ENDOCRINOLOGY RESEARCH AND CLINICAL DEVELOPMENTS

GREEN HEALER ANTI-DIABETIC NANOMEDICINE FOR THE MANAGEMENT OF DIABETES MELLITUS

Younis Ahmad Hajam, PhD
Rajesh Kumar, PhD
EDITORS

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Younis Ahmad Hajam, PhD
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Dedicated to Abdul Majeed Hajam and Raja Banoo,
the loving parents of the lead editor, Dr. Younis Ahmad Hajam

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Foreword

Professor (Dr.) O. P. Agrawal

It is my great pleasure to write the foreword for this book entitled “Green Healer Anti-Diabetic Nanomedicine for the Management of Diabetes Mellitus” compiled and edited by Dr. Younis Ahmad Hajam and Dr. Rajesh Kumar. Diabetes has emerged as a serious public health problem in India and many other parts of the world – it needs integrative medicine approach for its prevention and management. Nano Medicine both as practiced in has emerged as a new approach for the treatment of diabetes. This book is rich and diverse in content; and presents a vaste range of articles on different key aspects associated with different aspects of a very common endocrino- metabolic disorder namely “Green Healer Anti Diabetic Nanomedicine for the Management of Diabetes Mellitus”.

The book is a compilation of various aspect of diabetes such as role of Melatonin loaded Nano-medicine, Nanomedicine as therapeutic strategy for Diabetic wound healing, Pharmacological and Biopharmaceutical Perspectives of Nanomedicine, Nanomedicines, anti-inflammatory agents for the treatment of diabetes etc.in diabetes, Nanopolyphenols: Perspective of their encapsulation and anti-diabetic effect, Antidiabetic Activity of Green Gold–Silver Nanocomposite, Overview of Nanomedicine and Diabetes, Nanomedicine and their Applications in Healthcare System: A Strategy to Control Metabolic Syndrome and related aspects.

I am optimistic that this compilation will be of immense interest to various categories of readers(students, teachers, researchers and other academicians) working in different basic as well as applied life sciences, I congratulate the editorial team and all contributors for putting together such an exhaustive compilation of excellent chapters on various aspects of “diabetes”. In my

view, this book has a lot of futuristic value and will further evolve as science on diabetes grows. I would like to encourage all readers of this book, especially those who may be stimulated by its insights and contents, to join the editors in further strengthening this fascinating, challenging and rewarding endeavor by sharing their feedback and expectations for future.

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Preface

Diabetes is a common disease in life. Its long-term hyperglycemia may cause damage to the various tissues and organs of the body and may lead to health complications. These complications will have a significant impact on patients, with diabetic complications involving acute metabolic disorders such as DKA and hyperosmolar hyperglycemia syndrome; there are some other chronic complications of diabetes such as diabetic nephropathy, diabetic retinopathy, diabetic cardiomyopathy, peripheral neuropathy, diabetic foot, segmental bone injury, and other complications. Diabetic complications are often irreversible, causing severe burdens and injury to patients both economically and physically. This book highlights the cutting-edge research being conducted on the subject and focuses on the challenges of increasing the prevalence of diabetes in the world and role of modern technologies for the management of diabetes.

Nanomedicine in healthcare contributes to a better understanding and controlled interactions with biological mechanisms at the molecular level leading to new pathways for diagnosis and treatment of human diseases, in line with the global evolution of medicine. Nanomedicine as a translational science has the goal to provide cost effective novel therapies and diagnostics using the enabling capacity of nanotechnology applied to medicines. This ambition is based on the fact that nanotechnologies provide the tools for analysis and manipulation of biological processes at the nanoscale, where diseases initiate and progress. The result is an increasingly better understanding of the molecular biology of diseases leading to new targets for more specific and earlier diagnostic and therapeutic treatments. These new options cause profound changes in healthcare systems by enabling more personalized, predictive, preventive and regenerative medicine. This book also comprehensively and critically summarizes the application of nanomedicine in therapeutics of diabetes and complications management, providing an insightful outlook for their further clinical translation.

The book will also provide a simple compendium for undergraduate and postgraduate students to understand the fundamental concepts of nanomedicines and their mechanistic approach with regard to the diabetes. Readers find an articulate package of knowledge compiled about diabetes, its complications and role of nanotechnology in the treatment of diabetes.

Acknowledgments

First and foremost, we are grateful to the Almighty for establishing us to complete this innovative book. We would like to express our heartfelt gratitude and respect to all contributors who have contributed to this book in the form of their chapters. Indeed, it is our utmost pleasure to acknowledge all the people behind the completion of this book. It was not possible to complete this work without their continuous encouragement and support.

