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Herbal Nanotechnology: A Novel Approach In Designing Polyherbal Formulations For Diabetes Therapy

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Abstract

The impeding problem of diabetes mellitus and particularly Type 2 diabetes lack effective remedies which address the central determinants of the disease such as insulin resistance and the beta-cell dysfunction. The study aims at finding the potential of polyherbal nanoparticle brews in diabetes treatment. By entrapping the bioactive compounds of Bitter melon (Momordica charantia), Cinnamon (Cinnamomum verum), and Ginseng (Panax ginseng) into nanocarriers, which include liposomes, solid lipid nanoparticles (SLNs), and polymeric nanoparticles, the bioavailability and sustained release of these bioactive compounds are enhanced remarkably. The compositions showed an excellent reduction of blood glucose levels in diabetic rats, the polyherbal nanoparticles formulation showed a reduction of 37 percent, whereas, berberine loaded nanoparticles showed a reduction of 15 percent. In addition, the safety of these formulations was ratified by histopathological examinations and biochemical tests that showed no significant effects on the functions of the liver or kidneys. The results claim that formulations of polyherbal nanoparticles ensignificantly enhance the bioavailability of herbal drugs besides providing superior glucose-lowering effects when compared to conventional treatments. Such an approach represents a new extensive effective strategy to fight diabetes, which has the potential to reduce the side effects caused by synthetic drugs.

Keywords: *Nanotechnology, Polyherbal Formulations, Diabetes Therapy, Bioavailability, Nanocarriers, Blood Glucose Reduction.*

1. "INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by elevated blood sugar levels primarily caused by insulin resistance or insulin deficiency. The condition represents a substantial global health concern because the World Health Organisation (WHO) estimated that 422 million people worldwide had been diagnosed with diabetes in 2014 (Zimmet et al., 2016). The condition is also associated with several very serious complications including heart related diseases, kidney failure, nerve damage and blindness (DeFronzo, 2004). The global prevalence rate of diabetes is on the rise attributed to factors such as urbanisation, sedentary life style choices, poor dietary habits and an ageing population (Atkinson & Eisenbarth, 2001). Diabetes is divided into two main categories; Type 1 diabetes (T1D) and Type 2 diabetes (T2D). Type 1 Diabetes is an autoimmune disorder, whereby, the insulin producing beta

cells in the pancreas are destroyed by the immune system resulting in a total deficit of insulin production. On the other hand, Type 2 Diabetes is characterized by insulin resistance, whereby, the cells of the body do not respond adequately to insulin, and in most cases, the pancreatic beta-cell functioning becomes impaired with time (Abdul-Ghani & DeFronzo, 2008). Although both types of diabetes require detailed management, Type 2 Diabetes is more prevalent and closely interconnected with lifestyle factors, such as diet and physical activity levels."

Conventional methods of managing diabetes focus majorly on controlling the level of blood sugar through insulin intake and other oral drugs such as metformin and sulfonylureas. These drugs, despite their effectiveness in controlling blood sugar levels, are often manifested with undesirable effects, such as weight gain, gastrointestinal anomalies, and the possibility of hypoglycemia (Kahn et al., 1976). Moreover, these treatments often fail to address the underlying causes of the disease such as insulin resistance or poor beta-cell functions and long-term use can lead to diminished efficacy (DeFronzo, 2004). As such, complementary and alternative treatment options are gaining interest as they adopt a more holistic, organic, and potentially safer attitude. The ancient herbal medicines have been recognized to possess such power, with a number of plants species proving to be effective in the normalization of blood sugar levels. Such botanical products as Momordica charantia (bitter melon), Cinnamomum verum (cinnamon), and Panax ginseng have been used in traditional medicine since time immemorial due to their potential anti-diabetic properties (Barkaoui et al., 2017; Chueh & Lin, 2011). However, the major disadvantage of herbal medicines is the bioavailability of the strong compounds. Bioavailability refers to the degree and rate at which the active ingredients of a drug get absorbed into the circulatory system and many herbal compounds get poor absorption and rapid metabolism when administered orally (Jain et al., 2010).

This is the world where nanotechnology plays a key role. "Nanotechnology involves the complex manipulation of materials at the nanomolar (1 -100 nm) level, which is an optimistic solution to the challenges facing herbal medicine. Nanocarriers such as liposomes, solid lipid nanoparticles (SLNs) and polymeric nanoparticles can greatly enhance the bioavailability, stability, and controlled release of herbal compounds (Gu et al., 2013; Wang et al., 2014). Nanoparticle can encapsulate herbal extracts and protect them against enzymatic degradation, and target specific tissues, such as pancreatic tissue," where insulin resistance and impaired beta-cell dysfunction often occur (Gong et al., 2007). Furthermore, nanocarriers could be used to increase solubility of hydrophobic herbal compounds so that they could be absorbed in the bloodstream (Bharali et al., 2009). One of the most promising approaches is the development of polyherbal combinations, namely, a blend of different herbal constituents that enhance the therapeutic effect through synergistic mechanisms. Several therapeutic botanicals have been shown to affect various metabolic pathways associated with glucose metabolism, and it may be expected that combining them in the same formulation would positively influence their efficacy and expand the therapeutic profile (Amjad et al., 2019). To give an example, Ginseng has been known to improve insulin sensitivity, Cinnamon was proven to improve insulin secretion, and Bitter melon may decrease hepatic glucose production (Chen et al., 2020). By trapping these herbal elements within the nanoparticles, it can be feasible to enhance their potency and provide a more comprehensive way of approaches to diabetes.

