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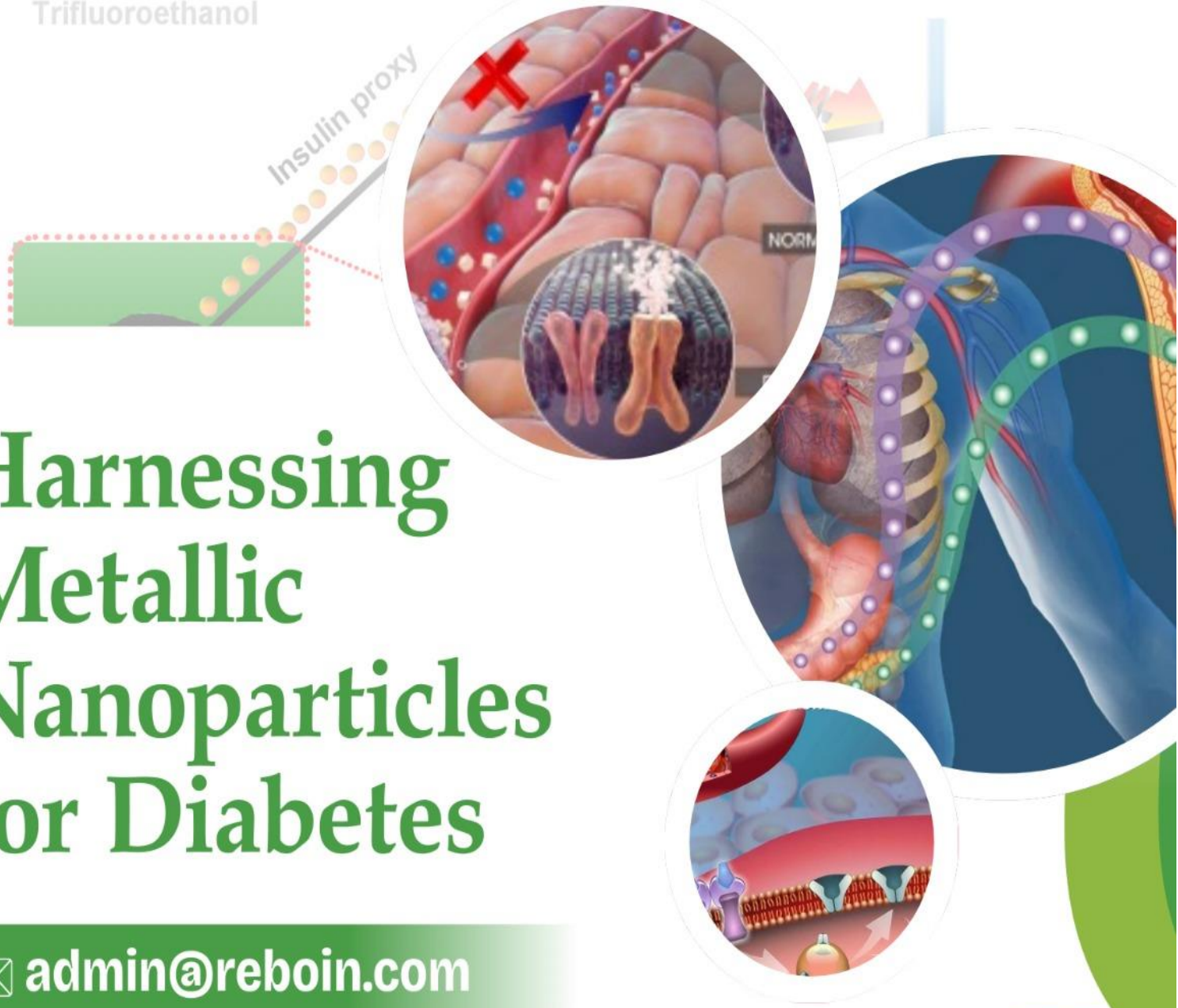

Harnessing Metallic Nanoparticles for Diabetes

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Harnessing Metallic Nanoparticles for Diabetes Management: A Comprehensive Review

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Abstract

Numerous studies on the use of nanoparticles in the medical field have been conducted. These studies have looked at the anti-diabetic and antibacterial properties of the particles as well as the use of nanoparticles in the early identification and treatment of cancer. This review is focused on plant-based synthesis, or the environmentally friendly production of different nanoparticles utilizing plant extracts. The antidiabetic properties of silver, copper oxide, gold, and zinc oxide nanoparticles as well as the production techniques from different plants and their extracts are the key points of emphasis in this review. This review also addresses nanotoxicity, or the toxicity resulting from the use of nanoparticles that interfere with vital physiological processes in the human body and pollute the environment by poisoning airborne and soil species.

