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Prospects for the convergence of polyphenols with pharmaceutical drugs in Type 2 Diabetes: challenges, risks, and strategies

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ABBREVIATIONS

ACCORD- Action to Control Cardiovascular Risk in Diabetes

ADA- Anti-Diabetic Agents

ADD- Advanced Drug Delivery

ADVANCE- Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation

BCS- Biopharmaceutics Classification System

CGM- Continuous glucose monitoring

CoQ_{10}- Coenzyme Q_{10}

DCCT- Diabetes Control and Complications Trial

DPP4- Dipeptidyl peptidase-4

EDS- Emerging delivery systems

EGCG- Epigallocatechin gallate

FDA- Food and Drug Administration

GLP-1- Glucagon-like peptide 1

GWAS- Genome-wide association studies

IDF- International Diabetes Federation

nCUR- Curcumin-laden nanoparticles

NPH- Neutral Protamine Hagedorn insulin

PGA- polyglycolic acid

PLA- polylactic acid

PLGA- Poly(lactic-co-glycolic) acid

PPARγ- Peroxisome Proliferator-Activated Receptor-γ

ROS-Reactive Oxygen Species

SGLT2- Sodium-glucose co-transporter-2

SMBG- Self-monitoring of blood glucose

STZ- Streptozotocin

T1DM- Type 1 Diabetes Mellitus

T2DM- Type 2 Diabetes Mellitus

UKPDS- United Kingdom Prospective Diabetes Study

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I. Abstract

Type 2 diabetes mellitus (T2DM) is a complex disease that can lead to a variety of life-threatening secondary health conditions. Current treatment strategies primarily revolve around tight glucose control that is difficult to achieve and often turns out to be dangerous due to possible hypoglycemic events. Numerous long-term studies have demonstrated that complex pathways, including low-grade inflammation due to fluctuating glucose levels, are involved in the progression of the disease and the development of secondary health conditions. Growing clinical evidence supports the effectiveness of using multiple medications, possibly in combination with insulin, to effectively manage T2DM. On the other hand, despite the huge, largely untapped potential therapeutic benefit of 'polyphenols', there remains a general skepticism of the practice. However, for any evidence-based clinical intervention, the balance of benefits and risks takes center stage and is governed by biopharmaceutics principles. In this article, we outline the current clinical perspectives on pharmaceutical drug combinations, rationale for early initiation of insulin, and the advantages of novel dosage forms to meet the pathophysiological changes of T2DM, emphasizing the need for further clinical studies to substantiate these approaches. We also make the case for traditional medicines and their combinations with pharmaceutical drugs and outline the inherent challenges in doing so, while also providing recommendations for future research and clinical practice.

Significance Statement

Type 2 diabetes is associated with life-threatening secondary health conditions that are often difficult to treat. This review provides an in-depth account of preventing/delaying secondary health conditions through combination therapies and emphasizes the role of effective delivery strategies in realizing the translation of such combinations. We will build the case for the importance of polyphenols in diabetes, determine the reasons for skepticism, and potential combinations with pharmaceutical drugs.

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II. Introduction

We have come a long way in our understanding of the pathophysiology of diabetes and its diagnosis, yet we remain far from cure. The world commemorated two important historical anniversaries in 2021 and 2023: the discovery of insulin and glucagon, respectively, which were discovered century ago. Despite significant efforts, and progress being made, diabetes continues to be a serious global health issue. Its management has been a challenge with no definitive treatment to cure diabetes or slow its progression. According to the International Diabetes Federation, approximately one in ten adults, equivalent to 537 million individuals globally, are affected by diabetes. According to projections, by 2030, this number will increase to 643 million (1 in 9 people), and by 2045, it will reach 784 million (1 in 8 adults). (IDF, 2022). This chronic metabolic condition is marked by imbalances in glucose and insulin levels, leading to potential long-term complications. Diabetes ranks among the leading causes of end-stage renal disease, blindness, and a variety of debilitating neuropathies due to microvascular pathology. Additionally, diabetes accelerates the onset of atherosclerotic macrovascular disease, causing end organ damage. Consequently, diabetic patients face an heightened risk of stroke, cardiac infarction, amputation of limbs, and other related ailments (Brownlee, 2001). Aside from its complications, diabetes is linked to numerous co-morbid conditions, such as hypertension, hyperlipidemia, obesity, chronic kidney disease, ischemic heart disease, etc. In its entirety, diabetes is a complex multifaceted disease involving multiple pathways. Rising morbidity and mortality rates underscore the need for a thorough comprehension of disease pathogenesis. An in-depth understanding of the disease enables the development of novel, safe, and effective approaches to target specific disease drivers via technological advances and research initiatives.

Type 1 diabetes mellitus (T1DM) is an autoimmune destruction of pancreatic β cells wherein there is little or no insulin depending on the rate of β cell destruction. On the other hand, T2DM is characterized by impaired pancreatic β-cell function, resulting in decreased insulin secretion and action. This leads to hyperglycemia, dyslipidemia, and insulin resistance (i.e., decreased sensitivity to insulin). Although no specific etiology has been pinpointed for T2DM, various factors are known to contribute to the development of the disease. Genetic factors play a significant role in disease onset and progression and can help to predict the likelihood and severity of developing complications. To date, the Genome-Wide Association Study (GWAS) has identified more than 550 signals associated with T2DM risk (Starling, 2021). Besides genetic factors, mitochondrial dysfunction, caused by metabolic abnormalities, also serves as a major causative factor in the disease development. This dysfunction majorly results in superoxide production which in turn activates 5 major pathways: polyol pathway flux, increased formation of AGEs (advanced glycation end products), increased expression of the receptor for AGEs and its activating ligands, activation of protein kinase C isoforms, and overactivity of the hexosamine pathway (Brownlee, 2001; Giacco, 2010). These pathways are involved in the pathogenesis of micro- and macro-vascular complications associated with diabetes. They

increase intracellular reactive oxygen species (ROS), activating a number of proinflammatory pathways (Giacco, 2010). ROS-induced oxidative damage of the pancreatic β-cells impacts both the quality and the quantity of insulin secretion, causing not only the disease initiation but also its advancement and associated complications (Giacco, 2010). Dysregulation of the epigenetic pathways results from crosstalk between different diabetogenic variables, including free radical stress, pro-inflammatory agents like cytokines, and fluctuating high glucose levels. Without altering the DNA sequence, these alterations change the expression of pathogenic genes in target cells, such as endothelial, vascular smooth muscle, retinal, and cardiac cells. Consequently, there is persistent expression of proinflammatory genes occurring in diabetics, even after normalization of their glycemic levels, as the result of these epigenetic modifications and biochemical alterations. This phenomenon is referred as "Hyperglycemic memory" or "metabolic memory"(Cooper, 2010; Reddy, 2015).

Diabetes Control and Complications Trial (DCCT, 1990), United Kingdom Prospective Diabetes Study (UKPDS) (UKPDS-33, 1998), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (Committee, 2001), and Action to Control Cardiovascular Risk in Diabetes (ACCORD Study Group, 2007) are various studies to name which have explored the role of glucose homeostasis in managing complications associated with diabetes. The evidence from these long-term trials and studies indicate that fluctuating hyperglycemia has long-term risks and that early achievement of euglycemia will have long-term benefits, particularly in delaying the advancement of the disease and avoiding the onset of long-term complications. This phenomenon has been called “legacy effect” by the UKPDS group (Folz, 2021). The follow up studies to above mentioned clinical trials showed that the period and extent of glycemic fluctuations alters the legacy effect, i.e., with exposure to extended period of glucose fluctuations, there is decreased effect of glycemic control. In addition, it was observed that microvascular complications are more likely to be addressed by long-term glycemic control than macrovascular complications (Folz, 2021). In addition to studying glucose fluctuation in patients with T2DM, the UKPDS, one of the seminal trials involving diabetes patients, was foremost to examine hemoglobin A1c (HbA1c) trajectories. HbA1c is synonymous with glycosylated hemoglobin, and its measurement indicates typical blood glucose levels over the past three months. Non-stable HbA1c trajectories were linked to an increased risk of microvascular events and mortality in diabetes individuals, independent of average HbA1c values. Thus, indicating that it may be beneficial to identify diabetes early, prioritize maintaining adequate glycemic control, and monitor the condition throughout time(Laiteerapong, 2017).

In addition to β-cell dysfunction and associated hyperglycemia, insulin resistance and hyperinsulinemia have been implicated in the development and progression of the disease. Extensive research has been conducted to determine the sequence of events in the progression of disease and it is the subject of debate as to whether insulin resistance precedes beta cell dysfunction or if β-cell overstimulation causing hyperinsulinemia is the

initial stage leading to insulin resistance and subsequently, obesity. This critical relationship, whether insulin resistance is downstream or upstream to hyperinsulinemia, is a key question in understanding disease mechanisms (Esser, 2020; Johnson, 2021; Shanik et al., 2008). Understanding the molecular mechanisms of the disease are important to identify and characterize the therapeutic targets. Insulin resistance is characterized by reduced sensitivity to insulin in key insulin-sensitive organs—namely the liver, skeletal muscle, and adipose tissue. Insulin resistance is caused by combination of genetic and environmental factors and is associated with a wide range of metabolic disorders such as T2DM, obesity, cardiovascular diseases, fatty liver disease, and polycystic ovary syndrome (PCOS). Multiple mediators, including cytokines, chemokines, and lipid metabolites, contribute to the development of resistance(James, 2021; Li, 2022). The mechanisms of insulin resistance are complex, not delving deeper into mechanisms, insulin resistance eventually leads to β-cell adaptation in terms of functional responsiveness and number of β-cells (Esser, 2020; Kahn et al., 2006). To overcome the resistance β-cells respond by secreting more insulin leading to compensatory hyperinsulinemia (secondary). This compensatory mechanism eventually exhausts β-cells leading to impaired glucose tolerance and T2DM (Kahn et al., 2006; Poitout and Robertson, 2008). Alternatively, some studies propose that primary hyperinsulinemia due to β-cell overstimulation might itself initiate disease progression, leading to insulin resistance and obesity (Del Prato et al., 1994; Johnson, 2021). Both scenarios are integral to the vicious cycle of disease progression and addressing both is crucial for effective management of the disease. In conclusion, achieving and maintaining euglycemic levels early in the disease process is crucial to prevent oxidative damage. Moreover, replicating the dynamic circulating insulin levels observed before the onset of diabetes is vital to prevent the development of hyperinsulinemia and insulin resistance (Figure 1). Routine diagnosis involves measuring circulating glucose in whole blood, plasma, or serum, which may include a fasting blood glucose test, random blood glucose test, and oral glucose tolerance test (OGTT). As mentioned in the foregoing sections, another gold standard to assess glycemic control is HbA1c, a widely used diagnostic measurement. HbA1c provides an average of blood glucose levels over the past 3 months, but it is limited in predicting the day-to-day glucose variability and does not predict or signify episodes of hypoglycemia. Evidence indicates that oscillating sugar levels, either sustained and/or acute glucose variations, contribute to the development of complications(Dandona, 2017). To develop better diabetes management strategies, it is essential to have a comprehensive understanding of glycemic fluctuations, including the frequency, duration, and severity of hypoglycemic events. Recent technological advancements enable the early diagnosis and management of disease progression. Self-monitoring of blood glucose (SMBG) is an integral component of T1DM disease management and in T2DM patients on insulin therapy. However, its application in newly diagnosed and non-insulin dependent T2DM management is still controversial. Integrating self-monitoring into T2DM management protocols necessitates careful consideration and standardization(Sia et al., 2021). Continuous glucose monitoring (CGM) devices, which can expedite treatment decisions, are currently available for widespread

commercial use. These devices measure interstitial glucose levels and can detect hypo and hyperglycemia, providing a thorough grasp of glycemic variability. The field is making progress in understanding the pathophysiological mechanisms and risk factors of the disease with the use of real-time metabolic monitoring, precise -omics tools, and genome-wide association studies (GWAS). They also pave the way for a more personalized approach to disease management. In the future, these techniques will offer new opportunities to enhance early diagnosis, and thus enhance clinical outcomes(Carr, 2022; Nathan, 2015; Pallares-Méndez, 2016).

This review emphasizes the significance of a comprehensive understanding of the disease and efficiently managing it, diverging from past approaches that focused solely on one aspect. While regulating blood glucose levels remains pivotal in diabetes management, addressing the underlying pathophysiology concurrently offers a more promising long-term approach. Multiple studies have underscored the importance of concurrently managing chronic low-grade inflammation alongside hyperglycemic fluctuation. The efficacy of polyphenols in combating the disease through multifaceted pathways is noteworthy. Moreover, the utilization of non-conventional dosage forms has addressed the shortcomings in the biopharmaceutical properties of polyphenols, thereby enhancing their capacity to combat the disease.

