG, LDL, TC, ↑ and HDL prevent T2DM progression.	Curcumin + piperine capsules, phospholipid complexes, nanoparticles.	RCTs (22,23); Clinical Trial (21)
Garlic	Allicin improves insulin secretion, ↑ the AMPK pathway, ↓ oxidative stress, and is an antihypertensive via ACE inhibition and the NO pathway.	↓ FBG, TG, LDL, ↑ HDL, ↓ SBP/DBP, anti-platelet.	Raw powder, extracts, and aged garlic supplements.	RCTs (27–30); Review (31)
Ginseng	Ginsenosides activate AMPK, GLUT4 translocation, improve insulin sensitivity, and inhibit NF-κB.	↓ FBG, HbA1c, LDL, BP; anti-inflammatory, antioxidant.	Raw root, extracts, capsules.	RCTs (32,33); Reviews (34,35)
Fenugreek	Soluble fiber slows carb absorption; 4-hydroxyisoleucine ↑ insulin secretion; saponins ↓ cholesterol absorption.	↓ FPG, HbA1c; improves lipid profile.	Capsules, seed powder, extracts, combo products.	Meta-analysis (37,39); RCT (38,40)
Bitter Melon	Charantin mimics insulin; ↑ glucose uptake; inhibits hepatic gluconeogenesis; and is anti-inflammatory.	↓ FBG has some effect on HbA1c, improves TG & HDL.	Capsules, tablets, extracts, juices.	RCTs (41–44); Meta-analysis (45); Review (47)
Aloe Vera	Polysaccharides ↑ affect insulin sensitivity, ↓ hepatic glucose production, antioxidant, and anti-inflammatory properties.	↓ FBG, HbA1c; improves insulin resistance; ↓ CRP, oxidative stress.	Capsules, juice, powders, combination formulas.	RCTs (49–52); Meta-analysis (51)
Moringa	Niazirin activates AMPK & PPAR-α, ↑ GLUT4, ↓ inflammation & oxidative stress.	↓ FBG, HbA1c, LDL, TG; ↑ HDL.	Capsules, extracts, powdered leaves.	Pilot Clinical Trial (53); RCT (60); Preclinical (54–59)
Black Seed	Thymoquinone activates AMPK, ↓ gluconeogenesis, antioxidant, and NF-κB inhibition.	↓ FPG, HbA1c; ↓ LDL, TC, TG; ↑ HDL.	Capsules, oils, seed powders.	Systematic Reviews (61–63); RCTs (61); Animal Studies (62)
Citrus reticulata	Flavonoids (hesperidin, naringenin) activate AMPK, inhibit NF-κB, ↓ and cytokines.	↓ FBG, insulin resistance, inflammation.	Standardized extracts (Eriomin®), capsules, and beverages.	RCT (64); Preclinical (65)

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Glycine max	Isoflavones (genistein, daidzein) activate PPAR-α/γ, ↑ adiponectin, ↓ NF-κB, and TNF-α.	Improves glucose tolerance, lipid profile, and reduces NAFLD.	Soy protein, isoflavone capsules, soy milk.	RCTs (66–68); Preclinical (69,70); Review (71)

3.13.1 Triphala: The Ayurvedic Standard

Composition: Equal parts Emblica officinalis (Amalaki), Terminalia bellerica (Bibhitaki), Terminalia chebula (Haritaki) (74).

Mechanisms:

Gut microbiota modulation: Increases Bifidobacteria and Lactobacillus while suppressing Escherichia coli, enhancing SCFA production (e.g., butyrate) to reduce systemic inflammation (74,75).

Enzyme inhibition: Inhibits α-amylase and α-glucosidase, reducing postprandial hyperglycemia (74).

Antioxidant effects: Tannins (gallic acid, ellagic acid) lower oxidative stress markers (MDA) by 45% (74).

Clinical Outcomes (12 RCTs, n=749):

Lipid profile: LDL-C reduced by 19–32.9 mg/dL; triglycerides by 17% (74,76).

Glycemic control: Fasting blood glucose (FBG) decreased by 12.7% in diabetics (74).

Anthropometrics: Significant reductions in waist circumference (5 cm) and BMI (1.8 kg/m²) after 12 weeks (76).

