https://doi.org/10.48047/AFJBS.6.13.2024.1522-1537

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Exploring Innovations in Stem Cell Therapy for Diabetes Mellitus: Current Insights and Future Applications

Chethan Kumar B.G[1, 2], Anil Kumar K.M[2], Ramya C M[3], Jayanthi M K[4], Akshaya Simha N[1], Ramith Ramu[1*]

[1]Department of Biotechnology and Bioinformatics, JSS Academy of Higher Education & Research, Mysuru – 570015, Karnataka, INDIA
[2]Department of Environmental Sciences, JSS Academy of Higher Education & Research, Mysuru – 570015, Karnataka, INDIA
[3]Department of Physiology, JSS Medical College, JSS Academy of Higher Education & Research, Mysuru – 570015, Karnataka, INDIA
[4]Department of Pharmacology, JSS Medical College, JSS Academy of Higher Education & Research, Mysuru – 570015, Karnataka, INDIA

Corresponding Author: Dr. Ramith Ramu
Department of Biotechnology and Bioinformatics, JSS Academy of Higher Education & Research, Mysuru – 570015, Karnataka, INDIA

Email: ramith.gowda@gmail.com

Article Info

Volume 6, Issue 13, July 2024

Received: 02 June 2024

Accepted: 30 June 2024

Published: 24 July 2024

doi: 10.48047/AFJBS.6.13.2024.1522-1537

ABSTRACT:

Diabetes mellitus is becoming more common worldwide which is a health risk, leading to significant morbidity and mortality. Despite advancements in pharmacotherapy and lifestyle modifications, managing diabetes remains a challenge due to its complex pathophysiology and associated complications. Stem cell treatment has become a potentially approach to a diabetes treatment, offering the potential to regenerate pancreatic beta cells, modulate immune responses, and improve tissue repair. This review article provides an overview of the current understanding of diabetes mellitus, discusses the mechanisms of action of various types of stem cells, and evaluates preclinical and clinical evidence supporting their therapeutic potential. Challenges such as immune rejection, tumorigenicity, and regulatory hurdles are addressed, along with future directions in stem cell therapy, including personalized medicine approaches and combination therapies. By highlighting the opportunities and obstacles in stem cell therapy for diabetes, this review aims to guide future research efforts toward developing safe, effective, and accessible treatments for diabetic patients worldwide.

1. INTRODUCTION

Diabetic mellitus is a chronic illness (Sreepathi et al ., 2024) that impairs protein, carbohydrate, and lipid metabolism. Insufficient insulin secretion is a defining characteristic, as it hinders the body's glucose use and results in hyperglycemia (Singh et al., 2016, Ramu et al., 2014). This is the most common endocrine disease globally; 40.9 million cases are expected in India by 2025, and the figure is expected to rise to 69.9 million by the same year 2019. Diabetes comes in two varieties type 1 diabetes and type 2 diabetes, according to guidelines that are regularly updated by the World Health Organization. However, distinguishing between them is challenging and lacking in defined guidelines (Chiefari et al., 2017, Maradesha et al., 2022). Diabetes interferes with macromolecule metabolism, (Sreepathi et al ., 2024) either by creating insufficient insulin or by using it inefficiently, which adversely affects the body's blood sugar regulation capacity (Kumar et al., 2020 Kumari et al.,2020, Martiz et al., 2022, Sreepathi et al,.2022). It crosses national borders, causing uncontrolled blood glucose levels and increased urine production (Katsarouet al., 2017, Firdose et al., 2023, Badiger et al., 2021). Based on the data from the World Health Organization, there was a notable increase in diabetes diagnoses, from 108 million in 1980 to 422 million in 2014. The classification of diabetes mellitus is tabulated in **Table 1**. pathophysiology in diabetes mellitus is shown in **Figure 1.**

Table 1. Classification of Diabetes

Diabetes type	Description
➢ Diabetes mellitus type 1 (T1DM)	β-Cell loss typically results in complete insulin insufficiency. Different levels of insulin resistance and chronic insulin insufficiency
➢ Diabetes mellitus type 2 (T2DM)	pregnant women with elevated blood glucose levels during pregnancy but without a history of diabetic mellitus
➢ GDM, or gestational diabetes mellitus	Diabetes runs significantly in families and affects both type 1 and type 2. A single gene mutation is the cause. The likelihood of a child acquiring this gene mutation is 50% if one of the parents carries it.
➢ Maturity-onset diabetes of the young (MODY)	A condition where autoimmune β-cell failure progresses slowly even when islet antibodies are present while the diabetes diagnostic.
➢ Latent autoimmune diabetes of the adult (LADA) ➢ Exocrine pancreatic diseases	Includes hemochromatosis, pancreatectomy, neoplasia, trauma, infection, and pancreatitis, among other conditions. Somatostatinoma, hyperthyroidism, glucagonoma, Cushing's disease, and other conditions
➢ Diabetes and gum disease connection for oral health	Diabetes increases the risk of gum and oral disease (Meenakshi et al., 2024) by impairing the body's ability to fight against infection.(Meenakshi et al., 2024) People with diabetes seem to have a higher prevalence and severity of gum disease (Meenakshi et al., 2024).

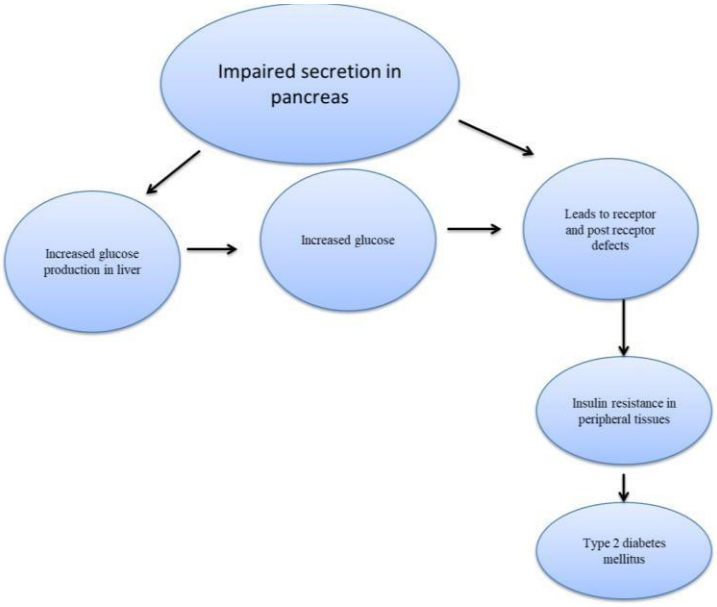

Figure 1. Pathophysiology of Type 1 Diabetic Mellitus **(Image courtesy: Ozougwu (2013)**

Modifying one's lifestyle is a crucial part of diabetes treatment. This includes controlling weight, modifying a diet, and engaging in regular exercise. Lifestyle modifications are critical because they improve overall metabolic health and insulin sensitivity (American Diabetes Association, 2020). Pharmacotherapy is crucial for many diabetic patients to maintain glycemic control. Oral antidiabetic drugs such as metformin, sulfonylureas, and DPP-4 inhibitors are often first-line therapies (Davies et al., 2018, Sajal et al., 2022, Patil et al., 2022, Swathi et al., 2016). Through several mechanisms, these medications raise insulin activity and decrease blood glucose levels. Insulin therapy is required when oral medications are insufficient. The cornerstone of diabetic therapy remains insulin, particularly for people with advanced type 2 or type 1 diabetes. However, while utilizing insulin therapy, there are problems with weight gain, hypoglycemia risk, and adherence. (Inzucchi et al., 2015, Patil et al.,2022).

