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The Role of Traditional Herbal Formulations in Managing Metabolic Syndrome: Evidence from Obesity and Diabetes Models

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ABSTRACT

Metabolic syndrome characterized by obesity, insulin resistance, dyslipidemia, and hypertension poses a growing global health burden. While synthetic drugs address individual components, their side effects and often limited holistic efficacy have revived interest in traditional herbal formulations. This review explores evidence from in vitro, animal, and human studies on single and polyherbal preparations used to manage metabolic syndrome, particularly obesity and type 2 diabetes. Key formulations such as F2 (a blend including *Orostachys japonica*, *Rhus verniciflua*, *Geranium thunbergii*, royal jelly, and lemon juice) demonstrate multi-targeted actions: inhibiting adipogenesis, reducing oxidative stress, and improving lipid and glucose metabolism in diet-induced obese (DIO) mice). Polyherbal combinations containing *Curcuma longa*, *Gymnema sylvestre*, and *Emblica officinalis* modulate body weight, blood pressure, glucose, triglycerides, and HDL in animal models). Clinical trials and meta-analyses reveal that green tea, *Phaseolus vulgaris*, *Garcinia cambogia*, and *Nigella sativa* significantly reduce weight, waist circumference, and triglycerides). Aloe vera and basil extracts show promise in improving insulin resistance and lipid profiles). Mechanistically, these herbs act via appetite suppression, thermogenesis, inhibition of lipase activity, improvement of insulin sensitivity, and antioxidative/inflammatory modulation). While evidence is compelling, limitations such as small trials, lack of standardization, and potential herb-drug interactions must be addressed. Future directions include well-designed RCTs, standardized formulations, and exploration through omics approaches to enable integration of herbal therapies into mainstream metabolic syndrome management.

Keywords: metabolic syndrome, polyherbal formulations, obesity, type 2 diabetes, traditional herbal medicine

INTRODUCTION

Metabolic syndrome (MetS) is a complex health condition characterized by a cluster of interrelated cardiometabolic disorders that include abdominal (central) obesity, elevated fasting blood glucose, dyslipidemia (typically high triglycerides and low HDL cholesterol), and hypertension[1–4]. These risk factors synergistically increase the likelihood of developing chronic diseases such as type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), and cardiovascular diseases (CVD), including heart attacks and strokes[5–7]. The prevalence of MetS has been rising at an alarming rate globally, primarily due to the increasing adoption of sedentary lifestyles, the widespread availability of calorie-dense processed foods, and the growing incidence of obesity across all age groups[8–10].

Conventional medical approaches to treating MetS often involve pharmacological agents that target individual components of the syndrome[11, 12]. For instance, antihypertensive medications manage blood pressure, lipid-lowering drugs such as statins reduce cholesterol levels, and insulin sensitizers like metformin help control blood glucose[13]. However, these monotherapies frequently fall short in addressing the multifactorial nature of MetS. Treating one symptom in isolation does not necessarily alleviate the systemic metabolic dysfunction that underlies the condition[13]. Additionally, long-term use of such medications can result in undesirable side effects—metformin, for example, is known to cause gastrointestinal discomfort in many patients, while statins have been associated with liver enzyme elevation and muscle pain[14]. Furthermore, the financial burden associated with polypharmacy in chronic conditions often poses a significant challenge, particularly in low- and middle-income countries.

In response to these challenges, there has been growing interest in complementary and integrative medicine, especially herbal therapies, as potential alternatives or adjuncts to conventional treatment strategies. Herbal

medicine, rooted in traditional systems such as Ayurveda, Traditional Chinese Medicine (TCM), and African folk medicine, has been used for centuries to treat metabolic imbalances. Herbs like *Azadirachta indica* (neem), *Trigonella foenum-graecum* (fenugreek), *Cinnamomum verum* (cinnamon), and *Momordica charantia* (bitter melon) have long been employed to support blood sugar control, reduce inflammation, and improve lipid metabolism[15]. These botanicals are believed to offer synergistic effects due to their multi-component nature, targeting multiple pathways involved in MetS pathophysiology while posing relatively fewer side effects compared to synthetic drugs[15].

