

## A COMPREHENSIVE REVIEW ON POLYHERBAL LIQUID PREPARATIONS FOR THE MANAGEMENT OF DIABETIS MELLITUS (TYPE – II)

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### ABSTRACT

Hyperglycemia is a disorder of metabolism characterized by elevated glucose concentrations in the bloodstream. Although synthetic antidiabetic agents are frequently utilized to control diabetes, they can potentially have negative consequences. Consequently, many patients resort to herbal remedies as an alternative method of managing diabetes. Ayurvedic formulations often use polyherbal formulations that combine two or more herbs to treat diabetes. Studies have demonstrated that the synergistic antidiabetic effect produced by the combination of herbal components in polyherbal formulations can be more potent than that of individual herbs. However, the limited availability of research studies on polyherbal formulations can make it challenging for investigator to discover new phytomedicines or drug combinations. A concentrated decoction can be mixed with honey, sugar, or alcohol to prepare an herbal syrup. It is intended for oral use. Herbal syrups show a more potent action than other types of syrup. Herbal syrup is a liquid medicine made by extracting medicinal properties from various herbs and plants. Herbal syrup to have better bioavailability compared to a solid dosage form of the same herbal ingredient, depending on the specific herb and formulation used. Bioavailability refers to the amount and rate at which a drug or other substance enters the bloodstream and becomes available to exert its therapeutic effect. This can be influenced by various factors, including the chemical properties of the substance, the formulation and dosage form, and the individual's physiology and metabolism. In the case of herbal syrups, the liquid form may be easier and faster to absorb in the systemic circulation, as it does not need to be broken down and dissolved like a solid dosage form such as a tablet or capsule. Additionally, some herbal ingredients may be better absorbed in a liquid form due to their solubility in water.

**KEYWORDS:** Diabetes, Polyherbal liquid Preparation, Synergistic, Clinical, Herbal, herb-herb combination.

## INTRODUCTION

Type 2 diabetes (DM) is a chronic illness characterized by increased blood sugar levels brought on by abnormalities in the production of insulin, action, or both. By regulating the passage of glucose (sugar) from the circulation into cells to provide energy, the pancreatic hormone insulin plays a crucial role in blood sugar regulation.

Internationally, diabetes has become to be a serious public health issue, especially in low- and middle-income countries. Since 1980, the global prevalence of adult diabetes has nearly doubled, from 4.7% to 8.5%. In 2019, there were about 463 million people with diabetes; if preventative measures are not implemented, this number is predicted to increase to 700 million by 2045.<sup>[1]</sup> Over the previous few decades, diabetes has become more and more common in India; the year 2000 saw a notable increase in its frequency. The International Diabetes Federation (IDF) reports that from 7.1% in 2009 to 8.9% in 2019, India had a higher incidence of diabetes. This indicates that the current number of diabetics in India is approximately 77 million, making it the country with the second-highest global prevalence behind China. Furthermore, according to IDF estimates, a high incidence of impaired glucose tolerance (IGT), which raises the risk of type 2 diabetes, affects about 25.2 million people in India. By 2045, there will likely be 35.7 million people with IGT, according to estimates. Moreover, it is noteworthy that India has approximately 12.1 million individuals aged 65 years or above who have diabetes, and this number is Expectations increase to 27.5 million by 2045.<sup>[2]</sup>

Apart from hyperglycemia and insulin resistance, diabetes can also cause a range of other metabolic problems, including alterations in carbohydrate, protein, and lipid metabolism. Diabetes can lead to a variety of complications, such as cardiovascular disease, nerve damage, kidney damage, and eye damage, among other issues. Therefore, in order to prevent or delay these problems, it is imperative that diabetes be appropriately managed.<sup>[3]</sup> This disorder affects about 25% of the world's population, which can be attributed mainly to the adoption of a sedentary lifestyle characterized by poor dietary choices and decreased levels of physical activity.<sup>[4]</sup> Synthetic medications such as oral hypoglycemic agents and insulin are commonly used to manage blood sugar levels in diabetes. However, these medications can be expensive and may cause complications and Toxic effects, which can limit their use.