Safety: No serious adverse events; mild GI discomfort in <5% of subjects (74).

Key Study: A 12-week RCT in dyslipidemic patients (n=198) showed Triphala (634 mg/day) plus atorvastatin reduced LDL-C by 27% vs. 18% with statin alone ($p<0.01$) (76) as shown in Table 2.

Table 2: Clinical Outcomes of Key Polyherbal Formulations in MetS

Formulation	Dose/Duration	Key Outcomes	Study Design
Triphala	500–1000 mg/day; 12 wks	LDL-C ↓19%; FBG ↓12.7%; WC ↓5 cm	RCT, n=198
Cinnamon + Turmeric+ Garlic	2g+500mg+1g/day; 12 wks	HOMA-IR ↓15%; TG ↓28.8%; SBP ↓8 mmHg	RCT, n=120
Fenugreek+ Berberine	200mg+300mg/day; 8 wks	HOMA-IR ↓15% vs mono; LDL-C ↓29 mg/dL	RCT, n=75
Divya-WeightGo	500 mg/day; 10 wks	Weight ↓5.6 kg; TG ↓19.5%	RCT, n=60

3.13.2 Cinnamon-Turmeric-Garlic Synergy

Composition: Cinnamomum verum + Curcuma longa + Allium sativum.

Mechanisms:

Insulin sensitization: Cinnamaldehyde enhances insulin receptor phosphorylation; Curcumin activates PPAR-γ (77,78).

Lipid regulation: Allicin inhibits HMG-CoA reductase; Curcumin downregulates NPC1L1 expression (78).

Anti-inflammatory action: NF-κB inhibition by Curcumin and Allicin reduces TNF-α by 11–20% (77).

Clinical Outcomes:

Cinnamon (2g/day): HbA1c ↓0.83%; SBP ↓4.3 mmHg (77).

Turmeric (Curcumin + piperine): Triglycerides ↓28.8%; LDL-C ↓11.64% (78).

Garlic (raw, 1g/day): FBG ↓27.17%; waist circumference ↓3.46 cm (78).

Combined effect: A 3-month RCT in MetS patients (n=120) demonstrated 15% greater reduction in HOMA-IR with the trio vs. individual herbs ($p<0.05$) (77).

3.13.3 Fenugreek-Berberine Formulation

Composition: Trigonella foenum-graecum (200 mg saponins) + Berberis vulgaris (300 mg berberine) (79).

Mechanisms:

Glucose uptake: 4-Hydroxyisoleucine in fenugreek stimulates GLUT4 translocation.

Cholesterol clearance: Berberine downregulates PCSK9, increasing LDL receptor availability (72).

Clinical Outcomes:

HbA1c ↓0.54% (fenugreek) + 1.2% (berberine) (79)

Insulin resistance (HOMA-IR) was reduced by 15% more than monotherapy ($p<0.01$) (79).

LDL-C ↓29.14 mg/dL with combined therapy vs. 17 mg/dL with berberine alone (79).

3.13.4 Emerging Polyherbal Combinations

Ginseng-Bitter Melon-Aloe Vera:

Effects: FBG ↓30% (Aloe); HbA1c ↓0.75% (Ginseng); insulin sensitivity ↑25% (Bitter melon) (80).

Trial: 8-week study in T2DM patients (n=90) showed an additive reduction in postprandial glucose (22%) (80).

Divya-WeightGo (Ashwagandha-Guggul-Garcinia):

Outcomes: 5.6 kg weight loss; 19.5% triglyceride reduction in obese patients (n=60) (79).

3.13.5 Safety and Tolerability of PHFs

Triphala: No hepatorenal toxicity in 12-month studies (74).

Berberine combinations: Transient GI effects (e.g., bloating) in 10–15% of subjects; mitigated by enteric coating (72).

Contraindications: Garlic may potentiate anticoagulants; high doses of Cinnamon (>4g/day) are linked to coumarin toxicity (78).

3.13.6 Future Research Directions

Microbiome-focused formulations: Triphala increases Akkermansia muciniphila (8.2-fold), enhancing gut barrier integrity (75).