Modern scientific research is increasingly validating these traditional claims. Preclinical studies using animal models and in vitro systems have elucidated numerous bioactive compounds within these herbs, such as flavonoids, saponins, alkaloids, and polyphenols[15]. These compounds have demonstrated anti-inflammatory, antioxidant, insulin-sensitizing, and lipid-lowering properties. Clinical trials have also provided promising results, with certain herbal formulations showing significant improvements in glycemic control, blood pressure, and lipid profiles among patients with T2DM or MetS[15, 16]. For instance, cinnamon has been shown to improve insulin sensitivity and lower fasting blood glucose, while fenugreek seeds may aid in reducing postprandial glucose spikes and triglyceride levels[17]. Despite the encouraging evidence, several limitations still hinder the widespread clinical adoption of herbal therapies. Many studies have small sample sizes, short durations, and lack standardized dosing or formulation protocols[17]. Moreover, herbal products can vary significantly in their phytochemical composition depending on cultivation conditions, preparation methods, and storage, which can affect consistency and reproducibility of therapeutic outcomes. Drug-herb interactions are also a concern, especially when used concurrently with conventional medications[18]. This review aims to provide a comprehensive synthesis of the current evidence on traditional herbal formulations used in the management of MetS, with a particular focus on obesity and diabetes models. It will explore their therapeutic potentials, mechanisms of action, limitations, and challenges in clinical translation. Additionally, it will highlight the importance of rigorous scientific validation, standardization, and regulatory oversight to facilitate the integration of effective herbal therapies into mainstream healthcare. Future research directions will also be discussed, including the need for large-scale randomized controlled trials and the application of systems biology and network pharmacology to unravel complex herb-drug interactions and optimize formulation efficacy.

Herbal Extracts & Formulations: Preclinical Evidence

F2 Polyherbal Formulation in DIO Mouse Model

The F2 polyherbal formulation represents a carefully standardized blend of ethanol extracts derived from five biologically active components[19]: *Orostachys japonica*, *Rhus verniciflua*, *Geranium thunbergii*, lemon juice, and royal jelly. This combination was specifically evaluated in a diet-induced obesity (DIO) mouse model to investigate its anti-obesity and metabolic regulatory effects[19]. Initially, mice were fed a high-fat diet (HFD) for five weeks to reliably induce obesity and mimic metabolic syndrome characteristics commonly observed in humans. Following obesity induction, the animals received oral administration of the F2 formulation at a dose of 46 mg/kg body weight for seven weeks[19]. The outcomes revealed substantial therapeutic potential: mice treated with F2 demonstrated a marked reduction in body weight gain compared to untreated controls. This was accompanied by an improved food efficiency ratio, indicating a more favorable balance between caloric intake and body weight. In addition, there was a significant reduction in white adipose tissue mass, a key indicator of visceral fat accumulation. These physiological improvements were supported by biochemical analyses showing lowered serum triglycerides and total cholesterol levels, suggesting effective lipid metabolism modulation. Moreover, insulin sensitivity was notably enhanced, as F2 treatment attenuated the insulin resistance typically induced by the high-fat diet, indicating a beneficial effect on glucose homeostasis[19].

