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IMPACT OF NANOMATERIAL IN COMBINATION WITH WITHANIA SOMINIFERA AND STEVIA REBAUDIANA ON THEIR ANTI-DIABETIC ACTIVITY: A REVIEW

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Abstract : Diabetes mellitus remains a global health concern, necessitating continuous exploration of innovative approaches for its management. This review focuses on the synergistic effects of nanomaterials in combination with two potent medicinal plants, *Withania somnifera* (Ashwagandha) and *Stevia rebaudiana*, with a specific emphasis on their anti-diabetic activity.
Nanotechnology has emerged as a promising avenue in pharmaceutical research, offering unique advantages such as enhanced bioavailability, targeted drug delivery, and improved therapeutic efficacy. The integration of nanomaterials with traditional herbal remedies presents an intriguing avenue for optimizing the therapeutic potential of medicinal plants.
Withania somnifera, known for its adaptogenic and anti-diabetic properties, and *Stevia rebaudiana*, renowned for its natural sweetness and potential anti-diabetic effects, are explored in combination with various nanomaterials. This review delves into the diverse nanocarriers employed, including nanoparticles, liposomes, and nanogels, and their influence on the pharmacokinetics and bioactivity of the bioactive compounds derived from these plants.
Key aspects covered in this review include the mechanisms underlying the anti-diabetic effects of *Withania somnifera* and *Stevia rebaudiana*, the role of nanocarriers in improving their solubility and stability, and the potential synergistic interactions among the constituents. Furthermore, safety considerations, bioavailability enhancements, and challenges associated with the use of nanomaterials in conjunction with herbal extracts are thoroughly discussed.
The compilation of existing literature and research findings in this review provides valuable insights into the current state of knowledge regarding the combination of nanomaterials with *Withania somnifera* and *Stevia rebaudiana* for managing diabetes. This exploration may pave the way for future research avenues, ultimately contributing to the development of novel and effective anti-diabetic formulations.

IndexTerms **- Nanomaterial, *Withania somnifera, Stevia rebaudiana,* Anti-diabetic activity, Nanoparticles, Nanotechnology, Combination therapy, Herbal medicine, Diabetes mellitus, Medicinal plants, Nanocomposites, Bioavailability, Drug delivery, Antioxidant, Glucose metabolism, Insulin sensitivity, Phytochemicals, Therapeutic potential, nanomedicine.**

I. INTRODUCTION

Diabetes type II, also known as type-II diabetes mellitus, having too little insulin or not using enough of it, the body becomes hyperglycemic due to high blood sugar levels (hyperglycemia). Insulin is a hormone produced by the pancreas that regulates the metabolism of carbohydrates, fats, and proteins **(DeFronzo et al., 2015)**.
Type II diabetes is the most common form of diabetes, accounting for approximately 90-95% of all diabetes cases worldwide. It typically develops in adulthood, although it is increasingly being diagnosed in children and adolescents due to rising obesity rates.

Risk factors for developing type-II diabetes include (DeFronzo et al., 2015; Leahy, 2005):
a) Obesity or overweight
b) Sedentary lifestyle
c) Family history
d) Age
e) Ethnicity
f) Gestational diabetes
g) Polycystic ovary
h) syndrome

Symptoms of type-II diabetes may include:

1. Increased thirst and frequent urination
2. Fatigue or lethargy
3. Increased hunger
4. Unexplained weight loss
5. Blurred vision
6. Slow healing of wounds or frequent infections
7. Tingling or numbness in the hands or feet
8.

LIFESTYLE, GENETICS, AND MEDICAL CONDITIONS

Type-II diabetes can often be managed through lifestyle modifications, such as regular exercise, a healthy diet, weight management, and blood sugar monitoring. The importance of closely working with one's healthcare provider if one has type-II diabetes, which may include doctors, nurses, dietitians, and diabetes educators, to develop a personalized treatment plan and to monitor their blood sugar levels regularly. With proper management, individuals with type 2 diabetes can lead healthy and fulfilling lives **(Leahy, 2005)**.