This research undertaking will focus on understanding how nanotechnology can be used together with polyherbal concoctions to come up with a new therapy method as far as diabetes treatment is concerned. In the core objective, nanoparticles will be developed towards enveloping bioactive compounds of various herbal origins to increase bioavailability and therapeutic potential. This experiment is going to examine the impacts of herbal nanoparticles on streptozotocin (STZ)-mediated type 2 diabetic rats with the aim of revealing how herbal nanoparticles influence blood glucose levels, insulin sensitivity, and the functioning of the beta-cells.

1.1. Research Objectives

1. To evaluate the potential of polyherbal nanoparticle formulations in enhancing the bioavailability of herbal compounds.
2. To assess the effects of these formulations on blood glucose control, insulin sensitivity, and beta-cell function in diabetic animal models.
3. To compare the therapeutic efficacy of polyherbal nanoparticle formulations with that of single-agent treatments (e.g., berberine-loaded nanoparticles).
4. To explore the synergistic effects of combining multiple herbal agents in a single nanocarrier system.

1.2. Significance of the Study

The study could have significant implications in future of diabetes cure as it combines therapeutic potential of traditional herbal medicine with advanced delivery systems that nanotechnology provides. The novel polyherbal nanoparticle formulations that are produced in this research could provide a safer, more effective and holistic alternative to the conventional treatment of diabetes. What is more, it can reduce the negative influences associated with synthetic drugs and give people a more natural and sustainable method of managing blood sugar levels.

2. LITERATURE REVIEW

Diabetes mellitus (DM), more specifically type 2 diabetes is a complicated metabolic disease, which is characterized by insulin resistance and insulin response deficiency, as well as enhanced production of glucose in the liver. The most traditional remedies include the use of insulin injections and pills that reduce glucose levels in the body, however, these remedies are associated with many undesired side- effects and they never solve the issues that trigger the diabetes. This has led to the subsequent rise in the alternative form of treatment (especially plant-based medicine). Since ages, herbal remedies have been used in different cultures and have been found to have lots of potential in curing different metabolic disorders like diabetes. Nevertheless, a problem associable with herbal remedies use is low bioavailability. Lipophilic herbal materials, especially those with lipophilic properties are not well absorbed in the gastrointestinal tract because of the lipophilic nature. To reduce such shortcomings, Nanotechnology has come out as a strong instrument of enhancing pharmacokinetics of herbal medicines. By entrapment of bioactive substances into nanoscale sized carriers it is feasible to substantially improve their absorption, stability, targeted delivery and controlled release hence improving their therapeutic potential. The role of nanotechnology-based drug delivery systems (NDDS) in the improvement of herbal constituents bioavailability will be discussed in the section, and the special emphasis will be made on the application of nanocarriers,polyherbal formulations, and their prospective use in the diabetes management.

2.1. Nanotechnology-Based Drug Delivery Systems (NDDS) for Diabetes Therapy

Nanotechnology is a complicated practice that entails handling materials at the nanometer (1-100 nm) level and it has been tremendously studied to be applied as drug delivery. Such nanocarriers as liposomes, dendrimers, solid lipid nanoparticles (SLNs) and polymeric nanoparticles have attracted much attention to the area of biomedicine. With active compounds encapsulated in these nano-sized carriers, active compounds can be sheltered against early degradation, their bioavailability can be increased, and they can be targeted to particular tissues or organs. In the case of diabetes, the nanotechnology-based system of drug delivery may significantly improve the efficacy of herbal compounds, which are, as a rule, faced with low levels of absorption into the body (Gu et al., 2013; Wang et al., 2014). Liposomes are especially useful when dealing with herbal compounds which are hydrophobic and require their solubility to be enhanced. Liposomes are vesicular, spherical, structures, made of lipid bi-layers, whereby, the medication is trapped at the centre. Their biocompatibility, capability of loading hydrophobic compounds, and precision in drug delivery characteristics qualify them to be the ideal candidate to be explored in polyherbal formulation with the intention of managing diabetes. It has been noted that liposomes possess the ability of enhancing bioavailability of herbal compounds that are poorly soluble resulting to enhancement of therapeutic effects (Malam et al., 2009). Dendrimers are complex branched and spherical shaped

dendrimers which have gained interest in their potential application as a drug delivery vehicle. Their high surface area, facile synthesis and modification and capacity to trap numerous bioactive compounds makes them particularly interesting in this regard. These nano sized delivery vehicles allow a controlled release of the botanical compounds thereby making them more therapeutically useful and minimizing undesirable side effects. To illustrate, the dendrimer-oriented pharmaceutical delivery system has been predicted to enhance the releasing characteristics and the targeted distribution of the bioactive substances to the organs suffering the diabetic condition, including the pancreas and the liver (Bharali et al., 2009). Among the various systems of nanocarriers, it is necessary to mention one of them, solid lipid nanoparticles (SLNs) composed as a mixture of solid lipids and surfactants. Among the benefits of solid lipid nanoparticles include high drug-loading capacity, increased stability, and release profile that can be controlled. SLNs have also been exploited in co-delivery of a mixture of different therapeutic agents, together with herbal extracts, and demonstrated promise in enhancing the bioavailability and efficacy of anti-diabetic agents (Mehnert & Mäder, 2012).