III. Treatment modalities

A. Anti-Diabetic (Non-Insulin) Agents (ADA)

Insulin is the mainstay management for T1DM whereas T2DM is primarily managed with Anti-Diabetic Agents (ADA). Currently, the US Food and Drug Administration (FDA) has approved several classes of drugs for the management of T2DM. These glucose-lowering medications are available in oral and injectable forms(American Diabetes Association Professional Practice Committee, 2022). They have various mechanisms and sites of action. These encompass sulfonylureas (and related insulin secretagogues), which stimulate pancreatic β cells and increase release of insulin; biguanides (metformin and others), are most commonly used first line of drugs in the management of T2DM which act on liver and reduce glucose production; another class of drugs are peroxisome proliferator-activated receptor-γ (PPARγ) agonists (thiazolidinediones), which act on the peripheral tissues sensitive to insulin and boost insulin sensitivity thus enhancing action of insulin; α-glucosidase inhibitors restrict the intestinal absorption of glucose; Gliflozins, or sodium-glucose co-transporter-2 (SGLT2) inhibitors, inhibit the kidneys from absorbing salt, which in turn causes the kidneys to excrete glucose; analogues of amylin delay emptying of the gastric content and suppress the secretion of glucagon to maintain glucose levels during fasting and postprandial. Last but not least, a novel class of incretin-based treatments known as Dipeptidyl peptidase-4 (DPP4) inhibitors (gliptins) and Glucagon-like peptide 1 agonists (GLP-1 analogs) have been shown to increase glucose-dependent insulin secretion, decrease glucagon secretion, and lessen hepatic glucose production. Different classes of commonly used antidiabetic agents with target organs, and mechanisms of action are illustrated in Figure 2. GLP-1 agonists, DPP4 inhibitors, SGLT2 inhibitors, and

the amylin group are relatively newer drug classes that demonstrate enhanced efficacy in regulating glucose levels(Ni et al., 2022). Antidiabetic drugs (non-insulin) approved by FDA which are available in the US market are listed in Table 1. Some novel agents that act on glucagon receptors(Novikoff and Müller, 2023) (e.g.LY2409021(Kelly et al., 2015)), free fatty acid receptors(Arora et al., 2021) (e.g. HWL-088(Chen et al., 2020)), monoclonal antibodies (LeFevre et al., 2022) (e.g. Teplizumab(Keam, 2023)) etc., are being explored and some have reached the clinical trial phase. Teplizumab is the first monoclonal antibody treatment, approved by FDA for T1DM. As the disease progresses, monotherapy may no longer be sufficient for management, therefore, a combination of medications maybe required to maintain glycemic levels. As different drugs have different sites and mechanisms of action, when used in combination, they have additive or synergistic effects to improve the glycemic profile. Clinical trials are currently being conducted to elucidate various combination drugs and their effects. For example, the clinical trial NCT00856284 studied the Efficacy and Safety of Alogliptin Plus Metformin compared to Glipizide Plus Metformin in Patients with T2DM; the clinical trial NCT00131664 Avandia™ + Amaryl™ or Avandamet™ compared with Metformin (AVALANCHE™ Study) (AVALANCHE). Randomized clinical trials with triple combination like STOP-OB(Kitazawa et al., 2020), PIONEER3(Rosenstock et al., 2019), EDICT(Abdul-Ghani et al., 2021; Abdul-Ghani et al., 2015) have shown efficacy in terms of blood glucose homeostasis, HbA1c levels, and body mass index (BMI). The EDICT study showed that combination therapy is better than sequential addition of the oral anti-diabetic drugs, by protecting β-cells and improving the insulin sensitivity in a 3-year follow-up study(Abdul-Ghani et al., 2021). Triple oral regimens defined as a combination of three oral anti-diabetic agents and is especially useful for patients with uncontrolled diabetes, who are hesitant to start insulin therapy(Downes et al., 2015). Triple combination agents available in the US market include: Qternmet XR and Trijardy XR. Table 2 lists the available combination forms of antidiabetic drugs in the US market. The use of multiple drugs increases the likelihood of disease management, but also associated side effects. This is especially true in the presence of co-morbid conditions. Therefore, these combination therapies should be used with caution. At times when the disease is difficult to manage with these agents, then they are combined with insulin (or its analogues) therapy(American Diabetes Association Professional Practice Committee, 2022; Downes et al., 2015; Padhi, 2020).

B. Insulin and its Analogues

Many T2DM patients have difficulty maintaining their HbA1c levels and glucose levels based on the American Diabetes Association (ADA) guidelines(American Diabetes Association Professional Practice Committee, 2022), consequently, insulin therapy is necessary. To reduce the increased risk of diabetic complications, it is important to manage baseline and postprandial glucose levels. Human insulin and insulin analogues are major sources of insulin preparations. Insulin analogues are further subdivided into further categories: rapid-acting insulin (aspart, lispro and glulisine), short-acting insulin (regular insulin), intermediate-acting insulin (Neutral Protamine Hagedorn (NPH) insulin), long-acting insulin (glargine, degludec, and detemir), and pre-mixed insulin (Novolog® Mix

70/30, Humalog® Mix 50/50, Humalog® Mix 75/25, etc.). Because insulin is unstable in the presence of digestive enzymes and has poor permeability across the intestinal walls into the systemic circulation, it is administered subcutaneously. The long- acting insulins are combined with short- or rapid-acting insulin analogues to meet basal and bolus insulin requirements. Long-acting insulin is expected to cover the inter-prandial phases, particularly overnight, whereas rapid or short-acting insulins are incorporated to oversee postprandial glucose levels. Based on individual's blood glucose levels and required level of control, basal insulins can be administered concurrently with oral antidiabetic agents. As injectable insulin is associated with hypoglycemia and weight gain, it is modified to provide enhanced glycemic control while minimizing side effects via reduced frequency of administrations and dosage of insulin(Sims, 2021). Insulin analogues can be used in conjunction with anti-diabetic medications, particularly GLP-1 receptor agonists, DDP-4 inhibitors, and SGLT-2 inhibitors. This may address many pathological complications associated with T2DM at lower insulin dosage needed and also decreasing the incidence of insulin associated side effects(Cahn, 2015). A systematic review on combination therapy has shown that basal insulin, when given in combination with rapid acting insulin or newer ADA agents are effective in the management of HbA1c levels(Cahn, 2015; Downes et al., 2015; Raccah, 2017). Table 3 lists the available forms of insulin and its analogues. New Insulin options that have been approved in market are: Semglee (Insulin Glargine-Yfgn), Tresiba (Insulin Degludec Injection), Toujeo (Insulin Glargine Injection), Xultophy (Insulin Degludec and Liraglutide Injection), iGlarLixi (Insulin Glargine and lixisenatide Injection). These have better efficacy in terms of duration, and thus, less frequent injections. Dosages can be adjusted by the individual, but they also show a similar side effect profile, as is seen with insulin. Once weekly insulin injections are undergoing clinical trials, for example, Basal insulin Fc, insulin Icodec, and Icosema (combination of Insulin Icodec and Semaglutide). These weekly basal insulins are efficacious and helpful if initiated early in the treatment process. In the advanced phase of diabetes, insulin is administered in conjunction with antidiabetic medications but further long-term studies are needed to fully comprehend the advantages and disadvantages of this approach.(Cheng, 2020).

Given the extensive literature detailing treatment strategies for managing T2DM, this review provides a concise overview of the treatment plan, focusing on key elements and current guidelines. Current treatment recommendations for T2DM emphasize not only the importance of lifestyle modifications but also advocate for a patient-centric approach. The "*Standards of Care in Diabetes*-2024" by the American Diabetes Association gives a comprehensive overview of the diabetes diagnosis, classifications, and management recommendations. The treatment plan should be chalked out taking into consideration various factors, including the potential risk of adverse effects from medications, the effectiveness of treatments, the presence of comorbid conditions such as cardiovascular or renal issues, and the risks of hypoglycemia and weight gain, particularly when insulin is included in the regimen(Committee, 2023). It is also vital to consider individual patient preferences, as well as the cost and accessibility of treatments, to ensure both efficacy and adherence. This holistic approach ensures that management strategies are both

personalized and practical, addressing the broad spectrum of factors impacting diabetic care. For individuals with established or high risk of atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and/or chronic kidney disease (CKD), the treatment plan should include agents that reduce cardiovascular and kidney disease risk, as recommended by recent guidelines(Committee, 2023). SGLT2 inhibitors and/ or incretin-based treatment such as GLP-1 RAs and dual GIP and GLP-1 receptor agonists are gaining momentum and being preferred in these patients due to their demonstrated cardiovascular and renal benefits as evidenced by many Cardiovascular and Kidney Outcome Trials. These agents not only aid in achieving individualized glycemic targets but also carry a lower risk of hypoglycemia and offer advantages in body weight management(Davies et al., 2022). Moreover, these drugs have shown the evidence of organ protection independent of their glucose lowering effects and have been shown to slow the progression to further complications, making them particularly valuable in the management of patients with complex comorbid conditions(Davies et al., 2022; Davies et al., 2018). Antidiabetic agents can be used in combination such that they are tailored to meet the specific needs of patients. Not all patients tolerate these agents well, and many individuals with T2DM may eventually benefit from insulin therapy. Insulin can be administered either alone or in combination with non-insulin antidiabetic agents. Treatment regimens can be adjusted, intensified, or modified as necessary to achieve individualized glycemic goals, in accordance with standard clinical guidelines. This flexibility in treatment planning allows for more personalized care, optimizing outcomes for patients with diverse therapeutic responses and tolerances(Committee, 2023).

IV. Recent Advances

A. Rationale for pursuing Novel Management Approaches

Although several potent hypoglycemic agents are available on the market, cure continues to remain elusive. Currently, ADA can address fluctuations in glucose levels via multiple pathways but does not prevent the progression of diabetic complications. Metformin (metformin HCl, belongs to Class III of Biopharmaceutics Classification System [BCS], highly soluble, and poorly permeable) is a first line medication used to treat T2DM. It functions by decreasing hepatic glucose production but it has poor bioavailability(Chen, 2020). Another group of anti-diabetics are Thiazolidinediones, “insulin sensitizers,” a peroxisome proliferator-activated receptor (PPAR) agonist. These are effective in glycemic control, have minimal risk of hypoglycemia and have atherosclerotic benefits surpassing other anti-diabetic drugs. Most importantly these drugs protect β-cells through their mechanism of action involving PPAR. The Thiazolidinediones belong to Class II of BCS, i.e., poor water solubility, with limited absorption. The major adverse side effect seen with thiazolidinediones is fluid retention, which raises the risk of cardiac failure. They carry the “black box” warning of congestive heart failure and myocardial ischemia. Sulfonylureas “secretagogues” are another class of drugs which act on β-cells, hence, they have a higher risk of hypoglycemia and lead to dysfunction of β-cells progressively when used for long-periods of time(Sola et al., 2015). GLP-1 receptor agonists (GLP-1RA) and DDP-4

inhibitors are new anti-diabetic drugs which increase the action of GLP-1. The DPP-4 inhibitors are all administered orally while GLP-1RA are mainly injectable as the GLP-1RA class of drugs are peptides and easily degraded in gastrointestinal tissue. Given the intricacy of disease and the adverse side effects associated with the medications, new treatment options need to be multi-factorial. The current new strategies supported by emerging delivery systems are designed to achieve an effective minimal therapeutic dose with reduced side effects(Padhi, 2020; Uppal, 2018).

B. Emerging Delivery Systems for Non-Insulin Agents

Emerging delivery systems (EDS) based approaches are advantageous for several reasons: achieving site-specific targets, increasing bioavailability by overcoming biological barriers, and minimal side effects at reduced dosages, therefore, enhancing the drug efficacy(Zhao et al., 2020). These EDS are mostly, based on size- (micro or nano-particulate); or composition (Polymeric based; Lipid- based); and or Vesicular system; (Dendrimer; Micelles; Spheres etc.) to overcome the challenges in the management of diabetes and in various other diseases. Polymeric nanoparticles are the most common platform being used to deliver antidiabetic drugs via encapsulation or conjugation. Effective delivery of pharmaceutical drugs or drug-like compounds have explored various natural and synthetic materials, some of which e.g., poly (lactic-co-glycolic) acid (PLGA), polyglycolic acid (PGA) and polylactic acid (PLA) are key components of several FDA approved products as they are biodegradable and metabolized by natural metabolic pathways rendering them non-toxic. The chemical and environmental modifications of the conventional available pharmacological drugs provide better glucose level management while simultaneously addressing concerns associated with standard conventional dosages(Alkahtani et al., 2024; Gomte et al., 2024; Vargason et al., 2021). Using these advanced drug delivery strategies, Metformin’s efficacy was enhanced, even at low dosages, and it has been shown to be effective in a variety of diseases besides diabetes. These include cancer, Parkinson's, and other inflammatory diseases(Chen, 2020). Another benefit of an advanced drug delivery system is a decrease in the number of injections and thus an increase patient compliance. Having a non-injectable, oral drug to increase compliance with enhanced bioavailability would be the main goal of drug delivery. On same lines, the FDA approved an oral formulation of semaglutide in 2014, by Nova Nordisk, which can be administered orally (Rybelsus). A recent review reports various strategies explored to deliver pramlintide, including co-delivery with insulin to avoid multiple injections and improve compliance(Kommera et al., 2024). Table 4 provides recent, non-exhaustive reports to best of our knowledge of advanced drug delivery strategies for various anti-diabetic drugs. A number of in-vitro-to-in-vivo studies examining the effects of these modified antidiabetic drug delivery techniques have been conducted to determine how these modifications increase the drug's efficacy, however this is also the fact that these strategies do not replace the need for insulin in advanced disease stages.

C. Emerging Delivery Systems for Insulin

In both T1DM and uncontrolled T2DM, patients often need repeated insulin injections subcutaneously. These injections cause local discomfort, show poor patient compliance, and are accompanied with side effects like hypoglycemia and weight gain. Moreover, it also fails to replicate normal, physiological endogenous insulin secretion. There is a plethora of research underway to develop strategies aimed at improving insulin delivery, ensuring it is administered as needed, at the appropriate site and in appropriate dosage forms, ultimately improving outcomes for patients(Kahn, 2014; Padhi, 2020). Different routes are being explored for insulin delivery: inhalation, buccal, transdermal, oral, vaginal, rectal etc(Shah et al., 2016; Sugumar et al., 2022). Inhaled insulin formulations approved by the FDA include Exubera®, and Afrezza®. Both are rapid-acting inhaled insulins approved suitable for both T1DM and T2DM patients. They can be used alone or as a combination therapy in conjugation with long-acting insulin. Exubera® (insulin human rdna origin) is linked with adverse effects such as hypoglycemia and a heightened risk of developing upper respiratory tract infections. Its usage is also contraindicated in smokers and people who have poor lung function. So, due to poor market uptake, it was discontinued 1 year after it was approved by FDA. Studies AFFINITY1 and AFFINITY-2 showed that Afrezza® (insulin human) is effective in lowering HbA1c with fewer episodes of hypoglycemia. This drug uses Technosphere® particle delivery, and this form can be used as an alternative to subcutaneous regular insulin. Like Exubera®, Afrezza® is associated with a decrease in lung compliance (Goldberg and Wong, 2015; Oleck et al., 2016). Dance 501, an inhaled formulation, is currently in clinical trials. The trial was halted in phase II due to insufficient enrollment. The Oral-lyn system delivers human regular insulin by spraying it into the oral cavity using the RapidMist™ device. Unlike inhalers, the formulation is absorbed by the buccal mucosa. Similar to Regular insulin, it has a rapid onset of action but for a shorter duration of action, and thus can be used as only prandial insulin. It has been approved to use in some countries like Ecuador and India. Clinical trials (NCT00668850 and NCT00948493) have been conducted but no results have been published to date. Transdermal delivery using microneedles, patches, ultrasound etc. are other routes being explored. Some of the clinical trials NCT00519623, NCT03544996, NCT01947556, NCT02272296, NCT01557907 etc. are being conducted to explore transdermal delivery. Transdermal delivery warrants long term studies to better understand penetration across the skin membranes, incidence of skin irritation etc., as well as the need to understand the risk of hypoglycemia and other side effects(Zhang et al., 2019). Another important innovation in insulin “smart” delivery is glucose responsive insulin delivery using glucose responsive moieties like glucose oxidase, phenylboronic acid, glucose-binding molecules, and charge-based responsiveness. Only one, glucose responsive system (MK-2640) has made it to clinical trials NCT02269735 but failed phase 1 trials, as it showed very low potency compared to regular insulin. This was due to the difference between species in preclinical and clinical studies(Krug et al., 2019). Recently, insulin-lipid nanoparticle complexes composed of phenylboronic acid have been reported to offer glucose responsive insulin. These complexes showed a prolonged duration of normoglycemia

compared to native insulin(Liu et al., 2023). However, long-term studies are needed to further validate this hypothesis. A study conducted on mice and minipigs with a glucose-responsive insulin patch demonstrated excellent results, showing the delivery system can have translational value in the future(Wang et al., 2019; Yu et al., 2020). Insulin delivery via glucose responsive nanogels demonstrated extended-release kinetics(Volpatti et al., 2020). This delivery strategy showed potential not only to deliver insulin but also used as carriers of islet cells for cell replacement therapy in diabetes(Volpatti et al., 2023). Numerous studies have been, and are being conducted, to develop novel glucose- responsive insulin delivery, with a potential translational value; however, the issues of controlled release, toxicity and efficacy are to be investigated and resolved in pre-clinical studies before moving on to clinical trials(Wang et al., 2020). Even though delivery of insulin via other routes is being explored, why is the peroral route is the preferred route? Is there any advantage of delivering insulin into the portal hepatic system?