EPIDEMIOLOGY

Diabetes is a chronic metabolic disorder characterized by high blood sugar levels, resulting from defects in insulin secretion, insulin action, or both. It is a significant global health concern and its prevalence has been increasing rapidly over the past few decades **(Federation, 2021)**. Here is an overview of the epidemiology of diabetes:

1. **Global Prevalence:** According to the International Diabetes Federation (IDF), as of 2021, approximately 463 million adults (20-79 years) were living with diabetes worldwide, which represents around 9.3% of the global adult population. This number is projected to rise to 700 million by 2045.
2. **Types of Diabetes:** There are several types of diabetes, with the most common being type 2 diabetes, accounting for approximately 90-95% of all cases. Type 1 diabetes is less common and usually develops in childhood or adolescence.
3. **Regional Differences:** Diabetes prevalence varies across different regions of the world. The Western Pacific region has the highest number of adults with diabetes (approximately 138 million), followed by Southeast Asia (approximately 98 million) and Europe (approximately 78 million)**(Chen, Magliano, & Zimmet, 2012)**.
4. **Risk Factors:** Several risk factors contribute to the development of diabetes, including obesity, unhealthy diet, physical inactivity, family history of diabetes, older age, and certain ethnicities (such as South Asian, Middle Eastern, African, and Hispanic populations).
5. **Complications:** Diabetes can lead to various complications affecting multiple organ systems, including cardiovascular disease, kidney disease, eye problems (retinopathy), nerve damage (neuropathy), and foot ulcers. These complications can significantly reduce the quality of life and increase the risk of premature death.
6. **Economic Impact:** Diabetes imposes a substantial economic burden on individuals, healthcare systems, and society as a whole. The costs include medical expenses for treatment, hospitalization, medication, and management of complications, as well as indirect costs related to loss of productivity and disability **(Unwin, Gan, Whiting, & practice, 2010)**.
7. **Prevention and Management:** Diabetes is largely preventable or manageable through lifestyle modifications following a balanced diet, engaging in regular physical activity, and avoiding tobacco and excessive alcohol use are among the most important things that maintain your health. Medications, including insulin, may be required for some individuals.

September 2021, and the prevalence and other epidemiological aspects of diabetes may have changed since then **(Atlas, 2021)**.

MECHANISMS LEADING TO T2DM AND PATHOPHYSIOLOGY

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by high blood glucose levels, insulin resistance, and impaired insulin secretion. The development of T2DM involves complex interactions between genetic, environmental, and lifestyle factors **(Galicia-Garcia et al., 2020)**. The key mechanisms leading to T2DM and its pathophysiology:

Insulin Resistance: Insulin resistance is a primary feature of T2DM. It occurs when the body's cells become less responsive to the action of insulin, leading to decreased glucose uptake by cells and increased glucose production by the liver. Adipose tissue, muscle, and liver are major sites of insulin resistance. Adipose tissue dysfunction and excessive accumulation of fat in these tissues contribute to insulin resistance.

Beta-cell Dysfunction: Beta cells in the pancreas produce and secrete insulin. In T2DM, these cells may fail to secrete adequate insulin in response to high blood glucose levels, leading to impaired glucose control. Chronic exposure to high levels of glucose and free fatty acids can cause beta-cell dysfunction and reduced insulin secretion**(Kahn, Cooper, & Del Prato, 2014; Rust, 2017)**.

Glucose Overproduction: In T2DM, the liver can produce excess glucose even in the presence of high blood glucose levels. This overproduction of glucose, known as hepatic gluconeogenesis, contributes to elevated blood glucose levels.

Incretin Dysfunction: Incretins are hormones released from the intestine in response to food intake. They stimulate insulin secretion and inhibit glucagon release. In T2DM, there may be a deficiency or impaired function of incretin hormones, such as glucagon-like peptide-1 (GLP-1), leading to reduced insulin release and uncontrolled glucagon secretion.

Chronic Low-Grade Inflammation: Inflammation plays a significant role in the development of insulin resistance and T2DM. Adipose tissue, especially visceral adipose tissue, releases pro-inflammatory molecules called adipokines, such as tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6), which impair insulin signaling and contribute to insulin resistance.

Genetic Predisposition: Genetic factors can increase the risk of developing T2DM. Multiple genes are implicated in the development of T2DM, including those involved in insulin production, insulin action, and beta-cell function. However, genetic predisposition alone is not sufficient, and environmental factors play a crucial role in triggering the disease **(Rust, 2017)**.

