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{Review Article}

Synergistic Potential of Polyherbal Combinations: An Integrative Review of Phytochemistry, and Therapeutic Applications

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Abstract:

Polyherbal preparations have been shown to be scientifically and therapeutic potential in the traditional and modern medicine, because they possess synergistic potential. Polyherbal in contrast to single-herb preparations: In contrast to single-herb preparations which generally focus on a limited number of pathways, polyherbal combinations have multiple biochemical and physiological effects and are more efficacious and provide a better therapeutic effect. The synergy of these formulations is achieved by their complementary nature like augmented bioavailability, multi-enzyme inhibition, antioxidant interactions and coordination of inflammatory and immunological responses. In vitro and in vivo studies have shown that polyherbal mixtures always have stronger antioxidant, antidiabetic, antimicrobial effects, hepatoprotective and anti-obesity effects in comparison to individual plant extracts. Such effects are credited to the varied phytochemical contents such as flavonoids, phenolics, terpenoids, alkaloids, and glycosides that all implement outstanding pharmacodynamic and pharmacokinetic interactions with one another. Also, polyherbal preparations have safer therapeutic profiles, as the possible toxicity of each herb is balanced and, therefore, the dose requirements are reduced by the synergistic effect. Though, there is a challenge of ensuring safety, quality and standardization because of plant material variability, multi-compound interactions and variability in extraction or processing technique. The regulatory mechanisms offered by WHO, AYUSH and international agencies are slowly turning into quality control, Good Manufacturing Practices (GMP), and evidence-based validation as key solutions to facilitate the acceptance of polyherbal therapeutics throughout the world. With the growing prevalence of chronic diseases in the global community, polyherbal formulations represent a promising, holistic, and economically feasible alternative towards comprehensive treatment of a disease and therefore, should be subject to further research in the form of mechanistic, analytical, and clinical studies.

Keywords: *Polyherbal formulations; Synergy; Phytochemicals; Antioxidant activity; Therapeutic applications*

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1. Introduction

The use of herbal medicine still remains central to health care in the world with the World Health Organization stating that close to 88 percent of the global population use herbal-based remedies to support their primary health care requirements [1]. The rising rate of chronic illnesses like diabetes, metabolic syndrome, inflammation, and oxidative-stress-related disorders has heightened the demand in natural therapeutic agents that are less dangerous and holistic than synthetic agents [2]. In the last 20 years, scientific studies across the world have grown enormously to confirm the pharmacological importance of medicinal plants and the number of bioactive phytochemicals, molecular pathways, and clinical evidence has increased [3]. The rediscovery of herbal studies is also evidenced by the increasing amount of dissatisfaction with the side effects, high price, and low long term efficacy of some synthetic medications [4]. Similarly, progress in analytical chemistry, pharmacognosy and systems biology has facilitated the more detailed examination of classical herbal systems, which has rendered herbal medicine more scientifically agreeable in contemporary pharmacotherapy [5]. Therefore, today, herbal medicine is a crucial point of contact between the traditional knowledge base and the modern evidence-based therapeutic practice [6].

Table 1. Mechanistic and Therapeutic Contributions of Major Polyherbal Components

Herb	Key Phytochemicals	Mechanistic Contribution	Therapeutic Outcomes
Moringa oleifera	Flavonoids, phenolic acids, glucosinolates	Antioxidant activity, enzyme inhibition (α-amylase, α-glucosidase), anti-inflammatory signaling modulation	Improves glycemic control, reduces oxidative stress, protects pancreatic β-cells
Murraya koenigii	Carbazole alkaloids (mahanimbine, girinimbine), essential oils	Enhances insulin secretion, antioxidant synergy, inhibits lipid peroxidation	Antidiabetic, hypolipidemic, hepatoprotective effects
Tinospora cordifolia	Alkaloids (berberine-like), diterpenoids, polysaccharides	Immunomodulation, antioxidant enhancement, NF-κB suppression	Anti-inflammatory, immunoprotective, antidiabetic activities
Curcuma longa	Curcuminoids (curcumin), turmerones	COX-2 and TNF-α suppression, ROS scavenging	Anti-inflammatory, antioxidant, anticancer potential
Azadirachta indica	Limonoids, quercetin, nimbin	Antimicrobial synergy, immunomodulation, glucose regulation	Antimicrobial, antidiabetic, hepatoprotective effects
Combined Polyherbal Effect	Multi-phytochemical matrix	Multi-target modulation, synergistic pharmacodynamics and pharmacokinetics	Superior efficacy, reduced toxicity, enhanced bioavailability

