Synergistic Effects of Nano-based Poly-herbal Formulations in Diabetes Management

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Abstract:

Diabetes mellitus is a chronic metabolic disorder marked by high blood sugar levels (hyperglycemia), mainly due to inadequate insulin production, insulin resistance, or both. It is broadly classified into Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent), with Type 2 diabetes being more common and strongly associated with obesity and sedentary lifestyles. According to the International Diabetes Federation, over 537 million adults globally are living with diabetes, and the number is expected to rise sharply, especially in low- and middle-income countries like India. Current treatment options, such as insulin injections and oral antidiabetic drugs, often show limited success. They may cause side effects like weight gain, gastrointestinal issues, and cardiovascular problems, and they generally do not address the root causes of the disease. These challenges have encouraged the exploration of alternative therapies. Polyherbal formulations, which combine multiple medicinal plants, are gaining attention as promising options. These formulations take advantage of the synergistic effects of various plant compounds, offering better glucose control with fewer side effects. When combined with nanotechnology, the benefits improve further. Nano formulations increase the solubility, stability, and absorption of herbal compounds, enabling targeted and sustained drug release. This reduces required doses and lowers toxicity. Polyherbal nanoparticles work through several mechanisms: they inhibit carbohydrate-digesting enzymes, enhance insulin release from pancreatic β-cells, improve insulin sensitivity, reduce inflammation and oxidative stress, and help maintain healthy lipid levels. Some commonly studied antidiabetic plant compounds include quercetin, curcumin, myricetin, berberine, ferulic acid, and glycyrrhizin. Though they have low oral bioavailability, this can be improved using nanocarriers like liposomes or polymeric nanoparticles. Studies using polyherbal nanoparticles have shown significant blood sugar reductions in animal models. In the future, new nanomaterials and personalized approaches may further enhance their use. Despite some challenges, nanobased polyherbal formulations hold strong potential as a modern strategy for managing diabetes effectively.

I. Introduction

Hyperglycemia, which can be caused by abnormalities in insulin secretion, action, or both, is a characteristic of diabetes mellitus (1). Type I diabetes, or insulin-dependent diabetes, and Type II diabetes, or non-insulin-dependent diabetes, or NIDDM , are the two forms of diabetes mellitus. Insulin production from β-pancreatic cells is insufficient in people with type 1 diabetes. However, Type 2 diabetes is directly linked to obesity and is defined by a gradual insulin resistance in the initial phase, which is followed by a decrease in the pancreatic hormone's ability to stimulate peripheral glucose disposal and suppress hepatic glucose production. Type I diabetes, sometimes referred to as immature diabetes, affects 5% of people with diabetes and is insulin-dependent. Type II diabetes is a non-insulin-dependent condition that often affects adults over the age of 40 (2). The International Diabetes Federation estimates that over 537 million adults are living with diabetes globally. Every country is seeing a rise in the number of persons with type 2 diabetes, with low- and middle-income nations housing 80% of those affected. In 2011, 4.6 million people died from DM. By 2030, 439 million individuals are predicted to develop type 2 diabetes. The environmental and lifestyle risk factors that contribute to type 2 diabetes cause significant regional variations in its incidence. According to predictions, within the next 20 years, there will be a significant increase in the prevalence of diabetes in adults, with type 2 DM becoming more common. Most of this growth is expected to occur in developing nations, where the majority of patients are aged 45-64 (3). The Diabetes Atlas 2006, released by the International Diabetes Federation, projects that 69.9 million Indians would have diabetes by 2025 if immediate preventive action is not taken, from the country's existing 40.9 million diabetics. .Type 1 diabetes involves autoimmune destruction of insulin-producing β-cells in the pancreas, while Type 2 diabetes is characterized by insulin resistance and β-cell dysfunction. In this disease, the pancreatic beta cells that produce insulin are attacked and destroyed by the immune system. A lack of beta cells might result in total insulin insufficiency. Because of this, blood tests for anti-IIA or anti-islet cell antibodies classify the condition as autoimmune. These result in the destruction of the pancreatic islets and lymphocytic infiltration. The disease can start quickly and spread over a few days to weeks, although the destruction might take longer. Rather than an absolute insufficiency, this syndrome is brought on by a relative lack of insulin (4). This indicates that there is not enough insulin produced by the body to meet requirements. Peripheral insulin resistance is accompanied by a beta cell deficit (5). When blood insulin levels are high but hypoglycemia or low blood sugar do not occur, this condition is known as peripheral insulin resistance. Changes in the insulin receptors that cause the activities of insulin may be the cause of this. The primary cause of insulin resistance is obesity. When oral medications are unable to provide enough insulin release over time, patients typically require insulin injections.