We are very much thankful to Dr. Dharmjit Singh Parmar, Vice Chancellor, Sant Baba Bhag Singh University, Jalandhar, Punjab, India, and Dr. Seema Rai, Department of Zoology, Dean, School of Studies in Life Science Guru Ghasidas Vishwavidayalaya (A Central University), Bilaspur, C G. 495009, India for their compliments, praise and blessing to the entire team of young researchers.

We are thankful to Dr. O. P. Agrawal, Former Vice-Chancellor, Jiwaji University, Gwalior, Madhya Pradesh for his constant support and encouragement.

We will also take this opportunity to express our sincere gratitude to NOVA Science Publishers, New York for their copious teamwork in publishing this work.

Support of our students, colleagues and family members is highly appreciable. Finally, we would like to put our head down in front of Almighty, who has given us courage, passion and strength for completing this work.

Chapter 1

Melatonin Loaded Nanomedicine for the Treatment of Diabetes

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Abstract

Melatonin is a hormone produced by the pineal gland that significantly regulates the sleep-wake cycle. It also acts as an antioxidant and anti-inflammatory agent, making it a promising therapeutic candidate for treating several diseases, including diabetes. *Nanomedicine* is an emerging field involving nanoparticles to deliver therapeutic agents to

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specific cells or tissues. Melatonin-loaded nanomedicine is a novel approach that offers targeted delivery of melatonin to cells and tissues, thereby enhancing its therapeutic efficacy. The history of nanomedicine dates back to the early 1960s, when the concept of nanotechnology was first introduced. Since then, significant advancements have been made in nanomedicine, leading to the development of various nano-carriers for drug delivery, including liposomes, dendrimers, and polymeric nanoparticles. Melatonin-loaded nanomedicine exerts its therapeutic effects through various cellular mechanisms, including the modulation of oxidative stress, inflammation, and insulin resistance. These mechanisms play a critical role in the pathogenesis of diabetes, making melatonin-based nanomedicine a potential treatment option for this disease. In preclinical studies, melatonin-loaded nanomedicine has been shown to improve glucose homeostasis, increase insulin sensitivity, and reduce oxidative stress in animal models of diabetes. These findings suggest that melatonin-based nanomedicine has the potential to be a safe and effective therapeutic option for the treatment of diabetes. Therefore, melatonin-loaded nanomedicine offers a promising therapeutic approach to treating diabetes. Its targeted delivery to specific cells and tissues and its antioxidant and anti-inflammatory properties make it a potential treatment option for this disease. Further research is needed to establish its safety and efficacy in humans, but the early results are promising. This book chapter reveals the potency and future scope of melatonin-based nanomedicine against *Diabetes mellitus*.

1. Introduction

The worldwide population is experiencing adverse health effects due to *diabetes mellitus*. *Diabetes* is a chronic disease characterized by the body's inability to regulate blood glucose levels properly. It affects millions of people worldwide and is associated with several complications such as cardiovascular diseases, neuropathy, and retinopathy. The pathogenesis of diabetes involves various mechanisms, including oxidative stress, inflammation, and insulin resistance. Therefore, developing therapeutic strategies that target these mechanisms has been a focus of research.

A lot of factors like life style, food habits etc. are playing key role in the development of diabetes in the human population (Trikkalinou et al., 2017; Lin et al., 2020). Different types of medicine are available for diabetes treatment. Nowadays, the nanotechnology arena flourishes as a remedy against *diabetes mellitus* (He et al., 2021; DiSanto et al., 2015; Simos et al., 2021). Nano-medicine is a field of research that involves the use of

nanoparticles to deliver therapeutic agents to specific cells or tissues. The use of nano-carriers for drug delivery offers several advantages, including enhanced bioavailability, improved pharmacokinetics, and targeted delivery to specific cells or tissues. Melatonin loaded nano-medicine represents a promising approach for the treatment of diabetes, offering a targeted delivery system that can regulate oxidative stress, inflammation, and insulin resistance.

Melatonin is a hormone produced by the pineal gland that plays a critical role in regulating the sleep-wake cycle. Apart from its basic role of regulating sleep and circadian rhythm, melatonin also serves as an anti-apoptotic agent, an anti-inflammatory agent, and an anti-cancer molecule. It is also known as the promising candidate for the treatment of several diseases, including diabetes. However, melatonin's clinical application has been limited by its poor bioavailability and short half-life. To address this issue, the development of melatonin loaded nano-medicine has been explored, providing a targeted approach for drug delivery with improved therapeutic efficacy. Melatonin plays an important role in viral infection, even attenuating corona virus (Bastani et al., 2021; Reiter et al., 2017; Talib et al., 2021; Zhang et al., 2020). As a result, melatonin is being used as nanomedicine to treat diabetes and its symptoms. Different types of nanocarriers, like lipid-based nanocarriers, niosomes for melatonin transfer, melatonin-loaded silica-based NPs, graphene and melatonin delivery, nanofibers and nanocapsules, chitosan-based NPs, synthetic polymeric nanoparticles for melatonin delivery are developing.