SGLT-2 inhibitors and GLP-1 receptor agonists are the modern therapies used for managing diabetes. (Zinman et al., 2015, Mahadev et al., 2022, Ramu et al., 2017) report that these drugs have different mechanisms of action and have been shown to enhance cardiovascular outcomes. To completely comprehend their long-term safety features and cost-effectiveness, more research is needed. (Powers et al., 2015). Reaching the right blood glucose levels without causing hypo or hyperglycemia episodes can be extremely challenging, especially in elderly and comorbid populations. Diabetic complications, which include neuropathy, nephropathy, and retinopathy, continue to represent a significant clinical burden (Patil et al., 2022, Maradesha et al., 2022).

Preventing and managing these consequences remains a major challenge in the treatment of diabetes, despite advancements in care. Furthermore, certain regions continue to impose restrictions on access to increasingly sophisticated medications and technological advancements, highlighting disparities in the cost and caliber of healthcare (Kahn et al., 2014). Resolving these disparities and ensuring equitable access to effective treatments are necessary to improve the prognosis of diabetic patients. Moreover, variations in the cost and quality of healthcare are highlighted by the fact that some areas still place limits on access to increasingly complex treatments and technological breakthroughs (Kahn et al., 2014). In regenerative medicine, stem cells are often used due to their unique properties; they are known to self-renew and get specialized into various cell types. Embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and

pancreatic progenitor cells are the few important cells that are used in stem cell therapy. In vitro modification of these cells into beta cells can create insulin, or they can be inserted into the pancreas to repair damaged tissue. Numerous preclinical experiments have demonstrated the efficacy of stem cell treatment in mitigating diabetic symptoms and improving glucose metabolism. For instance, (Lumelsky et al. 2001) successfully differentiated ESCs into insulin-secreting beta cells, opening up the possibility of an endless supply of cells for transplantation. Moreover, MSCs have been proven to contain immunomodulatory and anti-inflammatory qualities, protecting the pancreatic beta cells with type 1 diabetes against autoimmune destruction (Liu et al., 2019, Kalabharathi et al., 2021, Martiz et al., 2022).
At present, there are clinical trials to evaluate the effectiveness and safety of using stem cell-based treatments for diabetes. A notable study by (Shapiro et al. 2018) showed that transplanting progenitor cells from stem cells into individuals with type 1 diabetes was both safe and feasible, leading to blood sugar control and reduced reliance on insulin. Similarly, individuals with type 2 diabetes observed improvements in insulin production and blood sugar management after receiving a stem cell transplant from their bone marrow (Bhansali et al., 2017).

TYPES AND SOURCES OF STEM CELLS

Stem cell therapy is a potential treatment for diabetes mellitus that could lead to the regeneration of pancreatic beta cells and the restoration of insulin production. The therapeutic potential of many types of stem cells, each with distinct origins and benefits, has been investigated in diabetes. Embryonic stem cells, or ESCs, Early-stage embryos provide ESCs, which can differentiate into any kind of cell in the body, including beta cells, which are responsible for producing insulin (Kroon et al., 2008). Induced pluripotent stem cells, or iPSCs, can be created by reprogramming adult cells, including skin cells, to become pluripotent once more. They offer a potential autologous cell source for the treatment of diabetes by reducing the likelihood of immunological rejection (Tateishi et al., 2008). MSCs, or mesenchymal stem cells, are multipotent cells that are present in a variety of tissues, including adipose tissue. Despite their limited ability to differentiate into insulin-producing cells, MSCs have immunomodulatory and regenerative actions that promote beta-cell survival and function (Berman et al., 2010). Nostro et al. 2011 claim that pancreatic progenitor cells are more clearly committed to the beta cell lineage.

Embryonic stem cells: Because of their pluripotent nature, embryonic stem cells (ESCs) present a unique opportunity for regenerative medicine and show great promise in the treatment of diabetes mellitus. In individuals with diabetes mellitus, the pancreatic β-cells that produce insulin are either impaired or lacking, which results in insufficient control over glucose levels. Because ESCs may differentiate into other cell types, such as β-cells, that produce insulin, they offer a promising alternative (Rezania et al. 2014, Nivetha et al., 2022) conducted research that successfully proved the creation of functional β-cells from human ESCs, paving the path for their potential use in the treatment of diabetes. The insulin production of these ESC-derived β-cells was glucose-responsive, emulating the characteristics of natural β-cells. Furthermore, research by (Kroon et al (2008) has shown the capacity of pancreatic progenitors produced from embryonic stem cells to restore normoglycemia in models of diabetes in mice. The differentiation of embryonic stem cells is depicted in **Figure 2.**