At the molecular level, the F2 formulation exerted significant regulatory effects on adipogenic pathways within epididymal fat tissue[19]. There was downregulation of critical adipogenic transcription factors such as peroxisome proliferator-activated receptor gamma (PPARγ), sterol regulatory element-binding protein 1c (SREBP-1c), and adipocyte protein 2 (aP2), which collectively contribute to fat cell differentiation and lipid storage. Histological analysis of liver tissues further demonstrated reduced hepatic steatosis, highlighting F2's role in mitigating fatty liver development associated with obesity[19]. The analytical rigor of the study was ensured by employing validated ultra-performance liquid chromatography with diode-array detection (UPLC-DAD) assays to quantify and standardize the presence of reference phytochemicals including astragalin, ellagic acid, fisetin, fustin, and sulfuretin in the formulation[19]. This analytical control strengthens the reproducibility and quality of the herbal blend. Overall, the study underscores the synergistic action of F2's constituent compounds in targeting multiple facets of obesity and metabolic dysfunction, suggesting its promise as a natural therapeutic strategy for managing diet-induced obesity and associated metabolic derangements.

Other Polyherbal Combinations

A comprehensive review of the literature identified 25 animal studies investigating various polyherbal blends targeting metabolic syndrome (MetS) components, such as obesity, hypertension, dyslipidemia, and insulin resistance[20]. These studies primarily used rodent models that emulate human metabolic dysfunctions, offering valuable preclinical insights[20]. Among the most notable combinations were blends containing

Curcuma longa (turmeric), *Salacia reticulata*, *Gymnema sylvestre*, *Emblica officinalis*, and *Terminalia chebula*. These blends consistently demonstrated significant improvements in multiple metabolic parameters, including reductions in body weight, blood pressure, triglycerides, and fasting glucose levels, alongside increases in high-density lipoprotein (HDL) cholesterol in rodents[21]. Similarly, another combination consisting of *Glycyrrhiza uralensis* (licorice), *Rheum undulatum*, *Prunus persica*, and *Cinnamomum cassia* was reported to modulate all major components of MetS effectively, suggesting broad-spectrum benefits in metabolic regulation[22]. Additionally, traditional multi-herbal decoctions such as Lingguizhugan have shown potential synergistic effects, although detailed dosing data and pharmacokinetic profiles were often lacking, limiting the ability to fully evaluate their therapeutic window and efficacy[23].

Other polyherbal blends like red ginseng combined with *Polygonum multiflorum* or *Curcuma longa* with *Artemisia iwayomogi* also produced promising results, reinforcing the concept that herbal synergy can enhance therapeutic outcomes in metabolic disorders[24]. However, a common limitation across most studies was the absence of rigorous experimental design features, such as appropriate controls, randomized dosing, and clear dose-dependency assessments[24]. Many studies relied on single-dose experiments or lacked placebo groups, reducing the robustness of the conclusions. Moreover, standardization of herbal extracts and identification of active constituents were often insufficient, which hinders reproducibility and translational potential[25]. These shortcomings underscore the urgent need for improved experimental methodologies in polyherbal research, including validated phytochemical standardization, dose-response studies, and long-term safety evaluations. Addressing these gaps will enhance the scientific credibility of polyherbal formulations and facilitate their development into evidence-based therapeutics for metabolic syndrome and related disorders.

Single Herb and Compound Models

Recent preclinical studies have highlighted the synergistic potential of specific herbal blends and isolated phytochemicals in combating obesity and metabolic syndrome (MetS). For instance, formulations such as F2, which consist of multi-herbal mixtures, have demonstrated pronounced synergistic effects in animal models and in vitro systems. These blends often combine herbs with complementary actions, resulting in enhanced efficacy compared to individual components[26]. In several studies, such herbal combinations significantly reduced weight gain, adipocyte hypertrophy, and serum lipid levels in high-fat diet (HFD)-induced obese models[27]. These findings suggest that multi-compound herbal formulas may exert broad-spectrum metabolic regulatory effects, making them promising candidates for integrative obesity therapy[27]. This approach mirrors traditional medicinal systems where polyherbal prescriptions are frequently employed for complex disorders like obesity, which involve multiple dysregulated pathways.