This book chapter provides an overview of the physiology and pathophysiology of melatonin, the development of melatonin loaded nano-medicine, and its therapeutic effects against *diabetes mellitus*. It will also explore the different cellular mechanisms by which melatonin loaded nano-medicine exerts its therapeutic effects against various ailments, providing insights into its potential clinical applications.

2. Brief Account on *Diabetes Mellitus*

Diabetes mellitus is a chronic non-communicable condition which is characterised by hyperglycaemia pertaining to the inefficiency of body to produce sufficient amount of hormone insulin or to effectively use the produced insulin (Kerner et al., 2014). The long-term consequences of the disease persist because hyperglycaemia targets the endothelial cells which are primarily involved in protection against oxidative and inflammatory damage (Lorenzi and Cagliero, 1991). According to the 10th edition of the International

Diabetes Federation (IDF), diabetes is one of the 21st century's fastest-growing worldwide health emergencies. Diabetes is predicted to affect 537 million people worldwide in 2021, and 643 million by 2030 and 783 million by 2045 (International Diabetes Federation, 2021).

Type 1 is the less common form of diabetes which constitutes 5-10% of the total patients (Maahs et al., 2010) (Figure 1) and occurs because of autoimmune destruction of β-cells of the pancreas through T-cell mediated inflammatory response (insulitis) as well as a humoral (B-cell) response (Devendra et al., 2004).

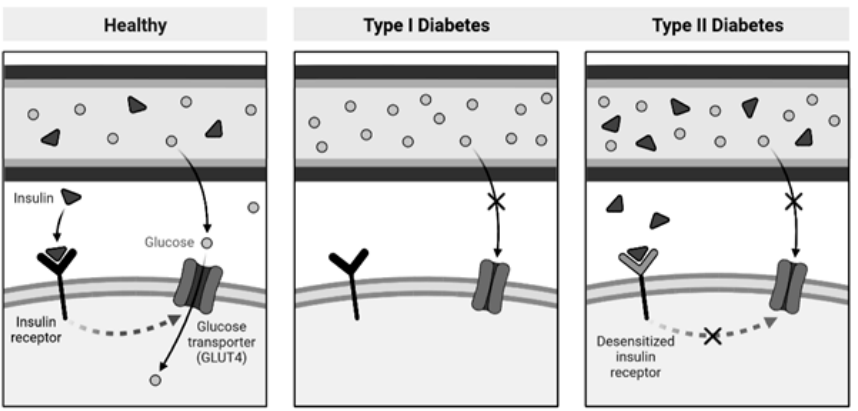

Figure 1. Pictorial representation of normal cell, type I and type II diabetes in human body.

Type 2 *diabetes mellitus* (T2DM), present in more than 95% of all diabetic adults, is characterized by insulin resistance and relative (as opposed to absolute) insulin insufficiency. Previously, this type of diabetes was referred to as adult-onset diabetes or non-insulin-dependent diabetes. The majority of patients are obese, which contributes to some degree of insulin resistance. Because hyperglycemia develops gradually and the initial stages are frequently not severe enough for the patient to notice any symptoms, this kind of diabetes often goes untreated for many years. Although weight loss and pharmacological treatment of hyperglycemia can partially cure insulin resistance, it is seldom returned to normal. Age, obesity, and lack of physical activity raise the risk of diabetes (American Diabetes Association, 2013).

3. Physiology and Pathophysiology of Melatonin

Melatonin is a circulating methoxy indole hormone primarily produced and secreted by the pineal gland at night. It is usually recognized as a pleiotropic and multi-tasking molecule (Figure 2). The retinal intrinsic photosensitive ganglion cells, whose projections to the suprachiasmatic nucleus (SCN) relay the ambient photoperiodic information, synchronize the biosynthesis to the light/dark cycle so that melatonin generation is restricted to the dark phase of the night (Canteras et al., 2011). Young and middle-aged people generate pineal melatonin, which works as an efficient chronobiotic agent capable of altering the phase and amplitude of circadian rhythms like the sleep-wake cycle (Arendt and Skene, 2005). The physiology of melatonin is a consolidative outcome of its daily and seasonal history of secretion profile besides its ontogenesis, vast actions, and consequent effects.