D. Is peroral route of administration better?

New concepts like weekly insulin injections, “closed loop” glucose sensing “smart” insulin delivery via implantable devices(Schaepelynck, 2019), and hydrogels(Heyns et al., 2023a) all address insulin deliverance via the various routes discussed above, but their safety, efficacy, cost burden and ease of usage are still not established. In addition, none of these formulations mimic endogenous insulin secretion. It is also worth noting that some stigma exists around the usage of these device-dependent delivery methods. This leads to a lower acceptance and compliance rate among the diabetic population, specifically T2DM. Noninvasive insulin delivery methods, specifically the peroral route, are preferrable because of the ease of administration and better dosage management, which steer towards improved efficacy. Additionally, the peroral route addresses hepatic glucose homeostasis. Liver has a substantial role in homeostasis of glucose. Insulin not only has direct action but also indirect effect on liver. The direct effect of insulin is on the liver is via glycogen metabolism, which eventually determines the amount of glucose produced by the liver. The indirect effect involves action of insulin on other insulin sensitive target tissues like adipose tissue, pancreatic α cells and the brain, which in turn act on hepatic glucose production. Studies have presented that insulin’s direct action on hepatic glucose production is more dominant than the indirect action(Edgerton, 2017). Under physiological conditions, as postprandial glucose levels increase, more insulin is secreted by pancreas is released into the portal vein and as a response to increased intraportal insulin levels, the net hepatic glucose uptake is heightened(Pagliassotti, 1992). Insulin stimulates glucose uptake and storage by other peripheral tissues such as muscles and adipose tissue, along with the inhibition of hepatic glucose uptake. In the liver, approximately half of the insulin is degraded and thus creates a gradient of insulin concentration between the hepatic portal and systemic circulations(Moore, 2003; Satake, 2002). The injectable insulins and their analogues fail to mimic the normal physiological pathway. As injectables cause higher systemic insulin concentrations than in portal or in liver sinusoids, which leads to peripheral hyperinsulinemia and decreased hepatic glucose uptake. By the time insulin reaches the liver via the systemic circulation, the insulin concentrations are too low for effective action.

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Thereby, peripheral insulin manages only peripheral glucose levels and does not impact hepatic glucose production. As the gradient between systemic and portal insulin concentrations reverses, peripheral hyperinsulinemia and “under-insulinization” of the liver occurs. This promotes insulin resistance and other metabolic abnormalities; thus, progression of diabetes. This can be avoided by selectively targeting hepatic glucose production using either, peroral insulin, drugs directly targeting the liver, or by infusing of insulin into portal vein(Edgerton, 2017; 2014; Kurtzhals et al., 2021). Researchers are working with insulin analogs which can target liver (Hepato-preferential insulin analogs), thus, mimicking closely the physiological state but much more work is needed to understand the safety profile of these drugs(Kurtzhals et al., 2021). Basal insulin peglispro (BIL; LY2605541) reached phase 3 clinical trials but was associated with undesired side effects and the product failed(Muñoz-Garach et al., 2017). With the peroral route, the portal-systemic insulin gradient is maintained and does not result in peripheral hyperinsulinemia; Thus, decreasing the incidence of complications associated with insulin resistance(Fonte, 2013). Peroral forms diminish the risk of hypoglycemia, which is commonly seen with parenteral insulin. Peroral insulin increases hepatic glucose uptake (stored as glycogen), provide indirect action of insulin on pancreatic α-cells, and regulates glucagon secretion. Thus, with any hypoglycemic event, glycogen stores are utilized and glucose is released(Arbit, 2017).

However, there are many barriers for peroral insulin delivery. These can be physiological barriers like pH and enzymes, or physical barriers like the mucosal layer, intestinal epithelium, and cellular tight junctions.(Gedawy et al., 2018). Many advances are being made to overcome these barriers and streamline insulin delivery. Similar to the antidiabetic drugs, variety of formulation strategies like nanoparticles, microparticles; hydrogels; GIT patches; ionic liquids; absorption enhancers; target-mediated delivery; microenvironment-responsive release; cell-penetrating peptides; oral robotic transport and more are being employed for oral insulin delivery(Gedawy et al., 2018; Ji et al., 2023; Xiao et al., 2020). Each of these strategies carries its own set of advantages and drawbacks in achieving an effective pharmacokinetic/pharmacodynamic (PK/PD) profile. One strategy currently under active exploration involves the ligand-targeted active delivery of drugs. This approach aims to achieve site-specific delivery, mitigate off-target effects, and thereby enhance the therapeutic effectiveness of the drug, insulin in this context(Zhao et al., 2020). A study exploring the use of Insulin-laden nanoparticles, transported non-competitively via transferrin receptors in the intestine using gambogic acid as its ligand, revealed a promising mechanism for tailoring the dosage regimen to individual needs(Ganugula et al., 2017). Another study employed naringenin as a ligand to facilitate folate receptor-mediated absorption of Insulin-laden nanoparticles. This approach demonstrated increased insulin loading and improved entrapment efficiencies(Heyns et al., 2023b).

Numerous studies investigating various strategies to deliver insulin perorally are ongoing, but only a handful have progressed to the clinical trial phase. Some of the oral insulin formulations which have reached clinical trials are Insulin tregopil (IN-105), ORMD-0801,

OI-338, ORA-2, HDV-1, Oshadi Icp, and TN20 etc. Clinical trials of IN-105 and ORMD-0801 have successfully reached phase 3 clinical trials. Both IN-105 (insulin Tregopil) and ORMD-0801 are prandial oral insulin. The NCT03430856 clinical trial compared the efficacy and safety of insulin Tregopil versus insulin Aspart in T2DM patients taking insulin Glargine and Metformin. This study demonstrated a good safety profile and early postprandial effects comparable to those of insulin Aspart, but its late postprandial effects were inferior to those of insulin Aspart(Lebovitz et al., 2022). ORMD-801 is currently in Phase 3 clinical trials and the optimal doses identified have been approved by the FDA. The most recent publication regarding ORMD-801 (NCT03467932), investigated the safety and efficacy of multiple doses of peroral insulin ORMD-801 in T2DM. The study demonstrated greater HbA1c reductions than placebo and was safe and well tolerated(Eldor et al., 2023). OI338 is the only basal peroral insulin approved lately, but its production was discontinued due to poor commercial viability. The doses required were high due to its low bioavailability(Halberg et al., 2019). Table 5 lists the different peroral insulin formulations in clinical trials.

V. Rationale for Early insulin initiation

At this juncture, it is important to acknowledge the debate concerning the early initiation of insulin at the time of diagnosis. T2DM is often not identified until the disease has progressed to a more advanced stage, as many experience mild to no symptoms. By the time diabetes is diagnosed, the body has typically been subjected to fluctuating glucose and insulin levels. These fluctuations result in significant pathophysiological changes including glucose intolerance, insulin resistance, hyperinsulinemia, and chronic low-grade inflammation. Continuous exposure to gluco- and lipo-toxicity, to reactive oxygen species and continuous demand of insulin production which results in β-cell dysfunction and eventually cell death(Matveyenko and Butler, 2008). This chronic exposure exert effects on β-cell mass and regenerative capacity, as well as metabolic memory(Hanefeld et al., 2020). In T2DM, unlike T1DM in which insulin therapy is initiated upon diagnosis, lifestyle modifications and the initiation of a single anti-diabetic agents, followed by combination therapy, and then insulin is added to the treatment protocol as a final step, all with the goal of reducing systemic glucose and HbA1c levels. This sequential therapy does not prevent the progression of β-cell deterioration or the onset of insulin resistance. In fact, some of these agents put a greater burden on the remaining β-cells to address the issues of glucotoxicity and lipotoxicity, thus resulting in a vicious cycle of disease progression and development of complications(Association, 2002; Hanefeld et al., 2020).

The foregoing sections discussed the importance in achieving glucose homeostasis and stable HbA1c trajectories that will influence the progression of the disease and in long run prevent the development of diabetic complications. The UKPDS study also demonstrated the advantages of early, intensive glucose control with insulin in preventing the onset of microvascular diseases such as retinopathy, nephropathy and neuropathy compared to treatments with non-insulin conventional agents. Follow-up research established a "legacy effect," showing that early intensive management of blood glucose yields long-term

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benefits, including reduced risk of myocardial infarction and overall mortality(Association, 2002; Holman et al., 2008).Numerous studies like DIGAMI, ORIGIN and other short- term studies tested short-term vs long-term insulin therapy in both uncontrolled newly diagnosed diabetic patients with severe hyperglycemia as well as was tested in controlled T2DM using long- term insulin therapy, assessing the impact of initiating insulin early in the management of disease(Raz and Mosenzon, 2013). Short term studies like ACCORD and ADVANCE trials didn't reduce cardiovascular events but longer term DCCT/EDIC have established reduction in the risk of cardiovascular events with intensive therapy(Holman et al., 2008). These studies have shown that early insulin initiation not only prevents disease progression but also reduces the incidence and severity of complications by increasing peripheral sensitivity and by protecting residual β-cell function(Chen et al., 2008; Investigators, 2013; Li et al., 2004; Retnakaran et al., 2010; Ritsinger, 2014). Early insulin therapy reduces the burden of glucotoxicity and lipotoxicity besides providing glycemic control, thus, preventing β-cell deterioration (a "disease modifying effect")(Alvarsson, 2003; Lingvay et al., 2009; Retnakaran and Drucker, 2008; Weng, 2008), and achieving what is called as "β-cell rest" (Owens, 2013; Raz and Mosenzon, 2013; Retnakaran and Drucker, 2008). Insulin had demonstrated various other roles like decreasing peripheral insulin resistance, acting on hepatic glucogenesis, inhibiting the production of reactive oxygen species (ROS) and also has anti-inflammatory effects that protect against endothelial dysfunction as seen in vascular disease(Chen et al., 2007; Dandona, 2007; Li et al., 2004; Owens, 2013). Early normalization of the metabolic events can prevent "metabolic memory" thus reducing disease associated complications. Despite the advantages of early insulin therapy in terms of improved HbA1c and fasting plasma glucose levels, factors such as fear of injections, concerns about hypoglycemia, weight gain, difficulties in managing the insulin regimen, social stigma, and cost act as barriers, preventing patients from initiating insulin therapy early in the course of the disease(Owens, 2013). A significant barrier in prescribing insulin as an initial treatment for T2DM is the association of severe hypoglycemic events with cardiovascular diseases in T2DM patients(Frier et al., 2011; Goto et al., 2013; Zoungas et al., 2010). Adding to these barriers, physicians' reluctance to initiate insulin acts as an impediment, as they anticipate poor patient compliance, are concerned about the patients' ability to maintain the insulin dosing regimen, or their inability to closely and regularly manage patient(Brod et al., 2014), a phenomenon called psychological insulin resistance(Brod et al., 2009; Woudenberg et al., 2012). As a result, early initiation of insulin is frequently delayed until other treatments have failed. Furthermore, the introduction of drugs such as SGLT-2 inhibitors and GLP-1 analogs has influenced treatment choices for T2DM, with both patients and doctors preferring these alternatives before beginning insulin therapy. As these drugs have demonstrated superior performance in terms of glycemic control, weight management, secondary complications management, and fewer side effects compared to other available treatments. As we know, a vast majority, if not all of these non-insulin hypoglycemic agents either work by increasing insulin secretion or by increasing the insulin sensitivity, in other words for these agents to act there is need for functional β-cells. However, as T2DM progresses, β-cells completely deteriorate leading to exogenous insulin

supplementation. Given the advantages of early initiation of insulin, alternative forms of insulin delivery methods are being actively explored to mitigate the risks linked with traditional insulin injections. Advanced drug delivery systems, such as peroral insulin administration may decrease the required dosage, thus reducing the risk of hypoglycemia—a common side effect associated with injectable insulin. The oral route of administration also tends to improve patient compliance, as it is less invasive and more consistent with routine medication-taking behaviors. Increased compliance can lead to more consistent management of blood glucose levels and overall better outcomes in diabetes care. Hence, having a peroral administration of insulin would not only be advantageous in terms of early initiation, but also enhances the efficacy and safety of diabetes management.