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1.1 Global relevance of herbal medicine

The need to cure patients has also brought herbal medicine to a forefront of healthcare practice in any part of the world because of its affordability, cultural commendation and variety of remedies [7]. Medicinal plants play a significant role in developing countries due to economic factors, however, even the developed countries experienced a sudden surge in the intake of herbal supplements in chronic disease control [8]. In many epidemiological researches, phytomedicines have been found to exhibit antioxidant, anti-inflammatory, immunomodulatory and metabolic regulatory properties which can be applied in long-term treatment [9]. In addition, medicinal plants possess a range of bioactive compounds, including alkaloids, terpenoids, flavonoids, glycosides, and phenolics, which individually add to the overall therapeutic effect due to multitarget effects [10]. The plant-based remedies are safer and less toxic than isolated chemical entities, which makes them suitable to be incorporated into complementary and alternative systems of medicine [11]. Research in herbal pharmacology has also been increasing and has further enhanced the knowledge of the molecular pathways mediated by the phytochemicals hence demonstrating its contribution to prevention of chronic diseases [12]. With the continuing growth of worldwide concern, herbal medicine is no longer seen as an isolated concept of a traditional practice, but as an important component of modern integrative healthcare [13].

1.2 Ancient versus modern development of polyherbal formulations.

Polyherbalism is an ancient notion related to the combination of various herbs supposedly involving an enhancement of therapeutic effectiveness due to the interaction between the effects of different herbs (polyherbalism) [14]. Multi-ingredient formulations were also used in Traditional Chinese Medicine, Siddha, and Unani systems to avoid complex disease pathways, decrease the toxicity and increase bioavailability [15]. As is known, in the past clinicians found that the combination of herbs would enable correction of several pathological conditions, a fact that was consistent with systems-based medicine [16]. Polyherbal preparations have found scientific interest in modern times and have been shown to have synergistic effects by studies that have been carried out with a scientific interest in pharmacological, biochemical and phytochemical studies [17]. The new global fields like network pharmacology and metabolomics now offer mechanistic descriptions of the old wisdom of combining multiple herbs [18]. The renewed interest in polyherbal recipes throughout the world has revitalized the study of polyherbal preparations, which are currently offered commercially as antidiabetic agents, antirheumatic agents, antigastrointestinal agents, antitransmissible agents, antithesclerotic agents, and antimetabolic agents [19]. Accordingly, the development of polyherbalism can be seen as the shift of the empirical traditional knowledge to the scientific practice of the evidence-based practice [20].

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1.3.Limitations of single-herb extracts

Although, single-herb preparations possess therapeutic properties, most of them have low concentrations of active constituents, which can not produce desirable pharmacological effects alone [21]. Most conditions, especially those related to the metabolism, inflammation, and even oxidative stress are multifactorial and demand an intervention that intervenes in a number of biochemical pathways at the same time which cannot be effectively achieved by single herbs [22]. In addition, plant extracts can demonstrate inconsistency in terms of geographical origin, seasonal factors, and mode of extraction with even the resulting clinical outcomes [23]. Even single-herb preparations cannot replace toxicity or side effects of single phytochemical, restricting their therapeutic target [24]. Moreover, the phytoconstituents of some plants cannot be absorbed and have inadequate systemic availability without bioenhancers, and in the absence of complementary herbs, they might exhibit poor pharmacokinetics [25]. The scientific literature also testifies that the use of one plant is not sufficient to regulate interconnected processes, including carbohydrate metabolism, lipid regulation, inflammation, and oxidative stress [26]. In turn, the weakness of single-herb treatment is the reason why more complex and synergistic herbal approaches are necessary [27].

1.4 Synchronous combination requirements.

The combination of herbs with others enables herbs to multiply the effects of the therapeutic action, reducing the risk of toxicity, and polyherbal formulations are better than single-plant extracts in numerous clinical applications [28]. Pharmacodynamic synergy is also present when a number of herbs share the same or complementary molecular targets and therefore create better pharmacological effects [29]. Pharmacokinetic synergy increases absorption, distribution, metabolism and excretion, which boost bioavailability of phytochemicals which otherwise might not be very active [30]. Research indicates that the combination of herbs can also have more effects than the actions of the constituents, particularly when used to address diabetes, oxidative stress, obesity, inflammation, and microbial infections [31]. Besides, the synergy assists in the countering of adverse reactions of some compounds where they are balanced with complementary herbs to enhance the overall safety [32]. Conventional recipes typically combine the so-called supporting herbs to enhance pharmacokinetic properties, the so-called catalysts to increase bioavailability and the so-called corrective herbs to decrease toxicity, which is validated in recent studies [33]. As the need to develop safer and multi-targeted therapeutic preparations increases, synergistic polyherbal preparations are scientifically justified, and clinically applicable, alternative solution [34].