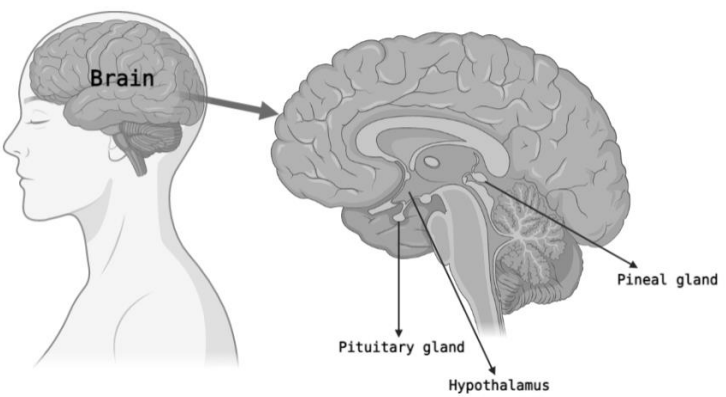

Figure 2. Location of pineal gland which is responsible for melatonin hormone synthesis.

Melatonin is a distinct molecule with reference to its characteristics and involvement in overall physiological processes with diverse mechanisms. It keeps checking on elementary cellular phenomena in almost all the varied cell types (Cipolla-Neto and Amaral, 2018; Suofu et al., 2017; Vriend et al., 2015; Majidinia et al., 2017). Numerous living things of various species, ranging from simple cyanobacteria to very complex birds and mammals, have been shown to contain melatonin. In high concentrations, it frequently acts as a potent antioxidant and a direct radical scavenger, while at lower physiological levels; it regulates redox-relevant enzymes (Reiter et al., 2001; 2003). The

hypothalamic suprachiasmatic nucleus (SCN), which creates circadian rhythms, is a traditional site of action where melatonin exerts its chronobiotic, phase-shifting, and sleep-inducing impact (Weaver and Reppert, 1996). Although it may also display autocrine or paracrine qualities, such as in the retina or stomach, the primary physiological functions of melatonin are tied to its hormonal characteristics (Tan et al., 2003).

The effects of melatonin are likely exerted by activating two inhibitory G-protein (Gi)-coupled receptors, MT1 and MT2, by inhibiting cAMP production (Nikolaev et al., 2021). Due to its unique characteristics, pineal melatonin acts through several mechanisms and in almost all levels of the organism's physiology. All physiological systems, like the central nervous system, cardiovascular system, reproductive system, immune system, respiratory system, endocrine system, bones, skin, etc., express the melatonin receptors MT1 and MT2. The human MT1 receptor is expressed abundantly in the SCN of the hypothalamus. However, the mRNA expression of MT1 and MT2 receptors is widely detected in the human brain and peripheral tissues, including the pancreatic islet of Langerhans (Ramracheya et al., 2008), where they are involved in the modulation of insulin and glucagon secretion from β-cells and α-cells respectively. It is essential to highlight that the effects of melatonin depend on several variables, including the timing and route of delivery, the strength and duration of the signal, the consistency of daily repetition, and the presence of melatonin receptors on the target organs (Cipolla-Neto and Amaral, 2018).

Human melatonin has a half-life of around 40 minutes in the blood after being converted to 6-hydroxy melatonin by cytochrome P450 isoforms, primarily CYP1A2. Then, in the liver and kidneys, it is conjugated to 6-sulfatoxymelatonin for later excretion through the urine (Ma et al., 2005). Owing to its amphiphilicity, melatonin exhibits receptor-mediated and non-receptor-mediated actions. In non-receptor mediated mode, it can pass through the cell, organelles, and nuclear membranes and, therefore, can directly interact with intracellular molecules. On the other hand, melatonin also presents receptor-mediated actions where it has to interact with both the membrane and nuclear receptors (Cipolla-Neto and Amaral, 2018).

The pancreas is a potential target tissue for melatonin because it inhibits forskolin- or high glucose-stimulated insulin secretion in rodent islet cells and rat INS-1 cells, a pancreatic β-cell line (Acuna-Castroviejo et al., 1994; Peschke et al., 2006). Melatonin sensitizes the β-cells response to glucagon-like peptide 1 (GLP-1), leading to increased insulin secretion (Kemp et al., 2002). It has been discovered that prolonged melatonin exposure through

drinking water helps rodents' aberrant glucose levels, such as hyperglycemia and insulinemia (Rasmussen et al., 1999; Agil et al., 2012). Similarly, long-term melatonin therapy is known to positively impact HbA1c levels in diabetic insomniacs (Garfinkel et al., 2011). Intriguingly, MT1 receptor deletion studies in mouse islet cells have shown that melatonin's effects on insulin release are predominantly mediated by MT1 receptors (Bahr et al., 2011).