2. Challenges in Current Diabetes Management

Current therapies, including insulin and oral hypoglycemic agents, often have limitations such as side effects, inadequate glycemic control, and failure to address underlying causes. For any patient whose diet and activity do not result in satisfactory glycemic control, oral treatment is recommended. In a considerable proportion of patients, oral hypoglycemic medications may lose their effectiveness even though the initial reaction may be favorable. Meglitinide, biguanide, thiazolidinedione, alpha-glucosidase inhibitors, and sulfonylurea are among the medications in this group. Some side effects of these medications include sulfonylurea, which can lead to weight gain because of hyperinsulinemia (6). Alpha-glucosidase inhibitors may cause diarrhoea; biguanides may cause weakness, fatigue, and lactic acidosis; and thiazolidinediones may raise LDL cholesterol levels. When the maximum dosage of an oral drug does not provide the best glycemic control, insulin is typically added to the agent. Hypoglycemia and weight gain are frequent side effects of insulin. Severe insulin therapy may also result in a higher risk of atherogenesis. The staggering rise in diabetes cases has made the disease a significant public health concern for India. It is now a global health concern that affects people from all walks of life in many different nations, and the oldest medical system in the world, ayurveda, is being considered as a potential treatment for diabetes. Despite the fact that various artificial medications have been created for patients, no one has ever been known to fully recover from diabetes (7). Current oral hypoglycemia medications have unfavorable side effects. As a result, the anti-diabetic properties of medicinal plants and their herbal formulation in the treatment of illness have received a lot of attention recently.The growing interest in complementary and alternative medicine, including herbal formulations, due to their potential to address multiple aspects of diabetes.

3. Polyherbal Formulations and Nano Technology

Polyherbal formulations involve combining multiple herbs, which may have synergistic effects, enhancing the therapeutic outcome (8). A polyherbal formulation (PHF) is a preparation of herbal medicine that treats illness by combining several herbs in a particular ratio. In Ayurveda and other traditional medical systems, PHFs are an ancient treatment approach. Because of its synergistic action and minimal adverse effects, the polyherbal formulation significantly controlled diabetes compared to the individual herb. In order to improve patient compliance and prevent repetitive administration, phytotherapeutics requires a scientific way to distribute the herbal medications over an extended period of time. This can be accomplished by creating innovative drug delivery systems (5). In addition to lowering the need for repeated doses, nanotechnology is one such method that helps to boost the therapeutic value by decreasing toxicity and enhancing bioavailability. It is a component of drug delivery systems that increase the therapeutic index by distributing the drug evenly throughout the body through the bloodstream and delivering it exclusively to designated locations. Among the many benefits of a medicine delivery system based on nanostructure (i) Because of their ultra-tiny volume, they can pass through the smallest and narrowest capillary vessels; (ii) penetrate cells and tissue gaps to reach target organs like the liver, spleen, lungs, spinal cord, and lymph ; and (iii) provide controlled release for a prolonged period of time (9) . These unique properties make nanostructured-based drug delivery systems a better option for drug delivery than conventional drug delivery systems. Animal experiments showed that the nanoparticles (NPs) enter the bloodstream and end up in organs like the kidney and liver. They can also protect the drug from degradation in the gastrointestinal tract and release the incorporated drug in a controlled manner, minimizing side effects (10).