2. Idea and Reason of Polyherbalism.

2.1 Polyherbal formulations (Ayurveda, TCM) have their historical origin.

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Polyherbal formulations are known to have a historical basis in ancient medicine systems like Ayurveda and Traditional Chinese Medicine (TCM). The textbooks of Ayurved such as the Charaka Samhita and Sarangdhar Samhita stressed the use of herbs in combination to make them more effective, have a balanced dosha action, and less toxic, making polyherbalism a fundamental treatment approach [35]. Likewise, multi-herb prescriptions in which jun-chen-zuo-shi (emperor-minister-assistant-envoy) concepts inform synergistic choice of herbs to act upon a number of physiological pathways has been long practiced in TCM [36]. These traditions acknowledge that diseases are multifactorial and ought to be remedied in multi-target therapies than single-component therapies [37]. The historical records of both systems indicate that the synergistic effect of using herbs increases harmonious therapeutic effect, broader pharmacological effect, and increases clinical safety [38]. Polyherbalism is therefore not a contemporary idea but a scientifically tested and proven development of centuries old medical wisdom [39].

2.2 PHFs (decoctions, churnas, extracts, etc.) definitions and classification.

Polyherbal formulations (PHFs) refer to medicinal preparations that include two or more plant substances that are intertwined in a given proportion to reach superior medicinal advantages [40]. They are categorized into various dosage types, such as decoction (kwatha), churnas (powders), asavas / aristas (fermented liquids), ghritas (medicated ghee), avalehas (confection) and pre-prepared extracts, depending on how they were prepared and their intended usage [41]. Capsules, tablets, suspensions, and hydroalcoholic extracts are also part of modern PHFs that are made with a controlled extraction technology to enhance pharmacological consistency [42]. Such classifications guarantee proper phytochemical extraction and stability and bioavailability that directly impact clinical outcome [43]. The classification is also useful in identifying the pharmacokinetic profile of the formulation, clinical appropriateness, shelf life and compliance by the patient [44]. Therefore, the standardization and therapeutic optimization rely on PHF classification [45].

2.3 Scientific explanation: principle of Sarangdhar Samhita.

One of the earliest scientific explanations of polyherbalism appears in the Sarangdhar Samhita (1300 A.D.), which claims that polyherbalism is more effective because herbs have a potentiation effect, which is synergetic [46]. It is emphasized in the text that, in most instances, many phytoconstituents are weak acting when applied as single agents but have markedly better effects when applied as a combination since they work complementarily [47]. It also stresses that a single herb can be a catalyst (bioenhancer) that enhances the absorption and metabolism of other constituents, as contemporary pharmacokinetic synergy notions [48]. This is in tandem with the modern scientific findings that there are numerous phytochemicals that act on interrelated biochemical pathways and have excellent therapeutic effects [49]. It is the Sarangdhar Samhita that therefore gives a good conceptual basis to multi-herb pharmacotherapy today, which is why the creation of standardized PHFs is being developed today [50].

2.4 Benefits of being superior to single-herb preparations.

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Compared to single-herb extracts, polyherbal preparations have multiple benefits: they provide multiple bioactive molecules that work on a variety of molecular targets, which enhances therapeutic effect [51]. They also minimize the chances of toxicity since any one or more complementary herbs can neutralize any one or more inappropriate or excessive effects of any one substance [52]. PHFs increase bioavailability via pharmacokinetic synergy, wherein some herbs have pharmacokinetic properties of increasing absorption, solubility, or metabolic stability of others [53]. Also, their spectrum activity, e.g., antioxidant, anti-inflammatory, antidiabetic, immunomodulatory, and hepatoprotective effects, is incorporated in one formulation [54]. PHFs have longer-lasting effects than single phytochemicals since they contain multiple components that reduce the need to increase dosage or cause drug tolerance [55]. These are the benefits that make PHFs the best therapeutic candidates of complex diseases [56].