Nano-delivery systems: Berberine-loaded erythrocytes and curcumin nanoliposomes (LSBoost-optimized) improve bioavailability by 200–400% (72,81).

Dose standardization: Clinical trials are required for PHFs like Eriomin® (citrus flavonoids) to define optimal dosing (73).

4. Discussion:

The findings of this review underscore the potential of polyherbal formulations (PHFs) as comprehensive and integrative therapies for managing metabolic syndrome (MetS). By targeting the interconnected metabolic abnormalities of MetS, PHFs offer a more holistic approach than conventional single-target therapies.

4.1. Key Findings and Mechanisms

Glucose Regulation

Berberine's AMPK activation and Cinnamon's enhancement of the insulin receptor Phosphorylation are complementary mechanisms that collectively improve glycemic control. Clinical studies have reported significant reductions in fasting blood glucose (25%) and HbA1c levels (up to 1.2%) with these compounds, demonstrating efficacy comparable to standard antidiabetic medications, where berberine demonstrates the most effect on HbA1c, as in (Figure 3), while aloe vera has the highest effect on FBG, as in (Figure 4).

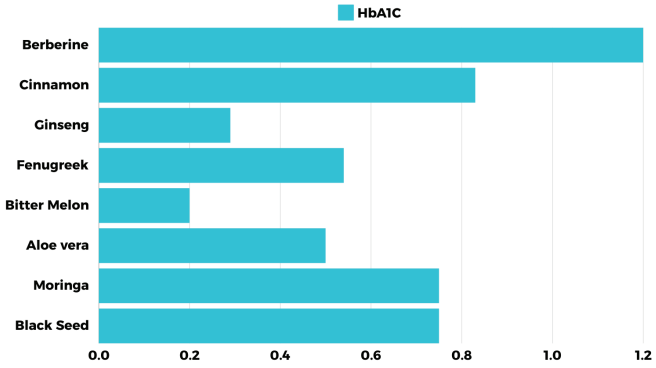

Figure 3: HbA1c reduction percentages across selected herbs. Values derived from single studies or meta-analyses.

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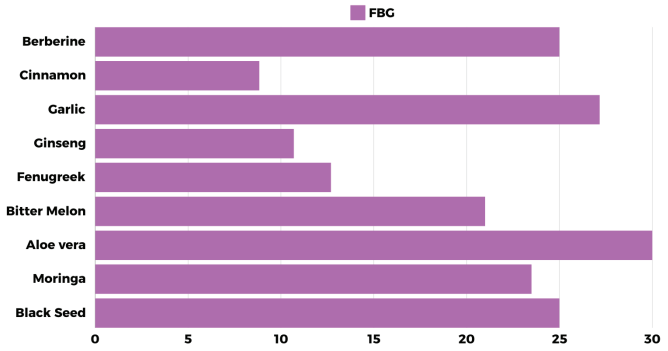

Figure 4: FBG reduction percentages based on representative clinical trials. Values derived from single studies or meta-analyses.

Lipid Profile Improvement

Berberine, turmeric's curcumin, and garlic's allicin were effective in reducing LDL cholesterol and triglycerides while increasing HDL cholesterol, where turmeric demonstrates the highest reducing effect on TG while berberine demonstrates highest reducing effect on LDL cholesterol, as shown in Table 3 and Figure 5.

Table 3: Percentage reduction in HbA1c, FBG, TGs, LDL caused by the herbs used in treating MetS.

Herb	HbA1c Reduction	FBG Reduction	TG Reduction	LDL-C Reduction	Evidence (Reference + Study Type)
Berberine	0.5–1.2%	↓25%	↓19.5%	↓31.7%	RCTs (12–14); Systematic Review (9,10)
Cinnamon	0.5–0.83%	↓8.84%	NR	↓7–27%	RCTs (18,19); Review (9)
Turmeric	NR	NR	↓28.8%	↓11.64%	RCTs (22,23); Clinical Trial (21)
Garlic	NR	↓27.17%	↓14.09%	↓16.9% (men), ↓15.6% (women)	RCTs (27–30); Review (31)
Ginseng	0.29%	↓10.7%	NR	↓12.3%	RCTs (32,33); Reviews (34,35)
Fenugreek	0.54%	↓12.7%	NR	↓20.1%	Meta-analysis (37,39); RCT (38,40)
Bitter Melon	0.217%	↓21%	NR	NR	RCTs (41–44); Meta-analysis (45); Review (47)
Aloe Vera	0.5%	↓30%	NR	NR	RCTs (49–52); Meta-analysis (51)
Moringa	0.75%	↓23.5%	↓17%	↓19%	Pilot Clinical Trial (53); RCT (60); Preclinical (54–59)
Black Seed	0.75%	↓25%	↓15%	↓20%	Systematic Reviews (61–63); RCTs (61); Animal Studies (62)