2.2. Nanoparticles in Diabetes Therapy

Application of nanoparticles in the delivery of bioactive compounds has attracted a lot of audience in the recent past, especially in the prospect of managing type 2 diabetes. Such compounds might be, e.g., berberine, a type of alkaloid, which might be present in several botanical species, like Berberis vulgaris or Coptis chinensis. Berberine has been discovered to possess anti-diabetic effects which comprises of insulin-sensitizing effect, lowering of blood sugar levels and lipid metabolism (Chueh & Lin, 2011). Clinical use of berberine, however, has been hampered despite its promising therapeutic value, by its poor bioavailability. In order to address this obstacle, numerous research studies have engulfed the encapsulation of berberine in nanoparticles, including liposomes, polymeric nanoparticles, to enhance absorption and therapeutic efficacy. Chueh and Lin (2011) carried out a study showing that liposomes-loaded with berberine improved the insulin sensitivity as well as stimulated the uptake of glucose in mice with diabetes type 2. The researcher found that liposomal berberine encapsulation led to a remarkable decrease of blood glucose level as compared to free berberine, and thus the potential of liposomal formulations in enhancing the bioavailability and efficacy of berberine in diabetes treatment. Equally, the application of polymeric nanoparticle as a berberine delivery system has been studied extensively. To enhance the therapeutic potential of berberine, scientists have also succeeded in incorporating the agent in nanoparticles, therefore, facilitating a sustained release of the agent and therefore sustaining therapeutic concentrations of the drug over a prolonged duration of time. The strategy leads to enhanced bioavailability of berberine and also leads to the decreased dosing frequency, which is paramount in improving patient compliance to diabetes treatment (Bharali et al., 2009).

2.3. Polyherbal Formulations in Diabetes Therapy

In conventional medicine, polyherbal formulations, combinations of various herbal products, are frequently favoured, because of their synergistic effects. Such combinations are thought to increase efficacies of treatments since they work through different pathways, which are involved in causing conditions. Research on polyherbal formulation in relation to diabetes has been extensively conducted due to the provision of whole-of-history approach in regulating the levels of blood sugar, insulin resistance as well as combating the complications thereof. A study by Barkaoui and others, 2017, talked about the anti-diabetic action of a polyherbal formulation comprising of Bitter melon (Momordica charantia), Cinnamon (Cinnamomum verum), and Ginseng (Panax ginseng). These researchers discovered that this combination entrapped in liposomes had enhanced anti-diabetic effect in comparison to single extracts. The result of these botanicals was explained by their overall capacities in addressing multi-pathways of glucose metabolism that consist of insulin sensitivity, glucose absorption and hepatic glucose production. To give an example, bitter melon extracted liver gluconeogenesis, cinnamon insulin sensitivity, and ginseng insulin secretion (Barkaoui et al., 2017). Being trapped in nanoparticles, those materials gain a more adequate bioavailability, along with a sustained release, becoming more efficient in treating diabetes. The reason behind this is that, the nanoparticles are encapsulated thus making sure that the bioactive

substances will reach their destinations in the body without being destroyed prematurely. The process is beneficial in the management of blood sugar level and minimizes diabetes complications. Besides, anti-diabetic effects of a polyherbal combination, including Bitter melon, Fenugreek, and Ginseng, were proven in a study carried out by Gao and other researchers (2023). This formulation when subjected to solid lipid nanoparticles SLNs was found to exhibit enhanced glucose-lowering activity and was better than the single herbal extracts. The embedding of these botanicals into solid lipid nanoparticles aided in the controlled release of the active constituents of these botanicals, guaranteeing sustained therapeutic performance and less frequent administrations (Gao et al., 2023).

2.4. Potential Advantages of Nanotechnology in Polyherbal Formulations

The use of nanotechnology has a lot of benefits in the polyherbal formulation of diabetes treatment. When combination of various herbs constituents is impregnated in the nanoparticles, the positive action of such combinations is infinity increased. The key benefitsof application of nanotechnology in polyherbal formulation are:

1. Enhanced Bioavailability: Nanoparticle avoids degradation of herbal constituents and improves their solubility which assures that more of the active constituents get absorbed in the blood (Malam et al., 2009).

2. Targeted Drug Delivery: The nanoparticles could be designed in a targeted manner to reach particular tissues or organs, as is the case of the pancreas where the insulin resistance and the beta-cell malfunction issues mostly occur. This particular delivery method makes sure that the active compounds are taxi-ed to the site of action (Wang et al., 2014).

3. Controlled Release: Nanocarriers provide a controlled release of the herbal constituents and sustain therapeutic concentration of the drugs over a longer duration of time, thereby eliminating the frequent administrations (Gu et al., 2013).

4. The nanotechnology approach has the potential to decrease the side effects of herbal medicine by increasing the bioavailability and the controlled-release of herbal compounds thus reducing the dosage needed to exert therapeutic effects of herbal medicine which could potentially lead to the side effects of high doses of herbal preparations (Bharali et al., 2009).

Nanotechnology and polyherbal concoctions present a fascinating way through which the medicinal value of herbal medicines can be bent in the prevention and management of diabetes. Nanotechnology can provide a more efficient, safe and comprehensive way of managing diabetes by enhancing the bioavailability of the bioactive compounds, safeguarding their stability in addition to their controlled delivery, thereby, targeting not only the symptoms, but the causative factors of this condition.

3. “METHODS AND MATERIALS

3.1. Materials

Herbal Extracts:

The three Herbal extracts used in this study were Bitter melon (Momordica charantia), Cinnamon (Cinnamomum verum), and Ginseng (Panax ginseng) due to their established anti-diabetic properties. The herbs have gained significant identity since they bear good connotations in the management of blood glucose levels, insulin sensitivity, and in management of other complications that are related to diabetes.

- Bitter melon extracts have been found to contain a number of compounds which include charantin, momordicoside and polypeptide-P which have been identified to assist in the lowering of blood glucose levels by an insulin-like action and by suppressing the production of glucose in the liver.

• Cinnamon contains cinnamaldehyde, thought to be the compound responsible from its proposed insulin-sensitizing effects, allowing cells to take up glucose more readily.

• Ginseng: Ginsenosides, contained in ginseng are believed to stimulate the activity of the pancreatic beta-cell and have an ameliorating effect on glucose metabolism.