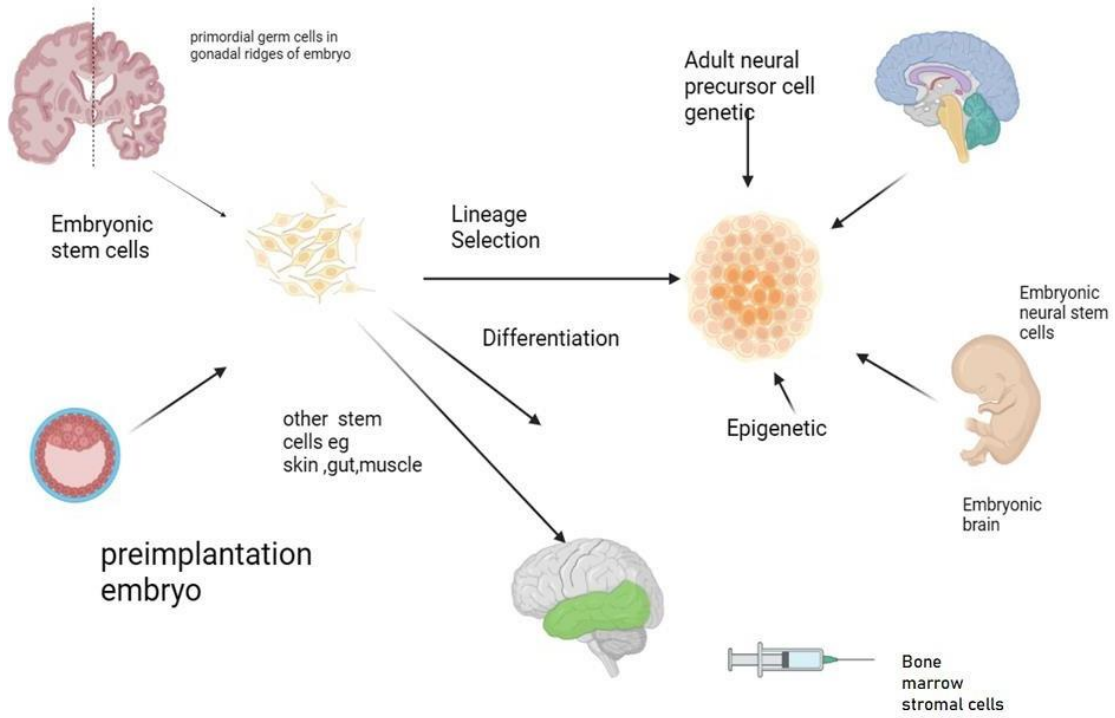

Figure 2: Different types of stem cells (Image courtesy: Rahman et al., 2022)

Induced pluripotent stem cells: In the field of regenerative medicine, especially the treatment of diabetes mellitus, induced pluripotent stem cells (iPSCs) have emerged as a promising substitute for embryonic stem cells (ESCs). Reprogrammed adult cells, usually skin or blood cells, are known as induced pluripotent stem cells (iPSCs). ESCs and iPSCs share the ability to differentiate into many cell types. iPSCs are advantageous in the context of diabetes mellitus in numerous ways. First off, because iPSCs are produced from adult tissues rather than embryos, they avoid the ethical difficulties surrounding the use of ESCs. By doing this, the ethical discussion around the annihilation of embryos is avoided. Furthermore, it is possible to create iPSCs from a patient's own cells, which lowers the possibility of immunological rejection and opens the door to customized therapy.

Studies have indicated that it is possible to create β-cells that produce insulin from iPSCs. Research conducted by (Maehr et al. 2009) and (Tateishi et al. 2008), for example, demonstrated the effective development of iPSCs into functional β-cells that can control blood glucose levels in animal models of diabetes. These results demonstrate the therapeutic potential of β-cells produced from iPSCs in the management of diabetes (Bharadwaj MR et al., 2024). Concerns about issues like the potential for tumorigenicity and genetic instability are still present with iPSCs. However, continuing studies seek to overcome these obstacles and realize iPSCs' full promise for diabetes treatment.

Mesenchymal stem cells (MSCs); are gaining popularity due to their potential for treating diabetes mellitus and providing a fresh take on regenerative medicine. MSCs are present in many adult tissues, such as bone marrow, adipose tissue, and the umbilical cord. Because of their immunomodulatory qualities and capacity for multipotent differentiation, MSCs are appealing targets for therapeutic interventions.

MSCs have been shown in numerous trials to have the ability to improve problems associated with diabetes. For example, Ezquer et al., 2016 found that by encouraging β-cell regeneration and lowering inflammation in pancreatic tissue, MSC transplantation enhanced pancreatic function and glycemic management in diabetic rats. Furthermore, it has been demonstrated

that paracrine factors derived from MSCs promote angiogenesis and increase blood flow in diabetic wounds, which speeds up the healing process (Ding et al., 2015). Additionally, MSCs have immunomodulatory properties that may help treat autoimmune types of diabetes, such as type 1 diabetes. MSCs can reduce autoimmunity and maintain β-cell function by interacting with immune cells and secreting anti-inflammatory cytokines (Bhansali et al., 2017). Although preclinical results are encouraging, issues including the best dosage, mode of administration, and long-term safety must be resolved before MSC-based treatments may be extensively used in clinical settings. However, studies are still being conducted to clarify the therapeutic mechanisms and maximize the effectiveness of MSC-based diabetic mellitus therapies.

Hematopoietic stem cells (HSCs): Hematopoietic stem cells (HSCs) are multipotent cells that can differentiate into any kind of blood cell, including platelets, white blood cells, and red blood cells. They are mostly found in the bone marrow. While HSCs have traditionally been linked to the production of blood cells, recent studies suggest that they may potentially provide therapeutic promise for the management of diabetes mellitus. Studies have shown that HSC transplantation can control the immune system and potentially prevent the autoimmune destruction of β-cells, which are responsible for producing insulin, in people with Type 1 diabetes mellitus (T1DM). Researchers hope to sustain insulin secretion and promote tolerance to pancreatic β-cells by resetting the immune system through HSC transplantation (Snarski et al., 2011). Additionally, in preclinical models of T1DM, HSC-derived regulatory T cells (Tregs) have demonstrated promise in reducing autoimmunity and maintaining β-cell activity (Tang et al., 2014, Kokila et al., 2023). HSCs may also aid in tissue regeneration and repair in diabetes-related disorders such as diabetic retinopathy and neuropathy. Preclinical research has shown that endothelial progenitor cells (EPCs) generated from hematopoietic stem cells (HSCs) can promote angiogenesis and vascular repair, which can help to mitigate the vascular problems associated with diabetes (Majumdar et al., 2012). Harnessing the therapeutic potential of HSCs for diabetes mellitus is still hampered by issues like the scarcity of HSC sources, the possibility of graft-versus-host disease (GVHD) after allogeneic transplantation, and the requirement for precise immunological regulation.

Adipose-derived stem cells (ADSCs): ADSCs represent a mesenchymal stem cell (MSC) subtype that may be extracted from adipose tissue, providing an easily obtainable and plentiful supply for applications in regenerative medicine. These cells have drawn a lot of interest lately because of their possible therapeutic use in treating a range of illnesses, including diabetes mellitus.

The potential of ADSCs in the treatment of diabetes mellitus has been investigated in several studies. The capacity of ADSCs to develop into several cell lineages, such as insulin-producing β-cells, presents a viable method for restoring β-cell bulk in individuals with diabetes (Rocha et al., 2014). Studies conducted by (Lee et al. 2013) showed that transplanting insulin-producing cells generated from ADSCs enhanced glucose metabolism and reduced hyperglycemia in animal models of diabetes. Additionally, ADSCs have immunomodulatory qualities that could help cure Type 1 diabetes mellitus, an auto-immune disease. ADSCs can inhibit autoimmune reactions and maintain β-cell function by secreting anti-inflammatory cytokines and modifying immune cell function (El-Badawy et al., 2016, Khadri et al., 2023).