Keywords

Nanoparticles, anti-diabetic activity, herbal extracts, nanoparticle synthesis, anti-diabetic potential, green synthesis.

1. INTRODUCTION

Nanotechnology research has come to the forefront because of its productivity. Nanoparticles are the foundation of this emerging field. Nanoparticles are very small particles ranging from 1 to 100 nm in diameter. Because the wavelength of visible light is shorter, an electron microscope is needed. There are many physical and chemical methods to produce nanoparticles, but the biggest drawback is that they are expensive and high risk when using chemicals that are not environmentally friendly and can cause great damage to the environment. Therefore, an alternative is to find environmentally friendly methods that promote the eco-friendly synthesis of nanoparticles [1] Nanoparticles can be produced by plants and microorganisms. Both plants and microorganisms have the potential to reduce metal ions into nanoparticles through green synthesis processes. Whole plants, plant tissues and fruits, plant extracts, microorganisms, and algae have been used to produce nanoparticles [2]. In plant-mediated green synthesis, phytochemicals derived from plant extracts are used as reducing and blocking agents. Nanoparticles are used to absorb limiting agents and stabilize the nanoparticles. Studies have shown that nanoparticles have excellent antibacterial properties that could potentially treat infections and antiproliferative properties that could definitely be used to treat cancer. It can also be used for diagnostic purposes [3]. Nanoparticles with a variety of functions can target and visualize tumor locations using imaging techniques, leading to early detection of cancer. Therefore, it has great potential in cancer diagnosis and treatment and will be a promising cancer treatment method in the near future [4]. Nanoparticles have a variety of applications, including chemical reaction catalysts, biomarkers, the cosmetics industry, sunglasses, and diagnosis and treatment of various diseases. Treatment goals. This review focuses on diabetic health and the antidiabetic potential of various nanoparticles. Diabetes mellitus is a metabolic disorder caused by a tendency for blood sugar levels to rise, inherited and/or acquired failure of the pancreas to produce insulin, or ineffectiveness of the insulin produced. This deficiency causes blood sugar levels to rise, damaging many body systems, especially blood vessels and nerves. Studies have highlighted the role of metals in glucose metabolism and the link between metal deficiencies and diabetes.

2. PLANT EXTRACTS AS A TRADITIONAL TREATMENT

Since all diseases occur naturally, plants that have anti-diabetic properties and can be used to treat diabetes have been studied. Since the studies were carried out in different ways, plant

species were grouped into groups such as plants with antidiabetic activity, plants with hypoglycemic activity, plants with alpha-glucosidase activity, plants with alpha-amylase activity, plants with glucose. Categorized as: A plant with tolerogenic, anti-diabetic and cardiovascular effects [5]. In a study on *Allium sativum L.*, rats were induced into streptozotocin diabetes and then exposed to various concentrations of garlic extract. Results showed that ethanol extract of garlic significantly reduced serum glucose, triglycerides, cholesterol, urea, uric acid, AST and ALT levels. Serum insulin levels were elevated in treated diabetic rats compared with control diabetic rats. Phenols, glycosides, alkaloids, terpenoids, flavonoids, carotenoids, etc., which have the best anti-diabetic effect [6]. In vitro studies testing the alpha-amylase and beta-glucoside activities of extracts from different parts of amla found that amla leaves are potentially active as β-glucosidase inhibitors, whereas stems and fruits are potential β-amylase inhibitors. The inhibitory activity of these two enzymes is considered important for diabetes drug development because they play an imporstant role in glucose uptake [3,6].

3. ANTIDIABETIC POTENTIAL OF DIFFERENT NANOPARTICLES

3.1 Silver Nanoparticles

Inhibition of carbohydrate-digesting enzymes (β-glucosidase and β-amylase) is an important goal in preventing rapid increases in blood glucose levels. *Tephrosia Tinctoria* silver nanoparticles exhibit greater alpha-amylase and alpha-glucosidase activities than the crude extract, but relatively less than the conventional drug acarbose. Glucose uptake analysis of AgNPs showed a maximum increase of 3.80 ± 0.028-fold compared to *Tephrosia Tinctoria* crude extract (2.61 ± 0.07) at 75 µg/mL [7]. Silver nanoparticles synthesized from *Allium cepa* exhibited significantly higher β-amylase inhibitory activity than acarbose at all concentrations tested. As the concentration of silver nanoparticles increased, the inhibition rate significantly increased in a dose-dependent manner. Silver nanoparticles synthesized from *Allium cepa* showed significant β-glucosidase inhibitory activity in a concentration-dependent manner. However, the activity was not significantly different from that of acarbose [8].