4. Role of Nanotechnology in Herbal Medicine

Nanotechnology in medicine involves manipulating materials on an atomic or molecular scale, especially to enhance drug delivery. Novel drug delivery systems (NDDS) such as polymeric nanoparticles, liposomes, phytosomes, microspheres, transferosomes, and ethosomes have made significant advances in plant therapeutics. According to reports, novel herbal formulations offer a number of benefits over conventional formulations, such as enhanced solubility and bioavailability, decreased toxicity, regulated drug administration, and preservation of plant active ingredients against deterioration. Drug delivery techniques at the nanoscale increase the effectiveness of herbal remedies and solve their drawbacks (11).

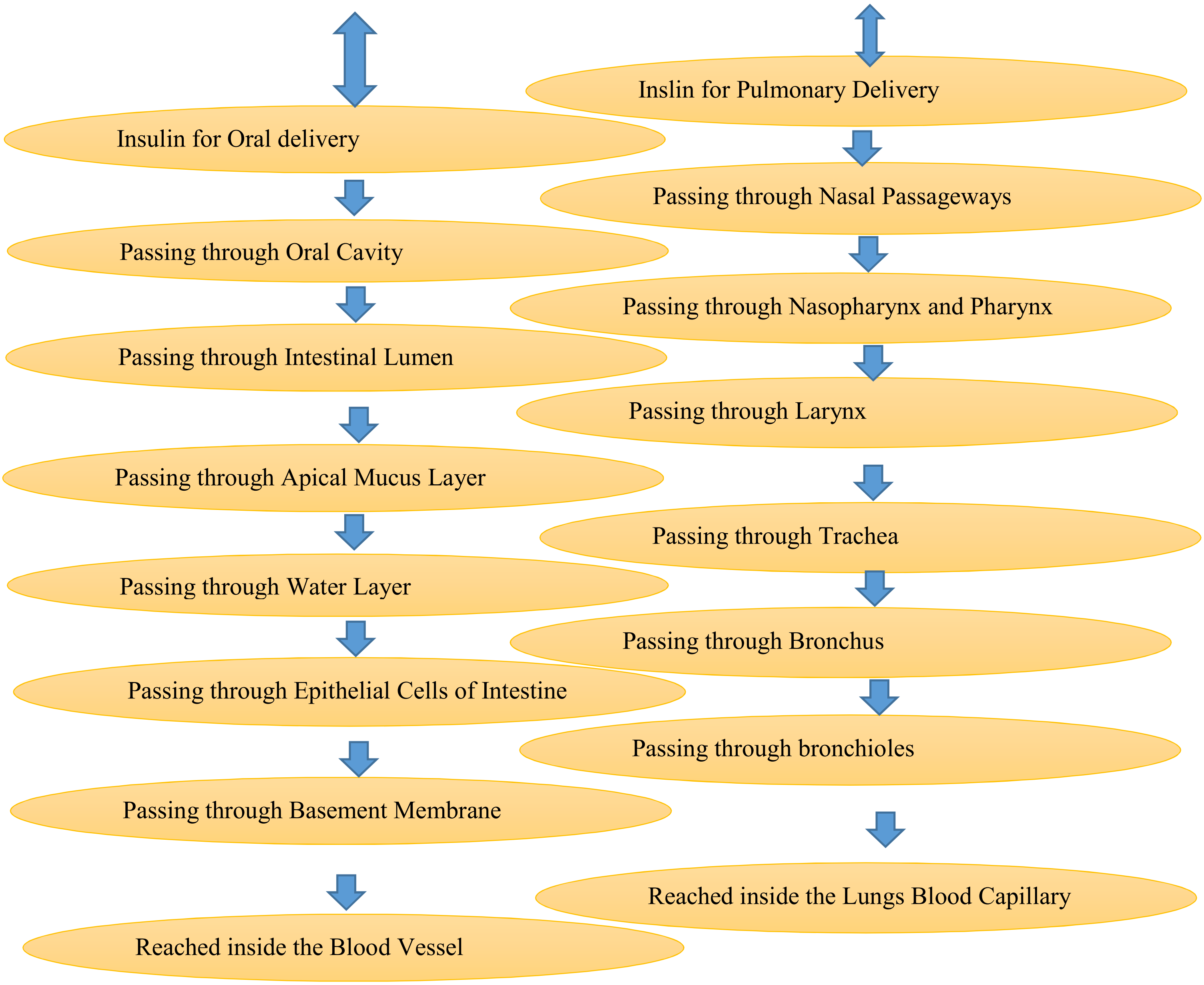
5. Roles and possible mechanism of nano-carriers in oral drug delivery system:

The physico-chemical characteristics of the medications (i.e., solubility, pKa, size, etc.) affect their bioavailability when taken orally. Depending on their size, several sites in the gastrointestinal tract (GIT) are used for the absorption of medications and particles. Intestinal macrophages phagocytose particles with a diameter of 1 µm, whereas particles smaller than 10 µm are carried by Peyer's patches, which are lymphatic islands found on the GIT. Enterocytes absorb nanoparticles (less than 200 nm) by endocytosis.(12) . The limited systemic bioavailability of medicines also affects their absorption and excretion due to efflux transporters including P-glycoprotein (Pgp) and enzymes produced on the surface of enterocytes. Because of their special characteristics, nanotechnology exposes the use of size-scale complex systems in a variety of sectors (6).

The delivery of the medication's active ingredient is one of the most researched applications of nanotechnology. Stable, biodegradable, non-toxic, non-inflammatory, non-thrombogenic, non-immunogenic, and able to pass through the reticuloendothelial system are all necessary for effective nanomedicine. Furthermore, nanomedicine ought to work with a variety of compounds, including proteins, nucleic acids, vaccinations, and tiny medications. Experimental evidence has demonstrated that nanoparticles with sizes ranging from 2 to 1000 nm can be used for imaging and therapeutic purposes.Moreover, nanotechnology may help with the intracellular and transcellular delivery of large macromolecules, the delivery of poorly water-soluble medications, the transcytosis of medications across the tight intestinal barrier, and the targeting of medications to a particular area of the gastrointestinal tract for oral administration. additionally, nanocarriers can be altered with certain ligands and directed to the receptors on the surface of epithelial cells to aid in the oral absorption of peptides and proteins. Poor absorption from the GIT is one of the many drawbacks of oral administration of several medications. By facilitating the adherence of nanocarrier to the mucosal epithelial membrane and aiding in the uptake of nanoparticles, bioadhesive polymers can help overcome such restrictions (13). Other than the oral delivery of drugs using nanocarriers, pulmonary means of delivery is also an efficient route (Fig. 1).

Oral Insulin Delivery Route using Nanocarrier

Pulmonary Insulin Delivery Route using Nanocarrie



6. Overview of Some Phytocompounds Having Antidiabetic Activity:

Plant parts such as leaves, fruit, seeds, flowers, exudate, bark, and roots can all contain phytocompounds that are used in raw or refined extracts or as nutritional supplements. Different sections of the same plant may contain different types of phytochemicals that are active. For instance, in Ficus capensis, the roots contain more tannins than the leaves, and the leaves have more flavonoids. Additionally, it has been noted that various plant parts can be used to treat various

illnesses. One well-known example is Mangifera indica, whose leaves heal lung disorders, coughs, and asthma, while its bark is used to treat diabetes and other ailments (14,15).
Phytomedicines, also known as plant-derived metabolites, have been shown in numerous studies to have positive effects on both type 1 and type 2 diabetes. These metabolites work through a variety of mechanisms (Figure 1), such as preventing intestinal glucose absorption by inhibiting intestinal glucosidase and pancreatic amylase, restoring functional cells, improving insulin secretion and expression, reducing insulin resistance, promoting glucose use, or preventing glucose production from liver cells, regulating carbohydrate and lipid metabolism, inhibiting the enzyme dipeptylpeptidase-4, and boosting antioxidant enzyme activity.