Growth factors and cytokines, which are paracrine factors derived from ADSC, have been demonstrated to enhance tissue regeneration, decrease inflammation, and promote angiogenesis. These effects may aid in the healing of diabetic complications, such as diabetic

neuropathy and impaired wound healing (Duscher et al., 2017, Satish et al., 2021). Even with the encouraging preclinical results, several issues must be resolved before ADSC-based treatments are implemented in clinical settings. These include assuring the security and effectiveness of human trials and refining techniques for cell separation, proliferation, and differentiation. The different stem cell types and their sources are tabulated in **Table 2**.

Table 2. Types of stem cells and their sources (SuPaul et al., 2011)

Type of Stem cell	Source	Advantages	Disadvantages
Embryonic stem cells	Embryo (Blastocyst)	Pluripotent	Ethical problems safety concerns tissue availability unpredictable differentiation
Fetal neural stem cells	Fetus	Multipotent (for neural cell types)	Ethical problems safety concerns tissue availability difficulty in directing relevant differentiation
Adult neural stem cells	Adult tissue (CNS)	Multipotent for neural cell types) Autologous-based therapy is Ethically favorable	safety concerns difficulty to extract
Adult non-neural stem cells	Adult tissue(various)	Autologous-based therapy Ethically favorable tissue availability	safety concerns lineage-restricted
Pluripotent stem cells	Adult tissue(various)	Pluripotent autologous-based therapy ethically favorable tissue availability	safety concerns

MECHANISM OF ACTION OF STEM CELLS

The therapeutic effects of stem cells in diabetes are underpinned by a complex web of cellular and molecular pathways. First off, stem cells can separate into β-cells that produce insulin. Examples of these cells are HSCs, iPSCs, MSCs, and ESCs. According to (Rezania et al. 2014), this differentiation potential can restore physiological insulin secretion and glucose homeostasis by replacing the β-cell mass, which is frequently lost in diabetes mellitus. Immunomodulatory actions of stem cells are especially important in Type 1 diabetes mellitus, which is mediated by the immune system. By secreting anti-inflammatory cytokines and modifying immune cell activity, MSCs and HSC-derived regulatory T cells (Tregs) have been demonstrated to reduce autoimmunity, control inflammation, and maintain β-cell function (Tang et al., 2014; Bhansali et al., 2017, Ramu, et al., 2016). Paracrine substances, including growth factors, cytokines, and extracellular vesicles, are secreted by stem cells and are essential for angiogenesis, tissue healing, and microenvironment regulation. According to (Ezquer et al. 2016 and Ding et al. 2015), these paracrine effects

support improved islet vascularization, improved pancreatic tissue regeneration, and improved β-cell survival and function.

By encouraging neovascularization, neuron regeneration, and wound healing, stem cell therapy may lessen the consequences of diabetes. While MSCs have shown effectiveness in improving diabetic neuropathy and retinopathy through their regenerative characteristics, endothelial progenitor cells (EPCs) produced from MSCs have been linked to improving angiogenesis and vascular repair (Majumdar et al., 2012; Duscher et al., 2017). With its many modes of action, such as β-cell regeneration, immunomodulation, paracrine effects, and tissue repair, stem cell therapy has enormous potential to cure diabetes mellitus.

Pancreatic β-cell regeneration is the main method by which stem cells exercise their therapeutic effects in diabetes mellitus. The capacity of ESCs and iPSCs to develop into β-cells that produce insulin makes them a renewable source for β-cell mass replenishment (Rezania et al., 2014). Likewise, it has been demonstrated that MSCs obtained from diverse origins, such as bone marrow and adipose tissue, can develop into cells that produce insulin, thereby enhancing endogenous insulin production and maintaining glucose homeostasis (Wang et al., 2016).

Immunomodulatory actions of stem cells are especially important in Type 1 d. melitus, which is mediated by the immune system. MSCs and HSC-derived regulatory T cells (Tregs) are crucial for reducing autoimmunity and preserving β-cell function because they release anti-inflammatory cytokines and regulate immune cell activity. (Tang et al., 2014; Bhansali et al., 2017). Additionally, it has been possible to create β-cells produced from iPSCs to avoid immune recognition, which presents a possibility for immune-tolerant cell replacement treatment (Mattapally et al., 2018).

Numerous paracrine substances, such as growth factors, cytokines, and extracellular vesicles, are released by stem cells and aid in tissue healing, angiogenesis, and microenvironmental regulation. These paracrine effects support improved islet vascularization, improved β-cell survival and function, and the regeneration of injured pancreatic tissue (Ezquer et al., 2016; Ding et al., 2015). Furthermore, it has been shown that factors originating from MSCs might facilitate wound healing, neovascularization, and nerve regeneration, which can help with diabetic consequences such as neuropathy and poor wound healing (Majumdar et al., 2012; Duscher et al., 2017).

To study the development of stem cell therapy in the treatment of d. melitus, preclinical data is essential. This includes animal studies that demonstrate efficacy, optimization of stem cell delivery techniques, and long-term safety and efficacy assessments. The effectiveness of stem cell therapy in retaining β-cell function and enhancing glycemic control in diabetes mellitus models has been demonstrated by numerous animal studies. Researchers have found, for instance, that transplanting various types of stem cells, such as mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), and induced pluripotent stem cell (iPSC)-derived β-cells, significantly improves blood glucose levels, insulin secretion, and histological markers of pancreatic regeneration in diabetic rodent models, such as mice and rats (Wang et al., 2016; Ezquer et al., 2016, Ramu et al., 2016). Subsequent clinical trials are informed by these preclinical investigations, which offer insightful information about the treatment potential of stem cells.

Improving stem cell delivery techniques is crucial to raising the effectiveness and security of stem cell treatment for diabetes mellitus. Several strategies have been investigated to enhance the function, engraftment, and survival of stem cells that have been transplanted. These consist of genetic alteration to improve homing and differentiation capacities, intravenous infusion, intrapancreatic injection, and encapsulation within biomaterials (Ding et al., 2015; Ezquer et al., 2016). Preclinical research on various delivery modalities has provided

important information about the advantages and disadvantages of each approach, as well as how effectively it works to encourage stem cell engraftment.

Evaluating the durability and potential side effects of stem cell therapy in diabetes mellitus requires long-term safety and efficacy studies. Extended follow-up periods in preclinical investigations facilitate a thorough assessment of animals treated with stem cells, encompassing evaluations of immunological response, glucose metabolism, β-cell function, and potential tumorigenicity. Additionally, pancreatic tissue integrity, vascularization, and inflammatory markers can be examined over time with longitudinal histological investigations (Mattapally et al., 2018; Duscher et al., 2017). Preclinical safety evaluations play a crucial role in shaping clinical trial designs and guaranteeing the successful conversion of stem cell therapy into safe and efficient treatments for individuals with diabetes.