VI. Role of Traditional Medicinal Knowledge

There are currently several traditional dietary compounds being evaluated for their role in the management of various diseases. Some of these include vitamins, minerals, botanical compounds, amino acids, polypeptides, polyphenols and live microbials(FDA, 2022). Polyphenols, the largest category of compounds naturally found in plant-based foods, are typically investigated for their role in various diseases like diabetes mellitus, cardiovascular diseases, obesity, Alzheimer's, Cancer, and chronic inflammatory conditions like arthritis are some of the few diseases to highlight (Corson, 2007). Many medical conditions can be treated by polyphenols, including cardiovascular, nephro-, anti-inflammatory, anti-microbial, hepato-, immunomodulatory, hypoglycemic, anti-atherosclerotic, and rheumatic conditions. They are studied in the management of various diseases because they play significant role by acting on oxidative stress pathways, on production of inflammatory cytokines and various other cell signaling pathways and in turn modulate inflammation which is essential to prevent ongoing inflammation in chronic inflammatory diseases like in inflammatory bowel diseases. Various dietary polyphenols act by modulating the gut microbiota and have role in diseases like metabolic disorders like obesity(Aloo et al., 2023). Berries have been shown to play major role in metabolic syndrome by acting on lipid metabolism, inflammation, oxidative stress, and other cell signaling pathways involved in the progression of the disease(Land Lail et al., 2021). In diseases like Alzheimer's these polyphenols provide neuronal protection(Grabska-Kobyłecka et al., 2023; Spencer, 2009). Some of the studies involving the role of polyphenols have entered the clinical trial phase like the clinical trial NCT04149288 studying the effects of the combination of two different types of olive oils in changing the risk factors of cardiovascular diseases. NCT01518764 is studying the effects of red wine polyphenols on insulin sensitivity, β-cell function, and microvascular functions. Many other clinical trials like NCT01568827, NCT02167555, NCT05428540, NCT04970589 are studying the effects of different forms of polyphenols in obesity, diabetes, and other co-morbid conditions. There is increasing interest in the use of polyphenols in the management of diabetes for their ability to target multiple pathways of disease progression.

Polyphenols such as resveratrol, quercetin, curcumin, epigallocatechin gallate, tannins, naringin, gingerol etc. show promise in managing T2DM by combating oxidative stress and chronic low-grade inflammation (Brownlee, 2001; Giacco, 2010). Besides playing the role of an anti-oxidant and an anti-inflammatory, polyphenols have a role on glucose and lipid metabolism, making them valuable in T2DM management(Kim, 2016; Menezes, 2022). Studies have shown that some polyphenols have an anti-diabetic effect via mechanisms like that of incretins. They either increase GLP-1 secretion, decrease breakdown by DDP-4 or increase sensitivity to insulin(Domínguez Avila, 2017). Many flavonoids such as resveratrol, Epigallocatechin gallate (EGCG) and other catechins, naringenin, quercetin etc., activate adenosine monophosphate- activated protein kinase (AMPK) via a similar mechanism of action as metformin(Momtaz et al., 2019). In addition to activating AMPK, the alkaloid berberine inhibits intestinal enzymes α-amylase and α-glucosidase(Derosa et al., 2022). Similar to thiazolidinediones, certain flavonoids such as naringenin(Goldwasser et al., 2010) and curcumin(Nishiyama et al., 2005), act on PPARγ and increase insulin sensitivity and secretion. Many nutraceuticals have actions on insulin secretion via increasing insulin sensitivity, acting on glucose synthesis and storage, and providing β-cell protection, etc., which further contribute to their antidiabetic potential(de Paulo Farias et al., 2021; Nie and Cooper, 2021; Sun et al., 2020). Another important mechanism of these polyphenols in diabetes is by modulating gut microbiota and positively influence cardiometabolic health. The gut microbiota help metabolize polyphenols into unique metabolites(Williamson and Clifford, 2017), which in turn activate intestinal sensors resulting in modulation of metabolism through crosstalk with various organs. More research is essential to elucidate the effect of polyphenols on intestinal microbiota and their action on glucose homeostasis(Villa-Rodriguez et al., 2019). Table 6 delineates clinical trials exploring the impact of various polyphenols on diabetes, obesity, and other metabolic syndromes. Notably, there are approximately 31 trials focusing on resveratrol, approximately 19 investigating curcumin, and 15 examining coenzymeQ_{10} (Co Q_{10}). Conversely, there are fewer than 10 trials each for naringin, ECGC, and quercetin. It's worth noting that a substantial portion of these trials either await publication of results or they have been prematurely terminated.

A. Limitations

Most polyphenols do not conform to standard drug classifications such as BCS(Dahan et al., 2009), Lipinski's Rule of Five(Lipinski, 2016), or the 4D approach to drug design and delivery(Davis and Illum, 1998). The BCS classifies drugs based on their solubility and intestinal permeability. Lipinski's rule of five evaluates a compound's drug likeliness based on criteria such as the number of hydrogen donors, molecular weight, LogP, and hydrogen acceptors. Finally, the 4D approach serves as a rationale for the design of drugs and delivery systems based on the drug and the disease in question. Interestingly, a vast majority, of polyphenols undergoing non-clinical and clinical research will not meet the druglike properties set through the foregoing standard theories of classification. For example, curcumin belongs to Class 4 of the BCS classification, which means curcumin has poor solubility and permeability. Similarly, resveratrol, and CoQ_{10} belong to BCS class

2 and have a poor 4D profile whereas, EGCG belongs to class 3 of BCS classification and fails to meet Lipinski's of 5 (Table 7). In addition, none of these compounds take a drug path of approval, and do not have an established dose regimen failing them for 4Ds. These inherent characteristics of polyphenols such as their large molecular structure led to poor bioavailability due to poor absorption across the intestinal wall, rapid metabolism by liver and kidney and high clearance. They also undergo various modifications by the intestinal flora leading to poor bioavailability(Manach et al., 2004). In addition, factors such as food matrix, digestive enzymes also interfere with the uptake of the compounds(Bohn, 2014; Duda-Chodak and Tarko, 2023). The poor solubility and permeability property add on to poor absorption and thus low bioavailability. Besides low bioavailability, they also face challenges in terms stability via the interactions with environmental factors like light, pH and temperature(Manach et al., 2004; Zhang et al., 2022a).

Like pharmaceutical drugs, low bioavailability of the polyphenols necessitates higher doses to achieve therapeutic effects, although the dosage needed is seldom investigated potentially compromising safety and compliance. Another aspect to high dosage is that the compounds which were shown to have protective mechanisms, but as the dose increases the same compound can induce DNA damage(Azqueta and Collins, 2016). Hence, we need to have optimized dosing to achieve maximum therapeutic benefit without any adverse effects. Advanced drug delivery strategies boost bioavailability and efficacy while decreasing dosage and dosing frequency. Recent advances in drug delivery assist in overcoming the pharmacokinetic drawbacks and achieving the desired therapeutic effect in the management of diabetes via target-specific absorption/action, prolonged release, and enhanced stability(Dewanjee, 2020; Ratnam, 2006; Rochlani, 2017). By improving the absorption of the encapsulated polyphenols, these delivery systems improve their bioavailability. In doing so, they protect these compounds from metabolic modifications in the intestine, liver, or kidneys. In addition, the advanced drug delivery systems enable the improved target tissue bioavailability leading to enhanced therapeutic outcomes at minimum effective doses with no/fewer side effects. The role of nano-formulated antioxidants is being studied, and many of these are undergoing clinical trials, however, further research is required to determine the dose, safety and clinical utility of these polyphenols.

As diabetes progresses, it necessitates the use of multiple therapeutic agents. Often, a single agent cannot effectively manage diabetes. Even though polyphenols have antioxidant and anti-diabetic properties, their use as a stand-alone treatment has not yet been established. A vast majority of polyphenols have been shown to exert therapeutic benefits, independent of glucose reduction (Dwivedi et al., 2022; Grama et al., 2013; Huang et al., 2020). The combination of currently available conventional pharmaceutical drugs and natural compounds may have a synergistic effect, resulting in enhanced disease management(Blahova, 2021; Khursheed, 2019). Table 8 lists some of the possible combinations being investigated for the treatment of the disease; however, relatively few studies have utilized combinatorial drugs. A recent review provided an in-depth analysis of

the literature on the effects of polyphenols on T2DM and offers some general recommendations on their use thereof. While the authors have recognized the potential of polyphenols in T2DM, they have identified some key issues that need to be considered in order to maximize the potential of polyphenols, e.g., variations in polyphenol sources, doses used in preclinical vs clinical trials, well designed research methodologies-in vitro, ex vivo, preclinical and clinical, careful selection of biomarkers (Menezes et al., 2022). Another paper by de Matos and Menezes, adds important aspect of how combination of lipophilic polyphenol-carbohydrate combinations via biotransformation or through synthetic approaches to polyphenol-c-glycosides presents an opportunity to managing T2DM (de Matos and Menezes, 2023). Both these papers call for more standardized and robust clinical trials to better assess the efficacy and safety of polyphenols in diabetes treatment.

VII. The Convergence of Polyphenols with Pharmaceutical Drugs- Underpinned by Effective Delivery Strategies

In advanced T2DM the deterioration of β-cells necessitates eventual insulin use, as anti-diabetic drugs can stress these cells and accelerate their decline. Successful diabetes management must focus on maintaining stable glucose levels, addressing vascular complications, countering oxidative stress and inflammation, and preserving β-cell health. The cyclical impact of metabolic memory involves oxidative radicals, inflammatory cytokines, and epigenetic changes(Darenskaya, 2021; Owens, 2013). ROS causes oxidative harm to β-cells, impairing their secretion and increasing insulin resistance due to hyperglycemia. This detrimentally affects the quantity and quality of insulin produced. Early glucose management and anti-inflammatory actions can mitigate β-cell damage. In contrast to existing antidiabetic drugs, early initiation of insulin might enhance glycemic control and safeguard β-cells, thus decelerating disease progression(Alvarsson, 2003; Retnakaran and Drucker, 2008; Weng, 2008). Recent research indicates that a GLP-1 estrogen conjugate in combination with insulin could not only maintain lower glucose levels with reduced insulin dosage but also enhance β-cell function (Sachs, 2020). The “CHANGE” study (NCT05040087) seeks to intensify diabetic medication based on glucose or HbA1c levels to preserve β-cell function and avert complications. Similarly, polyphenols offer protection against oxidative damage to β-cells. The synergy between insulin and polyphenols, when employed early in the disease, may effectively impede disease progression. A study demonstrated that co-administration of quercetin and insulin led to improved diabetes-related complications by reducing ROS production(Singh, 2018).

Recently, our lab explored the effects of a receptor-mediated peroral delivery strategy involving ligand-bound nanoparticle encapsulated curcumin combined with long-acting subcutaneous insulin in STZ-induced T1DM rats. The comprehensive studies demonstrated the significance of combined treatment in managing hyperglycemia and inflammation effectively(Dwivedi et al., 2022; Ganugula et al., 2023a; Ganugula et al., 2023b). The study has many interesting outcomes, in that a) curcumin-laden nanoparticles (nCUR) exerts superior efficacy at 50% lower dose compared to regular curcumin, b) nCUR combined with a single daily dose of long-acting insulin, showed superior glucose control

compared the respective individual treatments, c) while nCUR combined with insulin showed superior efficacy in controlling the secondary health conditions, particular microvascular complications, (Dwivedi et al., 2022; Ganugula et al., 2023a; Ganugula et al., 2023b). Notably, nCUR has an enduring effect on suppressing inflammation through many different mechanisms of action in different target tissues, e.g., eye, kidney. When compared with alternatives like oral curcumin, oral nano-curcumin, and long-acting insulin injections, the combined therapy of nCUR and insulin notably inhibited Piezo 1 in retinal layers, presenting an encouraging prospect for retinopathy treatment. Additionally, it successfully hindered the ROCK 1 signaling pathway, effectively arresting cataract development(Ganugula et al., 2023a). In the context of renal changes associated with diabetes, the combination therapy exhibited a reduction in P53 and P38 MAPK activity, which plays a crucial role in cellular stress responses and apoptosis, consequentially inhibiting downstream pro-inflammatory mediators and bolstering nephron protection(Ganugula et al., 2023b). Likewise, modulating the immunoinflammatory pathway proved effective in impeding the progression of diabetic peripheral neuropathy(Dwivedi et al., 2022). Together, the study highlights nCUR's ability to mitigate inflammation, oxidative stress, and vascular damage in prevention or delaying microvascular complications. These findings underscore the significance of combination therapy by showcasing synergistic action in targeting multiple signaling pathways, disrupting the disease cycle, and decreasing complications (Figure 3). Expanding on these insights, our ongoing investigations focus on utilizing a combination of ligand-targeted peroral insulin/CUR-laden nanoparticles in early-stage T2DM management. This innovative approach aims to replicate endogenous insulin function without overtaxing β-cells, potentially leading to enhanced glycemic control. The anticipated role of nCUR involves counteracting chronic low-grade inflammation, ultimately safeguarding β-cell function and potentially preventing complications.

VIII. Conclusion

Various cutting-edge technologies are undergoing pre-clinical trials: insulin pens/pumps, automated insulin delivery, and glucose-responsive insulin release systems (often referred to as “closed loop” or “artificial pancreas” systems). Promising approaches include implantable devices for the dual delivery of glucagon and insulin, regeneration of ß-like cell, transplantation of pancreatic islet cells, tissue engineering, gene therapy, and stem cell therapy. These strategies are theorized to offer enhanced efficacy in the management of T1DM, (characterized by the complete loss of ß- cells), as well as in very advanced T2DM (where there is complete decline in ß-cells). Although these hold promise for T1DM and advanced T2DM management, but they are extremely complex, expensive, associated with numerous complications such as rejection by the immune system(Melidoni, 2021) and need of removal of an implant or gels from the system(Mohanty, 2022). Even though T2DM management emphasizes glucose reduction like T1DM, but T2DM management appears to be much more complex. It is a multifaceted condition influenced by various factors and demands innovative approaches for effective management and prevention of secondary health conditions. Traditional management strategies such as dietary restriction, physical

activity, and weight loss have been demonstrated to reverse insulin resistance(Syeda et al., 2023). There is plethora of evidence to show that functional foods, and polyphenols have anti-diabetic, anti-obesity, ant-inflammatory, and antioxidant potential. Furthermore, dietary polyphenols, evident from research conducted on animals and cultures, demonstrated their role in preventing and managing diabetes by reducing ROS production, enhancing insulin signaling, revitalizing pancreatic islet β-cells, and promoting β-cell proliferation. A vast majority of supplements are being evaluated and undergoing clinical trials for their role in T2DM and in variety of other metabolic and cancerous conditions as listed in Table 6.

Utilizing advanced drug delivery systems, particularly nanotechnology, offers the potential to deliver, not only these diverse polyphenols but also hypoglycemic agents, including insulin, effectively as a stable and efficacious drug. Among these developments, peroral insulin delivery stands out due to its potential for enhanced compliance, reduced stigma, and cost-effectiveness. It alleviates the concerns of physicians and patients regarding injection. As perorally delivered insulin creates a portal vs systemic gradient leading to greater action on hepatic glucose, and thus better management of blood glucose levels without risk of hypoglycemic events. This is in opposition to subcutaneous insulin. Advanced drug delivery strategies are needed to overcome the issues of poor peroral bioavailability of insulin. After ensuring bioavailable forms, the next issue is determining the right medication and right dosage (single or in- combination), for which understanding physiologically based pharmacokinetic (PBPK) modeling is crucial. Currently peroral insulin using various strategies is being actively researched but most of these studies do not reach the clinical trial phase. This may be due to the fact that preclinical testing is done in T1DM models that do not mimic of T2DM pathophysiology. It is important to test peroral insulin in obese and non-obese T2DM models. Scaling the insulin formulations, especially in academic settings, is another important consideration.