Herbal medications are used to treat diabetes and generally improve the patient condition when combined with a healthy lifestyle. Recent papers have focused on their many antidiabetic qualities, which have drawn a lot of interest from researchers. In this context, Salehi et al. enumerated a number of antidiabetic plants that are widely utilized in many parts of the world and discussed the potential antidiabetic effects of their extracted phytocompounds. Some of these widely utilised plant-extracted chemicals have poor bioavailability. Some of them have been included in formulations of nanoparticulates in order to investigate the enhancements in their antidiabetic and bioavailability. Quercetin, curcumin, naringenin, resveratrol, ferulic acid, myricetin, liquiritin, and baicalin are examples of phenolic compounds; berberine and betanin are examples of nitrogenous compounds; glycyrrhizin, gymnemic acids, thymoquinone, etc (16).

6.1. Quercetin:

Apples, onions, tomato seeds, berries, citrus fruits, buckwheat tea, and fennel are among the plants that contain quercetin, a polyphenolic component. It is implicated in numerous antidiabetic actions, including insulin secretion and sensitization, glucose level improvement, and prevention of intestinal glucose absorption, according to studies that have shown that it has strong antioxidant and anti-inflammatory propertie . By activating adenosine monophosphate and preventing the formation of free radicals by blocking lipid peroxidation, quercetin promotes glucose transporter 4 (GLUT4), the primary facilitator of glucose uptake in skeletal muscles, adipose tissues, and other peripheral tissues. It also has anti-allergic, anticancer, anti-ulcer, cardiovascular protective, and retinopathy prevention properties. It can be applied to stop variations in body weight and blood sugar. One oral dose of 400 mg of quercetin decreased -glucosidase activity and reduced postprandial hyperglycemia in rats with type 2 diabetes.After more than eight weeks, a new meta-analysis of individuals with metabolic diseases found that quercetin can significantly lower plasma glucose levels at doses larger than 500 mg/day. Therefore, the treatment's duration and dosage are crucial elements that affect its efficacy. Quercetin is licensed for human usage and has been found to be securely tolerated up to 2000 mg/day. However, the gastrointestinal tract absorbs it poorly because of its poor solubility and only approximately 2% to 6.7% is absorbed after oral administration. Additionally, its plasmatic peak is reached in 0.7–7.0 h (17).

6.2. Curcumin:

Curcumin is the primary active curcuminoid and a natural polyphenol of turmeric. It is derived from the roots of Curcuma longa, which has been utilized for a long time in traditional Chinese and Ayurvedic medicine and has drawn a lot of interest due to its many health benefits, such as its anti-inflammatory, anti-hyperglycemic, and antioxidant qualities (18). Curcumin has been demonstrated in numerous studies to enhance insulin sensitivity, lower hyperglycemia, raise insulin levels, decrease pro-inflammatory mediators like tumor necrosis factor-} (TNF-}) and interleukin (IL-6, IL-1~) in diabetic patients, and boost their overall antioxidant capacity. It promotes adenosine monophosphate-activated protein kinase (AMPK) enzyme and inhibits glucose 6-phosphatase (G6Pase) activity (19). Na et al. found that patients with type 2 diabetes who were overweight or obese experienced reductions in body mass index (BMI), fasting blood glucose, glycosylated hemoglobin, insulin resistance index (HOMA-IR), and free fatty acids after taking 300 mg of curcumin orally for three months. There was a documented 18% decrease in glucose levels and an 11% decrease in glycosylated hemoglobin when compared to the baseline. The Food and Drug Administration (FDA) has approved curcumin as safe, and it is safe to use up to 8 g daily. Curcumin has a limited oral bioavailability of about 1% because of poor digestive absorption, which leads to excretion even though it is recognized safely and has a variety of physiological effects (15,20).