Changes in receptor density or polymorphisms are critical indicators of melatonin signaling failure in human disease. Neurodegenerative processes may lead to decreased receptor expression. Parkinson's disease (PD) patients have decreased MT1 and MT2 expression, particularly in the substantia nigra and the amygdala (Adi et al., 2010). Patients with Alzheimer's disease (AD) also have lower MT1 and MT2 densities in their cerebral cortex and pineal gland (Brunner et al., 2006).

4. Melatonin as Nano-Medicine

The application of nanotechnology to medicine is defined as nanomedicine. Nowadays, the use of nanosized particles for clinical purposes is more frequent. Drug-delivery systems give fresh potential to deliver more stringent, concentrated, and fine-tuned therapy, improving the molecular therapeutic efficacy of chemical agents while minimizing their adverse effects. This innovative field is devoted to the investigation, creation, and manipulation of various biomaterials at the nanoscale. Nanocarriers (NCs) are structures with two- or three-dimensional lengths more than or equal to 1nm and less than 100 nm (Laurent et al., 2008). However, less rigid definitions of "nanoscale" indicate that nanostructures smaller than 1000 nm may also be regarded as NCs (Jeevanandam et al., 2018). For biological use, it is crucial to be aware of the structural, behavioural, and functional alterations that occur when a material is compressed to reduce its size to the nanometric range and the difficulties in stabilizing NCs. A small indoleamine compound, melatonin (N-acetyl-5-methoxytriptamine), is secreted mainly by the pineal gland during darkness. However, it is also synthesized by most cells in the non-circadian way by which it is not released into the blood. Previously it has been reported that melatonin is possibly found in all living things, including plants and animals, and has been researched for various biological uses (Manchester et al., 2015; Salehi et al., 2019; Chuffa et al., 2019). When administered orally, melatonin has limited bioavailability and a short half-life as a type II agent with poor water solubility and high permeability (Li et al., 2017). Melatonin

effectively stabilizes cellular membranes, altering the activities of enzymes while enhancing cellular function. It also functions as an antioxidant, anticancer, and free radical scavenger (Reiter et al., 2017; Chuffa et al., 2019). Melatonin can have a variety of effects that are either receptor-mediated (e.g., through the MT1, MT2, and MT3 receptors) or receptor-independent (by directly interacting with intracellular or extracellular molecules). However, it has a varied route of administration but is commonly taken orally (Pandiperumal et al., 2008). A comprehensive study examined the different pharmacokinetics of nanosized melatonin delivery methods to address melatonin distribution to the skin via both *in vivo* and *in vitro* applications. This included liposomes, ethosomes, niosomes, polymeric nanoparticles (NPs), solid lipid NPs (SLN), and cyclodextrins (Zetner et al., 2016; Sanchez Milan et al., 2017) (Figure 3). Authors asserted that melatonin-loaded NCs were superior to traditionally delivered melatonin due to protection against early oxidation and improved drug penetration due to more appropriate exposure times. For COVID-19, where oxidative stress is a significant factor, nano-formulated melatonin has recently been proposed as a viable treatment (Martin et al., 2020). Figure 3 displays the many nanostructures that might be added to melatonin to boost its therapeutic potency and safety (Chuffa et al., 2021).

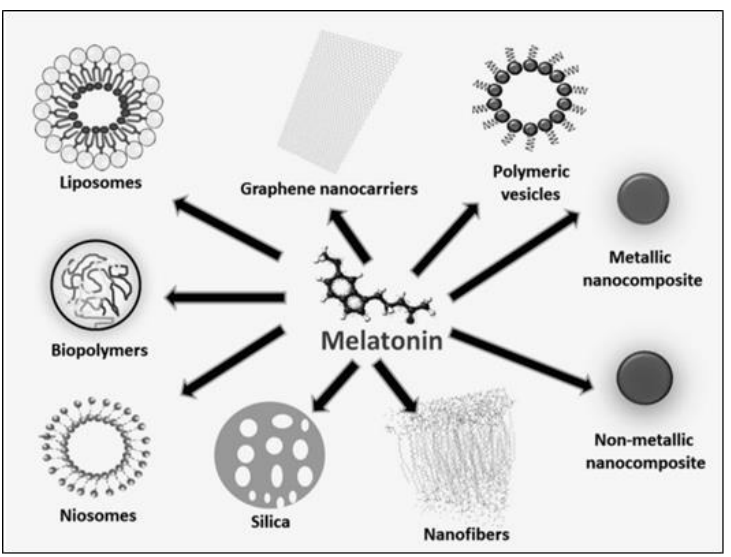

Figure 3. Lists the various melatonin-based nanostructures (Chuffa et al., 2021).