3.2 Copper Nanoparticles

Milk thistle extract CuO nanoparticles exhibit moderate levels of alpha-amylase enzyme inhibition. (35.5 ± 1.54%), with excellent urease inhibition effect at 200 µg/ml. (78.4±1.26%) at the same concentration and higher concentration of lipase inhibitory activity, i.e. (80.5-

0.91%) [9]. CuO nanoparticles from *Plectranthus amboinicus* leaf extract exhibit an alpha-amylase inhibitory activity of 94% at 500 µg/ml, which is higher than standard diclofenac sodium, which has an amylase inhibitory activity of 86% at 500 µg/ml [10].

3.3 Gold Nanoparticles

The alpha-amylase inhibitory effect of *Moringa oleiferaculanan* particles shows a 70% inhibitory effect at a concentration of 200 µg/ml, but is still low compared to the existing drug metformin, which shows a 96% inhibitory effect at the same concentration [11].

3.4 Zinc Nanoparticles

Treatment of mice with 100 mg/kg streptozotocin induced a hyperglycemic state in mice, while treatment of mice with *Hibiscus subdarrifa* ZnO nanoparticles restored glucose levels in mice after 14 days. ELISA analysis shows a severe imbalance between Th1 and Th2 cells. Here, Th1 represents an increase in cytokines and Th2 represents a decrease in cytokines in hyperglycemic mice. The mRNA expression levels of receptor genes such as IRA, GLUT 2 and GK were suppressed and diabetes induction increased the expression of PKLR, which was further regulated by PZN60, PZN100. Therefore, it was found that ZnO not only induced Th1 and Th2 cell function, but also induced the expression of insulin receptor and other genes in diabetic pancreas [12].

Anti-inflammatory, antioxidant, and insulin-sensitizing characteristics of these nanoparticles, provides clinical evidence of the anti-diabetic in the treatment of diabetes mellitus. Different applications utilized for research of different nanoparticles has been mentioned in **Table 1.**

Table 1 Activity of different metal nanoparticles and dose description

Nanoparticle type	Mechanism	Dose (mg/kg)	Reference
Gold	Anti-inflammatory, antioxidant, improves insulin sensitivity, protects pancreatic beta cells	0.5-1.5	13
Selenium	Improves glucose metabolism, enhances insulin signalling pathway	0.1-1	14
Zinc	Enhances insulin storage and its secretion, improving glucose uptake	1-10	15

Silver	Anti-bacterial, lowers blood glucose level, enhances wound healing	10	16

Each form of these nanoparticles has a distinct mechanism and uses. Though, additional research is crucial in real-time applications for the clinical use of these nanoparticles.

4. SYNTHESIS OF NANOPARTICLES AND UV-VIS SPECTROPHOTOMETER ANALYSIS

As discussed above, green synthesis of nanoparticles involves use of various microorganisms or plant extracts. In this review, green synthesis using plant extracts is discussed. The plant extracts have bioactive molecules or secondary metabolites such as terpenoids, flavonoids and phenols which act as stabilizing and reducing agents in green synthesis [9-11]. In the upcoming passages, the plant-extract based green synthesis of gold nanoparticles, silver nanoparticles, copper oxide nanoparticles and zinc oxide nanoparticles are described.

4.1. Synthesis of Gold Nanoparticles

One of the nanoparticles that exhibits the antidiabetic activity is gold nanoparticles (AuNPs). Some of the plant extracts used in its synthesis include *Moringa olifera, Fritillaria cirrhosa, Eclipta alba* and *Leucosida cericea. Moringa olifera* leaves extract has been used along with 1 mM auric chloride solution for the synthesis. The characterization test confirmed that the particles formed were gold nanoparticles with the shape being spherical, oval, and some of hexagonal shape having the diameter of 35-51 nm. Furthermore, it's antidiabetic activity was checked by the percentage of inhibition of α-amylase enzyme, which yielded positive results [13]. An increased concentration of nanoparticles led to the increased inhibition. *Fritillaria cirrhosa* can also be utilized for the same purpose. The formation of nanoparticles was confirmed using UV-Vis Spectrophotometry and the particles were found to be spherical with a diameter in the range of 40-45 nm. These nanoparticles were tested for its antidiabetic potential by using the nanoparticles on Streptozotocin (STZ) stimulated diabetic preclinical models, which showed that these nanoparticles were successful in regenerating the islets and β cells of the pancreas and thus, showing the antidiabetic activity [17]. Similar study was conducted using the gold nanoparticles synthesized by *Eclipta alba* plant extract on STZ induced apoptosis in RIN-5F cell lines. The nanoparticles obtained were spherical with