Beyond multi-herb formulas, individual phytochemicals and defined combinations also show considerable anti-obesity potential. A notable example includes the co-administration of berberine, catechin, and capsaicin, which collectively inhibited adipocyte differentiation in 3T3-L1 preadipocyte cells[28]. Each compound targets different cellular pathways—berberine modulates AMPK activity, catechins exhibit antioxidant effects, and capsaicin activates thermogenic pathways—highlighting their complementary mechanisms[29]. Moreover, a study involving L-carnitine combined with a herbal mixture demonstrated significant physiological benefits in HFD-fed rats[29–31]. This combination not only reduced body weight but also improved lipid profiles, enhanced antioxidant enzyme activity, and lowered oxidative stress markers. Such findings underscore the therapeutic promise of integrating nutraceuticals and bioactive plant compounds for managing metabolic dysfunction. These models offer valuable insights into the pharmacodynamic interactions among bioactive compounds, paving the way for future clinical applications that are both effective and safer than conventional pharmacotherapy.

Mechanisms of Action

The therapeutic efficacy of many herbal and natural compounds in treating obesity and metabolic syndrome is largely attributed to their diverse and complementary mechanisms of action[32]. One of the most commonly observed effects is appetite suppression, which leads to a significant reduction in overall energy intake[32]. This is often mediated through the modulation of central nervous system pathways involving neurotransmitters such as serotonin and dopamine, or through peripheral signals like leptin and ghrelin. Additionally, these compounds frequently enhance thermogenesis and elevate the basal metabolic rate by activating brown adipose tissue or inducing the expression of uncoupling proteins, thereby increasing energy expenditure even in the absence of physical activity[33]. These combined effects help create a negative energy balance that promotes fat loss over time.

Furthermore, several natural agents exert anti-obesity actions through direct modulation of lipid metabolism. Pancreatic lipase inhibition, for instance, reduces fat absorption in the gastrointestinal tract, thereby limiting caloric uptake from dietary fats[34]. Some compounds also improve insulin sensitivity, which is particularly beneficial for individuals with MetS. This is achieved through the regulation of adipokines like adiponectin and the facilitation of glucose transporter type 4 (GLUT4) translocation, leading to enhanced glucose uptake and reduced insulin resistance. Many of these herbs and phytochemicals also possess potent antioxidant and anti-inflammatory properties, which are crucial for mitigating oxidative stress and chronic inflammation—both

hallmarks of metabolic syndrome[34]. By neutralizing reactive oxygen species (ROS) and downregulating pro-inflammatory cytokines such as TNF-α and IL-6, these compounds help restore metabolic homeostasis and protect against obesity-related comorbidities. Collectively, these multifaceted actions make natural compounds valuable tools in both the prevention and management of metabolic disorders[35].

Clinical Evidence in Humans

Meta-Analyses and Systematic Reviews

A comprehensive 2019 meta-analysis encompassing 279 randomized controlled trials (RCTs) investigated the effectiveness of plant-derived products in managing obesity and metabolic syndrome (MetS)[36]. This large-scale review highlighted a significant impact of various botanical agents on key metabolic indicators such as body weight, body mass index (BMI), waist-to-hip circumference, and lipid profiles. Notably, several plants including *Camellia sinensis* (green tea), *Phaseolus vulgaris* (white kidney bean), *Garcinia cambogia*, *Nigella sativa* (black cumin), puerh tea, *Irvingia gabonensis*, and *Caralluma fimbriata* demonstrated statistically and clinically meaningful reductions in body weight and metabolic risk markers[37]. The findings underscored the potential of phytotherapeutic interventions as complementary strategies in the clinical management of obesity and its associated complications.

Among these botanicals, *P. vulgaris* and *N. sativa* emerged as particularly efficacious. *P. vulgaris*, through its α-amylase inhibitory properties, contributed significantly to reductions in body weight, likely by reducing carbohydrate absorption and promoting satiety[38]. On the other hand, *N. sativa* showed strong lipid-modulating effects, especially in lowering triglyceride levels, suggesting its potential for managing dyslipidemia in MetS[38]. These outcomes offer promising directions for future clinical trials and pharmacological development, but also highlight the need for caution due to the heterogeneity in trial quality and intervention protocols. Systematic reviews such as this provide valuable aggregated evidence but call attention to critical gaps in long-term safety data, dosage standardization, and the mechanisms underpinning observed effects.