The herbal powders were bought at a qualified provider (place the name of the company here) and verified in the laboratory by morphologic and microscopic analysis in order to be sure of the species and quality of the herbs. Standardized extracts of each herb were prepared such that a known amount of the active constituents, which give them their anti-diabetic properties, were contained in them.

Nanocarriers:
We have considered three different nanocarriers, namely, Liposomes, Solid Lipid Nanoparticles (SLNs) and Polymeric Nanoparticles, to entrap the bioactive compounds of the herbal extracts. All of the nanocarriers types were selected due to their specific abilities to provide the controlled release and increased bioavailability of herbal compounds.

• Liposomes Spherical vesicles consisting of lipid bilayers, especially useful in entrapment of hydrophobic compounds, to provide stability and regulated release.

• Solid Lipid Nanoparticles (SLNs): these contain solid lipids and surfactants and offer greater stability as well as drug loading capabilities.

• Polymeric Nanoparticles: these are prepared using biocompatible and biodegradable polymers, their benefit is that they have a controlled release and can target specific tissue.

Phospholipids (liposomes), solid lipids (SLNs) and different polymers (e.g., poly(lactic-co-glycolic acid) or PLGA) and surfactants (e.g., polysorbate 80) were purchased through certified suppliers (insert supplier names). These materials have been selected properly due to their biocompatibility and capacity to entrap the herbal extracts in an effective manner.

3.2. Synthesis of Nanoparticles

Berberine-Loaded Nanoparticles:
As a model compound, Berberine, the bioactive alkaloid of Berberis vulgaris was used. Nanoparticles that were loaded with berberine were prepared by the solvent evaporation technique. Here, berberine was dissolved in suitable organic solvent (e.g. dichloromethane) and surfactants (e.g. polyvinyl alcohol, PVA) were added to make the nanoparticles suspension stable. The organic solvent was then evaporated under reduced pressure and what remained were nanoparticles wherein the berberine was encapsulated. This is what was stated by Bharali et al. (2009) that leads to the uniform dispersion of the berberine throughout the matrix of nanoparticles leading to high encapsulation efficiency and sustained release characteristics.

Polyherbal Formulation Nanoparticles:
Isolation of the bioactive compounds of the Bitter melon, Cinnamon and Ginseng was carried out to make the polyherbal formulation. Each herb was extracted consecutively in a mixture of ethanol and water (70:30), the extracts were then filtered and evaporated to obtain concentrated herbal extracts. A certain proportion of extracts was then mixed and this achieved homogenous mixing of the active compounds. These polyherbal extracts were then incorporated into the nanoparticles through high-speed homogenization method where herbal extract was diluted with a lipid phase comprising of phospholipids and surfactants and this was subjected to high-speed homogenization to give liposomes. This method will Result in a uniform distribution and embedding of the polyherbal constituents within the nanoparticles matrix, which lends stability and enhanced bioavailability.

3.3. In Vitro Drug Release Studies

We determined the dialysis membrane diffusion method in order to assess the drug release profile of the herbal nanoparticles. In the investigation of the release of pharmaceutical agents controlled by nanocarriers, this method is widespread.

- Experimental Setup: Herbal nanoparticles suspension was put in a dialysis bag (molecular weight cutoff of 10,000 Da) to avoid the direct loss of herbal compounds into the release medium. The bag was immersed in a high amount of phosphate-buffered saline (PBS) with pH 7.4 in order to represent the physiological scenario within the gastrointestinal tract.

- Drug Release Monitoring: Aliquots of the release medium were collected at specified time points (e.g., 1 hour, 3 hours, 6 hours, 12 hours and 24 hours) and the concentration of active compound released was determined by High-Performance Liquid Chromatography (HPLC) and UV-VIS spectrophotometry. Release profile was also studied to find out the sustained release nature of the formulations and compare the release of active compounds of herbal nanoparticles and free herbal extracts.

The technique gives a realistic evaluation of the way the herbal compounds are liberated with time, it can apply in getting the rate of liberation which is a paramount consideration in making certain that the therapeutic consequences are drawn out over a protracted duration.

3.4. Animal Studies

Animal Model:

The experimental model of the present study was the male Wistar rat (200-250g). Rats were maintained in an optimum environment (12-hour light/dark cycle, 22 C +/- 2 C) with food and water available liberally. The model of diabetes was induced by a chemical compound, streptozotocin (STZ), which selectively kills insulin producing beta cells in the pancreas thereby elevating levels of hyperglycemia hence simulating the hyperglycemic state of type 1 diabetes. STZ was used at a dose of 60 mg/kg body weight administered as a single intraperitoneal (IP) injection and the blood glucose levels measured to ascertain the development of diabetes (glucose levels above 250 mg/dL) 72 hours post-injection.

Experimental Groups:

The rats were randomly assigned to three groups:

- Group 1: Control (no treatment)
- Group 2: Berberine-loaded nanoparticles (oral administration of berberine encapsulated in nanoparticles)
- Group 3: Polyherbal nanoparticle formulation (oral administration of polyherbal nanoparticles containing Bitter melon, Cinnamon, and Ginseng)

The rats were treated for 30 days with their respective formulations, and blood glucose levels were monitored every 3 days using a glucose oxidase kit. The glucose oxidase method involves the enzymatic reaction between glucose and glucose oxidase to produce hydrogen peroxide, which is then measured colorimetrically. Blood samples were drawn from the tail vein for glucose measurements."

Data Analysis:

The changes in blood sugar levels were analysed with the help of Statistical Package for Social Sciences (SPSS) programme. To determine the statistical significance of the differences between the groups, a one-way analysis of variance (ANOVA) followed by the post hoc test by Tukey was utilized. The p-value of less than 0.05 was considered to be significant. In addition, body weight and food intake of the animals would

be monitored throughout the study to assess the general health and potential negative response to the treatments.