2.5 Up-to-date relevance in chronic disease.

The chronic illnesses include diabetes, obesity, inflammation, arthritis, cancer and metabolic syndrome with multifactorial pathophysiology that cannot be efficiently treated using single-target synthetic medications [57]. Polyherbal preparations offer the multi-target mode of therapy through regulation of oxidative stress, mediators of inflammation, enzymes of metabolism and immune reactions as a whole [58]. It is being increasingly proven that PHFs exhibit better antihyperglycemic, antioxidant, anti-inflammatory, and organ-protective action than isolated plant extracts [59]. The relevance of PHFs to synergies via pathway-level modulation continues to be confirmed by the existence of multiple modern analytical platforms, such as network pharmacology, metabolomics, and systems biology [60]. With increasing prevalence of chronic diseases in the world, PHFs are safe, cheap and physiologically comprehensive therapeutic options that support the trend of integrative medicine [61]. Therefore, polyherbalism is still very applicable in the contemporary healthcare systems [62].

3. Polyherbal Combination Synergy.

3.1 The definition and forms of synergy.

Harmony in polyherbal formulations is defined as the effect where the two or more plant constituents interact to give an overall therapeutic effect exceeding the individual effects [63]. The presence of this improvement is attributed to the fact that the various phytochemicals interact with interdependent biochemical pathways leading to an increase in efficacy, decrease in toxicity, and bioavailability [64]. Pharmacodynamic synergy is synergy between herbs that acts on the same physiological target, e.g. enzymes, receptors or signaling pathway, in a complementary or reinforcing manner [65]. Another phenomenon, called pharmacokinetic synergy, is where one herb increases the absorption, distribution, metabolism or elimination of another, thus increasing systemic availability and therapeutic effectiveness [66]. All these mechanisms justify the effectiveness of polyherbal preparations over single-herb preparations in complicated diseases [67]. Synergy is now backed by both the ancient wisdom and the present molecular medicine [68].

3.2 Additive and synergistic and antagonistic interactions.

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The interactions of herbs may be additive, synergistic and antagonistic based on the combined effect of two or more herbs [69]. Additive interactions happen when the joint effect equals the sum total of individual effects, and there is no further improvement to the effect of overlapping with the baseline [70]. Synergistic interactions result in a higher therapeutic effect than the anticipated additive effect, which is a positive herb-herb interaction by way of multi-target regulation or improved bioavailability [71]. Antagonistic interactions decrease the therapeutic activity, which is the occurrence of one herb opposing the action of another or creating competition at the metabolic or receptor locations [72]. The importance of these interactions is to comprehend how to develop effective polyherbal formulations, how to avoid adverse interactions and how to maximize therapeutic success [73]. Studies demonstrate that the vast majority of the Ayurvedic and TCM combinations, which are designed well, deliberately take advantage of synergy and reduce antagonism [74].

3.3 Methods to measure synergy

Scientific assessment of herbal synergy is based on quantitative approaches e.g., the Combination Index (CI) which is a mathematical evaluation to determine whether or not a pair of herbs produce synergistic (<1), additive (=1) or antagonistic (>1) effects [75]. Another method is known as isobolographic analysis in which a dose-response curves of herbal combinations are visually or statistically compared to determine synergism [76]. Fractional Inhibitory Concentration (FIC) index has been popularly used in antimicrobial and enzyme-inhibition research to determine the interactions between two agents, where FIC values [?]0.5 is considered synergistic activity [77]. These are pharmacological and microbiological models of the adapted form which offer objective methods to test traditional herb-herb compatibility knowledge [78]. More recently, computational biology and network pharmacology have enhanced the measurement of synergy through multi-compound interactions over molecular pathways [79]. Therefore, synergy analysis currently incorporates both the experimental and computation analysis [80].

3.4 Literary examples of herb-herb synergy.

Classical polyherbal interactions between medicinal plants have been proven by numerous studies that have observed synergistic interactions between plants. As an example, Piper nigrum (black pepper) allows Curcuma longa curcumin to have a higher bioavailability by inhibiting hepatic and intestinal metabolism via the action of piperine; a form of potent pharmacokinetic synergy [81]. Murraya koenigii in combination with Moringa oleifera presents a better antidiabetic and antioxidant effect through a combination of the plant in regulating a-glucosidase, lipid peroxidation and inflammatory mediators than either plant alone [82]. Likewise, there is synergistic antihyperglycemic and pancreatic b-cell-protective properties of Tinospora cordifolia with Gymnema sylvestre [83]. Trikatu (ginger, black pepper, long pepper) is a classic Ayurvedic combination, which boosts digestion and intake of drugs, whereas Guduchi + Turmeric have a drug-enhancing effect, which works in synergy to enhance immune and anti-inflammatory responses [84]. This kind of evidence is a strong argument in favor of the rationale of polyherbal formulations in both the traditional and modern setting [85].