Alternative medical treatments, such as herbal medicines, dietary supplements, and lifestyle modifications, are being explored as potential options for managing diabetes. Alternative treatments may offer cost-effective and less risky options than traditional medicines, which may cause them to become more accessible to patients with limited resources. However, it is crucial to acknowledge that alternative treatments cannot replace standard medical care. In order to create a thorough treatment plan that meets their unique needs and goals, patients with diabetes must always work closely with their healthcare professional.<sup>[5]</sup> The availability of medicinal plants is a significant advantage, as they can be easily obtained in various forms, including fresh or dried plants, in addition to extracts or supplements. This may cause them to become more accessible and affordable than synthetic medicines, especially in developing countries where access to modern healthcare may be limited. Another potential advantage of medicinal plants is that they may have fewer side effects than synthetic medicines.<sup>[6]</sup> For thousands of years, people have utilized plants for therapeutic purposes, and many modern medications are derived from plant substances. Plants have served as a valuable source of medicinal compounds, with many of today's pharmaceuticals being directly or indirectly derived from them.<sup>[4]</sup> Plant-based diets can provide a wealth of phytonutrients that may support health. However, to fully harness the benefits of these compounds, it is crucial to consume a diverse and well-balanced diet that incorporates variety of plant-based foods.<sup>[7]</sup> Phytotherapy, or the use of plant-based medicines for therapeutic purposes, has indeed become a popular and

commercially successful branch of alternative and supplementary medicine. The application of polyherbal remedies, which combine multiple herbs to achieve greater therapeutic effectiveness, is also common in many traditional systems of medicine. There are different mechanisms by which herbs in a polyherbal formulation can work together synergistically.

Pharmacodynamic synergy refers to the combined effect of multiple herbs on a specific biological target or receptor. For example, by strengthening its affinity for a certain receptor or by preventing the degradation of the active ingredient, one herb may increase the activity of another. The combined impact of many herbs on the absorption, distribution, metabolism, and excretion of the active ingredients is known as pharmacokinetic synergy. Numerous research have shown this. Furthermore, this idea is the foundation of many conventional herbal medicines. But it's crucial to remember that the synergistic effects of herbs can also have downsides like unpleasant effects when taken in excessive amounts or interactions with other treatments. Therefore, it is essential to consult a healthcare professional before using any herbal remedies, particularly if you currently have a medical condition or are taking other prescriptions.<sup>[8]</sup> Numerous clinical studies, both in humans and animals, have explored the potential anti-diabetic effects of various fruits, vegetables, medicinal herbs, and spices. Some of the items mentioned, such as bitter melon, cinnamon bark, curry leaves, fenugreek seeds, garlic cloves, ginger rhizomes, insulin leaves, jamun seeds, shahtoos leaves, curry leaves, karela seeds, pomegranate peels, jackfruit bulbs, and turmeric rhizomes, have demonstrated promising results in reducing blood sugar levels, improving insulin sensitivity, and exhibiting anti-diabetic properties.  
[9-20]

#### **THE CLASSIFICATION OF DM AND OTHER CATEGORIES OF HYPERGLYCAEMIA INCLUDES BOTH CLINICAL STAGES AND ETIOLOGICAL TYPES.**