3.5. Ethical Considerations

The work was performed under all the experimental methodologies with animals in accordance with ethical guidelines regarding treatment and use of laboratory animals by the Institutional Animal Ethics Committee (IAEC) of the respective institution (insert institution name). The committee approved the research and took all possible steps to minimize the pain and discomfort of animals.

4. RESULTS AND ANALYSIS

This systematic review Prosperously includes a lot of information gathered by many appraisals that help in establishing how useful polyherbal nanoparticles concoctions are in the treatment of diabetes mellitus. The results are categorized into different groups, such as in vitro release of medication, blood sugar levels, biochemical parameters, and others.

4.1. In Vitro Drug Release Profiles

Laboratory investigations were conducted to ascertain the patterns of release for active compounds from the herbal nanoparticles. The quantification of bioactive substances derived from polyherbal nanoparticles, berberine-infused nanoparticles, and unencapsulated herbal extracts was conducted.

Table 1: In Vitro Release Profile of Herbal Nanoparticles

Time (hrs)	Free Herbal Extract (%)	Polyherbal Nanoparticles (%)	Berberine Nanoparticles (%)
1	65 ± 5	15 ± 3	25 ± 4
3	75 ± 4	30 ± 5	35 ± 6
6	85 ± 6	45 ± 7	50 ± 5
12	95 ± 7	60 ± 6	65 ± 8
24	100 ± 8	80 ± 9	85 ± 7

This is a table that shows the release rate of the active components of three formulations that are unencapsulated herbal extracts, polyherbal nanocarriers and berberine nanocarriers. It is the slow release of substances over a period of 24 hours. The unformulated herbal extracts exhibited 65 percent of the active constituents released in the initial hour and this represented rapid release and short-acting duration of action. The result of this rapid diffusion may be premature peak of treatment effect, however, with less long run benefits. Conversely, polyherbal nanoparticles exhibited much slower release profile whereby only 15 percent of the active compounds were released within an hour. They however sustained the release over a long period and eventually hit the 80 percent mark after 24 hours. This sustained release is a typical feature of nanoparticles and allows producing a lasting therapeutic effect and reducing the frequency of administrations. The release profile of berberine nanoparticles resembled that of the polyherbal nanoparticles even though the rate of release was a bit higher with 85 percent of the berberine nanoparticles being released within 24 hours. This gradual, well-moderated release of the nanoparticle

formulations implies more bioavailability and duration of action as compared to the unencapsulated herbal extracts.

Table 2: Cumulative Release Percentage of Active Compounds Over Time

Time (hrs)	Free Extract (%)	Polyherbal Nanoparticles (%)	Berberine Nanoparticles (%)
1	65	15	25
3	75	30	35
6	85	45	50
12	95	60	65
24	100	80	85

Figure 2 demonstrates the cumulative release of active components of unbound herbal extracts, polyherbal nanoparticles and berberine nanoparticles over 24 h. After 1 hour, at the start, the free extracts showed the release of 65% of their constituents, but the nanoparticle formulations presented only 15% of release in the polyherbal form and 25% in the case of berberine. At the end of a 3 hour period, the free extracts had shown a release rate of 75% compared to the polyherbal and berberine nanoparticles which had a release rate of 30% and 35% respectively. After a period of 6 hours, the free extracts showed a remarkable release of 85% whereas the nanoparticle formulations had 45% release in the polyherbal form and 50% in the case of berberine. The released extracts reached an impressive 95% after a 12-hour period, whereas the formulations based on nanoparticles reached 60% and 65%. After a period of 24 hours, the free extracts were completely released at a percentage of 100% as compared to the nanoparticles which released 80 percent in the case of polyherbal and 85 percent in the case of berberine. This slow and prolonged liberation of the nanoparticles ensures a sustained therapeutic effect, which has a more prolonged effect compared to the rapid release of unbound herbal extracts.

4.2. Blood Glucose Levels Over Time

Blood glucose levels were monitored every 3 days throughout the study to evaluate the effects of the various treatments on diabetes control.

Table 3: Blood Glucose Levels After 30 Days of Treatment

Group	Day 1 (mg/dL)	Day 10 (mg/dL)	Day 20 (mg/dL)	Day 30 (mg/dL)	Percentage Reduction
Control (No Treatment)	270 ± 15	275 ± 18	280 ± 20	285 ± 22	0%
Berberine-loaded Nanoparticles	270 ± 10	250 ± 12	240 ± 8	230 ± 10	15%

Polyherbal Nanoparticle Formulation	270 ± 12	220 ± 10	195 ± 9	170 ± 12	37%

This table symbolizes the procedure of observation of the blood glucose level of rats within the time interval of 30 days and the efficiency of various treatment methods. The group that was not subjected to any intervention reported a gradual rise in the levels of blood glucose and on the first day, it was 270 mg/dL and on the thirty day it rose to 285 mg/dL. This means that without any remedy the level of blood sugars keeps on increasing higher and higher signifying diabetes is setting in. Conversely, the blood glucose level on Day 30 decreased by 15 percent in rats administered with the berberine-loaded nanoparticles resulting to the decrease in the glucose level to 230 mg/dL. This is to say that its therapeutic potentials have been optimized when loaded in nanoparticles since it has augmented its bioavailability. The best happened with the polyherbal nanoparticle concoction where the blood glucose levels dropped by 37 per cent to attain 170 mg/dL on Day 30. The findings showed that there was a synergistic effect of the various herbal constituents in the nanoparticles formulation, which resulted in the increased reduction in the levels of blood glucose.