5. History of Nano-Medicine

According to the National Institutes of Health in the United States, nanotechnology is the study and manipulation of matter at scales between one and one hundred nanometers (nm), where novel phenomena allow for novel applications (Nano, 101). Fundamentally, nanotechnology aims to circumvent issues with small-molecule drugs, such as their subpar drug profiles and limited tissue penetration. The notion that it would be feasible to alter the properties of drugs by arranging them differently as nanoparticles has been around for a long time, even though nanotechnology is a relatively new topic.

Paul Ehrlich and Richard Feynman, two influential Nobel laureates who played inspirational roles in the 20th century, passed away many years before the science of nanomedicine was developed. However, the problems they posed for later generations of scientists are still evident today. Many people consider Feynman the originator of nanotechnology (Feynman, 1960) during his 1959 lecture to the American Physical Society, "Plenty of Room at the Bottom," where he encouraged colleagues from physics and biology to investigate nanodomains of their relative field of research interest. Ehrlich's work is based on the concept of targeted therapeutics, which he named "magic bullet" or "Zauberkugel," a drug that would be specifically directed at the target without having an impact on healthy host cells (Valent et al., 2016). This once-novel concept has undoubtedly been realized with the arrival of licensed nanomedicines on the market for clinical therapy that has proven targeted effects.

Interestingly, colloidal solutions of iron-carbohydrate nanoparticles had been utilized clinically for ten years before Feynman's call to arms and 25 years before Norio Tanaguchi first invented and popularised the word "nanotechnology" in 1974 (Bayda et al., 2020). Iron sucrose was first approved in Switzerland in 1949 as an IV treatment for iron deficiency (Nikravesh et al., 2020). The first FDA-licensed nanomedicine is commonly considered INN (Salvioni et al., 2019), a PEGylated liposome carrier containing doxorubicin, which is a deadly anticancer drug. A PEGylated version of asparaginase was approved in 1994 for treating acute lymphoblastic leukemia. The risk of cardiotoxicity is seven times lower with liposome loaded with doxorubicin than the free drug, and its circulation half-life is 100 times longer (Cheng et al., 2012).

The understanding of biological interactions at the nanoscale in medicine has advanced. It soon became apparent that newly developed nanomaterials would be extremely useful for diagnosing and treating disease (Mitchell et al.,

2020). In 2000, the National Nanotechnology was launched by the US National Science and Technology Council (NSTC). This federal initiative promoted research on the nanoscale and helped establish nanomedicine as a new field of study (Mitchell et al., 2020; Weissig et al., 2021).

The advancement of this field's research has resulted in the creation of several nanoparticle preparations that fall into three primary categories: lipid-based, polymeric, and inorganic (Friedrichs and Bowman, 2021).

Nowadays, numerous fields of traditional medicine and newer ones like gene therapy and CAR-T are the subjects of nanomedicine research. One significant application of nanomedicine has recently been observed during the vaccine preparation against COVID-19. This is the development of a nano-pharmaceutical vaccine with liposomal nanoparticles as SARS Cov-2 mRNA carriers (Friedrichs and Bowman, 2021).

The field of nanomedicine is currently developing and holds great therapeutic potential. In addition, it is crucial to recognize the challenges associated with nanomedicines and to make ongoing efforts to close the numerous research gaps in this area.

6. Different Nano-Careers for Melatonin Delivery

There are different forms of melatonin based nanoparticles developing day by day. Some of the melatonin based nano-particles presented in Figure 4.

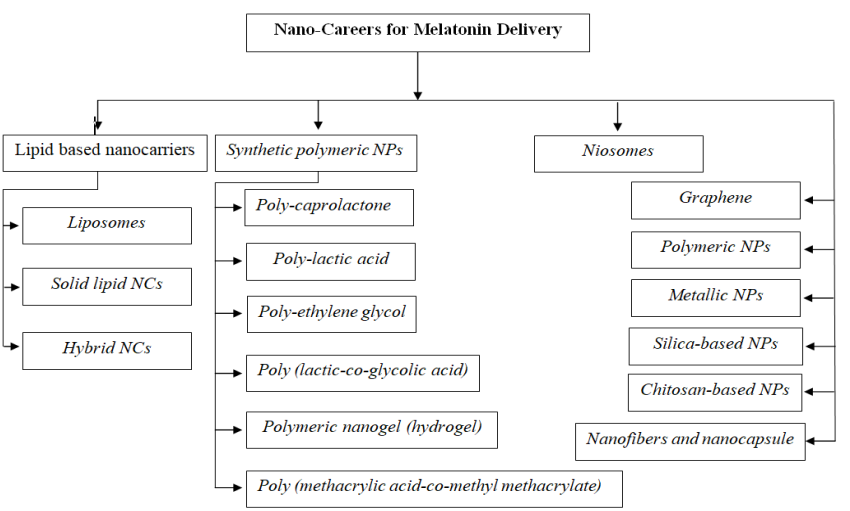

Figure 4. Different types of nano-careers for melatonin delivery.