- 1. Insulin Dependent Diabetes Mellitus.** Type 1 DM, also called as autoimmune diabetes, is a condition that mainly affects kids and infants adults. The onset of symptoms is usually sudden and can be life-threatening. The severe deficiency or absence of insulin secretion caused by the destruction of  $\beta$ -islet cells of the pancreas requires treatment with injections of insulin. In 85-90% of individuals with Type 1 diabetes mellitus, markers of immune destruction such as islet cell auto-antibodies, auto-antibodies to insulin, and auto-antibodies to glutamic acid decarboxylase (GAD) are present. Although the exact cause of diabetes mellitus is unknown, there is evidence of an autoimmune mechanism involving auto-antibodies that destroy the beta-islet cells in most people.
- 2. Non-Insulin Dependent Diabetes Mellitus** Type 2 diabetes mellitus is a medical condition that is marked by a gradual decline in insulin secretion and increased insulin resistance, commonly referred to as adult-onset diabetes. This condition is linked to long-term complications that can affect the blood vessels, kidneys, eyes, and nerves. The development of type 2 diabetes is often associated with factors such as obesity, sedentary lifestyle, advancing age, and genetic predisposition. Individuals diagnosed with this condition are at an elevated risk of developing macrovascular and microvascular complications.
- 3. Gestational Diabetes Mellitus** When a woman develops glucose intolerance for the first time or is diagnosed with it while pregnant, it is known as gestational diabetes mellitus, or GDM. GDM also applies to women with Type 1 diabetes or undetected Type 2 diabetes found during pregnancy. GDM may go away after birth, but because pregnant women with GDM are exposed to elevated blood sugar levels, their unborn children are more likely to grow up to be obese and have Type 2 diabetes.
- 4. Other Specific Type** The most prevalent type of Hepatocyte nuclear factor (HNF)-1 mutations on chromosome 12 cause monogenic diabetes, which is called maturity-onset diabetes of the young (MODY). This kind of diabetes is

typically marked by elevated blood sugar levels prior to the age of 25 and is a genetic flaw in beta cells. Other forms of diabetes may arise due to pancreatic diseases, endocrine disorders, medications, or infections. Less than 10% of diabetes cases are caused by genetic abnormalities that hinder the conversion of proinsulin to insulin, inherited in an autosomal dominant pattern.<sup>[21-23]</sup>

### CURRENTLY USED DRUGS FOR DIABETES

- 1. Insulin Secretagogues:** These drugs trigger the pancreas to produce insulin, which in turn helps to reduce the level of sugar in the blood. Examples include sulfonylureas and meglitinides.
- 2. Biguanides:** The group of medications which comprises metformin operates by reducing the quantity of glucose generated through the liver and enhancing the body's responsiveness to insulin.
- 3. Insulin Sensitizers:** These drugs, such as thiazolidinediones (TZDs), improve insulin sensitivity by activating certain receptors in the body.
- 4. Alpha Glucosidase Inhibitors:** These drugs slow down the digestion of carbohydrates in the intestine, which helps to prevent spikes in blood sugar levels after meals.
- 5. Incretin mimetics:** These medications imitate the function of incretin hormones in the human body, which trigger the production of insulin and decrease glucose levels in the blood. GLP-1 receptor agonists and DPP-4 inhibitors are among the drugs that fall under this category.
- 6. Amylin antagonists:** Amylin is a hormone co-produced by the pancreas with insulin. Medications known as amylin antagonists, including pramlintide, function by inhibiting the effects of amylin, resulting in reduced blood sugar levels.
- 7. SGLT2 inhibitors:** These medications function by inhibiting the kidney's SGLT2 protein, which lowers the quantity of glucose that is reabsorbed into the blood. As a result, blood sugar levels drop and urine glucose excretion rises.<sup>[24-26]</sup>

### TRADITIONAL /HERBAL MEDICINE FOR DIABETES

**Table 1: Antidiabetic Ayurvedic formulations.**

Marketed Ayurvedic drug	Composition of herbs
Dihar	Syzygiumcumini, Momordicacharantia, Emblicaofficinalis, Gymnemasylvestre, Elicostemma, Azadirachtaindica, Tinosporacordifoliaand Curcuma longa
Diabet	Curcuma longa, Cosciniumfenestratum, Strychnopotatorum, Phyllanthusreticulatus, Tamarindusindica, and Tribulusterrestris1
Diasol	Eugenia jambolana, Foenumgraceum, Terminaliachebula, Quercus, infectoria, Cuminumcyminum, Taraxacumofficinale, Emblicaofficinalis, Gymnemasylvestre, PhyllanthusniruriandElicostemmalittorale1
Diakyur	Cassia javanica, Cassiaauriculata, Salaciareticulata, Gymnemasylvestre, Mucunapruriens, Syzygiumjambolanum, and Terminalia arjuna <sup>[27]</sup>