CLINICAL TRIALS OF STEM CELLS FOR THE TREATMENT OF DIABETES MELLITUS

Clinical trials are done to evaluate the transition of stem cell therapy for Diabetes mellitus from preclinical research to clinical practice (Trounson & McDonald, 2015). According to Dominicici et al. (2006), Phase II/III trials analyze efficacy and long-term outcomes, while Phase I/II trials largely focus on safety and feasibility assessments.

Phase I/II Trials: In a limited patient population, phase I/II trials aim to look for the safety, viability, and initial efficacy of stem cell therapy (Jansen et al., 2010). The purpose of these trials is to ascertain the best dosage schedule, mode of administration, and possible side effects of stem cell transplantation. Phase I and II trials also evaluate patient selection criteria, delivery strategies, and the viability of cell production. Researchers intensively monitor patients for immunological responses, adverse events, and tumorigenicity related to stem cell therapy during Phase I and II trials. The occurrence of infections, immunological rejection, and ectopic tissue development are examples of safety endpoints. The evaluation of transplanted stem cells' engraftment, survival, and functionality, together with their influence on β-cell function and glycemic control, is done through feasibility endpoints.

Phase II/III Trials: Using a larger patient population, phase II/III trials assess the effectiveness and long-term results of stem cell therapy by building on the results of phase I/II trials (Uccelli et al., 2008). The purpose of these trials is to determine whether stem cell transplantation offers therapeutic advantages over conventional medical therapy. Improvements in β-cell function, insulin independence, glycemic management, and a decrease in complications associated with diabetes are examples of efficacy endpoints.

Phase II and III trials must include long-term follow-up evaluations to determine the sustainability and duration of treatment effects and to track any delayed adverse events or disease progression. Stable glycemic control, avoiding complications from diabetes, and guaranteeing the long-term tolerability and safety of stem cell therapy are the key goals of long-term outcomes.

CHALLENGES AND CONSIDERATIONS

The clinical translation of stem cell therapy presents a variety of challenges and issues, from logistical obstacles to moral conundrums. In order to guarantee the safety, effectiveness, and moral purity of stem cell-based therapies, these issues must be resolved.

1. Immune Rejection: One major obstacle to the long-term application and engraftment of trans-plant stem cells is host immunological responses. Immune rejection may impair the results of therapy and cause transplant failure. Immunosuppressive treatment, immunological regulation, and the creation of immune-tolerant stem cell sources are methods to lessen immune rejection (Dominici et al., 2006).

2. Tumorigenic Potential: The capacity of stem cell therapy is overshadowed by the possible occurrence of stem cells developing into tumors like teratomas of malignant transformation. Extensive preclinical testing and extensive observation time are necessary to assess the carcinogenicity potential of stem cell-derived medicinal products. Besides, methods that lower tumorigenicity—for example, characterization of cells and genetic modification—could avoid flawed treatments (Trounson & McDonald, 2015).

3. Standardization of Protocols: The gap in set protocols for the processes of stem cell isolation, differentiation, growth, and implantation leads to a lower clinical research quality that is not reproducible and can't be compared. To this extent, standardization attempts are geared toward developing universal procedures for the administration and control of stem cells while also providing for quality assessment and regulatory control measures (Uccelli et al., 2008).

4. Regulatory Hurdles: Many hurdles restricting swift clinical translation also exist in addition to regulatory obstacles in the course of stem cell therapy development. Besides all these, this also involves stringent post-market surveillance, clinical trial approval steps, and cell manufacturing practices. The concerns of patient security as well as the moral course of clinical experimentation are interlinked with the laws and guidelines that provide for best practices (for instance, GMP laws) and ethical supervision (Jansen et al., 2010).

5. Ethical Considerations: The problem with the use of HESCs (human embryonic stem cells), fetal tissues, and gene editing technology to conduct stem cell therapies is complicated by the problems that are of an ethical nature. Ethical issues such as informed consent, patient autonomy, and ethical questions surrounding the use and distribution of technology, as well as the moral standing of human embryos, are all well-described in the topic of bioethics. Since stem cell research and clinical practice inevitably have to address ethical questions and operate based on ethical norms, ethical management should be an imperative.

THE FUTURE OF STEM CELL THERAPY

Stem cell therapy for the case of diabetes mellitus may well be revolutionary and might lead to advances in the prospect of methods of treatment and improving diabetes patient outcomes. Better adaptations to stem cell engineering methods, individual treatment regimes, association therapy, the use of biomaterials, and immunomodulation are key issues of priority.

1. Enhanced Stem Cell Engineering Techniques: The therapeutic potential of stem cells can be enhanced because new methods, including genetic engineering, induced pluripotent stem cells (iPSCs), and cellular reprogramming, are being developed. Due to the development of cells from the stem modified with an accessory for the improvement of engraftment, survival, and differentiation, the gene modification process is permitted. Additionally, targeted microenvironmental cues and biomimetic scaffolds are capable of affecting stem cell behavior, thereby promoting cell regeneration and healing in these tissues (Fischbach et al., 2013).

2. Personalized Medicine Approaches: Personalized medicine plans are designed after patient characters are identified using individualized medicine approaches, for example, by comparing genetic background and illness development rate to the response to the drugs used. There is a possibility of somatic cell-derived patient-specific PSCs that can serve as a basis for drug screening, cell-based medicine, and individual disease modeling platforms. Through the use of personalized medicine techniques, patients would face fewer unwanted and unnecessary side effects and more successful treatments because those approaches would consider the patient’s uniqueness (Tang et al., 2014).

3. Combination Therapies: Concurrent therapy that blends autologous stem cell infusion with the application of growth factors, drug addicts, and immunomodulators promises to

yield additional benefits through the joint course of action. The beneficial results of stem cell therapy in treating diabetes mellitus and its pathogenic routes like inflammation, oxidative stress, or metabolic unsoundness may be boosted by combining it with other therapies (Bhansali et al., 2017).

4. Biomaterial-Based Strategies: The biomaterial-based models that utilize biomaterials' unique properties to prolong implanted stem cells' transport, residence, and performance are the way to go. Biomaterial scaffolds enable cellular interaction and function in 3D, like natural extracellular, by offering them a matrix that resembles their own ECM. Also, as it was presented by (Ezquer et al. 2016), the task of biomaterials as the controlled release agent that delivers the medicines and other bioactive elements to the site of injury can be easily performed.

5. Advancements in Immunomodulation: The objective of advanced immunomodulation practices is to increase transplant acceptance and prevent immune rejection. Immune checkpoint blocking treatments, mesenchymal stem cell (MSC) immunomodulation approaches, and regulatory T cell (Treg)-based therapies are among the highly prospective tools for regulating immune responses and inducing transplant acceptability. Through applying the deceitful abilities of stem cells, researchers can improve the efficiency and safety of stem cell treatments for diabetes mellitus (Tang et al., 2014).