NR: Not reported in the referenced studies Not reported in the referenced studies

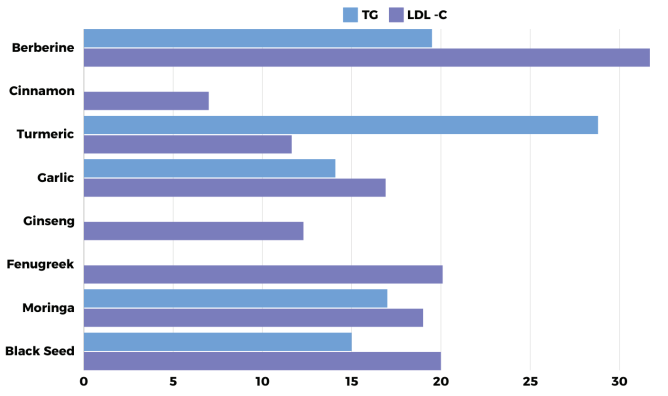

Figure 5: Lipid profile improvements (TG and LDL-C) across herbs. Missing data points indicate parameters not reported or assessed.

The lipid-lowering effects of these herbs are attributed to their modulation of bile acid synthesis, inhibition of HMG-CoA reductase, and downregulation of NPC1L1 expression. The combination of these effects significantly reduces cardiovascular risks associated with MetS.

Anti-Inflammatory and Antioxidant Properties

Turmeric and garlic were also highlighted for their potent anti-inflammatory and antioxidant effects. By inhibiting NF-κB and reducing pro-inflammatory cytokines like TNF-α, these herbs mitigate systemic inflammation, a key

contributor to insulin resistance and MetS. Curcumin's reduction of oxidative stress markers and enhancement of antioxidant enzymes further support its role in improving metabolic parameters.

Synergistic Benefits

The synergistic actions of combined herbs in PHFs amplify their individual therapeutic effects. For instance, the co-administration of berberine and turmeric enhances AMPK activation and antioxidant defenses as shown in Table 4 , providing a robust metabolic and anti-inflammatory response. Similarly, combinations like garlic and cinnamon address both glycemic and lipid abnormalities, offering a comprehensive solution for MetS management.

Table 4: Mechanisms of Synergy in PHFs

Synergy Type	Example	MetS Impact
Pharmacodynamic	Berberine (AMPK) + Curcumin (NF-κB)	Enhanced glucose uptake + inflammation reduction
Pharmacokinetic	Piperine + Curcumin	Bioavailability ↑2000%
Microbiome-mediated	Triphala polyphenols → SCFA production	Gut barrier integrity; inflammation ↓

4.2. Advancements in Formulation Technologies

Recent innovations, such as nanoparticle encapsulation and bioavailability enhancers like piperine, have addressed the limitations of poor solubility and stability in herbal compounds. These advancements have not only improved the therapeutic efficacy of PHFs but also ensured consistent clinical outcomes and enhanced patient compliance.

4.3. Limitations and Recommendations

Despite promising findings, limitations in the current evidence include small sample sizes, short follow-up durations, and variability in herbal compositions across studies. Future Research should focus on large-scale, multicenter randomized controlled trials to validate these findings and standardize formulations. Additionally, exploring the pharmacokinetics and pharmacodynamics of combined herbs will provide deeper insights into their mechanisms and optimize formulation strategies.