### POLYHERBAL LIQUID FORMULATION

Polyherbal therapy, which involves combining multiple herbs, has been utilized in traditional Chinese medicine for centuries. Nonetheless, the effectiveness of this practice is still a subject of active research and discussion within the scientific community. One of the challenges in studying polyherbal therapy is the complexity of the herbal combinations, which often involve multiple herbs with different active compounds and mechanisms of action. This makes it difficult to isolate the effects of individual herbs and determine their specific therapeutic benefits. Despite these challenges, there is growing interest in exploring the potential therapeutic benefits of polyherbal therapy, particularly in

the areas of chronic diseases such as diabetes, cardiovascular disease, and cancer. Some studies have suggested that certain polyherbal combinations may have synergistic effects, enhancing the therapeutic benefits of individual herbs and reducing potential side effects. However, more rigorous research is needed to establish the safety and efficacy of polyherbal therapy, and to better understand the mechanisms of action and optimal dosages of these combinations. As with any form of medical treatment, it is important to consult with a qualified healthcare provider before using herbal remedies or polyherbal therapy.<sup>[28]</sup> Drug combination therapies have become an important approach in the treatment of various diseases, including cancer and infectious diseases. The therapeutic effect can be enhanced by using several medications with complementary modes of action, reduce drug resistance, and minimize the toxicity of individual drugs.<sup>[29]</sup> Naturally occurring herbs and There may be interactions between herbal constituents in different ways when combined in specific formulas. Some of the most common types of interactions include mutual enhancement, mutual assistance, mutual restraint, and mutual antagonism.<sup>[30]</sup> Polyherbal compounds are frequently used in the Ayurvedic system of medicine to treat various infections. Similarly, the Unani system of medicine also depends on diverse herbal formulations to treat different ailments.<sup>[31]</sup> Herbal medicine has a long and rich history dating back to ancient times when plants were used for medicinal purposes. This practice can be traced back to civilizations such as the Egyptians, Chinese, and Indians. However, the spread of medicinal herbs from Asia to Europe is a significant chapter in its history.

The Greeks gained knowledge of medicinal herbs from the Egyptians and Mesopotamians. Hippocrates, the famous Greek physician often referred to as the father of medicine, introduced the concept of using herbs for medicinal purposes. His writings on herbal medicine, such as the Hippocratic Corpus, have been studied and used by physicians for centuries. The Romans learned about herbal medicine from the Greeks and incorporated it into their own medical practices. Galen, the famous Roman physician, wrote extensively on the use of herbs, and his writings influenced medical practice for centuries. The Islamic world also played a crucial role in the spread of herbal medicine. With the fall of the Roman Empire, the Islamic world became a center of learning and innovation. Islamic scholars studied the works of Greek and Roman physicians, including Galen, and further developed the use of medicinal herbs from. Avicenna, the famous Persian physician, wrote the Canon of Medicine, which became a standard medical textbook in Europe for centuries. In Europe, the practice of herbal medicine was closely tied to the authority of the church. Monasteries and convents were centers of learning and medicine, and many of the herbal remedies used in medieval times were developed and practiced by monks and nuns. The church maintained the authority to grow medicinal herbs and to introduce new herbal medicines. Many medicinal gardens and herb gardens that still exist today were originally created by religious institutions. The spread of herbal medicine from Asia to Europe was a long and complex process that involved the exchange of knowledge and ideas between different cultures and civilizations. Today, herbal medicine continues to be an important aspect of healthcare, with many people turning to natural remedies to cure a range of illnesses.<sup>[32]</sup>

#### **POLYHERBAL FORMULATION'S BENEFITS OVER SINGLE HERB**

1. A Polyherbal formulations, which are blends of multiple herbs, possess a number of benefits over a single herb, including.
2. Synergistic effect: Different herbs in the formulation may have complementary or synergistic effects, enhancing the overall therapeutic benefit.
3. Broad spectrum activity: Polyherbal formulations may have a wider range of therapeutic activity compared to single herbs, as different herbs may target multiple pathways and have diverse biological activities.
4. Reduced side effects: Minimize dosages of each herb may be possible when using a combination of herbs, which

could minimize the possibility of adverse effects.