2. CONCLUSION

Lastly, the topic of stem cell therapy for diabetes that possesses a transformative capacity and lets direct patient outcomes considerably improve is one of the most important ones to be discussed. There is a need for creative and innovative solutions because, across the globe, diabetes is becoming more intense because of various causes like genes (genetic) and lifestyle changes. Stem cells can reinforce tissue repair, modulate immunological responses, and regenerate pancreatic β-cells in such a way that they offer an important strategy for overruling the complexities of diabetes.

The field of clinical translation constantly undergoes investigation to cope with the mentioned hurdles and challenges, such as immune responses that can have adverse effects, standardized protocols, regulatory procedures, and ethical dilemmas, despite facing these obstacles. These hindering factors can only be dealt with through better stem cell engineering techniques, exploiting the possibilities of personalized medicine and relying on combination therapies for stem cells, using bioengineering approaches, and exploring the avenues of immunomodulation. In concert with scientists, physicians, regulatory agencies, and ethical review groups, stem cell pregnancy for diabetes mellitus is promising for the future. To capture the full capability of stem cell-based therapies to change the course of diabetes treatment, scientists must receive sustained and long-term research funding, the preclinical and clinical evaluations must be detailed, and comprehensive, and ethical standards must be respected and adhered to. The final purpose is to deliver inexpensive, safe, and effective therapy to all patients worldwide that decreases patients' symptoms and improves their quality of life.

Acknowledgements

All the authors thank JSS Academy of Higher Education and Research (Mysore, Karnataka, India) for their kind support and encouragement.

Conflict of Interest

The authors have declared that there is no conflict of interest.

3. REFERENCES

1. American Diabetes Association. (2022). Standards of medical care in diabetes—2022 abridged for primary care providers. Clinical Diabetes. 40(1), 10-38.
2. Berman, D. M., Willman, M. A., Han, D. (2010). Mesenchymal stem cells enhance allogeneic islet engraftment in nonhuman primates. Diabetes. 59(10), 2558–2568.
3. S Badiger, A., R Maruthi, K., Naik Bajpe, S., Ramu, R., & Jayadev, K. (2021). Urinary Tract Infection–A Review on Its Prevalence and Recent Advances.
4. Bhansali, A., Upreti, V., Khandelwal, N., Marwaha, N., Gupta, V., Sachdeva, N., and Ramakrishnan, S. (2009). Efficacy of autologous bone marrow–derived stem cell transplantation in patients with type 2 diabetes mellitus. Stem cells and development. 18(10), 1407-1416.
5. Bhansali, S., Dutta, P., Kumar, V., Yadav, M. K., Jain, A., Mudaliar, S., ... & Sharma, R. R. (2017). Efficacy of autologous bone marrow–derived mesenchymal stem cell and mononuclear cell transplantation in type 2 diabetes mellitus: a randomized, placebo-controlled comparative study. Stem cells and development. 26(7), 471-481.
6. Bharadwaj, M. R., Mythreyi, R., Basalingappa, K. M., Gopenath, T. S., & Gobianand, K. (2024). Stem cell's potential role in the treatment of diabetes mellitus. In Stem Cells and Signaling Pathways (pp. 359-383). Academic Press.
7. Chiefari, E., Arcidiacono, B., Foti, D., & Brunetti, A. (2017). Gestational diabetes mellitus: an updated overview. Journal of endocrinological investigation. 40, 899-909.
8. Classification of diabetes mellitus. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.
9. Davies, M. J., D'Alessio, D. A., Fradkin, J., Kernan, W. N., Mathieu, C., Mingrone, G., & Buse, J. B. (2018). Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 41(12), 2669-2701.
10. Ding, J., Wang, O., Guo, X., Jiang, L., Zhou, J., Zhang, L., & Yao, X. (2015). Transplantation of bone marrow mesenchymal stem cells on collagen scaffolds for the functional regeneration of injured rat uterus. Biomaterials. 52, 407-418.
11. Dominici, M., Le Blanc, K., Mueller, I., Slaper-Cortenbach, I., Marini, F., Krause, D., ... & Horwitz, E. (2006). Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 8(4), 315-317.
12. Duscher, D., Atashroo, D., Maan, Z. N., Luan, A., Brett, E. A., Barrera, J., & Longaker, M. T. (2017). Ultrasound-assisted liposuction does not compromise the regenerative potential of adipose-derived stem cells. Stem Cells Translational Medicine. 6(9), 1979-1988.
13. El-Badawy, A., El-Badri, N., & Abo-Elela, M. (2016). Characterization of wound exudate-derived mesenchymal stem cells: a potential therapy for chronic wound healing. Cytotherapy. 18(1), 41-53.
14. Ezquer, F., Bahamonde, J., Huang, Y. L., Ezquer, M., & Konofagou, E. E. (2016). Paracrine effect of mesenchymal stem cells in tissue repair is mediated by extracellular vesicles. Advances in regenerative medicine: Role of nanotechnology, and engineering principles. 96.
15. Fischbach, M. A., Bluestone, J. A., & Lim, W. A. (2013). Cell-based therapeutics: the next pillar of medicine. Science translational medicine. 5(179), 179ps7-179ps7.
16. Firdose, N., Raj, R., Gangadharappa, B. S., Ishika, G. V., & Ramu, R. (2023). Effect of selective serotonin reuptake inhibitors on blood glucose in euglycemic and

streptozotocin-induced diabetic albino Wistar rats. International Journal of Health and Allied Sciences. 12(4), 6.