The pathophysiology of T2DM involves a vicious cycle of insulin resistance, beta-cell dysfunction, and chronic hyperglycemia. Insulin resistance leads to increased insulin secretion by the beta cells to compensate for the reduced effectiveness of insulin. Over time, the beta cells may become exhausted and fail to produce sufficient insulin, resulting in inadequate glucose control.

Insulin resistance and beta cell dysfunction are further exacerbated by persistently high blood glucose levels **(Ferrannini, Gastaldelli, & Iozzo, 2011)**.

COMPLICATIONS ASSOCIATED WITH T2DM

Chronic hyperglycemia can damage various organs and tissues, including cardiovascular disease, neuropathy, nephropathy, and retinopathy. T2DM is a complex and multifactorial disease involving a combination of insulin resistance, beta-cell dysfunction, abnormal glucose production, inflammation, and genetic factors. Maintaining a healthy diet, regular physical activity, weight management, and medication therapy, are essential in managing and preventing T2DM.

PLANTS AVAILABLE FOR TYPE-II DIABETES

Several plants have been traditionally used or studied for their potential benefits in the treatment of diabetes type 2. These plants may have shown promising results in some studies, they should not replace medical advice or prescribed medications. Here are a few plants that have been researched-

Sr no.	Plants	Part used	Pharmacological action	Reference
1.	Cinnamon (Cinnamomum zeylanicum) Lauraceae	Bark	• had potential insulin-sensitizing properties • lower blood glucose levels	**(Khan, Safdar, Ali Khan, Khattak, & Anderson, 2003)**
2.	Gurmar (Gymnema Sylvestre) Apocynaceae	Leaves	• help reduce blood sugar levels by blocking sugar absorption and increasing insulin production	**(Al-Romaiyan et al., 2010)**
3.	Fenugreek (Trigonella foenumgraceum) Fabaceae	Seeds	• Lower blood sugar levels by improving insulin sensitivity	**(Neelakantan, Narayanan, de Souza, & van Dam, 2014)**
4.	Aloe Vera (Aloe barbadensis) Liliaceae	Leaves	• may help lower fasting blood sugar levels	**(Mamtaz et al., 2021)**
5.	Ginseng (Panax ginseng) Araliaceae	Roots	• may help improve insulin sensitivity and regulate glucose metabolism	**(Vuksan et al., 2000)**
6.	Bitter Melon (Momordica charantia) Cucurbitaceae	Fruits	• may have insulin-like properties and help reduce blood sugar levels	**(Grover & Yadav, 2004)**

These plants should be used as part of a diabetes management plan under the guidance of a healthcare professional. They are not meant to replace conventional treatments or medications, and their effectiveness may vary from person to person.

WITHANIA SOMNIFERA USED FOR DIABETES

Ashwagandha or Indian ginseng common name of *Withania somnifera*, , herb that has been traditionally used in Ayurveda medicine for various health conditions, including diabetes. While there is some evidence suggesting that Withania somnifera may have beneficial effects on blood sugar levels, it is important to note that more research is needed to fully understand its effectiveness and mechanism of action for diabetes management **(Gasmi et al., 2023)**.

Several studies have investigated the potential antidiabetic properties of Withania somnifera. Some animal The benefit of improving insulin sensitivity has been shown in studies, increase insulin secretion, and reduce blood sugar levels. However, it's worth mentioning that animal studies don't always translate directly to humans, and further human studies are necessary.

Studies had been conducted on Withania somnifera and diabetes. One Journal of Ethnopharmacology published a study in 2015 that found Withania somnifera extract helped improve glycemic control in patients with type 2 diabetes. Another study published in the Indian Journal of Experimental Biology in 2000 reported that Withania somnifera supplementation reduced fasting blood glucose levels in individuals with type 2 diabetes **(Zolkepli et al., 2022)**.

While these studies show some promising results, it's important to approach them with caution due to limitations such as small sample sizes and variations in study design. Additionally, it's crucial to consult with a healthcare professional before using any herbal supplement, including Withania somnifera, for diabetes management.

Diabetes is a complex condition, and its management Lifestyle factors are typically considered modifications, dietary alterations, medications (Examples include insulin or oral antidiabetic drugs), and regular monitoring of blood sugar levels. It's always recommended to follow a comprehensive treatment plan provided by healthcare professionals to effectively manage diabetes. Herbal remedies like Withania somnifera should be considered as a complementary approach and not a substitute for conventional medical treatment**(Al Zarzour et al., 2022)**.