A deeper understanding of the disease demonstrates that T2DM is complex, and each patient needs a customized treatment approach. Combining peroral insulin with polyphenols offers a comprehensive treatment approach that targets the disease's pathophysiological aspects. To guarantee this combination's long-term compatibility, safety, and optimization, more research is required. The potential interactions between polyphenol metabolites and insulin analogs should be thoroughly examined to determine whether they exhibit additive, synergistic, or potentially antagonistic effects, such as food allergies. For now, polyphenols are not drugs and do not have an established clinical utility. They are not prescribed by physicians, and they are largely restricted to the oral route of administration as supplements.

In addition, preclinical research should always consider the dose conversion factors and assess the feasibility of such dose translation to humans. This becomes even more important, when it comes to non-conventional dosage forms such as nanoparticles, where the drug-loading/entrapment efficiency has a determinantal role in translation. For example, for a high dose drug/druglike that has limited loading/entrapment will influence the excipient dump and safety and may never translate. On the other hand, compliance is very loosely

defined, for example, something compliant in humans may not be in rodents and vice versa. Systematic studies establishing drug-like properties could change the fate of these molecules, such that a long-acting dosage form such as subcutaneous depot, e.g., microparticle, in situ gels can control low-grade inflammation over several weeks to months on single administration.

Notes

M.A., R.G. and M.N.V.R.K. are inventors on patent applications related to the technology described in the manuscript (exclusively licensed to Peroral Bioscience, Inc.,). M.N.V.R.K. is a non-paid scientific advisory board member and M.A. is a shareholder of Peroral Biosciences, Inc.

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Data Availability Statement

This review article contains no datasets generated or analyzed during the current study

Authorship contribution

Wrote or contributed to the writing of the manuscript: Allamreddy, Arora, Ganugula, Friend, Basu, and Kumar. All authors have read, edited, and approved the final version.

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TABLE 1: ANTIDIABETIC DRUGS AVAILABLE IN MARKET [a]

CLASS	DRUG	AGENT	YEAR approved by FDA	FORMULATION TYPE/ INGREDIENT/ ROUTE	COMMON SIDE EFFECTS
BIGUANIDES	Metformin	Glumetza/ Fortamet/ Glucophage	1995	Tablet, film-coated salt of the metformin, Oral	• Diarrhea • Indigestion • Nausea/Vomiting • Flatulence • Fatigue • Headache
THIAZOLIDINEDIONES	Rosiglitazone	Avandia*	1999	Tablet, maleate salt of Rosiglitazone, Oral	• Fluid Retention • Weight Gain • Heart Failure • Anemia • Upper Respiratory Tract Infection
	Pioglitazone	Actos	1999	Tablet, Pioglitazone Hydrochloride, Oral	
SGLT2 INHIBITORS	Canagliflozin	Invokana	2013	Tablet, film coated anhydrous Canagliflozin, Oral	• Vaginal Yeast Infections • Urinary Tract Infections • Dysuria • Dyslipidemia • Renal Impairment • Hyperphosphatemia
	Dapagliflozin	Farxiga	2014	Tablet, film coated Dapagliflozin propanediol, Oral	
	Empagliflozin	Jardiance	2014	Tablet, film coated Empagliflozin, Oral	
	Ertugliflozin	Steglatro	2017	Tablet, film coated Ertugliflozin Pidolate, Oral	
	Bexagliflozin	Brenzavvy	2023	Tablet, film coated Bexagliflozin, Oral	
SULFONYLUREAS	Glipizide	Glucotrol XL	1984	Tablet, extended release, Glipizide, Oral	• Hypoglycemia • Weight Gain • Headache • Dizziness
	Glimepiride	Amaryl	1995	Tablet, Glimepiride, Oral	
	Glyburide	DiaBeta, Glynase	1984	Tablet, Glyburide, Oral	

MEGLITINIDES	Repaglinide	Prandin	2013	Tablet, Repaglinide, Oral	• Hypoglycemia • Weight gain • Headache • Upper Respiratory Tract infection
	Nateglinide	Starlix	2009	Tablet, coated, Nateglinide, Oral	
DPP-4 INHIBITORS	Sitagliptin	Januvia	2006	Tablet, film coated, Sitagliptin Phosphate, Oral	• Upper Respiratory Infection • Headache •Acute Pancreatitis •Hypoglycemia
	Saxagliptin	Onglyza	2009	Tablet, film coated, Saxagliptin Hydrochloride, Oral	
	Linagliptin	Trajenta	2011	Tablet, film coated, Linagliptin, Oral	
	Alogliptin	Nesina	2013	Tablet, film coated, Alogliptin Benzoate, Oral	
ALPHA-GLUCOSIDASE INHIBITORS	Acarbose	Precose	1995	Tablet, Acarbose, Oral	• Stomach Pain • Diarrhea • Flatulence • Abnormal Liver Tests
	Miglitol	Glyset	1996	Tablet, coated, Miglitol, Oral	
GLP1 RECEPTOR AGONIST	Exenatide	Byetta/ Bydureon/ Bcise	2005/ 2012/ 2017	Byetta - Suspension, synthetic peptide Injection. BYDUREON BCISE extended-release- a sterile injectable suspension of exenatide extended-release microspheres	• Pancreatitis • Hypoglycemia, • Acute Kidney Injury • Hypersensitivity Reactions, • Acute Gallbladder Disease • Signs of a Thyroid Tumor • eye problems caused by diabetes (retinopathy)
	Liraglutide	Victoza	2010	Solution, Liraglutide peptide produced by recombinant D NA technology,	

				Injection	• Contraindicated in patients with- Multiple Endocrine Neoplasia syndrome type 2 (MEN 2), or a family history of medullary thyroid carcinoma • Do not use in patients with Diabetic Ketoacidosis
	Dulaglutide	Trulicity	2014	Solution, Dulaglutide, a recombinant DNA, is an injection of a fusion protein made up of two disulfide-linked chains, that are identical to one another and have an N-terminal GLP-1 homolog sequence, Injection	
	Albiglutide	Tanzeum	2014	Powder and solvent for solution, Albiglutide is a recombinant DNA produced polypeptide, Injection	
	Lixisenatide	Adlyxin	2016	Solution, lixisenatide, Injection	
	Semaglutide	Rybelsus/ Wegovy	2019/ 2021	Solution, Semaglutide is a recombinant DNA produced polypeptide, Injection	
AMYLIN ANALOGUE	Pramlintide	Symlin	2005	Solution, Pramlintide Acetate, Injection	• Hypoglycemia • Headache • Dizziness • Fast heart rate •Vision Problems
DUAL GLP-1 RECEPTOR/GIP RECEPTOR AGONISTS	Tirzepatide	Mounjaro	2022	Solution, Tirzepatide is a dual GIP/GLP-1 seensitizing polypeptides, Injection	• Risk of Thyroid C-Cell Tumors • Stomach pain • Difficulty in breathing or swallowing • Fast heartbeat • Flatulence

					• Heartburn

[a] Source: https://pubchem.ncbi.nlm.nih.gov/

TABLE 2: COMBINATION OF ANTIDIABETIC DRUGS AVAILABLE IN MARKET[a]

DRUG 1	DRUG 2	COMBINATION	AGENT	YEAR approved by FDA
BIGUANIDE	SULFONYLUREA	Metformin and Glyburide	Glucovance	2004
		Metformin; Glipizide	Metaglip	2005
	THIAZOLIDINEDIONES	Metformin; Pioglitazone	Actoplus Met/ Actoplus Met XR	2005
		Metformin; Rosiglitazone	Avandamet	2002/ Discontinued[b]
	DPP-4 INHIBITORS	Metformin; Sitagliptin	Janumet	2007
		Metformin; Linagliptin	Jentadueto	2012
		Metformin; Alogliptin	Kazano	2013
		Metformin; saxagliptin	Kombiglyze XR	2010
	SGLT2 INHIBITORS	Metformin; Canagliflozin	Invokamet/ Invokamet XR	2014
		Metformin; Dapagliflozin	Xigduo XR	2014
		Metformin; Empagliflozin	Synjardy/ Synjardy XR	2015
		Metformin; Ertugliflozin	Segluromet	2017
	MEGLITINIDE	Metformin; Repaglinide	PrandiMet	Discontinued[c]
SULFONYLUREA	THIAZOLIDINEDIONES	Glimepiride; Pioglitazone	Duetact	2006
		Glimepiride; Rosiglitazone	Avandaryl	Discontinued[b]
DPP-4 INHIBITORS	THIAZOLIDINEDIONES	Alogliptin; Pioglitazone	Oseni	2013
	SGLT2 INHIBITORS	Linagliptin; Empagliflozin	Glyxambi	2015
		Sitagliptin; Ertugliflozin	Steglujan	2017
		Saxagliptin; Dapagliflozin	Qtern	2017
BIGUANIDE / SGLT2 INHIBITORS	DPP-4 INHIBITORS	Empagliflozin; Linagliptin; Metformin	Trijardy XR	2020
		Metformin; Saxagliptin; Dapagliflozin	Qternmet XR	2019

[a] Source: https://www.drugs.com/drug-class/antidiabetic-agents.html
[b] FDA discontinued because of safety concerns or effectiveness.

[c] Unclear why this medication was discontinued

TABLE 3: VARIOUS FORMS OF INSULIN

INSULIN TYPE	AGENTS	SUPPLIER	YEAR approved by FDA
RAPID ACTING	Insulin Lispro (HUMALOG/ADMELOG)	Eli Lilly/Sanofi	1996/2017
	Insulin Lispro abbc (LYUMJEV/HUMALOG JUNIOR KWIKPEN)	Eli Lilly	2020/ 2017
	Insulin Glulisine (APHIDRA)	Sanofi	2004
	Insulin Aspart (NOVOLOG/FIASP)	Novo Nordisk	2001/ 2019
	Oral Inhalation- Insulin Regular (AFREZZA)	MannKind	2014
SHORT ACTING	Human Insulin Regular (HUMULIN R/ NOVOLIN R/ VELOSULIN R)	Eli Lilly/Novo Nordisk	1982/ 1991/ 1999
INTERMEDIATE ACTING	Human Insulin NPH (HUMULIN N/ NOVOLIN N)	Eli Lilly/ Novo Nordisk	1982/ 1991
LONG ACTING	Insulin Glargine (LANTUS/TOUJEO/ BASAGLAR)	Sanofi/Eli Lilly	2000/ 2018/ 2015
	Insulin Glargine -yfgn (SEMGLEE)	Viatris and Biocon	2021
	Insulin Glargine-aglr (REZVOGLAR)	Eli Lilly	2021
	Insulin Detemir (LEVEMIR)	Novo Nordisk	2005
ULTRA-LONG-ACTING INSULIN	Insulin Degludec (Tresiba) (shortage in USA[a])	Novo Nordisk	2015
PRE-MIXED INTERMEDIATE ACTING (NPH) AND SHORT ACTING (REGULAR)	HUMULIN 70/30, HUMULIN 50/50, NOVOLIN 70/30	Eli Lilly/Novo Nordisk	1989/ 1992/ 1991
PRE-MIXED INTERMEDIATE ACTING (LISPRO PROTAMINE SUSPENSION) AND RAPID ACTING (LISPRO)	HUMALOG MIX 50/50, HUMALOG MIX 75/25	Eli Lilly	1999
PRE-MIXED INTERMEDIATE-ACTING (ASPART PROTAMINE SUSPENSION) AND RAPID ACTING (ASPART)	NOVOLOG MIX 70/30	Novo Nordisk	2001
PREMIXED INSULIN/GLP-1 RA PRODUCTS	Insulin Glargine and Lixisenatide – (SOLIQUA)	Sanofi	2016
	Degludec and Liraglutide – (XULTOPHY)	Novo Nordisk	2016
COMBINATION ASPART AND DEGLUDEC	RYZODEG 70/30 (shortage in USA*)	Novo Nordisk	2015

[a] Due to shortage of FlexTouch delivery device expected until December 2024

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TABLE 4: RECENT REPORTS ON DRUG DELIVERY OF ANTIDIABETIC DRUGS

DRUG	DRUG DELIVERY SYSTEM	COMMENTS
Metformin	Polylactic-co-glycolic acid (PLGA)	The investigation carried out on diabetic rats in an experimental model of periodontal disease revealed that the clearance rate of Metformin encapsulated in PLGA was slower than that of Metformin alone.(Pereira et al., 2021)
	Hyo-deoxycholic Acid-Modified Metformin Liposomes	The Liposomes had enhanced the hypoglycemic effect of metformin. It also demonstrated that Hyo-deoxycholic acid plays a suitable role as an excipient.(Hu et al., 2023)
	In-situ Biopolymer-based Floating Gel	It was shown that with the use of in-situ gel can result in a sustained delivery of metformin, hence enhancing the drug's absorption.(Wiwattanapatapee et al., 2023)
	Bio-conjugated Metformin-Gold Nanoparticles (GNPs)	The conjugated gold nanoparticles demonstrated greater antiglycation activity (at lower doses) and a lower side-effect profile than the pure metformin antiglycation drug (when used at higher doses). This is because the nanoparticles require a lower dosage than pure metformin.(Alenazi et al., 2022)
	Metformin Hydrochloride loaded Lipid Vesicles (MH-LLV)	The lipid vesicles demonstrated an encouraging extended-release formulation with pharmacokinetic properties, and enhanced antihyperglycemic potentials.(Ossai et al., 2021)
	Metformin hydrochloride mucosal nanoparticles enteric-coated capsule (MH-MNPs-EC) based on metformin hydrochloride chitosan mucosal nanoparticles (MH-CS MNPs)	The mucosal nanoparticles exhibited excellent intestinal adherence and also considerably extended the metformin's residence duration in the intestine. Comparing the nanoparticles enteric coated capsules to commercially available metformin enteric capsules, the nanoparticles enteric coated capsules demonstrated a superior therapeutic effect.(Lu et al., 2022)
	Metformin Hydrochloride encapsulation into gelatin/sodium alginate nanoparticles using BÜCHI nano spray dryer B-90	The in-vitro studies with metformin encapsulated nanoparticles showed sustained release profile of metformin and the animal studies showed a notable drop in blood glucose levels.(Shehata and Ibrahima, 2019)
Repaglinide and Metformin	Amberlite resin based floating microspheres	Floating microspheres extended drug release compared to plain drug and had a superior blood glucose lowering effect profile.(Jain et al., 2021)
Repaglinide	Chewable Repaglinide encapsulated niosomes tablets	Comparing tablets to traditional medications, a significant drop in blood glucose levels was seen.(Fouad et al., 2023)
Nateglinide	Niosomal encapsulation of Nateglinide	Niosomes showed significant improvement in the rate and extent of the hypoglycemic effect compared with the unprocessed drug.(Sultan et al., 2018)
Pioglitazone	Chitosan/PEG blended PLGA biocompatible nanoparticles	An in vivo study revealed that the nanoparticle formulation improved drug bioavailability and blood glucose lowering profile.(Sharma et al., 2022)
	Pioglitazone-Loaded PLGA Nanoparticles	The PK-PD characteristics of the nanoparticles were superior. It revealed an extremely slow drug release profile, a greater percentage of