17. Inzucchi, S. E., Bergenstal, R. M., Buse, J. B., Diamant, M., Ferrannini, E., Nauck, M., & Matthews, D. R. (2015). Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 38(1), 140-149.
18. Jansen, B. J., Gilissen, C., & Roelofs, H. (2010). Functional differences between mesenchymal stem cell populations are reflected by their transcriptome. Stem Cells and Development. 19(4), 481-490.
19. Kahn, S. E., Cooper, M. E., Del Prato, S., Pathan, I., & Nathanson, D. (2014). A multicenter, randomized, placebo-controlled trial assessing the efficacy, safety, and tolerability of glycogen synthase kinase 3 inhibitors in the treatment of type 2 diabetes. Diabetes Care, 37(5), 1232-1239.
20. Katsarou, A., Gudbjörnsdottir, S., Rawshani, A., Dabelea, D., Bonifacio, E., Anderson, B. J., ... & Lernmark, Å. (2017). Type 1 diabetes mellitus. Nature reviews Disease primers. 3(1), 1-17.
21. Khadri, M. N., Ramu, R., Simha, N. A., & Khanum, S. A. (2024). Synthesis, molecular docking, analgesic, anti-inflammatory, and ulcerogenic evaluation of thiophene-pyrazole candidates as COX, 5-LOX, and TNF-α inhibitors. Inflammopharmacology, 32(1), 693-713.
22. Kroon, E., Martinson, L. A., Kadoya, K., (2008). Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells in vivo. Nature Biotechnology. 26(4), 443–452.
23. Kumar, R., Saha, P., Kumar, Y., Sahana, S., Dubey, A., & Prakash, O. (2020). A Review on Diabetes Mellitus: Type1 & Type2. World Journal of Pharmacy and Pharmaceutical Sciences. 9(10), 838-850.
24. Kumari VB, C., Huligere, S. S., Shbeer, A. M., Ageel, M., MK, J., & Ramu, R. (2022). Probiotic potential Lacticaseibacillus casei and Limosilactobacillus fermentum strains isolated from dosa batter inhibit α-glucosidase and α-amylase enzymes. Microorganisms. 10(6), 1195.
25. Kokila, N. R., Mahesh, B., Ramu, R., Roopashree, B., & Mruthunjaya, K. (2023). α-Amylase inhibitory potential of Thunbergia mysorensis leaves extract and bioactive compounds by in vitro and computational approach. Journal of Biomolecular Structure and Dynamics. 41(24), 14887-14903.
26. Lee, R. H., Seo, M. J., Reger, R. L., Spees, J. L., Pulin, A. A., Olson, S. D., ... & Prockop, D. J. (2013). Multipotent stromal cells from human marrow home to and promote repair of pancreatic islets and renal glomeruli in diabetic NOD/scid mice. Proceedings of the National Academy of Sciences. 103(46), 17438-17443.
27. Liu, M., Han, Z. C., & Zhang, X. (2019). Mesenchymal stem cells: biology and clinical potential in type 1 diabetes therapy. Journal of Cellular and Molecular Medicine. 23(2), 125–136.
28. Lumelsky, N., Blondel, O., Laeng, P., Velasco, I., Ravin, R., & McKay, R. (2001). Differentiation of embryonic stem cells to insulin-secreting structures similar to pancreatic islets. Science. 292(5520), 1389–1394.
29. Maehr, R., Chen, S., Snitow, M., Ludwig, T., Yagasaki, L., Goland, R., & Melton, D. A. (2009). Generation of pluripotent stem cells from patients with type 1 diabetes. Proceedings of the National Academy of Sciences. 106(37), 15768-15773.
30. Mahadev, M., Nandini, H. S., Ramu, R., Gowda, D. V., Almarhoon, Z. M., Al-Ghorbani, M., & Mabkhot, Y. N. (2022). Fabrication and evaluation of quercetin

nanoemulsion: A delivery system with improved bioavailability and therapeutic efficacy in diabetes mellitus. Pharmaceuticals, 15(1), 70.

31. Maradesha, T., Patil, S. M., Phanindra, B., Achar, R. R., Silina, E., Stupin, V., & Ramu, R. (2022). Multiprotein inhibitory effect of dietary polyphenol rutin from whole green jackfruit flour targeting different stages of diabetes mellitus: defining a bio-computational stratagem. Separations. 9(9), 262.
32. Maradesha, T., Patil, S. M., Al-Mutairi, K. A., Ramu, R., Madhunapantula, S. V., & Alqadi, T. (2022). Inhibitory effect of polyphenols from the whole green jackfruit flour against α-glucosidase, α-amylase, aldose reductase and glycation at multiple stages and their interaction: Inhibition kinetics and molecular simulations. Molecules. 27(6), 1888.
33. Majumdar, M. K., Thiede, M. A., Mosca, J. D., Moorman, M., & Gerson, S. L. (2012). Phenotypic and functional comparison of cultures of marrow-derived mesenchymal stem cells (MSCs) and stromal cells. Journal of Cellular Physiology. 176(1), 57-66.
34. Mattapally, S., Pawlik, K. M., Fast, V. G., Zumaquero, E., Lund, F. E., Randall, T. D., & Ortega, P. V. (2018). Human leukocyte antigen class I and II knockout human induced pluripotent stem cell–derived cells: universal donor for cell therapy. Journal of the American Heart Association. 7(24), e010239.
35. Meenakshi, S., Monisha Jeyasingh., Dishi Sangati., Sreeshyla H S., Raghunath N., Ramith Ramu., (2024). Improving nutritional status of elderly patients with dentures circumventing challenges. African Journal of Biological Sciences. 6(11), 721-728.
36. Meenakshi, S., Pavitra, T., Raghunath, N., Sumana, K., Praveen Rai., Ramith Ramu (2024). Exploration of unique microbial communities in oral and denture microbiomes. African Journal of Biological Sciences. 6(5), 5111-5135.
37. Meenakshi Srinivasa Iyer., Monisha. Jeyasingh., Dishi Sangati., Sreeshyla H S., Raghunath Nagasundara Rao., Ramith Ramu (2024). Improving nutritional status of elderly patients with dentures circumventing challenges. African Journal of Biological Sciences.6(11), 1241-1248.
38. Martiz, R. M., Patil, S. M., Thirumalapura Hombegowda, D., Shbeer, A. M., Alqadi, T., Al-Ghorbani, M., ... & Prasad, A. (2022). Phyto-computational intervention of diabetes mellitus at multiple stages using isoeugenol from Ocimum tenuiflorum: A combination of pharmacokinetics and molecular modelling approaches. Molecules. 27(19), 6222.
39. Nivetha, N., Martiz, R. M., Patil, S. M., Ramu, R., Sreenivasa, S., & Velmathi, S. (2022). Benzodioxole grafted spirooxindole pyrrolidinyl derivatives: Synthesis, characterization, molecular docking and anti-diabetic activity. RSC advances, 12(37), 24192-24207.
40. Nostro, M. C., Sarangi, F., Ogawa, S., et al. (2011). Stage-specific signaling through TGFβ family members and WNT regulates patterning and pancreatic specification of human pluripotent stem cells. Development. 138(5), 861–871.
41. Navya Sreepathi., Jayanthi, M K., Nagma Firdose., Ashwini P., Meenakshi S., Akshaya Simha, N., Reshma Mary Martiz., Vasantha Kumar., Ramith Ramu., (2024). Molecular Docking and Simulation of Rhodanine and Rhodanine-3-AceticAcid Derivatives as Potential Aldose Reductase Inhibitors. African Journal of Biological Sciences. 6(12), 135-144.
42. Navya Sreepathi ., Jayanthi M K., VenuDakshinamurthy., Ashwini P., Raghunath N., Akshaya Simha, N., Reshma Mary Martiz., Vasantha Kumar., Ramith Ramu., (2024). In Silico Analysis of Rhodanine and Rhodanine Acetic Acid Derivatives as Inhibitors of Xanthine Oxidase. African Journal of Biological Sciences. 6(12), 145-156.
43. Powers, M. A., Bardsley, J., Cypress, M., Duker, P., Funnell, M. M., Hess, Fischl, A., & Vivian, E. (2015). Diabetes Self-management Education and Support in Type 2 Diabetes: A Joint Position Statement of the American Diabetes Association, the

American Association of Diabetes Educators, and the Academy of Nutrition and Dietetics. The Diabetes Educator. 41(4), 417-430.