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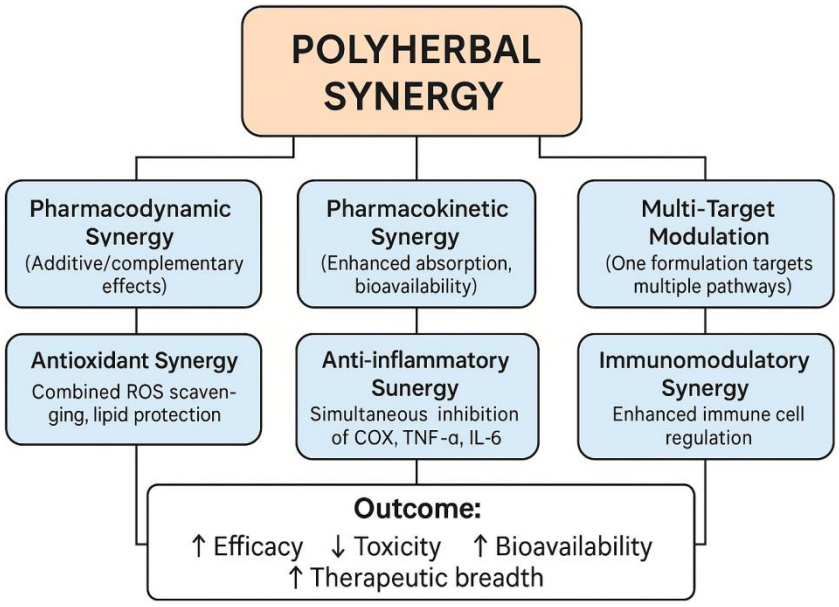

Figure 1. Mechanistic Basis of Synergistic Interactions in Polyherbal Formulations

3.5 Significance of synergy in the success of therapeutic measures.

The therapeutic superiority of polyherbal formulations is focused on its synergy that allows multi-target modulation in multifactorial diseases (diabetes, obesity, inflammation, and cancer) [86]. Pharmacodynamic synergy enables herbs to act together in a coordinated way to alter a wide range of enzymes, receptors, and signalling pathways to produce extended and more therapeutic effects than individual isolated compounds [87]. Pharmacokinetic synergy also advances the effect of the treatment by promoting absorption, decreasing degradation of active phytochemicals, and increasing bioavailability [88]. Synergy also enables the use of lower dosages of each of the herbs, which decreases toxicity and also lowers chances of adverse-drug interactions [89]. Pharmacological research results interest in modern systems biology and network pharmacology establish that PHFs multi-component interactions replicate the complexity of biological systems, hence can provide maximized therapeutic efficacy [90]. In general, the effective polyherbal formulations are developed based on synergy, and it becomes inevitable in the contemporary phytomedicine studies [91].4. Mechanistic Basis of Polyherbal Synergism

4. Mechanistic Basis of Polyherbal Synergism

4.1.Development of multi-targeted pathway interventions

Polyherbal preparations have the potential to control numerous biochemical pathways at once, enabling them to tune including glucose metabolism, lipid regulation, oxidative stress response interacting pathways, and mitochondrial pathways [92]. PHFs interact with multiple enzymes, signalling proteins, and transcription factors simultaneously, causing a therapeutic effect at the systems level, unlike single compounds, which only bind to isolated receptors [93]. This multi-target action proves to be especially useful in complex, ongoing diseases when there is a combination of several, pathogenic

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mechanisms. PHFs thus offer a wider and long term therapeutic response by treating the entire range of disease physiology [94].

4.2 Synergy (e.g., a-amylase, a-glucosidase) Enzyme inhibition.

A combination of several herbs is more effective in enzymes that break down carbohydrates i.e. a-amylase and a-glucosidase than a single extract [95]. Synergistic combinations positively impact competitive and non-competitive binding of enzymes using a variety of phytochemical classes such as flavonoids, alkaloids and phenolic acids. This leads to sluggish carbohydrate digestion, lower postprandial glucose spikes and better glycemic control [96]. The synergistic effect between the inhibitory activities of each herb is higher than the aggregate effect of the herbs, indicating actual enzymatic synergy [97].

4.3The antioxidant synergy (ROS scavenging, lipid peroxidation inhibition) is displayed at.