6.3. Myricetin:

Fruits, berries, vegetables, teas, wine, and plants belonging to the Myricaceae (bark of Myrica nagi) and other families, including the Anacardiaceae, Pinaceae, Primulaceae, and Polygonaceae, are the primary sources of myricetin, a naturally occurring polyphenolic component. The Food and Agriculture Organization (FAO) and the U.S. Flavor and Extract Manufacturer Association (FEMA) have approved it as safe for use as an ingredient in beverages.

Its antidiabetic properties were reported in both in vitro and in vivo studies (21). Myricetin significantly inhibited -glucosidase and -amylase in an in vitro investigation published by Tadera et al. . Myricetin has been demonstrated to enhance the antioxidant properties of the enzymes glutathione peroxidase and xanthine oxidase as well as renal functioning in diabetic rats (22).

6.4. Berberine:

The alkaloid berberine is a member of the isoquinone group (23). It has been used to treat a number of illnesses, including diabetes, and can be found in a variety of plants, such as Phellodendron amurense, Berberis vulgaris, Coptis deltoidei, Coptis teetoides, and Berberis amurense. Berberine lowers glycated hemoglobin, plasma triglycerides, total cholesterol, postprandial blood glucose, and fasting blood glucose, according to studies. Berberine uses a variety of methods to produce its hypoglycemic effects. The AMPK pathway is triggered, glucokinase is regulated, glucose transporter activity is increased, glucose uptake is improved, gluconeogenesis is inhibited, glycolysis is promoted, insulin resistance is reduced, and receptor sensitivity is increased (24).

6.5. Ferulic Acid:

Numerous commonly consumed foods, including cereals, whole-grain foods, bananas, coffee, orange juice, eggplant, bamboo shoots, beetroot, citrus, cabbage, broccoli, and spinach, contain ferulic acid, a phenolic phytochemical that is well-known for its potent antioxidant and antidiabetic effects. According to reports, ferulic acid increases insulin secretion and cell sensitivity to insulin while inhibiting glucosidase {Citation}. After oral administration, ferulic acid is quickly absorbed (about 90%) and reaches its plasma peak concentration in 30 minutes (25).

6.6. Glycyrrhizin

Glycyrrhizin, a triterpenoid saponin that is more than 30 times sweeter than saccharose but does not raise blood sugar levels, is taken from the roots of several Glycyrrhiza species, including Glycyrrhiza uralensis, Glycyrrhiza glabra, and Glycyrrhiza inflata. Since of its many benefits, such as its antidiabetic and antioxidant qualities, and since the FDA has classified it as generally recognized as safe (GRAS), glycyrrhizin has been used for a long time in herbal medicine. It has been shown to decrease the postprandial rise in blood glucose and to upregulate GLUT4 and the peroxisome proliferator-activated receptor gamma (PPAR-). Although glycyrrhizin is highly soluble, its low and partial absorption makes it weakly accessible after oral dosing (26).

7. Case Studies of Specific Nanobased Polyherbal formulation in Diabetes.

A. Polyherbal Formulations with Documented Synergistic Effects:

Herbal Ingredients	**Dosage Form**	**Experimental Protocol**	**Mechanism of Action**	**Reference**
Momordica charantia, Trigonella foenum-graecum, Nigella sativa, and Ocimum sanctum	silver nanoparticle	Streptozotocin-induced Wistar albino rat model.	antidiabetic effect by attenuating the necrosis of pancreatic tissues	(27)
Andrographis paniculata, *Andrographis alata,* Adhatoda *zeylanica,* Gymnema sylvestre, Syzygium cumini, and *Justicia glabra*	Chitosan nanoparticle		reduced the serum glucose level	(28)
Momordica charantia, *Trigonella foenum-graecum* and *Withania somnifera*	Lyophilized hydro-alcoholic extracts	streptozotocin-induced diabetic rat model	destruction of islets of Langerhans, which results into decrease in serum insulin level	(29)
Tinospora cordifolia and Syzygium cumini	Nanosuspension	wistar albino rats	elevation in blood glucose level	(30)