6.1. Lipid Based Nanocarriers

These nanosystems are composed of rows of lipid materials to deliver biological materials or drugs to target cell types (Teixeira et al., 2017). Melatonin does not have very strong solubility in water, so lipid-based nanocarriers are used to increase its bioavailability for the cell (Proietti et al., 2014). There are three types of nanocarriers: liposomes, solid lipid NPs, and hybrid nanocapsules. Each type of lipid-based nanocarrier has unique characteristics and can penetrate various physiological barriers (Carbone et al., 2014).

6.1.1. Liposomes NPs as Carriers of Melatonin

Liposomes are composed of a bilayer of phospholipids used as nanocarriers for hydrophilic, hydrophobic, and amphiphilic materials (Laouini et al., 2012). Liposomes can be created using reverse-phase evaporation, ethanol injection, high-pressure homogenization, and detergent dialysis (Zhang et al., 2017). It is reported that liposomes have lower stability, very high cost, and low carrier capacity (Teixeira et al., 2017; Nogueira et al., 2015). However, the stability of the liposome can be increased with the help of zwitterionic polymers (Lin et al., 2019; Zhang et al., 2019; Cao et al., 2012). Natural polysaccharides like chitosan can enhance the stability of melatonin-loaded phosphatidylcholine liposomes (chitosomes) (Gonçalves et al., 2012). Melatonin-loaded ethanolic liposomes (ethosomes) develop a net negative charge on the surface and prevent the aggregation of ethosomes (Dubey et al., 2007).

6.1.2. Lipid Formed Nanocarriers for Melatonin Transport

Solid lipid nanoparticles are intracellular drug carriers composed of solid fat cores. To maintain a solid state in the core at body temperature, lipids with a melting point above 40ºC. A mixed composition of solid and liquid lipids enhances the stability and drug loading capacity (Souto et al., 2009). A solid lipid nanocarrier is used for hydrophobic compounds' topical, oral, systemic, ocular, and pulmonary delivery (Teixeira et al., 2017). Exogenous melatonin can be used for the treatment of sleep disorders. Delivery of melatonin through dermal or ocular routes is not an easy job. Tursilli et al., (2006) observed 19.6% degradation of un-capsulated melatonin and, on the other hand, 5.6% degradation of tristearin-phosphatidylcholine capsulated melatonin (7 mg) due to photolysis. In addition, Kanikkannan et al. (2002), Priano et al. (2007), and Hatem et al. (2018) separately obtained results that showed sustained release of melatonin after trans-dermal applications.

6.1.3. Lipids and Polymers Based Nanoparticles for Melatonin Administration

In nanocarriers, lipids show high loading capacity, and polymers regulate efficient drug release (Hallan et al., 2016). Hybrid NCs were formed to obtain the properties of lipid and polymeric particles (Teixeira et al., 2017). Melatonin-loaded LPN has been shown to have antioxidant and antiapoptotic properties in liver microsomes (Pohlmann et al., 2010; Schaffazick et al., 2008), an in vitro antioxidant assay (Külkamp et al., 2011), pulmonary cells (Charo et al., 2015), nematodes (Charo et al., 2019; Charo et al., 2015). In the treatment of paraquat-induced oxidative stress in alveolar A549 cells, melatonin-loaded LPN shows less cytotoxicity and genotoxicity as compared to free melatonin (Charão et al., 2015). Charão et al., (2019) observed in their results that the fluorescence intensity of SOD-3 enzymes encoding strains increased after melatonin-loaded LPN delivery.

6.2. Niosomes for Melatonin Transport

Nisosomes are another type of nanocarrier. Nisosomes are more stable than liposomes but somewhat leakier than liposomes and can decrease in size when frozen (Bartelds et al., 2018). For example, liposomes can be used for dermal delivery to a specific target in the brain delivery of hydrophilic or lipophilic drugs (Chen et al., 2019). According to Priprem et al. (2018), melatonin-loaded lysosome gel aids in the smooth handling of melatonin pharmacokinetics. Melatonin-loaded nisosomes are a better choice for protecting or treating UV-induced skin damage than sun-screams (Arslan et al., 2017).