Polyherbal blends offer the advantage of a high concentration of antioxidant molecules (phenolics, flavonoids, tannins) that act in a synergistic fashion in neutralizing reactive oxygen species (ROS) in relation to pure antioxidants [98]. Synergy is observed in which a single phytochemical replenishes another, or as a radical scavenging agent that enhances the stability of antioxidant enzymes, including SOD, CAT, and GPx [99]. It is also an effect of cooperation that enhances cellular defense mechanisms, inhibiting lipid peroxidation and tissue oxidative damage. Consequently, PHFs have high cytoprotective and anti-aging effects [100].

4.4 COX, TNF-a, IL-6 synergy in inflammation regulation.

Various mediators are involved in the regulation of inflammation, and polyherbal formulations control simultaneously COX enzymes, NF-kB, and cytokine release (TNF-a, IL-6, IL-1b) [101]. Phenolics, terpenoids and alkaloids herbs are synergistic in suppressing pro-inflammatory signaling and enhancing anti-inflammatory mediators [102]. The combined modulation of this is much more effective to decrease chronic inflammation as compared to the individual herbs. It is also observed that the multi-compound effects reduce tissue damage and speed up the healing processes [103].

4.5 Immunomodulatory synergy

Polyherbal preparations improve the innate and adaptive immunity by acting synergistically to stimulate the macrophages, NK cells and T-lymphocytes [104]. There are those that induce phagocytosis and others enhance antibody or cytokine homeostasis. The result is a homeostatic response of host defense that is caused by this coordinated modulation and is not over stimulated by the immune system. This synergy would be of particular use in chronic infections, metabolic conditions and immune-suppressed conditions [105].5. Pharmacological Activities of Polyherbal Combinations

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5.1 Antioxidant Activity

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Polyherbal formulations show strong antioxidant activity due to the presence of diverse phytochemicals such as flavonoids, phenolics, tannins, and alkaloids that act through complementary mechanisms [106]. These combinations enhance free radical scavenging, metal chelation, and stabilization of endogenous antioxidant enzymes like SOD, CAT, and GPx [107]. In vitro studies using DPPH, ABTS, FRAP, and nitric oxide scavenging assays consistently report greater activity from polyherbal systems than single-herb extracts [108]. In vivo models demonstrate reduced lipid peroxidation, improved hepatic antioxidant capacity, and protection against oxidative tissue damage when synergistic herbal mixtures are administered [109]. Such findings highlight that antioxidant synergy is a key therapeutic advantage of polyherbal formulations [110].

5.2 Antidiabetic Activity

Polyherbal combinations exert potent antihyperglycemic effects through multi-targeted mechanisms including α-amylase and α-glucosidase inhibition, enhanced glucose uptake, and improved insulin sensitivity [111]. They modulate key enzymes of carbohydrate metabolism, reduce postprandial glucose spikes, and improve pancreatic β-cell function through antioxidant and cytoprotective actions [112]. Several studies show enhanced GLUT-4 translocation, improved adiponectin expression, and restoration of hepatic glycogen stores after polyherbal treatment [113]. Animal model evidence indicates that combinations such as *Tinospora cordifolia* + *Gymnema sylvestre* or *Moringa oleifera* + *Murraya koenigii* outperform individual herbs in controlling fasting and postprandial glucose levels [114]. These effects collectively contribute to better glycemic regulation and protection against diabetes-associated complications [115].