Mehani is a polyherbal formulation containing *Tinospora cordiofolia, Curcuma longa Trigonella foenum gracum Emblica officinale and Salacia oblonga.*	Silver Nanoparticles (AgNPs) and Iron Nanoparticles (FeNPs)	absorbance was read at 540nm by using UV Spectroscopy	Inhibition of Alpha amylase	(31)
Combined flavonoid-rich extract from fruits of *Citrullus colocynthis* (L.) *Momordica balsamina* and *Momordica dioica*	Phytosomes	Streptozotocin-nicotinamide-induced diabetic rats	Sustained release of the flavonoid High antidiabetic efficacy of 100 mg/kg per day of the phytosomes than 250 mg of the free methanolic extract	(32)
Azadirachta indica, *Hibiscus rosa-sinensis*, *Murraya koenigii*, *Moringa oleifera*, and *Tamarindus indica* aqueous leaves extract Mulberry leaf and Pueraria lobata ethanolic extracts	Zinc oxide nanoparticles (ZnONPs) Selenium nanoparticles (SeNPs)	In vivo hypoglycemic effect in diabetic rats	Exhibition of appreciable α-amylase and α-glucosidase inhibitory activity Significant hypoglycemic effects with decrease in blood glucose	(33)
Polyherbal Formulation Containing Tinospora cordiofolia, Curcuma	Iron nanoparticles (FeNPs)	In vitro _-amylase inhibitory assay	Equivalent _ amylase enzyme inhibitory activity	(20)

longa Trigonella foenum gracum, Emblica officinale, and Salacia oblonga methanolic extract			(70.48%) to the standard ascorbic acid (73.87%) at the maximum concentration of 250 _g/mL	

8. Future Perspectives and Opportunities

Emerging technologies in the field of nanomedicine are opening new avenues for improving the efficacy, safety, and precision of polyherbal formulations used in diabetes management. The development of novel nanomaterials, such as dendrimers and polymeric nanoparticles, has the potential to enhance the bioavailability and targeted delivery of phytoconstituents, thereby minimizing systemic side effects and maximizing therapeutic outcomes. The concept of personalized medicine further extends this innovation, allowing customization of polyherbal nanoparticle formulations based on individual genetic, metabolic, and microbiome profiles to achieve patient-specific therapeutic responses. Moreover, integrating these advanced polyherbal nanoparticles with conventional antidiabetic drugs could offer synergistic effects, resulting in improved glycemic control and reduced drug resistance. Despite these promising prospects, substantial research gaps remain, necessitating further studies to elucidate the long-term safety, pharmacokinetic behavior, optimal phytochemical combinations, and underlying molecular mechanisms of polyherbal nanoparticles. Such investigations will be crucial for translating these emerging technologies into clinically viable and standardized therapeutic interventions.

9. Conclusion

The global prevalence of diabetes continues to rise, presenting a significant challenge to healthcare systems worldwide. Current management strategies, including insulin and oral hypoglycemic agents, often fall short due to limitations such as side effects, inadequate glycemic control, and the inability to address the multifactorial nature of the disease. In this context, nanobased polyherbal formulations have emerged as a promising alternative, offering a multi-targeted approach to diabetes management by combining the therapeutic benefits of multiple herbs with the advanced delivery capabilities of nanotechnology. The future of nanobased polyherbal formulations in diabetes management is highly promising. Continued research and development, along with rigorous clinical evaluation, are essential to fully realize their potential. Emerging technologies, such as new nanomaterials and advanced drug delivery systems, could further enhance the efficacy and safety of these formulations. By addressing the current challenges and exploring new opportunities, nanobased polyherbal formulations could revolutionize diabetes care, offering a more effective, multi-targeted, and patient-centered approach to managing this complex disease.

In conclusion, the synergistic effects of nanobased polyherbal formulations hold great promise for transforming diabetes management. With ongoing innovation and research, these formulations could become a cornerstone in the fight against diabetes, providing a safer and more effective alternative to current therapies.

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