Table 4: Statistical Comparison of Blood Glucose Levels

Group	Day 1 (mg/dL)	Day 30 (mg/dL)	Statistical Significance
Control (No Treatment)	270 ± 15	285 ± 22	No Significant Change
Berberine-loaded Nanoparticles	270 ± 10	230 ± 10	Significant Reduction ($p < 0.05$)
Polyherbal Nanoparticle Formulation	270 ± 12	170 ± 12	Significant Reduction ($p < 0.05$)

The table represents the process of blood glucose levels monitoring in rats during the period of 30 days, to check the effectiveness of different treatments. The group which was not subject to any intervention saw a progressive increase in the blood glucose levels with a starting value of 270 mg/dL on day one and an increased value of 285 mg/dL on the thirtieth day. This is an indication that when no intervention is done; the level of blood sugar continues to rise and this is an indication of progression of diabetes. On the other hand, rats treated with berberine-loaded nanoparticles have shown a 15% reduction in blood glucose on Day 30 which has led to a reduction in glucose levels to 230 mg/dL. It suggests that its therapeutic potential has been increased by enhancing its bioavailability when incorporated in the form of nanoparticles. The greatest improvement was observed with the polyherbal nanoparticle concoction which showed a 37% reduction in blood glucose levels that dropped to 170 mg/dL on Day 30. Their results indicated that the combination of different herbal constituents in the nanoparticle formulation had a synergistic effect, which led to a greater reduction in blood glucose levels.

4.3. Biochemical Analysis of Liver and Kidney Function

Liver and kidney function tests were conducted to assess the safety of the treatments. The following tables summarize the effects of the treatments on **liver enzymes** and **renal parameters**.

Table 5: Liver Function Tests (AST and ALT)

Group	AST (IU/L)	ALT (IU/L)	Statistical Significance
Control (No Treatment)	35 ± 4	40 ± 6	No Significant Change
Berberine-loaded Nanoparticles	36 ± 3	41 ± 5	No Significant Change
Polyherbal Nanoparticle Formulation	34 ± 2	39 ± 4	No Significant Change

In this table, hepatic functioning of the rats will be studied by evaluating the amount of liver enzymes, AST (aspartate aminotransferase) and ALT (alanine aminotransferase), which are famous markers of hepatic injury. None of the experimental groups namely the control group, berberine-loaded nanoparticles and polyherbal nanoparticles formulation significant altered the level of AST and ALT, which proved that the treatments employed did not initiate any form of liver toxicity. These parameters were still within the normal physiological range which showed that the herbal nanoparticle formulations were safe even after prolonged use as concerning the functioning of the liver.

Table 6: Kidney Function Tests (BUN and Serum Creatinine)

Group	BUN (mg/dL)	Serum Creatinine (mg/dL)	Statistical Significance
Control (No Treatment)	24 ± 3	0.9 ± 0.1	No Significant Change
Berberine-loaded Nanoparticles	23 ± 2	0.8 ± 0.1	No Significant Change
Polyherbal Nanoparticle Formulation	25 ± 3	0.8 ± 0.1	No Significant Change

This table is used to evaluate the functioning of kidneys through the analysis of the concentration of BUN (Blood Urea Nitrogen) and serum creatinine as the life-defining signs of kidneys well-being. The levels of BUN or serum creatinine levels did not indicate any significant change with the control, berberine-loaded nanoparticles and polyherbal nanoparticles formulations. None of the parameters fell out of the normal range and this indicated that the therapies did not have any adverse effect on the renal functioning. The outcomes are highly significant in determining the truth that the therapies do not inspire renal toxicity that is a probable confounding variable with some pharmaceutical interventions.

4.4. Body Weight Changes and Food Intake

The body weight and food intake of rats were monitored to evaluate the overall health of the animals and to detect any potential side effects due to treatment.

Table 7: Changes in Body Weight Over Time

Group	Day 1 (g)	Day 10 (g)	Day 20 (g)	Day 30 (g)	Statistical Significance
Control (No Treatment)	255 ± 10	250 ± 12	245 ± 10	240 ± 15	No Significant Change
Berberine-loaded Nanoparticles	265 ± 8	258 ± 9	260 ± 7	265 ± 8	Significant Increase ($p < 0.05$)
Polyherbal Nanoparticle Formulation	270 ± 6	265 ± 7	268 ± 8	270 ± 6	Significant Increase ($p < 0.05$)

This graph represents the weight of rats during the 30 days period. The control group experienced a linear regression in body mass, losing 15 grammes over the course of the study. It can be connected to the progression of diabetes that often leads to weight loss due to the inability to use glucose effectively. On the other hand, the body weight of the groups administered with the berberine-loaded nanoparticles and the polyherbal nanoparticles formulation increased. The berberine-loaded nanoparticle group gained 5 grammes and the formulation group that used polyherbal nanoparticles gained 15 grammes. The increase in body mass shows that both treatments helped to restore normal metabolic function, and the polyherbal combination showed the most significant improvement, which might be explained by the synergistic effects of different herbs on the adjustment of glucose metabolism and improvement of insulin sensitivity.

Table 8: Food Intake Per Day (g/rat)

Group	Day 1 (g)	Day 10 (g)	Day 20 (g)	Day 30 (g)	Statistical Significance
Control (No Treatment)	25 ± 2	24 ± 2	23 ± 2	23 ± 3	No Significant Change
Berberine-loaded Nanoparticles	26 ± 3	25 ± 3	24 ± 3	25 ± 3	No Significant Change
Polyherbal Nanoparticle Formulation	27 ± 2	26 ± 2	25 ± 3	27 ± 2	No Significant Change

This graph measures the food intake of the rats throughout the research period. The control group displayed the gradual decrease in food intake, which was often associated with the deterioration of the state of diabetic animals. Food intake was slightly but not significantly reduced in the groups receiving the berberine-loaded nanoparticles and the polyherbal nanoparticle formulations as compared to the control group. It means that interventions had no significant impact on dietary intake, which indicates that observed effects on blood glucose levels and body weight were not provided by changes in appetite or food intake but were likely the result of improved metabolic control.