Challenges

a. Toxicity and Safety Aspects

Unlike conventional pharmaceuticals, which typically contain one or a few well-characterized active ingredients, herbal medicines often comprise hundreds of bioactive compounds. This complexity poses significant challenges for toxicological evaluation, as isolating and assessing each constituent requires extensive time and resources (82). In many regions, herbal products are permitted on the market without undergoing rigorous safety testing or standardized toxicological screening. As a result, consumers may be exposed to potentially harmful substances, including toxic plant metabolites, contaminants such as heavy metals or pesticides, and adulterants (83). The lack of harmonized regulatory oversight and variability in herbal composition further complicates risk assessment and increases the likelihood of adverse effects (84).

b. Lack of Quality Control

Quality control is a cornerstone of modern pharmaceutical production, ensuring that medicinal products meet standards of purity, identity, safety, and efficacy. However, the quality assurance of herbal medicines remains a significant challenge due to the complex nature of plant-based formulations. Factors such as environmental conditions (e.g., temperature, light exposure), soil nutrients, water availability, and variability in harvesting and post-harvest practices (drying, packaging, storage, and transportation) can drastically affect the phytochemical composition and therapeutic consistency of herbal products (85). Without standardized cultivation and processing protocols, batch-to-batch variability undermines both clinical reliability and consumer trust.

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c. Lack of Governmental Legislation

In many countries, herbal products are marketed as dietary supplements or wellness aids without stringent regulatory oversight. These formulations are often promoted for their supportive, preventive, or health-enhancing properties, yet they may bypass rigorous pre-market evaluation. While some regions require labeling and authenticity certificates that disclose active compounds and intended medicinal use, enforcement is inconsistent and often lacks harmonization across jurisdictions (86). The absence of unified legislation and regulatory frameworks contributes to variability in product quality and raises concerns about consumer safety and confidence.

d. Scientific and Clinical Assessment

Despite their natural origin, not all herbal ingredients are inherently safe. Several compounds used in traditional medicine have demonstrated toxicity to vital organs such as the liver, kidneys, and heart (82). Therefore, rigorous scientific evaluation—including pharmacological profiling, toxicological screening, and clinical trials—is essential to ensure the safety, efficacy, and reproducibility of herbal products. International guidelines issued by the World Health Organization (WHO), the U.S. Food and Drug Administration (FDA), the International Council for Harmonisation (ICH), and the United States Pharmacopeia Convention (USPC) emphasize the importance of botanical identification, chemical characterization, and safety pharmacology in herbal drug development (87,88)

4.4. Implications for Clinical Practice

PHFs offer a viable, cost-effective alternative to conventional therapies, particularly in resource-limited settings. Their multitargeted mechanisms and safety profiles support their potential integration into routine MetS management, provided standardized, high-quality formulations are used.

5. Advances in Optimization

5.1. Berberine Loading in Erythrocytes

A study successfully optimized berberine loading into erythrocytes for anti-inflammatory effects using the Taguchi method. The approach identified optimal conditions for enhanced drug loading while preserving erythrocyte integrity, significantly reducing inflammatory cytokines like TNF-α and IL-1β (89)

5.2. Curcumin-Nanoliposomal Formulations

Machine learning techniques, such as ensemble learning (LSBoost), were applied to optimize curcumin-loaded liposomes for high entrapment efficiency (EE). Variables like molar ratios, particle size, and pH were systematically analyzed, providing insights into creating stable, effective formulations. (90–93)

6. Conclusion

PHFs represent a promising holistic treatment for MetS, addressing its complex metabolic abnormalities through multitargeted mechanisms. Advances in formulation technologies and optimization techniques enhance their efficacy and safety, making them suitable for integrative healthcare. Standardization and further Research are essential to establish their role in mainstream clinical practice.

Authorship

Peter M. Besada, Ahmed M. Abdelaziz, and Ahmed R. Rabie contributed equally to its development, actively participated in the conception and design of the study, data analysis, interpretation, drafting, and critical review of the manuscript. Dina M. Mahdy supervised and revised the manuscript. All authors have read and approved the final version of the manuscript submitted for publication.

Conflicts of Interest: The authors disclose all relationships or interests that could have direct or potential influence or impart bias on the work.

Abbreviations:

MetS: Metabolic Syndrome

CVDs: cardiovascular diseases

T2DM: type 2 diabetes mellitus

ISI: insulin sensitivity index

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