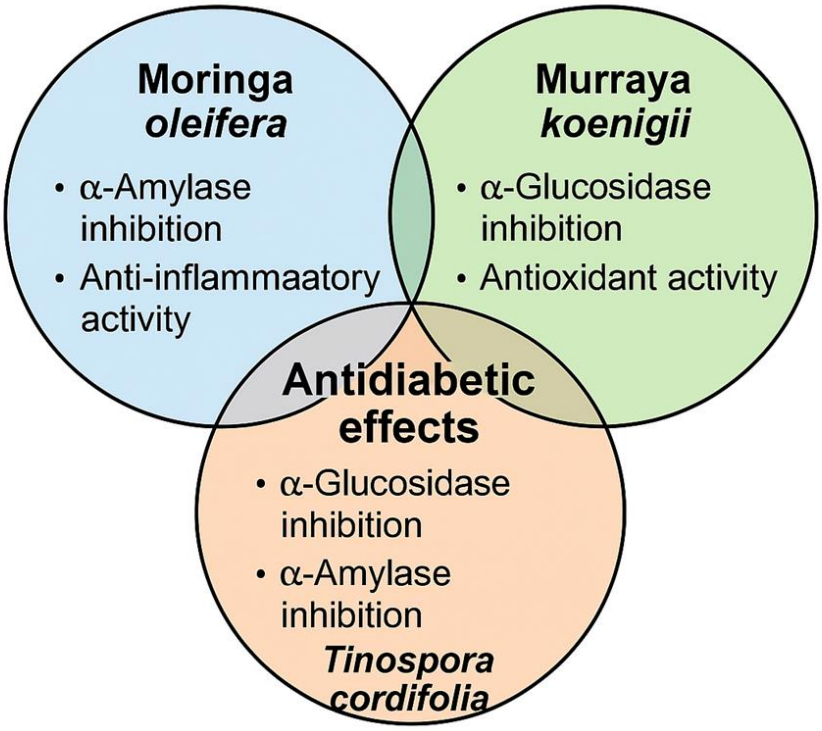

Figure 2. Synergistic Antidiabetic Effects of *Moringa oleifera*, *Murraya koenigii*, and *Tinospora cordifolia*

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5.3 Anti-inflammatory Activity

The anti-inflammatory activity of polyherbal preparations is more pronounced because the action of phytochemicals suppressing pro-inflammatory cytokines like TNF-a, IL-1b and IL-6 and stimulating the anti-inflammatory response is combined [116]. They regulate intracellular signals cascades, such as NF-kB, COX-2, LOX, and MAPK, and inhibit the production of nitric oxide and synthesis of prostaglandins [117]. In vitro macrophage models and in vivo studies of carrageenan induced paw edema show synergetic effect of herbs combined with carrageenan in inhibiting inflammatory reactions [118]. This combination results in an improved edema decrease, less oxidative stress indicator, and quick tissue healing in comparison with herb-only interventions [119].

5.4 Antimicrobial Activity

Polyherbal blends are broad-spectrum antimicrobial agents that form synergistic interactions that help to disrupt the bacterial membranes, interfere with the quorum sensing and cripple the microbial enzyme systems [120]. Phytochemical combinations improve antimicrobial activity against microbes by acting at multiple sites in microbial cells leading to permeability, and blocking efflux pumps [121]. Research indicates that polyherbal mixtures are associated with very low minimum inhibitory concentrations (MICs) when compared with single extracts, which is an indicator of great synergistic potential [122]. There are also formulations that are resistance-modifying agents, which regain microbial vulnerability to the traditional antibiotics by blocking resistance mechanisms [123]. This research indicates that they are promising in the management of drug resistant infections [124].

5.5 Hepatoprotective Activity

Polyherbal preparations have hepatoprotective effects that inhibit oxidative stress, prevent lipid peroxidation, stabilize cell membranes, and stimulate detoxication processes [125]. A synergistic action of alkaloids, flavonoids, and triterpenoid phytochemicals regulates hepatic enzymes AST, ALT, ALP, and bilirubin in the restoration of normal biochemical balance in the liver in the event of hepatotoxicity [126]. The effect of polyherbal formulations in vivo using CCl4-, paracetamol-, and alcohol-induced liver damage shows high hepatoprotection in the former [127]. These mixtures also enhance hepatic mitochondrial repair and repopulation of hepatocytes, which leads to the recovery of the liver in the long term [128].

5.6 Anti-obesity Effects

Polyherbal formulations have anti-obesity effects because they suppress pancreatic lipase activity, thus lowering the absorption of fatty foods in the diet [129]. Some herbs interactively inhibit the formation of adipose tissue by reducing the expression of PPAR-g and C/EBP-a transcription factors and the lipid accumulation of adipocytes [130]. They additionally advance lipid metabolism by increasing the activation of AMPK, fatty acid oxidation, and decreasing serum triglycerides and LDL levels [131]. Research indicates that anti-obesity herbs in their combinations achieve higher weight loss, visceral fat, and metabolic value than the individual plant extracts [132]. Such activities

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render polyherbal preparations good alternatives when it comes to treating obesity [133].6. Safety, Toxicity, and Standardization of Polyherbal Formulations

6. Safety, Toxicity, and Standardization of Polyherbal Formulations

6.1 Requirement of toxicity assessment.

Toxicity assessment is critical to polyherbal products since interaction of several herbs may lead to unpredictable results, alterations in potency or even cumulative toxicity [134]. Although herbs themselves can be considered a safe method, the interaction of the synergy or metabolite effect can result in an increase in toxicity or change in pharmacokinetics. Toxicity testing assists the determination of safe dosage ranges and organ specific risk as well as long-term safety consequences. It also facilitates that heavy metals, pesticides, microbial load or adulterants are not present. As the consumption of polyherbal supplements increases in the whole world, scientifically verified safety is compulsory to guarantee protection of the health of the people [135].