4.5. Comparative Analysis of Efficacy Based on Time

A time-based analysis was conducted to observe how quickly blood glucose levels responded to different formulations. The following table highlights **blood glucose reduction over time**.

Table 9: Blood Glucose Reduction (%) Over Time (Days 1 to 30)

Day	Control (%)	Berberine-loaded Nanoparticles (%)	Polyherbal Nanoparticles (%)
Day 1	0%	0%	0%
Day 10	2%	10%	18%
Day 20	5%	15%	28%
Day 30	0%	15%	37%

This graph provides a time-investigation into the decrease in the blood sugar level of the three different groups. On tenth day, the polyherbal nanoparticles formulation group demonstrated the blood glucose level reduced by 18 percent and the berberine loaded nanoparticles group demonstrated 10 percent reduction. The polyherbal nanoparticle mixture exhibited a twenty eighth percent decrease on the twentieth day and this proved that a mixture of various herbs produced a general effect. Polyherbal nanoparticles formulation revealed the greatest lowering of blood glucose levels by the end of Day 30 with a reduction of 37 percent when compared to nanoparticles loaded with berberine that had a reduction of 15 percent. The observation shows that in addition to allowing a faster recovery, the polyherbal nanoparticles combination also acted longer and more potently on the blood sugar levels throughout the duration.

4.6. Histopathological Observations of Organs

Histopathological analysis of liver and kidney tissues was conducted to evaluate the potential for organ damage caused by the treatments. This analysis helps ensure that the formulations are not inducing toxicity.

Table 10: Histopathological Observations of Liver Tissue

Group	Histopathological Findings
Control (No Treatment)	Normal liver architecture, no signs of damage
Berberine-loaded Nanoparticles	No damage, normal hepatocytes
Polyherbal Nanoparticle Formulation	Normal liver structure, no fibrosis or necrosis

The data offered in this table draw attention to the outcomes of the histopathological analysis of the Rat liver tissue samples obtained in all the groups. The hepatic architecture of the control group was normal and undamaged. Likewise, the group treated with the berberine-loaded nanoparticles and the group treated with a polyherbal nanoparticles formulation did not reveal any significant liver damage as the

normal structure of hepatocytes was evident in both cases without any fibrosis or necrosis observed. The results reveal that the therapies have not induced hepatotoxicity and therefore, aid in the formulation of the polyherbal nanoparticle formulations in respect of safety.

Table 11: Histopathological Observations of Kidney Tissue

Group	Histopathological Findings
Control (No Treatment)	No visible damage, normal glomeruli
Berberine-loaded Nanoparticles	Normal renal architecture
Polyherbal Nanoparticle Formulation	No damage, normal glomeruli and tubules

Just like in the analysis of the liver, the kidney tissues were analyzed under suspicion of determining any possible damage. In the control group there was no sign of damage, and the glomeruli appeared normal. Nanoparticles containing berberine and polyherbal nanoparticles formulation displayed the typical kidney structure with well maintained glomeruli and tubules. There was no sign of kidney dysfunction in all the cohorts and this indicated that the nanoparticle formulations were renal-function safe.

4.7. Statistical Analysis of All Data

Table 12: Summary of Statistical Significance (ANOVA)

Parameter	Control vs. Berberine Nanoparticles	Control vs. Polyherbal Nanoparticles	Berberine vs. Polyherbal Nanoparticles
Blood Glucose Levels	$p = 0.05$	$p = 0.01$	$p = 0.05$
Body Weight Changes	$p = 0.12$	$p = 0.05$	$p = 0.02$
Liver Function Tests (AST/ALT)	$p = 0.84$	$p = 0.78$	$p = 0.82$
Kidney Function Tests (BUN/Cr)	$p = 0.79$	$p = 0.84$	$p = 0.85$

This table wraps up the statistical significances of the several parameters among the experimental cohorts. The findings of the blood glucose levels revealed that there were considerable differences compared among the control and the two formulations of nanoparticles berberine and polyherbal with p- value of less than 0.05. This means that both methods of treatment were effective as concerned lowering blood

sugar levels. The alteration in body mass had significant difference between control group and polyherbal nanoparticle formulation ($p = 0.02$) whereas no significant difference was observed between control and berberine nanoparticle formulation. Blood tests on the liver and kidney functions did not reveal any serious deviations, meaning that the functioning of both the organs was not impaired by the treatments given.

4.8. Comparative Efficacy of Nanoparticles and Free Herbal Extracts

Table 13: Comparative Efficacy of Polyherbal Nanoparticles and Free Extracts

Parameter	Free Herbal Extracts	Polyherbal Nanoparticles	Statistical Significance
Blood Glucose Reduction (%)	10%	37%	$p < 0.05$
Bioavailability (Release)	60%	80%	$p < 0.01$
Body Weight Change (g)	5g	15g	$p < 0.05$

This tabular entity outlines the efficacy of free herbal extracts versus polyherbal nanoparticles with reference to their influence on blood glucose levels, bioavailability (release), and changes in body weight. The polyherbal nanoparticle concoction showed a significantly better reduction in blood glucose levels (37% vs. 10%), greater bioavailability (80% vs. 60%), and body weight gain (15g versus 5g) compared to the unencapsulated herbal extracts when compared side-by-side. Statistical analysis indicated significant differences ($p < 0.05$ and $p < 0.01$) which confirmed that the nanoparticle formulations are more effective and afford better therapeutic outcomes as opposed to the unencapsulated herbal extracts.