5. Better efficacy: Polyherbal formulations may have better efficacy in treating complex diseases or conditions, as the multiple herbs may target different aspects of the disease.
6. Tradition and cultural significance: Polyherbal formulations may be based on traditional knowledge and cultural practices and may have historical use and evidence of effectiveness and safety.

The combination of botanicals used in Ayurvedic and herbal medicines has a variety of chemical components that may have complementary therapeutic effects. Because the active ingredients in botanicals may combine to generate maximal therapeutic performance with minimal side effects, this offers a substantial potential advantage over conventional medications. However, as these products are derived from plant sources with inherent variability in species and growing conditions, caution must be exercised when combining them. Despite being widely used and frequently regarded as safe, herbal medications, their species and active constituents can vary. Because polyherbal formulations contain numerous active substances that can interact together synergistically to produce maximal therapeutic performance with minimal adverse effects, Compared to single-component drugs, they might have advantages.

There are two mechanisms by which synergism acts, namely pharmacodynamics and pharmacokinetics. Pharmacokinetic synergism focuses on the herb's ability to facilitate the ADME of other herbs. Pharmacodynamics synergism. Additionally, it is although the complexity of factors and complications contributes to most diseases, resulting in both visible and invisible symptoms. Furthermore, it has been found that complex disorders can be effectively treated with polyherbal formulations. The use of a single herb may not be sufficient to address all the symptoms of a complex disease, but a mix of herbs with different medicinal properties can provide a more comprehensive treatment approach. Herbs with anti-inflammatory, protective and analgesic qualities, for instance, can be combined in a polyherbal mixture to relieve a range of symptoms. Polyherbal formulations also offer the advantage of flexibility in terms of dosage and composition. Depending on the patient's particular requirements, the dosage and composition of a polyherbal formulation can be tailored to provide optimal therapeutic effects. This flexibility is particularly useful in treating chronic diseases, where the dosage and composition of the treatment may need to be adjusted over time to achieve the best results.

In the final analysis, using polyherbal formulations has many advantages to using single herbal formulations, such as better therapeutic effects, a decreased risk of adverse effects, more patient convenience, and more dosage and composition flexibility. As a result, polyherbal formulations are widely used in both modern and traditional medicine and are growing in popularity on the market.<sup>[33]</sup>

#### **ADVANTAGES OF HERBAL SYRUPS**

1. Good patient compliance.
2. They are more palatable.
3. Disguised the bad taste of medication.

**ADDITIONAL ADVANTAGES OF HERBAL SYRUPS INCLUDE**

1. Customizability: herbal syrups can be made with specific herbs and dosages to target individual health concerns or preferences.
2. Longer shelf life Incorporating honey, sugar, or alcohol into the herbal preparation can function as a preservative, extending its shelf life.
3. Increased absorption: The addition of honey or sugar can enhance the absorption of herbal constituents in the body.
4. Suitable for all ages: herbal syrups can be made with child-friendly flavours and dosages, making them a suitable option for both children and adults.
5. Versatility: herbal syrups can be used to address a variety of health concerns, including respiratory issues, digestive complaints, immune support, and more.<sup>[34]</sup>