		entrapment efficiency, longer storage duration, and an appropriate particle size.(Todaro et al., 2022)
	Pioglitazone-Loaded PEG-PLA/PLGA-based Nanoparticles	The study demonstrated the effectiveness of nanoparticles in reducing inflammatory response via PPAR- (observed in atherosclerosis).(Groner et al., 2023)
Glipizide (GPZ)	O-Carboxymethyl chitosan (O-CMC) nanoparticles (NPs)	In vivo studies demonstrated that glipizide nanoparticles are superior to pure and commercially available glipizide in ameliorating various T2D-related biomarkers.(El-Dakroury et al., 2023)
Gliclazide	PLGA Based second-generation nanocrystals (SGNCs) Carriers	The results of the study showed that gliclazide nanocrystal carriers result in a faster initial release, followed by a delayed release with enhanced bioavailability. This allows for more effective gliclazide administration in T2DM patients.(Panda et al., 2019)
	Solid Lipid-Based Gliclazide Nanoparticles	In-vitro, Pharmacokinetics, Pharmacodynamic, and subacute toxicity studies demonstrated that gliclazide-loaded nanoparticles have a greater anti-diabetic effect than raw gliclazide powder.(Nazief et al., 2020)
	Self-nanoemulsifying drug delivery system (SNEDDS) of gliclazide (GCZ)	Studies conducted in vivo showed that SNEDDS significantly reduced blood glucose levels and increased bioavailability by twofold when compared to plain drug suspension. These findings suggest that a lipid-based system could be a good alternative for treating diabetes.(Patel et al., 2019)
Linagliptin and Gliclazide	Linagliptin and gliclazide di-loaded extended-release nanoparticles	After 8 hours, the nanoparticles formula released over 80% of both medicines, and over 24 hours, it demonstrated good extended release.(Rahi et al., 2021)
Glimepiride	Nano particles of glimepiride via spray freezing into cryogenic liquid (SFCL)	The study demonstrated a 1.79-fold increase in the bioavailability of GP after oral administration of SCFL nanoparticles.(Gaber et al., 2022)
	Nano emulsion (NE) system for transdermal administration of glimepiride	Using ex vivo permeation, skin irritation, and in vivo pharmacokinetics, transdermal NE-based Glimepiride gel showed promise as an replacement for oral conventional medication in the management of T2DM.(Abdallah et al., 2023)
Semaglutide	Sodium N-[8-(2-hydroxy-benzoyl) amino] caprylate (SNAC)	For oral delivery of semaglutide, the most promising absorption enhancers are sodium caprylate/caprate and their derivatives. These are oral GLP-1Ras approved by the FDA.(Bucheit et al., 2020)
Saxagliptin and Dapagliflozin	Electro sprayed tri-layer poly (D, l-lactide-co-glycolide) nanoparticles	The hybrid nanoparticle-based drug delivery system demonstrated distinct and controllable sustained release profiles.(Zhang et al., 2022b)
Exedine-4	Chitosan-PLGA microspheres	Experiments conducted in vivo revealed that exendin-4-loaded microspheres significantly enhanced osseointegration and bone formation around implants in rats with T2DM without affecting blood glucose levels.(Shi et al., 2022)

	Exenatide-loaded inside-porous PLGA microspheres	Studies conducted both In-vitro and in animals demonstrated the drug's favorable release characteristics.(Zhai et al., 2020)
	Exenatide Loaded PLGA Microparticles Prepared by Ultra-Fine Particle Processing System	High encapsulation efficiency and sustained release for two months were demonstrated by the microparticles, and the PK experiments showed that three weeks following a single injection of dimpled microparticles, the effective drug concentration could be sustained.(Zhu et al., 2019)
	Exenatide loaded Biotinylated Trimethylated Chitosan/HP- 55 Nanoparticles	Exenatide was successfully delivered orally via Bio-TMC/HP-55 nanoparticles, improving patient compliance.(Guo et al., 2022)
Liraglutide	Liraglutide loaded PLGA nanoparticles	The Lira-loaded PLGA nanoparticles were optimized to successfully maintain Lira's natural structure and has shown potential for oral administration.(Ismail et al., 2019)

TABLE 5: ORAL INSULIN IN CLINICAL TRIALS

INSULIN	STUDY TITLE	NCT NUMBER	TRIAL PHASE, STATUS	TECHNOLOGY	COMPANY
Oral insulin 338 (OI338)	Trial to Compare NNC0123-0000-0338 in a Tablet Formulation and Insulin Glargine in Subjects with Type 2 Diabetes Currently Treated with Oral Antidiabetic Therapy	NCT 02470039	II, completed	Microemulsion system, Gastrointestinal permeation enhancement technology (GIPET™)	Novo Nordisk A/S
	Effect of Food on the Pharmacokinetics of NNC0123-0000-0338 in a Tablet Formulation in Healthy Subjects	NCT 02304627	I, completed		
ORMD-0801	Study to Evaluate the Efficacy and Safety of ORMD-0801 in Subjects with T2DM	NCT 04606576	III, active, not recruiting	Enteric coating; enzyme inhibitor; permeation enhancer	Oramed (Israel)
	A Study to Evaluate the Effect of ORMD-0801 in Patients with T2DM	NCT 04564846	II, completed		
	A Study of Oral Insulin to Reduce Liver Fat Content in Type 2 Diabetes Patients with Nonalcoholic Steatohepatitis (NASH)	NCT 04616014	II, completed		
	A Study to Assess the Safety and Efficacy of Oral Insulin in T2DM Patients with Nonalcoholic Steatohepatitis (NASH)	NCT 04618744	II, completed		
	A Phase 3 Study to Evaluate the Efficacy and Safety of ORMD-0801 in Subjects with Type 2 Diabetes Mellitus	NCT 04754334	III, recruiting		
	Effectiveness of Oral Insulin in Unstable Type 1 Diabetes Patients	NCT 00867594	II, completed		
	A Study of Single and Multiple Doses of Oral Insulin or Placebo in Subjects with Type 2 Diabetes Mellitus	NCT 02954601	II, completed		
	A Study to Evaluate the Efficacy and Safety of ORMD-0801 (Oral Insulin) in Patients with	NCT 03467932	II, completed		

	Type 2 Diabetes Mellitus				
	A Study to Compare ORMD-0801 Once Daily to ORMD-0801 Three Times Daily in Subjects with Type 1 Diabetes	NCT 04150107	II, completed		
	A Study to Evaluate the Efficacy and Safety of ORMD-0801 (Oral Insulin) in Patients with Type 2 Diabetes Mellitus	NCT 03467932	II, completed		
Oshadi Icp	Efficacy Safety and Tolerability of Multiple Doses of Oshadi Icp (Oshadi Oral Insulin) in patients with T1DM	NCT 01973920	II, completed	Silica-based nanoparticles with combination of proinsulin, c-peptide, and a polysaccharide	Oshadi (Israel)
	Safety and Tolerability of Oshadi Icp in Patients with T1DM	NCT 01772251	I/II, completed		
IN-105 (Insulin Tregopil)	Effect of Dosing Time and Meal on IN-105 (Insulin Tregopil) PK and PD	NCT 03392961	I, completed	Polyethylene glycol side chain with enhancer sodium caprate (PEGylation)	Biocon, India
	Comparison of Insulin Tregopil (IN-105) With Insulin Aspart in T2DM Patients	NCT 03430856	II/III, completed		
TN20	Immune Effects of Oral Insulin in Relatives at Risk for T1DM (TN20)	NCT 02580877	II/ completed	Human recombinant insulin crystals	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
	Oral Insulin for Prevention of Diabetes in Relatives at Risk for Type 1 Diabetes Mellitus (TN07)	NCT 00419562	III/ completed		
	The Diabetes Prevention Trial of T1DM (DPT-1)	NCT 00004984	III, completed		
	Primary Intervention with Mucosal Insulin (Pre-POINT)	NCT 02620553	I/II, completed	insulin crystals (Lilly Pharmaceuticals) in microcrystalline cellulose	Technical University of Munich
	Pre-POINT-Early Study	NCT 02547519	II, completed	insulin crystals (Lilly Pharmaceuticals) in microcrystalline cellulose	Technical University of Munich
Fr1da	Fr1da Insulin Intervention	NCT 02620072	II, active, not	insulin crystals (Lilly	Technical University of Munich

			recruiting	Pharmaceuticals) in microcrystalline cellulose	
ORA2	A Two-Part Study of Peroral Insulin in T2DM	NCT 00990444	I/II, suspended	Dextran matrix capsule with insulin	BOWS Pharmaceuticals AG (Zug, Switzerland)
HDV-I (Hepatic Derived Vesicles)	Study of Two Doses of Oral HDV-Insulin and Placebo with Background Metformin Treatment in Patients with T2DM	NCT 00814294	II/III, completed	Liver-targeted liposomal insulin vesicles	Diasome Pharma
Oral Insulin-CNAB	Oral Insulin: A Comparison with Subcutaneous Regular Human Insulin in Patients with T2DM	NCT 00982254	I, completed	Noncovalent interaction of insulin with drug-carrier molecule monosodium N-(4chlorosalicyloyl)-4-aminobutyrate (4-CNAB)	Emisphere Technologies, Inc.
Oral Insulin (N11005)	A Study Evaluating the Bioavailability of Oral Insulin (N11005)	NCT 04975022	I, completed	No published data	Beijing Hospital

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TABLE 6: COMMON POLYPHENOLS IN DIABETIC CLINICAL TRIALS

NATURAL PRODUCTS ROLE IN DIABETES	**NCT Number**	**PHASE**	**STUDY TITLE**	**PRIMARY OUTCOMES MEASURED**	**SECONDARY OUTCOMES MEASURED**
RESVERATROL • **Anti-inflammatory** • **Anti-oxidant** • **Anti-aging** • **Anti-carcinogenic** • **Anti-angiogenic** ↑phosphorylation of AMPK/ ↑SIRT1→↑ islet mitochondrial activities and ↓ROS levels. ↑SIRT1 and ↓ NF-κB activity→↑insulin sensitivity ↓glucose production and ↑lipolysis	NCT-01038089	Not applicable	Pilot Study of The Effects of Resveratrol on Endothelial Function in Subjects with T2DM	The primary outcome was the measurement of flow-mediated brachial artery dilation.	Blood indicators for oxidative stress, insulin resistance, and inflammation make up the secondary outcome measure.
	NCT-01638780	Not Applicable	Resveratrol and T2DM	The study's primary goal is to determine whether addition of resveratrol can improve overall and insulin sensitivity in muscle in T2DM patients.	The investigators' secondary objective is to determine if the enhanced insulin sensitivity can be attributed to an increase in muscle mitochondrial oxidative capability and a decrease in intrahepatic and cardiac lipid content.
	NCT-01677611	Phase 1	Effects of Resveratrol in Patients with T2DM	The primary result assessed how 12 weeks of oral resveratrol affected the expression of SIRT1 in skeletal muscle.	Measures of AMPK, p-AMPK, and GLUT4 expression levels, energy expenditure, levels of physical activity, the distribution of skeletal muscle fiber type composition and abdominal adipose tissue composition, body weight, HbA1c, plasma lipid sub-fraction, adiponectin levels, and insulin sensitivity are the secondary outcomes.
	NCT-01997762	Phase 4	Can Resveratrol Improve Insulin Sensitivity and Preserve Beta Cell Function Following Gestational Diabetes?	Improving insulin sensitivity and preserving beta cell function is the primary objective.	Secondary outcome to evaluate recruitment rates, treatment adherence, change in insulin sensitivity, change in liver function, change in c-reactive protein, change in glycated hemoglobin, and change in serum lipid levels.
	NCT-01881347	Not Applicable	Effects of Resveratrol on Endothelial	Measuring the baseline change in Brachial artery flow-	The secondary outcome assesses how resveratrol