approximately 26 nm diameter and they prevented the β cell damage in the cell lines, indicating that these nanoparticles possess antidiabetic activity [18].

4.2. Synthesis of Silver Nanoparticles

The silver nanoparticles (AgNPs) have also imparted promising results for the antidiabetic properties. Silver nanoparticles were synthesized using *Lonicera japonica* leaf extract and characterized to confirm and determine its morphology. UV-Vis spectrophotometry indicated the absorption band at 435nm and transmission electron microscopy of the particles revealed that these particles were spherical and hexagonal with an average size of 53 nm. The antidiabetic activity was checked by the inhibition of α-amylase and α-glucosidase. These nanoparticles indicated IC50 value of the nanoparticles to be 54.56 µg/ml and 37.86 µg/ml for α-amylase and α-glucosidase respectively [19]. Another effective study was successful at synthesizing spherical AgNPs of an average size of about 48 nm using *Punica granatum* leaf extract. These nanoparticles showed a resonance peak at 415 nm on characterization by UV-visible spectrophotometry. These particles exhibited IC50 value of 65.2 µg/ml and 53.8 µg/ml for inhibition against α-amylase and α-glucosidase, respectively [20]. Wahab et al., observed that the size of the nanoparticle is indirectly proportional to the effective inhibition of α-amylase enzyme [16].

4.3 Synthesis of Zinc Oxide Nanoparticles

Ficus Palmate leaves have been useful for the synthesis of zinc oxide nanoparticles (ZnONPs) with an absorption peak observed in the range of 340-380 nm by UV-Vis spectrophotometry with roughly spherical shape and demonstrated α-amylase and α-glucosidase inhibition with IC50 value of 70.07 ± 0.07 µg/ml and 68.49 ± 0.43 µg/ml, respectively [21]. ZnONPs of *Areca catechu* leaves extract were found to be spherical in shape with an average diameter range of 20-40 nm and an absorption peak at 371nm. The findings revealed that the concentration of ZnONPs was inversely proportional to the glucose uptake with an IC50 for α-amylase as 52.64 µg/ml [22]. Moreover, it is reported that the temperature used in the synthesis process and the size of the nanoparticle played an important role in the antidiabetic activity. Based on the findings of this research, it was concluded that smaller the size of the ZnONP, the more efficacy against the diabetes [23].

4.4 Synthesis of Copper Nanoparticles

Copper nanoparticles (CuNPs) have also been known to demonstrate antidiabetic activity. *Dioscorea bulbifera* tuber extract has been used for the copper nanoparticle synthesis. The

spherical shaped CuNPs demonstrated significant antidiabetic activity by inhibition of α-amylase and α-glucosidase [24]. A plant *Strobilanthes cordifolia* leaf extract was also utilized for the preparation of CuNPs and check its antidiabetic potential. These nanoparticles had maximum absorption peak at 438 nm in UV-vis spectroscopy and spherical shape. Moreover, the IC50 value for inhibitory effect for α-amylase is 38.23 µg/ml while for α-glucosidase is 47.75 µg/ml [25].

5. NANOTOXICITY

A wide range of other properties of nanoparticles make it suitable for various applications. Nanomaterials are used in a variety of industries including textile, pharmaceuticals, and medical equipment. They are widely used in coatings, medical procedures, diagnostics, cosmetics, sunscreens, food packaging and other applications. Though, overuse of nanoparticles has been associated to 'nanotoxicity' or 'nanoparticle toxicity'. These terms refers to the biokinetic evaluation of manmade nanostructures and nanomaterials, which takes into account many aspects including physiological, physicochemical, molecular, and other factors. Nanoparticles cause nanotoxicity in two aspects- internal cause and external cause. The microscopic size and high surface-to-volume ratio of nanoparticles, leading to alterations in their properties both chemically and physically, have attracted the attention of researchers in nanotechnology. Comparing the nanoparticles to their corresponding particles at higher scales, the nanoparticles have distinct physical, chemical, and biological properties [26,27].