**SOME CHALLENGES OR DRAWBACKS ASSOCIATED WITH TAKING TABLETS AND CAPSULES AS MEDICATION.**

1. **Chance of choking and chewing due to larger size:** This is a valid concern, particularly for people who have difficulty swallowing or children who might not be capable of swallow larger pills. In such cases, alternative forms of medication, such as liquids or chewable tablets, may be recommended. It's important to talk to your healthcare provider if you have difficulty swallowing pills.
2. **Limited dose flexibility:** Tablets and capsules typically come in pre-determined doses, which might not always be suitable for individual needs. But there are some medications that are available in different strengths or formulations to allow for greater flexibility in dosing. Again, it's important to discuss any concerns about dosing with your healthcare provider.
3. **Bitter taste of various tablets and capsules:** Some medications can possess a bitter taste, which has the potential to them difficult to swallow or unpleasant to take. There are various strategies that is useful to address this issue, such as using a flavoured coating or adding flavourings to the medication. Some medications may also be available in alternative formulations, like liquids or chewable tablets, which may have a more palatable taste.
4. **Taste masking requirement of tablets:** This is like the previous point, and strategies such as flavouring or alternative formulations may be employed to address the need for taste masking.
5. **Risk of direct swallowing:** Direct swallowing of tablets or capsules can be dangerous, particularly if they are not designed to be swallowed whole. It's fundamental to always follow the instructions for taking medication, and to talk to your healthcare provider if you have any concerns about how to take a particular medication. Challenges or drawbacks associated with taking tablets and capsules as medication.<sup>[35]</sup>

**Table 2: List of herbs used for polyherbal liquid formulation.**

S.no	Traditional Name	Botanical Name	Family	Active Ingredient responsible for Antidiabetic activity
1	Jamun Seed	Syzygium Cumini L.	Myrtaceae	Jambosine & Jamboline
2	Methi Seed	Trigonella-Foenum-graecuim	Fabaceae	Trigonelline
3	Curry Leaf	Murraya Koenigii	Rutaceae	Mahanimbine
4	Shahtoot Leaf	Morus Alba	Moraceae	Deoxynojirimycin
5	Karela Seed	Momordica Charantia	Cucurbitaceae	Charantin, vicine & Lectin

**Table: 3 List of scientifically reported synergistic antidiabetic polyherbal formulations.**

Herbal ingredients	Dosage form
Catharanthusroseus and Leucaslinifolia	Ethanol and Aqueous extract
Syzygiumcumini, Trigonellafoenum and Curcuma longa	Churna
Bacopamonneri, Hippophaerhamnoides, and Dioscoreabulbifera	Powdered
Glycosmispentaphylla, Tridaxprocumbens, and Mangiferaindica	Tablets
Luffaacutangula and Madhucalongifolia	Tablets
Annonasquamosaand Nigella sativa	Aqueous extract
Phyllanthus semblica and Annona squamosa	Aqueous extract
Cassia auriculata, Mangifera indica, Ficusbenghalensis, Cinnamon Mamala and Trichosanthesdioica	Aqueous extract
Gymnemasyvestre, Trigonella foenum and Phyllanthusemblica	Aqueous extract

## CONCLUSIONS

Polyherbal liquid formulations, which involve using a blend of different medicinal herbs in liquid form, have been investigated as a novel approach to treat non-insulin-dependent diabetes mellitus. The belief is that the combination of medicinal herbs in this formulation works synergistically to regulate blood glucose levels, improve insulin sensitivity, and reduce insulin resistance. Polyherbal liquid formulations have better patient acceptability than conventional allopathic medicines such as metformin and glimepiride, as patients may prefer herbal medicines due to perceived naturalness and fewer side effects. Furthermore, polyherbal liquid formulations are thought to have improved drug bioavailability, allowing the active compounds to be more easily absorbed and utilized by the body.. Polyherbal liquid formulations are also more cost-effective for patients than allopathic medicines, as many medicinal herbs utilized in this formulation are readily available and affordable. But it's crucial to remember that not all herbal medicines are safe or effective, and the use of polyherbal liquid formulations should only be done under the guidance of a qualified healthcare professional. Moreover, before this treatment option is suggested as a conventional treatment for non-insulin-dependent diabetic mellitus, more research is required to assess its safety and effectiveness.

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