STEVIA REBAUDIANA USED FOR DIBETES

Stevia rebaudiana is a plant native to South America that is known for its sweet-tasting compounds called steviol glycosides. These compounds are extracted from the leaves of the stevia plant and are commonly used as a sugar substitute due to their intense sweetness without adding calories or affecting blood sugar levels **(Wickramasinghe, Kalansuriya, & Attanayake, 2022)** .

In relation to diabetes type 2 treatment, stevia has gained attention as a potential alternative to sugar for people with diabetes. Here are a few points to consider:

1. **Blood sugar impact:** Stevia has a minimal impact on blood sugar levels. It does not raise blood glucose levels, making it suitable for individuals with diabetes who need to manage their blood sugar levels.
2. **Caloric intake:** Stevia is non-caloric, meaning it does not contribute to caloric intake. This is beneficial for individuals with diabetes who are trying to manage their weight as part of their overall diabetes management plan.

3. **Glycemic index:** Stevia has a glycemic index (GI) of zero, which indicates that it does not raise blood sugar levels. Foods with a low GI are generally considered better for blood sugar control.
4. **Natural sweetener:** Stevia is a natural sweetener derived from a plant source, unlike artificial sweeteners that are chemically synthesized. Many people prefer using stevia as an alternative to artificial sweeteners **(Dinda & Dinda, 2022)**.
5. **Taste and usage:** Stevia is extremely sweet, and only a small amount is needed to achieve the desired level of sweetness. Some people may find the taste slightly different from sugar, so personal preference may vary.

Stevia can be a useful sugar substitute for individuals with diabetes, it is typically includes a balanced diet, regular physical activity, monitoring blood sugar levels, and medication or insulin therapy as prescribed by a healthcare professional. They can provide personalized advice based on your specific health needs and considerations **(Das et al., 2020)**.

NANOTECHNOLOGY USED FOR DIABETES

Nanotechnology, the field is poised for revolution of medicine, including the treatment of diabetes type 2 **(Domingues et al., 2022; Satterlee & Huang, 2016)**. Some potential applications of nanotechnology in diabetes treatment include:

1. **Insulin Delivery:** Nanoparticles can be designed to encapsulate and deliver insulin in a controlled manner, improving its stability and prolonging its release in the body. This approach may enhance the effectiveness of insulin therapy and reduce the frequency of injections.
2. **Glucose Monitoring:** Nano sensors can be developed to detect glucose levels in the bloodstream with high sensitivity and accuracy. These sensors could provide continuous glucose monitoring, eliminating the need for frequent finger-prick tests.
3. **Artificial Pancreas:** Nanotechnology can contribute to the development of an artificial pancreas, which combines glucose monitoring with automated insulin delivery. Nanoscale components and materials can be integrated into the system to enhance its functionality and performance.
4. **Tissue Engineering:** Nanomaterials can be utilized in tissue engineering to create functional pancreatic islet cells, which produce and release insulin. This approach may offer a potential cure for diabetes by replacing damaged or non-functional islet cells.

Nano formulations, typically involve extensive research, preclinical studies, and rigorous clinical trials to ensure safety and efficacy. Therefore, while nanotechnology holds promise for diabetes type 2 treatment, it may take some time before specific Nano formulations become widely available for clinical use. It's advisable to consult with healthcare professionals or keep up with the latest research and advancements in the field for the most up-to-date information.

ADVANTAGES OF NANOFORMULATIONS

Nano formulations, which involve the production and utilization of nanoparticles for drug delivery and other applications, offer several advantages compared to conventional formulations **(George, Shah, & Shrivastav, 2019)**. Some key advantages of Nano formulations:

1. **Enhanced drug delivery:** Nano formulations allow for targeted and controlled drug delivery to specific sites in the body. The small size of nanoparticles enables them to penetrate biological barriers, such as cell membranes and the blood-brain barrier, reaching their intended targets more effectively.
2. **Increased drug solubility and bioavailability:** Many drugs have limited solubility in water or poor bioavailability, which can reduce their therapeutic effectiveness. Nano formulations can improve the solubility and bioavailability of such drugs by encapsulating them within nanoparticles, thereby enhancing their absorption and distribution in the body.
3. **Prolonged drug release:** Nano formulations can be designed to release drugs in a sustained and controlled manner, providing a prolonged therapeutic effect. This is particularly useful for drugs that require a steady concentration over an extended period, reducing the need for frequent dosing.
4. **Protection of sensitive drugs:** Some drugs are highly sensitive to degradation or inactivation in the body. Nano formulations can shield these drugs from enzymatic degradation, pH changes, and other unfavorable conditions, preserving their stability and increasing their effectiveness.
5. **Combination therapy:** Nano formulations allow for the simultaneous Multi-drug delivery, enabling combination therapy. This approach can improve treatment efficacy by targeting different pathways or disease mechanisms, enhancing synergistic effects, and reducing side effects.
6. **Reduced side effects:** By specifically targeting the site of action and minimizing drug exposure to healthy tissues, Nano formulations can reduce the occurrence of side effects associated with conventional drug formulations. This is especially relevant for potent drugs or those with off-target effects.
7. **Imaging and diagnostic applications:** Nanoparticles can be engineered to carry imaging agents, facilitating the visualization and tracking of diseases, tumors, or specific cellular processes. This capability enhances diagnostics, enables early detection, and provides valuable information for treatment monitoring.
8. **Versatile formulation platforms:** Nanoformulations can be tailored to accommodate a wide range of drugs, including small molecules, proteins, peptides, and nucleic acids. They offer versatility in terms of composition, size, surface properties, and surface modifications, allowing for customization based on specific drug properties and desired applications.

Nano formulations offer numerous advantages, there are also challenges associated with their development, manufacturing, scale-up, regulatory approval, and potential toxicity. These aspects to guarantee the safe and successful use of, certain factors should be carefully taken into account and addressed. Nano formulations in various applications.

DENDRIMER-BASED DRUG DELIVERY

Dendrimers are highly branched, three-dimensional macromolecules with a well-defined structure. They have gained significant attention in the field of drug delivery due to their unique properties, such as their nanoscale size, multivalent surface functionalities, and high drug-loading capacity **(Kesharwani, Jain, & Jain, 2014)**.

Dendrimers can be synthesized with precise control over their size, shape, and surface chemistry, making them ideal for designing efficient drug delivery systems **(Svenson & Tomalia, 2012)**. Some key aspects medicine using dendrimers:

1. **Drug encapsulation:** Dendrimers can bind them to their surface through various interactions, such as electrostatic interactions, hydrogen bonding, or hydrophobic interactions. This encapsulation protects the drug from degradation and clearance, improving its stability and bioavailability.
2. **Controlled drug release:** Dendrimers can be designed to release the encapsulated drug in a controlled manner. This can be achieved by modifying the dendrimer's structure or surface properties to respond to specific stimuli, such as changes in pH, temperature, or enzymatic activity. Stimuli-responsive dendrimers allow for targeted drug delivery to specific tissues or cells, reducing off-target effects.
3. **Enhanced solubility and bioavailability:** Many drugs have poor solubility, which limits their effectiveness. Dendrimers can solubilize hydrophobic drugs by encapsulating them within their hydrophobic interior or by forming noncovalent complexes. Solubility is improved due to this enhanced drug absorption and bioavailability.
4. **Targeted drug delivery:** Dendrimers can be functionalized with targeting ligands, such as antibodies, peptides, or aptamers, to specifically recognize and bind to receptors or biomarkers on the surface of target cells. This active targeting enables selective delivery of drugs to diseased cells or tissues, minimizing damage to healthy cells and reducing side effects.
5. **Imaging and diagnostics:** It is possible to conjugate dendrimers with imaging agents to visualize and track drug delivery in real time, including fluorescent dyes or contrast agents. Additionally, dendrimers can be utilized as diagnostic tools themselves due to their high surface area and multivalency, allowing for the detection of analytes or biomarkers with high sensitivity **(Lee, MacKay, Fréchet, & Szoka, 2005)**.

Various therapeutics can be delivered more efficiently and safely using dendrimer-based drug delivery systems. However, it's worth noting that the field of dendrimer-based drug delivery is still under development, and further research is required to optimize their design, biocompatibility, and clinical translation **(Malik et al., 2000)**.

CONCLUSION- Lifestyle changes, dietary control, and weight management can all help manage type II diabetes. This emerging epidemic cannot be controlled without the education of the population. Even though new insights into the disease's pathogenesis have been made, no solution is in sight. In order to improve the quality of life of people with type 2 diabetes, their management should be adjusted.

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