The toxicity of nanoparticles is significantly influenced by their size and surface resulting in due to complicated bio physicochemical interactions at the bio-nano interfaces. When a nanoparticle enters the body, its physicochemical properties allow it to interact with the body's components; this is known as the enteropathy factor, or internal cause. Moreover, the interaction of nanoparticles with blood composition causes blood coagulation once they enter the blood circulation. The external source of toxicity is surface contamination, which occurs when lipopolysaccharide or bacterial endotoxin are absorbed by nanoparticles and generate a hazardous reaction. Most nanoparticles are expected to have harmful effects on the human body through a variety of pathways, including oxidative stress, inflammation, protein corona and interactions with internal components [26-29].

Metal nanoparticles (MNPs) release into the atmosphere and the terrestrial environment might cause toxicity in soil and airborne species. At concentrations >30µg mL, it has been observed that AgNPs hinder the growth of bacterial strains (*Staphylococcus* genus).

Additionally, MNPs have been shown to have harmful effects on terrestrial plants, including a decrease in plant growth, a reduction in seed germination, and changes to photosynthesis and mineral nutrition. Release of MNPs in aquatic environment leads to toxic effects on aquatic life [27,30,31]. The research indicates that humans are exposed to significant health risks if they consume, inhale, or unintentionally come into contact with MNPs while packaging and processing. It even encompasses blood coagulation, lung tumours, cardiovascular disorders, lysosomal damage and induced cytotoxicity [32]. Research on silver nanoparticles showed that these materials are largely deposited in organs and are not soluble. Even for consumers, such inadvertent migration through packaged goods may give rise to a number of severe health risks [31]. Silica nanoparticles (SiNPs) are widely produced nanoparticles in the world and are utilized in all facets of daily life. According to the estimates in 2002, around 500 000 tons of synthetic silica and silicates in a size range between one and several μ m were produced annually. These nanoparticles are used in food, consumer goods and agriculture [33]. CuNPs are significantly more harmful to lung cells by inducing oxidative lesions and destroying DNA. The outcomes showed that the copper oxide nanoparticles broke down into copper ions, and that free metallic copper ions suppress healthy cells. The physicochemical characteristics of these copper ions, particularly their solubility inside cells, have a significant impact on their cytotoxicity. Copper oxide nanoparticles also induce neurotoxicity and hepatoxicity [34]. MNPs have harmful effect on vital organs such as kidneys, liver, lungs, and brain. As of now, nanoparticles toxicity is being examined utilizing human malignant growth cells or immortalized cells [30-34].

Mitigating the nanotoxicity of nanoparticles involves several key strategies. First, optimizing the size and shape of nanoparticles is crucial; smaller or irregularly shaped particles can have higher toxicity, so designing nanoparticles with less harmful dimensions or geometries can help mitigate these risks. During manufacturing, ensuring high purity and using safer synthesis methods—such as green chemistry approaches—can limit the presence of harmful byproducts. It is also essential to coat nanoparticles with biocompatible compounds. For instance, adding polyethylene glycol (PEG) or other stabilizers can help reduce toxicity. Additionally, protective coatings and encapsulation methods, such as using polymer shells or biodegradable matrices, can shield nanoparticles from interacting with biological systems. The development of eco-friendly synthesis methods for carbon nanotubes reduces the risk of contamination and adverse effects. During application, implementing rigorous exposure controls, like using protective coatings or encapsulation, can prevent direct contact with toxic

nanoparticles. Regular monitoring, such as assessing the impact of silver nanoparticles in water systems, helps track their environmental effects and inform mitigation strategies. Adhering to regulatory guidelines and investing in research, such as exploring biodegradable nanoparticles, further supports the safe integration of nanotechnology into various fields while minimizing potential risks. Collectively, these strategies contribute to the development of nanoparticles with reduced toxicity, balancing their benefits with minimized health and environmental risks. For example, AuNPs are first nanoparticles that are approved by USFDA as nanomedicine and nanocarrier. The results of the research showed that chemically produced gold nanoparticles smaller than 20 nm are extremely harmful to stem cells because they change the hydromethylation and methylation patterns of cellular DNA [35]. Though, more research in terms of clinical studies, physiological effects, doses, drug delivery, bioavailability, and targeted therapy is needed before utilizing nanoparticles for clinical purposes.