6.3. Melatonin-Loaded Silica-Based NPs

Silica at the nano-scale has unique properties that can be used in drug delivery for cancer treatment (Achilleos et al., 2008). Based on the many unique properties of silica NPs, they can be used in diagnosis, therapy, the formation of biosensors, enzyme supporters, cellular uptake, etc. (Bitar et al., 2012).

6.4. Graphene and Melatonin Delivery

Graphene is a derivative of carbon, which is commonly used for bio-sensing and electrochemistry (Novoselov et al., 2012). Graphene oxide (GO) can perform as a drug carrier because of its hydrophobic nature (Usman et al., 2018). Melatonin combined with doxorubicin in a graphene nanocarrier has anti-osteosarcoma effects while being less toxic to normal cells. It increases apoptosis and down regulates the human telomerase catalytic subunit (Niu et al., 2021).

6.5. Nanofibers and Nanocapsule

Biochemically, as a result, developing wound-healing formulations is a difficult task (Mirmajidi et al., 2021)—replacement and maintenance of cells that may be damaged due to disease (Rahmani et al., 2017). Mirmajidi et al., (2021) developed chitosan (Cs)-polycaprolactone/polyvinylalcohol melatonin /chitosanpolycaprolactone three-layer nanofiber for dressing different kinds of wounds like diabetic ulcers, trauma, and burns. Li et al. (2019) developed melatonin-loaded bacterial cellulose nanofiber suspensions that dissolute more rapidly than free melatonin and have 2.4 times higher bioavailability than free melatonin for a slow release of melatonin in the retinas of rabbits. Bessone et al. (2020) prepared a nanosystem. Melatonin-loaded ethyl-cellulose nanocapsules showed their effectiveness in drug delivery in retinal ganglion cells.

6.6. Chitosan-Based NPs

Chitosan nanoparticles are synthesized by N-deacetylation of chitin, which is commonly used to deliver drugs, genes, or proteins into the cell (Almaaytah et al., 2018). The most common formulation for synthesizing Chitosan NPs is ionotropic gelation via interactions of positively charged amino sugar monomers and negatively charged polyanions (e.g., tripolyphosphate, hexametaphosphate, or dextran sulfate) (Rassu et al., 2018; Saeed et al., 2020). Chitosan is primarily composed of lectin, a natural lipid mixture of phosphatidylethanolamine and phosphatidylcholine. This formulation enhances the bio-adhesion and penetration of nanoparticles. Lectin/chitosan nanoparticles have an efficient potential for wound healing in in-vitro

(Blaževi´c et al., 2016; Romi´c et al., 2019) and in vivo conditions (Lopes et al., 2020). Lecithin/chitosan nanoparticles have a positive charge, which plays a vital role in release and permeability. This property of lecithin/chitosan nanoparticles is utilized to inhibit the growth of human glioblastoma U87MG cells (Yadav et al., 2017). Hafner et al. (2015) obtained results that indicated lecithin/chitosan-based nanoparticles have long-term stability after lyophilization.

6.7. Polymer Based Nanoparticles for Melatonin Transport

Polymeric nanoparticles are biodegradable and contain drugs in adsorbed, chemically linked form or encapsulated in nanocarriers. They are used for efficient, targeted drug delivery, to improve circulation time, and to have fewer side effects. Some polymeric nanoparticles do not undergo phagocytosis in the cell (Ahlawat et al., 2018). Different polymeric nanoparticles are available with unique characteristics such as size, morphology, surface charge, loading capacity, penetration efficiency, etc. These entire features have a central role in nanoparticles' pharmacokinetics and pharmacodynamics. Different situations require different requirements for the characteristics of polymeric nanoparticles. So, the choice of polymeric NP depends on what kinds of drugs are encapsulated or the purpose of drug delivery (Amgoth et al., 2019). So, if we want to use polymeric NPs for melatonin delivery, we must first study the physicochemical characteristics of melatonin.

6.7.1. Polycaprolactone/Melatonin

De Oliveira Junior et al. (2019) reported a melatonin-loaded polycaprolactone (PCL). For delivery of melatonin into the brain through the nose for the treatment of glioblastoma, PCL is a better choice. PCL is synthesised by the nanoprecipitation method and delivered through an intranasal route. U87MG cells show high cytotoxicity toward melatonin-loaded PCL nanoparticles. This selective response of melatonin-loaded PCL NPs is useful for glioblastoma treatment (Oliveira Junior et al., 2019). PCL NPs showed very good results in the transdermal delivery of melatonin. Massella et al. (2017) observed the continued and controlled release of melatonin.

6.7.2. Poly-Lactic Acid/Melatonin

Melatonin loaded PLA is applicable for treatment of constitutive and induced bone anomalies (Ghosh, 2021). With the help of HPLC, Martins et al. (2017)