6.2 Acute, sub-acute and chronic toxicity investigations.

The acute toxicity studies are used to identify the immediate adverse effects after one high dose administration that will help in establishing the LD50 and safe starting doses in humans [136]. Sub-acute trials provide the effect of repeated dosing with 28-30 days, which gives an insight into biochemical, hematological, and histopathological changes. Chronic toxicity studies take a period of at least 90 days or more to identify cumulative toxicity, carcinogenicity, reproductive effects as well as metabolic disruptions [137]. Such tests are based on the OECD standards and provide a complete safety profiling prior to clinical application. This is especially important in polyherbal formulations, where there is multi-compound complexity and therefore the need to conduct tiered toxicity testing is required [138].

6.3 Herb-drug interactions

Polyherbal preparations can also affect the absorption, excretion, or metabolism of conventional drugs, particularly those that are activated via CYP450 enzymes and P-glycoprotein transporters [139]. Certain herbs may enhance the pharmacological effects, resulting in exaggerated therapeutic or side effects and other may suppress the action of drugs or diminish its effects. Such interactions are the most important in the circumstances that involve long-term medication like diabetes, high blood pressure, and anticoagulant therapy. Therefore, it is critical to learn about herb-drug pharmacodynamics and pharmacokinetics so that, when combining polyherbal preparations with allopathic medications, one could co-administer the medications safely [140].

6.4 Problems of polyherbal standardization.

Natural variability of the plant raw material, variability in phytochemical content, and the multi-herb formulations make standardization of polyherbal formulations difficult [141]. The level of phytoconstituents is highly affected by environmental conditions, seasons of harvesting, storage and means through which they are extracted. In contrast

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to single-compound pharmaceuticals, PHFs have to be analyzed in a fingerprint-like manner (HPTLC, HPLC, LC-MS) to provide consistency of batches to batches. Also, synergistic reactions make it more difficult to identify marker compounds to control quality. These complications require powerful quality control mechanisms and tested protocols of analysis [142].

6.5 Good Manufacturing Practices (GMP) for PHFs

GMP provides assurance of the purity, safety and efficacy of polyherbal formulations through regulating the source of raw materials, processing, environmental regulation, documentation and testing [143]. Effective GMP practices minimize contamination, adulteration, microbial load, and heavy metal. It is also geared towards correct identification of plant species, standardized extraction and reproducible formulation. GMP Pharmaceutical of herbal products fits the manufacturing in relation to the world standards of quality and the improvement of clinical acceptability. Polyherbals that are exported to controlled markets in GMP have to be compliant in order to be exported [144].

6.6 Regulatory considerations (WHO, AYUSH, FDA)

Regulations of polyherbal preparations vary among regions though they often stress on safety, effectiveness, standardisation, and accurate labeling. WHO sets international standards of quality control of herbs as well as toxicity research and production procedures [145]. In India, regulatory approval is environmental, and it is necessary to meet the requirements of Ayurvedic Pharmacopoeia and determine safety evidence. Under DSHEA, the U.S FDA regulates the herbal preparations as dietary supplements, which must be labeled honestly and subject to post-market surveillance. All these frameworks are what make PHFs comply with internationally acceptable safety and quality standards prior to their use by the population [146].

7. Conclusion

Polyherbal preparations represent a scientifically and traditionally justified method of multi-target therapy, which is more effective than that of single-herb preparations. Their synergistic effects are owed to the multi-activity of their different phytochemicals that interact to regulate metabolic, inflammatory, oxidative, and immunological processes. Modern experimental models have yielded evidence that the combination of herbs increases the pharmacodynamic performance and pharmacokinetic performance, decreases toxicity, and also increases therapeutic reliability. The combination of the old tradition with the new methods of analysis has reinforced the scientific basis of polyherbal synergism. Although they have a tremendous potential, there are still issues concerning safety, standardization and regulatory adherence. Further studies with more effective tools like network pharmacology, metabolomics and molecular docking will better understand their mechanisms and formulate optimally. Polyherbal combinations are one of the potential solutions to the current healthcare system, especially as the world is being plagued by the rise of chronic and lifestyle-related diseases, which polyherbal combinations appear to address effectively and affordably, being more holistic, cheaper, and safer than conventional therapies.

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