6. CONCLUSION

Nanoparticles demonstrate transformative potential in diabetes management. Additionally, nanotechnology might facilitate advanced glucose monitoring, wound healing, and mitigation of diabetic complications like nephropathy through renal-targeted systems. While promising, scalability, long-term safety, and regulatory hurdles remain critical considerations for clinical translation. Overall, nanomedicine offers a paradigm shift toward personalized, efficient, and patient-friendly antidiabetic strategies.

Acknowledgment

Not Applicable

Conflict of Interest

Not Applicable

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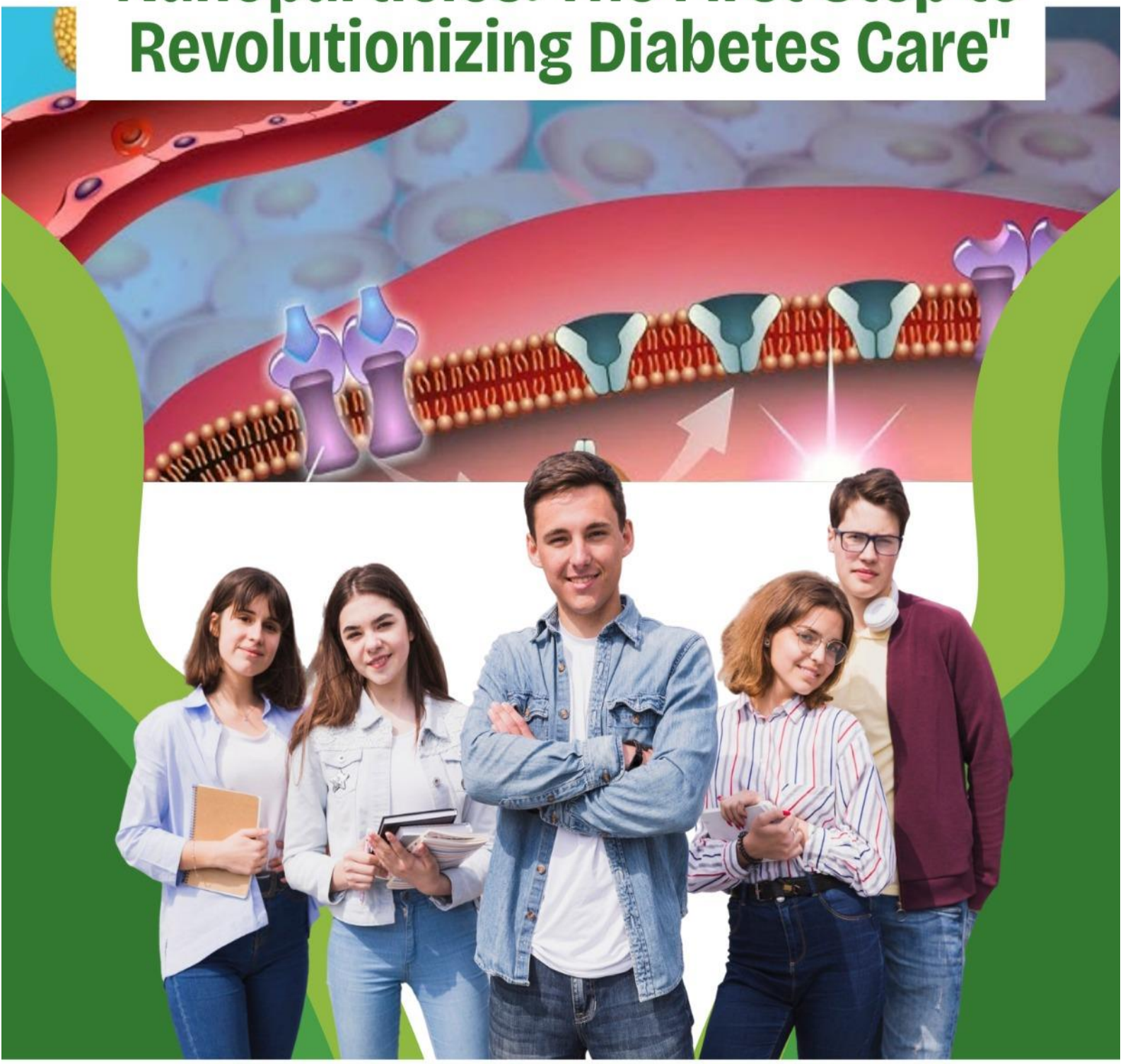

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