Single-Herb Trials

Individual herb-based clinical trials have provided further insight into the potential efficacy of specific botanicals in the management of obesity and metabolic risk factors. For example, green tea catechins, particularly epigallocatechin gallate (EGCG), have shown consistent benefits in reducing body weight (standardized mean difference [SMD] −0.75), BMI (−1.2), waist circumference (−1.71 cm), and total cholesterol levels (−0.43)[39]. These effects are likely attributable to enhanced fat oxidation, increased energy expenditure, and improved lipid metabolism[40]. Similarly, *Phaseolus vulgaris* extracts have demonstrated moderate but significant improvements in weight (SMD −0.88), mainly through inhibition of starch digestion and appetite suppression[41]. *Nigella sativa* has shown strong triglyceride-lowering effects (SMD −1.67), possibly due to its bioactive compound thymoquinone, which exerts antioxidant and anti-inflammatory properties[42].

Other botanicals like *Irvingia gabonensis*, *Cissus quadrangularis*, and *Caralluma fimbriata* have also shown promising outcomes in smaller trials, particularly in supporting weight loss[43]. These herbs are believed to act via diverse pathways including appetite suppression, modulation of adipogenesis, and improvement of insulin sensitivity[43]. Additionally, *Aloe vera* gel supplementation has been linked to reductions in fat mass and improvements in glycemic control and lipid profiles, especially in obese or prediabetic individuals. *Ocimum basilicum* (basil leaf) has demonstrated hypoglycemic effects in patients with type 2 diabetes mellitus (T2DM), reducing both fasting and postprandial glucose levels[44]. Despite these encouraging findings, the overall evidence base is constrained by the limited scale and duration of these studies, necessitating more robust, long-term trials to validate efficacy and determine safety across diverse populations.

Safety & Limitations

Despite their promising therapeutic profiles, plant-derived anti-obesity agents are not without limitations. Most clinical trials conducted so far have been of relatively short duration, typically less than 12 weeks, and generally report good tolerability with few adverse events. However, the long-term safety of these botanicals remains largely unexamined[45]. Potential herb-drug interactions, especially in patients on multiple medications for comorbid conditions such as diabetes, hypertension, or dyslipidemia, are insufficiently documented. This lack of pharmacovigilance is a significant concern given the increasing use of herbal products as complementary or alternative therapies[45].

Moreover, the methodological rigor of many studies in this field is variable. Issues such as small sample sizes, lack of randomization, inadequate blinding, and inconsistent outcome reporting hinder the ability to draw definitive conclusions[46]. Another major limitation lies in the absence of standardized extracts, making it difficult to compare results across studies or replicate findings[46]. The quality and composition of herbal supplements can vary widely depending on geographical origin, processing methods, and storage conditions[46]. These limitations highlight the urgent need for more rigorous, large-scale randomized controlled trials with standardized formulations and robust safety monitoring protocols. Only then can the true potential and applicability of these botanicals in clinical practice be accurately assessed.

DISCUSSION

Multi-Targeted Synergy

Herbal formulations composed of multiple botanicals have demonstrated promising efficacy in the management of obesity-related metabolic disorders due to their ability to exert simultaneous effects on several biological targets[47]. These natural mixtures often contain bioactive compounds that work in concert to modulate key physiological processes such as adipogenesis, glucose homeostasis, inflammation, and oxidative stress[47]. The synergistic or additive interactions between these compounds can enhance therapeutic efficacy beyond what is achievable with single-ingredient interventions. This multi-targeted mechanism is particularly valuable in complex diseases like obesity, where multiple pathways are dysregulated. For example, certain polyherbal formulations can inhibit adipocyte differentiation while also improving insulin sensitivity and reducing pro-inflammatory cytokines, offering a holistic therapeutic benefit[48].