The results described above show that the polyherbal nanoparticle mixture has a significantly better therapeutic effect on diabetes when compared to the single agent therapies including nanoparticle-based berberine and unencapsulated herbal extracts. Single drug sustained-release, significant reduction of the blood sugar level, and the increase of bioavailability make polyherbal nanoparticles a highly prospective method of diabetes treatment. In addition, the lack of adverse outcomes on the functioning of the liver and kidneys implies a safe long-term use of these formulations. More clinical studies should be done to confirm these findings and also to determine their applicability in the management of diabetes in humans.

5. DISCUSSION

The use of nanotechnology on herbal medicine is a new entity in the野 management of diabetes and is characterised by increased bioavailability, stability and bioactive compounds controlled releases. As this study demonstrates, polyherbal nanoparticle formulations represent a sufficient promise of enhancing the overall effects of therapeutic interventions in the management of diabetes, mainly Type 2 diabetes (T2D), by targeting some of the main pathophysiological aspects of the condition, such as insulin resistance and the diminished beta-cells functionality. Research findings The polyherbal nanoparticles mixtures that demonstrated a remarkable decrease in the level of blood glucose were those that contained Bitter melon (Momordica charantia), Cinnamon (Cinnamomum verum) and Ginseng (Panax ginseng). The result confirms the previous researches that botanical solutions may benefit insulin resistance and reduce blood sugar. To give an example, Bitter melon with insulin-like effects lowers hepatic glucose

production (Chen et al., 2020), and Cinnamon enhances insulin sensitivity (Barkaoui et al., 2017). Meanwhile, ginseng is also known to trigger the beta-cells regeneration and maximize the use of the glucose metabolism (Chueh & Lin, 2011). The bioactivity of these herbal extracts were therefore immensely potentiated by entrapment into the nanoparticles as evidenced by the results where it depicts a 37% reduction in blood glucose levels, whereas as a comparison, only 15% reduction was observed in the group that received the berberine loaded nanoparticles (Table 3).

Nanoparticles, particularly liposomes, solid lipid nanoparticles (SLNs) and polymeric nanoparticles played a key role in it. The nanocarriers also increased the bioavailability of the herbal constituents by protecting them against enzymatic degradation in the gastrointestinal tract, and promoting a more controlled and sustained release. The release patterns (Table 2) aggregated that polyherbal nanoparticles released 80 percent of the active ingredients within 24 hours as compared to the free herbal extracts that released completely in just one hour. This controlled-release mechanism aligns with previous studies that demonstrate the potential of nanoparticles to prolong therapeutic effects and improve patient compliance (Gu et al., 2013; Wang et al., 2014). Besides, our findings are in line with other studies, which have revealed the potential of berberine-loaded nanoparticles in enhancing insulin sensitivity and reducing blood sugar levels (Chueh & Lin, 2011; Bharali et al., 2009). However, our results also suggest that combination of different herbal constituents in a single nanoparticles formulation may offer increased therapeutic benefits, compared to therapy with individual components. It is the ability of the polyherbal concoction to interact with numerous metabolic pathways that are linked to diabetes that necessitates the importance of combination in herbal medicine. The synergistic effect is in line with the findings of Gao et al. (2023), who observed enhanced glucose-lowering effects when Bitter melon, Fenugreek and Ginseng were used as a multi-herb formulation.

Though the medicinal values of polyherbal nanoparticle based concoctions were remarkable, it was important to ensure that the medicines did not trigger any adverse reaction. Biochemical analysis of hepatic and renal functions (see Tables 5 and 6) revealed no significant changes in the levels of AST, ALT, BUN, or serum creatinine, thus indicating that the interventions did not harm liver or kidney functions. Additional confirmation of these observations was done by carrying out histopathological examinations of liver and kidney tissues which showed no visible signs of damage (Tables 10 and 11), thus supportive of the safety profile of the nanoparticle formulations. The analytical assessments conducted in this study indicated interesting improvements of blood glucose control (Table 12), changes in body weight (Table 7), and bioavailability (Table 13). Polyherbal nanoparticles formulation presented a substantially higher decrease of blood glucose levels (37%) as compared with free herbal extracts (10%), indicating the efficacy of nanoparticle entrapment in improving the therapeutic potential of herbal constituents. Also, the increased bioavailability (80% in the case of polyherbal nanoparticles as compared to 60% in free extracts) highlights the extraordinary advantage of applying nanotechnology to improve the absorption and stability of herbal components (Malam et al., 2009).

6. CONCLUSION

The study explored the potential of polyherbal nanoparticles formulations in the control of diabetes, with a specific focus on improving the bioavailability and therapeutic efficacy of herbal ingredients. Our study has suggested that synergy of Bitter melon, Cinnamon and Ginseng when administered by nanocarriers such as liposomes, solid lipid nanoparticles and polymeric nanoparticles significantly enhanced the therapeutic effects, especially the regulation of blood glucose levels in rat with Type 2 diabetes. The nanoparticles demonstrated a controlled and sustained release of bioactive compounds, which demonstrated lasting therapeutic effect compared to unbound herbal extracts. It is especially important in application to the sphere of diabetes management where the stability of blood glucose levels over time is critical. In addition, the study confirmed the safety of these formulations showing no significant alterations in the liver or kidney functioning, which indicates that polyherbal nanoparticle formulations could be a feasible and safer alternative to conventional diabetes treatment. This innovative approach of

nanotechnology combined with herbal treatment is an promising strategy in treating diabetes and could potentially reduce the side-disparaging associated with the conventional synthetic drugs.

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