44. Patil, S. M., Martiz, R. M., Satish, A. M., Shbeer, A. M., Ageel, M., Al-Ghorbani, M., ... & Ramu, R. (2022). Discovery of novel coumarin derivatives as potential dual inhibitors against α-glucosidase and α-amylase for the management of post-prandial hyperglycemia via molecular modelling approaches. Molecules. 27(12), 3888.
45. Patil, S. M., Martiz, R. M., Ramu, R., Shirahatti, P. S., Prakash, A., Kumar, B. P., & Kumar, N. (2022). Evaluation of flavonoids from banana pseudostem and flower (quercetin and catechin) as potent inhibitors of α-glucosidase: An in-silico perspective. Journal of Biomolecular Structure and Dynamics, 40(23). 12491-12505.
46. Patil, S. M., Shirahatti, P. S., & Ramu, R. (2022). Azadirachta indica A. Juss (neem) against diabetes mellitus: A critical review on its phytochemistry, pharmacology, and toxicology. Journal of Pharmacy and Pharmacology. 74(5), 681-710.
47. Ramu, R., Shirahatti, P. S., Zameer, F., Ranganatha, L. V., & Prasad, M. N. (2014). Inhibitory effect of banana (Musa sp. var. Nanjangud rasa bale) flower extract and its constituents Umbelliferone and Lupeol on α-glucosidase, aldose reductase, and glycation at multiple stages. South African Journal of Botany, 95, 54-63.
48. Ramu, R., Shirahatti, P. S., Nayakavadi, S., Vadivelan, R., Zameer, F., Dhananjaya, B. L., & Prasad, N. (2016). The effect of a plant extract enriched in stigmasterol and β-sitosterol on glycaemic status and glucose metabolism in alloxan-induced diabetic rats. Food & function. 7(9), 3999-4011.
49. Ramu, R., S. Shirahatti, P., Zameer, F., Lakkappa Dhananjaya, B., & MN, N. P. (2016). Assessment of in vivo antidiabetic properties of umbelliferone and lupeol constituents of banana (Musa sp. var. Nanjangud Rasa Bale) flower in hyperglycaemic rodent model. PLoS One. 11(3), e0151135.
50. Ramu, R., Shirahatti, P. S., Anilakumar, K. R., Nayakavadi, S., Zameer, F., Dhananjaya, B. L., & Prasad, M. N. (2017). Assessment of nutritional quality and global antioxidant response of banana (Musa sp. CV. Nanjangud Rasa Bale) pseudostem and flower. Pharmacognosy research, 9(Suppl 1), S74.
51. Rezania, A., Bruin, J. E., Arora, P., Rubin, A., Batushansky, I., Asadi, A., ... & Kieffer, T. J. (2014). Reversal of diabetes with insulin-producing cells derived in vitro from human pluripotent stem cells. Nature biotechnology. 32(11), 1121-1133.
52. Rocha, A., Oliveira, F., Azevedo, L. F., Reis, R. L., & Sousa, N. (2014). Adipose-derived stem cells isolated from different adipose tissues present different therapeutic potential. Stem Cell Reviews and Reports. 10(5), 760-770.
53. Shapiro, A. M. J., Pokrywczynska, M., Ricordi, C., & Clinical Islet Transplantation Consortium. (2018). Clinical pancreatic islet transplantation. Nature Reviews Endocrinology, 14(5), 268–277.
54. Singh, N., Kesherwani, R., Tiwari, A. K., & Patel, D. K. (2016). A review on diabetes mellitus. The Pharma Innovation. 5(7, Part A), 36.
55. Satish, A.M., M. K., J., Gangadhar, T.V., & Ramu, R. (2021). Evaluation of Wound Healing Activity of Catharanthus Roseus Aqueous Extract in Adult Albino Rats. International Journal of pharma and Bio Sciences.
56. Sreepathi, N., Jayanthi, M. K., Chandra, S. J., Bajpe, S. N., & Ramu, R. (2022). Probiotic intervention in the treatment of diabetes mellitus: a review. J. Pure Appl. Microbiol. 6, 1519-1529.
57. Putta, S., Sastry Yarla, N., Kumar Kilari, E., Surekha, C., Aliev, G., Basavaraju Divakara, M., ... & Lakkappa Dhananjaya, B. (2016). Therapeutic potentials of triterpenes in diabetes and its associated complications. Current topics in medicinal chemistry. 16(23), 2532-2542.

58. Snarski, E., Milczarczyk, A., Halaburda, K., Torosian, T., Paluszewska, M., Urbanowska, E.,& Dwilewicz-Trojaczek, J. (2011). Independence of exogenous insulin following immunoablation and stem cell reconstitution in newly diagnosed diabetes type I. Bone Marrow Transplantation. 46(4), 562-566.
59. Su, Paul & Loane, Clare & Politis, Marios. (2011). The Use of Stem Cells in the Treatment of Parkinsons Disease. Insciences J. [Case Reports]. 1. 10.5640/insc.0103136.
60. Sajal, H., Patil, S. M., Raj, R., Shbeer, A. M., Ageel, M., & Ramu, R. (2022). Computer-aided screening of phytoconstituents from Ocimum tenuiflorum against diabetes mellitus targeting DPP4 inhibition: A combination of molecular docking, molecular dynamics, and pharmacokinetics approaches. Molecules. 27(16), 5133.
61. Tang, Q., Adams, J. Y., Penaranda, C., Melli, K., Piaggio, E., Sgouroudis, E. & Bluestone, J. A. (2014). Central role of defective interleukin-2 production in the triggering of islet autoimmune destruction. Immunity. 31(2), 215-227.
62. Tateishi, K., He, J., Taranova, O., (2008). Generation of insulin-secreting islet-like clusters from human skin fibroblasts. Journal of Biological Chemistry, 283(46), 31601–31607.
63. Trounson, A., & McDonald, C. (2015). Stem cell therapies in clinical trials: progress and challenges. Cell Stem Cell.17(1), 11-22.
64. Uccelli, A., Moretta, L., & Pistoia, V. (2008). Mesenchymal stem cells in health and disease. Nature Reviews Immunology. 8(9), 726-736.
65. Wang, L., Tran, I., Seshareddy, K., & Weiss, M. L. (2016). Detrimental effects of rat mesenchymal stromal cell pre-treatment in a model of acute kidney rejection. Cytotherapy.18(2), 147-159.
66. Zinman, B., Wanner, C., Lachin, J. M., Fitchett, D., Bluhmki, E., Hantel, S., & Johansen, O. E. (2015). Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 373(22), 2117-2128.0.