Standardization techniques, such as Ultra Performance Liquid Chromatography with Diode-Array Detection (UPLC-DAD), have significantly advanced the reproducibility and quality control of herbal preparations[49]. These analytical tools allow for the consistent quantification of bioactive markers, ensuring batch-to-batch uniformity, which is essential for clinical reliability and regulatory approval. A standardized formulation, such as the referenced F2 compound evaluated in peer-reviewed studies, illustrates the potential of integrating advanced analytical chemistry into herbal medicine development. As a result, combining traditional ethnopharmacological knowledge with modern standardization techniques holds promise for optimizing the therapeutic potential of multi-herbal regimens[49].

Challenges to Clinical Translation

Despite growing evidence supporting the efficacy of herbal formulations, several critical challenges hinder their clinical translation. A primary concern is the lack of comprehensive standardization practices across formulations[50]. Many herbal products on the market lack rigorous quality control measures, resulting in inconsistencies in bioactive compound content and therapeutic potency. Quantifying bioactive markers and establishing dose consistency is vital for translating preclinical success into reproducible clinical outcomes. Moreover, randomized controlled trials (RCTs) exploring herbal interventions often suffer from small sample sizes, poor methodological rigor, or short durations, making it difficult to draw definitive conclusions about long-term safety and efficacy[51].

Safety remains another major hurdle. Herb–drug interactions, especially those involving cytochrome P450 enzymes, may alter the pharmacokinetics of co-administered drugs, leading to adverse effects or therapeutic failure[52]. These interactions require thorough pharmacovigilance and mechanistic profiling. Furthermore, regulatory ambiguities—such as whether a product is classified as a supplement or a drug can influence the stringency of clinical trial design and approval pathways[52]. Without clear classification, navigating global regulatory frameworks becomes complex. Finally, the mechanistic understanding of herbal therapies is still evolving. Systems biology approaches, including genomics, proteomics, and metabolomics, combined with advanced in vitro and in vivo models, can provide much-needed clarity on the molecular underpinnings of herbal efficacy, paving the way for more informed clinical applications.

Future Directions

The future of herbal medicine in managing metabolic disorders lies in the integration of herbal blends with conventional care and lifestyle interventions. This approach includes conducting well-designed integrative clinical trials that evaluate herbal formulations alongside standard pharmacotherapies and personalized diet and exercise programs. These studies should be powered to detect long-term clinical benefits and safety outcomes. Additionally, pharmacokinetic investigations are essential to understand how herbal compounds are absorbed, metabolized, and eliminated, as well as to establish dose-response relationships. This information will support dose optimization and minimize toxicity, enhancing clinical reliability and regulatory acceptance.

Innovations in formulation technologies—such as nanoencapsulation and the use of bioenhancers—are also promising avenues to improve the bioavailability and therapeutic efficacy of herbal compounds. Furthermore, advances in precision medicine provide opportunities to tailor herbal interventions based on an individual's genetic background or metabolic profile, increasing the likelihood of treatment success. Personalized herbal medicine, informed by omics data and systems biology, could revolutionize how these natural therapies are prescribed. Lastly, synthesizing global evidence through meta-analyses and integrating ethnopharmacological wisdom into clinical guidelines can support broader primary care adoption. This multidimensional strategy will help bridge the gap between traditional practices and evidence-based medicine, enabling herbal therapies to play a more prominent role in modern healthcare.

CONCLUSION

Traditional herbal formulations offer promising multi-target therapies for metabolic syndrome, with strong preclinical data and emerging clinical support. Their complex activity profile—spanning adipogenesis inhibition, lipase activity, insulin signaling, and inflammation—provides a compelling case for broader adoption. However, realization of their full potential demands rigor: standardized preparation, robust clinical trials, safety evaluation, mechanistic studies, and regulatory pathways. With these foundations, herbal formulations may become valuable tools in combating the metabolic syndrome epidemic.

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