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			Function in T2DM	mediated dilatation is the main goal.	supplementation affects the expression of proteins, the generation of nitric oxide, and the functionality of mitochondria.
	NCT-01451918	Phase 2	Regulation of Intestinal and Hepatic Lipoprotein Secretion by Resveratrol	The main objective is to assess the effect of resveratrol on ApoB 100 and ApoB 48 production in humans.	Secondary outcome measures the change in insulin sensitivity with resveratrol treatment
	NCT-02549924	Phase 2	Effect of Administration of Resveratrol on Glycemic Variability in Individuals with Type 2 Diabetes Mellitus	The primary outcome is to measure glycemic excursions using continuous glucose monitoring.	Secondary outcome measurement includes Fasting glucose, Post prandial glucose, HbA1C, Total cholesterol, triglycerides, HDL-C, LDL-C, VLDL-C, ALT, AST, Creatinine, Blood pressure, body, and fat visceral %.
	NCT-04449198	Early Phase 1	Type 1 Diabetes, Endothelin, and Skeletal Muscle Mitochondrial Dysfunction: The Role of Sirtuin-1	The primary objectives are to quantify the changes in skeletal muscle mitochondrial function and the area under the curve (AUC) for cutaneous vascular conductance (CVC).	Changes in Pulse Wave Velocity (PWV), Post Occlusive Reactive Hyperemia (PORH), and Percentage Flow-Mediated Dilation (FMD) are examples of secondary outcome measures.
	NCT-03762096	Not applicable	Short Interval Resveratrol Trial in Cardiovascular Surgery (SIRT-CVS)	Primary outcome is to measure the change in endothelial function by measuring nitric oxide synthase levels in heart tissue.	Secondary outcome is to measure the effect of resveratrol on key molecular signals that determine endothelial function, caveolar makeup and function, as well as cytoprotective signaling and responses in the heart.
	NCT-02129595	Not applicable	Resveratrol and First-degree Relatives of T2DM Patients	The study's main goal is to look into insulin sensitivity in first-degree relatives of T2DM patients, both generally and in relation to specific muscles.	Examining whether a lower intrahepatic and cardiac lipid content and enhanced muscle mitochondrial oxidative capability are responsible for the improved insulin sensitivity is the secondary goal. Additionally, the

					researchers hope to look at how resveratrol affects the uptake of glucose in brown adipose tissue in a portion of the subjects.
	NCT-05172947	Not applicable	Effect of Resveratrol and Pharmacist Intervention on Diabetes Mellitus and Its Neuropathic Complication	Primary objective is to assess neuropathic pain by various neuropathic pain assessment tools and Nerve conduction studies will be performed to assess the effect of interventional therapy.	Secondary objective to assess the glycemic status and to assess the effect of the interventions on metabolic changes.
	NCT-02565979	Not applicable	Long-term Resveratrol and Metabolism	The main goal of the study is to examine if 6 months' resveratrol supplementation can improve glucose tolerance in overweight/obese individuals.	The secondary objectives is to investigate whether resting energy metabolism, intra-hepatic lipid content, physical performance, body composition and quality of life change by 6 months resveratrol supplementation.
	NCT-01354977	Phase 2	Effect of Resveratrol on Age-related Insulin Resistance and Inflammation in Humans	The primary outcome includes measuring peripheral insulin sensitivity by determining the rate of glucose uptake.	Secondary outcome is to determine hepatic insulin sensitivity by measuring endogenous glucose production, muscle mitochondrial function, measuring inflammatory and anti-inflammatory markers in adipose tissue assessment of cognitive function.
	NCT-02247596	Phase 2	Effects of High-Dose Resveratrol in Non-Diabetic Obese Males	Examining the effects of two weeks of oral resveratrol on resting energy expenditure and insulin sensitivity in male individuals who were obese but did not have diabetes was the main goal of the study.	Blood pressure, glycated haemoglobin (HbA1c), and plasma lipid sub-fraction were among the secondary variables.
	NCT-02244879	Phase 3	Effects of Resveratrol on Inflammation in	This study's primary goal is to look into the effect of	Secondary outcome measured included metabolic, oxidative

			Type 2 Diabetic Patients	resveratrol on inflammatory mediators in T2DM patients in vivo, by measuring the values of high-sensitivity CRP (C-reactive protein).	markers, body composition, and bone mineral density.
	NCT-01593605	Not applicable	Resveratrol-Leucine Metabolite Synergy in Pre-diabetes	Primary objective of the study is to evaluate the effect of resveratrol on glucose control.	Secondary measure includes the metabolic markers.
	NCT-01158417	Not applicable	Resveratrol in T2DM and Obesity	The main goal is to find out how resveratrol affects the production of ROS and the pro-inflammatory transcription factor NF-kB.	The secondary goal is to determine whether, in comparison to placebo, resveratrol stimulates the incretin system and increases GIP and GLP-1 secretion/release.
	NCT-01714102	Not applicable	Resveratrol and the Metabolic Syndrome	Primary outcome measures reduction on insulin resistance.	Secondary outcome measures reduction in serum cytokines/chemokines, reduction in blood pressure, reduction lipid values, reduction in crown like structures and adipose tissue mass, changes in HOMA-IR, variations in adipose tissue and stool gene expression.
	NCT-01150955	Not applicable	Potential Beneficial Effects of Resveratrol	Primary objective is to measure metabolic parameters.	Secondary outcome measures pathways of substrate metabolism.
	NCT-02704494	Early Phase 1	Resveratrol's Effects in Diabetic Nephropathy	Primary outcome measures urine albumin and serum creatinine.	Secondary outcome measures Fasting blood sugar, Glycosylated hemoglobin, Liver aminotransferases (ALT and AST), Serum insulin level, and number of patients with adverse events.
	NCT-01302639	Not applicable	Dietary Polyphenols and Lipid Oxidation	Primary outcome is to measure postprandial fat oxidation	Not specified
	NCT-00937222	Not applicable	Effects of Peanut and	The primary outcome measure is	Serum lipids, glucose, HbA1c,

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			Peanut Butter Consumption on Blood Lipids and Glycemic Control in Adults with T2DM	HDL-C.	anthropometrics, and blood pressure are measured by the secondary outcome.
	NCT-02216552	Phase 2 Phase 3	Resveratrol for the Treatment of Non-Alcoholic Fatty Liver Disease and Insulin Resistance in Overweight Adolescents	Changes in liver triglyceride content as assessed by MRS and improvements in insulin resistance as assessed by the area under the glucose excursion curve during an oral glucose tolerance test using 75 grams are examples of primary outcome measurements.	Not specified
QUERCETIN • **Anti-inflammatory** • **Anti-obesity** • **Anti-hyperlipidemic** • **Neuro-protective** • **Anti-hypertensive** • **Anti-atherosclerotic** ↑glucose uptake, ↑phosphorylation of PI3K/Akt signaling pathways, interacts with PPARγ receptor, ↑plasma adiponectin levels, ↓TNF-α production. Improves β-cells action.	NCT-01839344	Phase 2	Effects of Quercetin on Blood Sugar and Blood Vessel Function in T2DM.	Principal metrics include resultant glucose tolerance after being tested for maltose tolerance.	Area under the glucose curve is measured by the secondary outcome.
	NCT-00065676	Phase 2	Investigating the Use of Quercetin on Glucose Absorption in Obesity, and Obesity with Type 2 Diabetes	Primary outcome measures quercetin effect on glucose absorption.	Not specified
	NCT-01881919	Early Phase 1	Effect of Quercetin Supplements on Healthy Males: A Four-Week Randomized Cross-Over Trial	Primary objective is to measure the risk of getting hyperuricemia assessed by the measure of plasma uric acid.	Secondary outcome is to measure urinary uric acid level, Blood pressure, Blood glucose, and Metabolomic and metabonomic profiling of blood plasma.
	NCT-02760017	Not applicable	Bauhinia Forficata in Diabetic Patients	Primary outcome measures glycated hemoglobin levels, and fasting glucose levels.	Secondary objective of the study is to assess plasma inflammatory parameters levels, plasma oxidative stress parameters levels, and plasma endothelin-1 levels.
CURCUMIN	NCT-02529982	Not applicable	Curcumin Supplementation and Patients with Type 2 Diabetes	Primary outcome measures fasting blood sugar, insulin, HbA1c, Homeostatic Model Assessment	Secondary outcome measures total capacity antioxidant, Malondialdehyde, BMI and waist

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• **Anti-inflammatory** • **Anti-carcinogenic** • **Anti-oxidant** • **Immuno-modulatory** • **Hypoglycemic** • **Anti-rheumatic effects** NF-kB →↓inflammatory cytokines→↑insulin sensitivity ↓postprandial glucose, ↓Lipid peroxidation, ↓ Leptin and ↑ adiponectin				of Insulin Resistance and change in pancreatic B-cell function.	circumference.
	NCT-01052025	Phase 4	Curcumin Therapy in Patients with Impaired Glucose Tolerance and Insulin Resistance	Primary outcome measures the efficacy of curcumin on the delay of degenerative beta-cells in pancreas for protection of T2D in patients with impaired glucose tolerance (Pre-diabetes).	Secondary outcome is to examine the efficacy of curcumin on the reduction of blood sugar level, lipid profile, insulin resistance status and oxidative stress status in Pre-diabetes patients.
	NCT-01052597	Phase 4	Curcumin for Type 2 Diabetic Patients	Primary objective of the study is to assess the effectiveness of curcumin on reduction of atherosclerotic events and risks in T2DM patients.	. Secondary outcome is to assess the effectiveness of curcumin on the reduction of blood sugar, glycosylated hemoglobin (HBA1c), lipid profile, and insulin resistance.
	NCT-04528212	Phase 4	Fenofibrate Versus Curcumin in T2DM Patients	Primary outcome measures Fetuin A protein and human Sirtuin1 a Protein – Recombinant human SIRT1 protein.	Measures of secondary outcomes Triglyceride and total cholesterol values.
	NCT-05753436	Phase 2	Curcumin's Effect on Diabetic Patients with Atherosclerotic Cardiovascular Risk	Primary outcome measures Atherosclerotic cardiovascular diseases risk score, blood glucose level, lipid profile, blood pressure and heart rate.	Secondary outcome measures concentration of tumor necrosis factor alpha, malondialdehyde, international normalized ratio and serum ferritin levels.
	NCT-02529969	Phase 2 Phase 3	Effects of Curcumin Supplementation on Lipid Profile and Inflammatory Markers of Patients with T2DM	Primary outcome measures triglyceride.	Secondary outcome measures C-reactive protein.
	NCT-02908152	Phase 2 Phase 3	Curcumin Supplement in Nonalcoholic Fatty Liver Patients	Primary outcome measures Hepatic steatosis.	Secondary objective is to evaluate the Glucose, HbA1c, ALT, and AST.
	NCT-05407467	Phase 1 Phase 2	KurCoSmart Effects on	Primary outcome measures fasting	Secondary outcome measures Body Mass

			People with Type 2 DM	and prandial blood glucose, HbA1c level, inflammation degree; and insulin resistance.	Index and Blood pressure.
	NCT-03262363	Phase 2 Phase 3	Curcumin on NFE2L2 Gene Expression, Antioxidant Capacity and Renal Function according to rs35652124 in Diabetic Nephropathy	Changes in the expression of Gen NFE2L2, antioxidant capacity, and renal function at three and six months are the primary outcome measures.	Not specified
	NCT-03917784	Phase 4	Effect of Oral Supplementation with Curcumin on Insulin Sensitivity in Subjects with Prediabetes	Primary objective is to assess HOMA-IR, HOMA-Beta, and Mastuda index.	Secondary outcome measures weight, height, waist circumference, hip circumference, and levels of insulin, triglycerides, cholesterol, HDL cholesterol, LDLD cholesterol, uric acid, creatinine, urea, ALT, ALP, LDH, glycosylated hemoglobin and total bilirubin.
	NCT-01646047	Not applicable	Diabetes Visual Function Supplement Study (DiVFuSS)	Primary outcome measures changes in visual function.	Secondary outcome measures changes in serum markers and changes in retinal structure.
	NCT-03866005	Not applicable	Prospective Study of Adjunctive Carotenoids Plus Anti-oxidants in Anti-VEGF Treated Diabetic Macular Edema (PROACTIVED ME)	Primary outcome measures best-corrected visual acuity, SD-OCT macular subfield thicknesses and required number of anti-VEGF injections.	Secondary outcome measures changes in serum markers and changes in retinal structure.
	NCT-03542240	Not applicable	Effects of Curcumin Supplementation on Gut Barrier Function in Patients with Metabolic Syndrome	Changes in intestinal permeability and intestinal barrier function are measured by the primary result.	Not specified

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	NCT-02834078	Not applicable	Effect of BGG on Glucose Metabolism and Other Markers of Metabolic Syndrome (Glucogold)	Primary outcome evaluates change in oral disposition index and change in glycated hemoglobin.	Secondary outcome measures change in fasting blood sugar and change in Body Mass Index.
	NCT-04742829	Not applicable	Effects of a Therapy with INTRAVIT® Tablets in Patients with Diabetic Retinopathy	Primary outcome measures number of participants with signs of improvement/worsening of diabetic retinopathy, in a certain stage of diabetic retinopathy according to the ETDRS modified AAO 2003, with improved/worsened visual acuity, and with improved/worsened macular edema.	Secondary outcome measures number of patients with improved/worsened blood parameters related to diabetes.
	NCT-04378972	Not applicable	Anti-inflammatory Effect of Curcumin, Homotaurine, Vitamin D3 on Human Vitreous in Patients with Diabetic Retinopathy	Primary outcome is to evaluate pro-inflammatory cytokines.	Not specified
EGCG (Epigallocatechin Gallate) • **Anti-oxidant** • **Anti-inflammatory** ↓ insulin resistance, protecting β-islet cells, +insulin-signaling pathway, and ↓ inflammation.	NCT-00867555	Not applicable	Green Tea, High in Epigallocatechin Gallate (EGCG) and Postprandial Fat Oxidation	Primary outcome measures postprandial fat oxidation.	Not specified
	NCT-01360567	Phase 3	The Effect of Green Tea Extract on Type 2 Diabetes with Hyperlipidemia	Primary outcome measures percent change of HOMA insulin resistance and TG.	Secondary outcome measures percent change of HbA1C and Cholesterol.
	NCT-02147041	Phase 2 Phase 3	The Effect of Extract of Green Tea on Obese Women and Obese Related Hormone Peptides	Primary objective of the study is to assess composite of anthropometric measures.	Secondary outcome measures hormone peptide change, biochemical characteristic change, traditional Chinese medicine syndrome classification and quality of life.

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	NCT-01302639	Not applicable	Dietary Polyphenols and Lipid Oxidation	Primary outcome measures postprandial fat oxidation.	Not specified
	NCT-00567905	Phase 2 Phase 3	Effect of Green Tea Extract on Type 2 Diabetes (GTT-DM)	The main outcome measure was the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR).	The secondary result measures blood sugar, creatinine, uric acid, aspartate and alanine aminotransferases, HbA1C, and plasma lipoproteins (triglycerides, cholesterol, HDL and LDL cholesterol), BMI, and WC.
	NCT-05349903	Not applicable	Impact of Slowly Digestible Carbohydrates on the Gut-brain Axis	Primary outcome measures postprandial glycemic response, and postprandial plasma gut hormone response.	Secondary outcome measures gastric emptying rate, appetite ratings (Visual Analog Scale, VAS), food intake of the next meal and breath hydrogen (fermentability).
	NCT-01923597	Phase 2	Effect of Green Tea (Epigallocatechin Gallate) on Albuminuria in Patients with Diabetic Nephropathy.	The effect of green tea (epigallocatechin gallate) on nephropathy and albuminuria in diabetic patients is the primary outcome studied.	The effect of green tea (epigallocatechin gallate) on blood pressure, blood glucose regulation, oxidative stress, plasma metabolites, and plasma lipids in patients with diabetic nephropathy is measured by a secondary outcome.
NARINGIN • **Anti-oxidant** • **Anti-inflammatory** • **Anti-apoptotic** • **Anti-ulcer** • **Anti-osteoporotic** • **Anti-carcinogenic** ↑insulin signaling. ↑ PPARγ →↓blood glucose and cholesterol.	NCT-03928249	Not applicable	Therapeutic Intervention of Eriocitrin in the Reduction of Hyperglycemia in Pre-diabetic Individuals	Primary outcome measures fasting glycemia.	Secondary outcome measures rate of change in plasma glucose concentration, in plasma HbA1c, in plasma insulin concentration, in plasma lipid concentration, in plasma hepatic enzymes, in plasma inflammatory parameters and in anthropometric parameters.

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↑hepatic glycolysis and glycogen concentration, ↓ hepatic gluconeogenesis	NCT-06005142	Not applicable	Therapeutic Intervention of Eriomin Associated with Metformin in the Control of Hyperglycemia in Pre-Diabetic Patients (Eriomin+Met)	Primary outcome measures fasting glycemia.	Secondary outcome measures rate of change in plasma glucose concentration, in plasma HbA1c, in plasma insulin concentration, in plasma lipid concentration, in plasma hepatic enzymes, in plasma inflammatory parameters and in anthropometric parameters.
	NCT-03527277	Not applicable	Orange Juice And Sugar Intervention Study (OASIS)	Primary outcome measures Low density lipoprotein cholesterol, apolipoprotein B, de novo lipogenesis, hepatic triglyceride, and endogenous glucose production.	Secondary outcome measures rate of change in plasma glucose concentration, in plasma HbA1c, in plasma insulin concentration, in plasma lipid concentration, in plasma hepatic enzymes, in plasma inflammatory parameters and in anthropometric parameters.
COENZYME Q_{10} • **Anti-oxidant** • **Energy production** • **Anti-inflammatory** • **Cardio-protective** **Inhibition of lipid peroxidation** Reduces mitochondrial oxidative stress. ↑insulin sensitivity ↓ oxidative stress.	NCT-03111433	Phase 2	Efficacy of Coenzyme Q10 in Pediatrics with T1DM	Principal measurements of the outcome variation in the concentration of soluble adhesion molecules between cells	Not specified
	NCT-02622672	Phase 2 Phase 3	Water-soluble Ubiquinol Supplementation on Blood Glucose, Lipids, Oxidative Stress, and Inflammation in Diabetes	Primary outcome measures fasting glucose.	Secondary metrics for outcomes LDL-C, HDL-C, MDA, catalase, superoxide dismutase, glutathione peroxidase, hs-CRP, high sensitivity interleukin, and high sensitivity C-reactive protein are the lipoprotein-cholesterol (LDL-, HDL-, and GPx) that are measured.

	NCT-02796378	Phase 4	Living With Statins - Interventional Exercise Study (LIFESTAT)	Primary objective is to assess the physical performance measured by VO2-max.	Secondary outcome measures myalgia, difference in muscle strength, difference in glucose metabolism and difference in mitochondrial function.
	NCT-02255682	Phase 4	Living With Statins - The Impact of Cholesterol Lowering Drugs on Health, Lifestyle and Well-being (LIFESTAT)	The main goal is to evaluate the myalgia differences.	Secondary outcome measures difference in VO2-max, difference in muscle strength, difference in glucose metabolism and difference in mitochondrial function.
	NCT-02984813	Phase 1	Safety and Efficacy of Antioxidants and Anti-inflammatory Agents in Glaucoma and Diabetic Retinopathy	Primary outcome measures flavoprotein fluorescence index.	Secondary outcome measures Visual acuity and Humphrey visual field testing (24-2).
	NCT-05429229	Phase 2	Effect of Topical Antioxidants in Dry Eye Disease and Diabetic Retinopathy	Primary outcome measures baseline changes in tumor necrosis factor alpha levels, in levels of interleukin 8, in levels of interleukin 6, in levels of interleukin 10, in total antioxidant capacity, and in lipo-peroxides levels in tear film at 30 days.	Secondary outcome measures Visual acuity and Humphrey visual field testing (24-2).
	NCT-02062034	Phase 2	Efficacy of Ubiquinone and Combined Antioxidant Therapy in Non-proliferative Diabetic Retinopathy	Primary outcome measures oxidative stress markers.	Secondary outcomes evaluate the progression and reversal of non-proliferative diabetic retinopathy as well as indicators of mitochondrial dysfunction.

	NCT-00703482	Phase 2	A Randomized, Double-Blind, Placebo-Controlled Study Assessing the Effect of Fenofibrate, Coenzyme Q10 and their co-administration on Ventricular Diastolic Function in Patients with Type 2 Diabetes	Primary outcome measures evolution of the E'/E septal ratio.	Measures of the secondary outcome include the degree of LVDD severity, changes in the left and right atrium volumes, sizes, LVEDD and LVESD, LVEDV and LVESV, LV mass, LV ejection fraction, IVRT, tissue Doppler E'/A' ratio, and PV doppler parameters.

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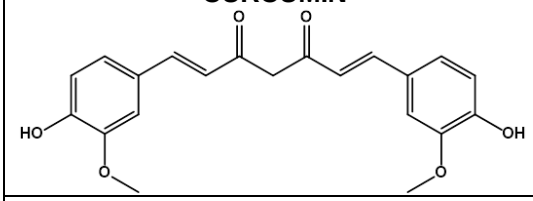
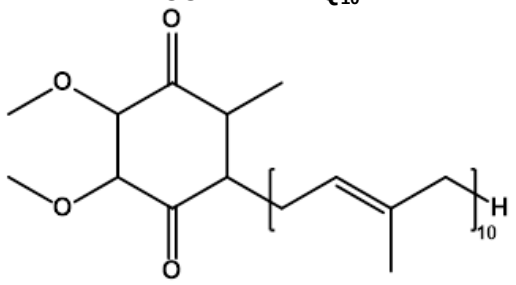
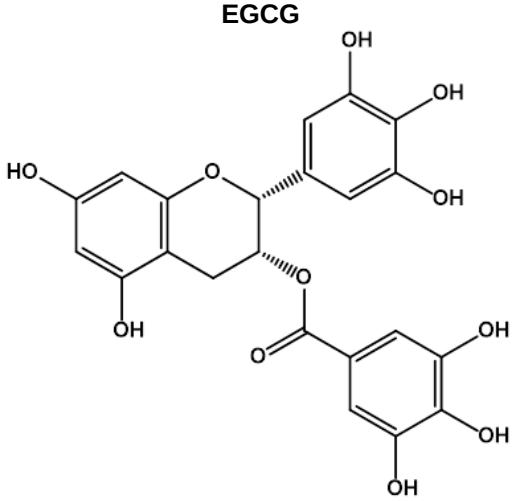
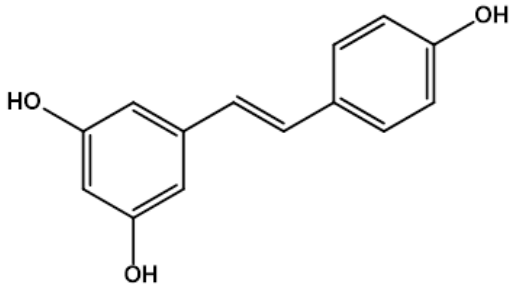
TABLE 7: PROPERTIES OF SELECTED POLYPHENOLS

COMPOUND	PROPERTIES	RULES
CURCUMIN 	Hydrogen bond acceptors (sum of Ns and Os)- 6 Hydrogen bond donors (sum of OH and NHs)- 2 Molecular weight-368.38 XlogP3-AA- 3.2	**Number of Lipinski's rules broken**- 0 **BCS class** -IV **4Ds** ☹
COENZYME Q_{10} 	Hydrogen bond acceptors (sum of Ns and Os)- 4 Hydrogen bond donors (sum of OH and NHs)- 0 Molecular weight-863.34 XlogP3-AA- 19.4	**Number of Lipinski's rules broken**- 2 **BCS class** -IV **4Ds** ☹
EGCG 	Hydrogen bond acceptors (sum of Ns and Os)- 11 Hydrogen bond donors (sum of OH and NHs)- 8 Molecular weight-458.3 XlogP3- 1.2	**Number of Lipinski's rules broken**- 2 **BCS class** -III **4Ds** ☹
RESVERATROL 	Hydrogen bond acceptors (sum of Ns and Os)- 3 Hydrogen bond donors (sum of OH and NHs)- 3 Molecular weight-228.4 XlogP3-AA- 3.1	**Number of Lipinski's rules broken**- 0 **BCS class** -II **4Ds** ☹
NARINGENIN	Hydrogen bond acceptors (sum of Ns and Os)- 14 Hydrogen bond donors (sum of OH and NHs)- 8 Molecular weight- 580.5	**Number of Lipinski's rules broken**- 3 **BCS class** – II **4Ds** ☹

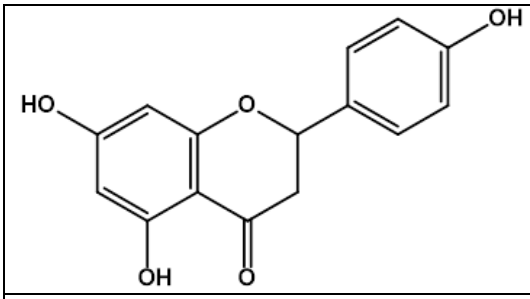
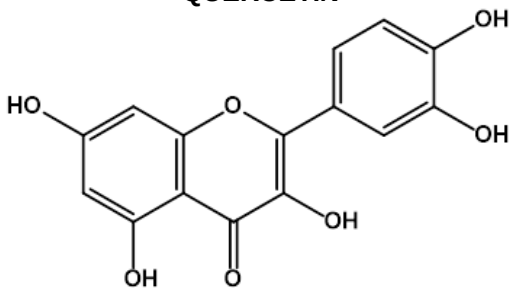
	XlogP3-AA- -0.5	
QUERCETIN 	Hydrogen bond acceptors (sum of Ns and Os)- 7 Hydrogen bond donors (sum of OH and NHs)- 5 Molecular weight- 302.23 XlogP- 1.5	**Number of Lipinski's rules broken**- 0 **BCS class** – II **4Ds** ☹

TABLE 8: COMBINATION THERAPIES WITH POLYPHENOLS AND ANTI-DIABETIC AGENTS

NATURAL PRODUCT	ANTIDIABETIC AGENT	REMARK
CURCUMIN	**GLIMEPIRIDE**	In this work, normal and diabetic rats were used to investigate the combination's PK and PD effects. By blocking the CYP2C9 enzyme, the combination of glimepiride and curcumin enhanced the bioavailability of glimepiride. This suggests that, when given at the right dose, curcumin may be helpful as an adjuvant to glimepiride in diabetic patients.(Rani, 2012)
CURCUMIN	**METFORMIN**	In macrophages and microglia, curcumin amplifies the anti-inflammatory actions of metformin, suggesting possible synergistic effects in peripheral and central pain pathways. Nevertheless, the synergistic interaction does not seem to be linked to severe CNS adverse effects.(Dasuni Wasana, 2022)
CURCUMIN	**METFORMIN**	Curcumin and metformin may work in concert when it comes to oxidative stress, increased PON 1 levels, and dyslipidemia. Consequently, it might be a useful strategy for preventing diabetic complications, especially cardiovascular problems..(Roxo, 2019)
CURCUMIN-LADEN NANOPARTICLES and METFORMIN		PEGylated PLGA nanoparticles (NPs) encapsulating Metformin and Curcumin. The findings showed that the formulations showed dose-dependent cytotoxicity against T47D cells and that, in contrast to the other groups, NPs had a more synergistic antiproliferative effect and greatly slowed down the proliferation of cancer cells. Thus, the combinational therapy has potential as a breast cancer treatment.(Farajzadeh, 2018)
CURCUMIN-LADEN NANOPARTICLES	**LONG-ACTING INSULIN**	PLGA-GA2 based curcumin nanoparticles. These studies demonstrated that combination therapy with curcumin and insulin reduces hyperglycemia and inflammation thus providing improved management of T1DM and its associated complications.(Dwivedi et al., 2022; Ganugula et al., 2023a; Ganugula et al., 2023b)
CURCUMIN-LADEN NANOPARTICLES	**LONG-ACTING INSULIN**	Glucose-responsive microgel based on chitosan, comprising conventional insulin and Curcumin-laden nanoparticles. The research presented a potentially useful drug delivery method that can provide two medications with different physicochemical characteristics at the same time in a formulation that has physiological and pathological significance. (Heyns et al., 2023a)
QUERCETIN and GLIBENCLAMIDE NANOGELS		Quercetin and glibenclamide-loaded chitosan nanogels. The study's goals were to create and describe a nanogel formulation that contained quercetin and glibenclamide and to look into the combination's penetration characteristics.(Chellappan, 2019)

INSULIN and QUERCETIN NANOPARTICLES		Lyotropic liquid crystalline nanoparticles loaded with insulin and quercetin. The combination approach reduced the generation of reactive oxygen species that cause issues related to diabetes and greatly enhanced the oral absorption of insulin and quercetin.(Singh, 2018)
RESVERATOL	**DAPGLIFLOZIN**	Resveratrol activated the PI3K/Akt pathway, which in turn decreased FoxO1 activation, hence preventing dapagliflozin-induced kidney gluconeogenesis. This study offered a prospective course of action to enhance SGLT2 inhibitors' ability to effectively lower blood glucose levels in the treatment of T2DM.(Sun, 2021)
RESVERATROL	**PIOGLITAZONE**	In addition to its anti-inflammatory effects, the combined therapy raised overall antioxidant capacity and lowered levels of peroxisome proliferator-activated receptors, which were caused by STZ-DM induction. Thus, a potential combo treatment to address problems associated with insulin resistance and diabetes.(Tamimi, 2023)
RESVERATROL	**GLIBENCLAMIDE**	The purpose of this study was to determine how glibenclamide and resveratrol affected the xenobiotic metabolizing enzyme activities in the livers of rats given STZ-induced diabetic treatment. Additionally, there may be dietary supplement-drug interactions with resveratrol and berberine. (Bozcaarmutlu, 2022)
RESVERATROL and METFORMIN NANOPARTICLES		Resveratrol-encapsulated polycaprolactone nanoparticles (R@PCL NPs) which is linked to metformin R@PCL-T/M NP. The in-vivo studies showed that the enhanced treatment efficacy can be attributed to the increased permeability of the nanotherapeutics across retina and sustainability of the two drugs' pharmacological effects in the retinal pigment epithelium. Consequently, a therapeutic agent able to target the retina and treat complex diseases of the posterior segment with enhanced efficacy.(Nguyen, 2023)
EPIGALLOCATECHIN GALLATE	**EXENDIN-4**	The study revealed that the combination of EGCG and exendin-4 has beneficial metabolic effects on mice with diabetes who consume a high-fat diet. Consequently, EGCG along with GLP-1 might be a beneficial supplement in conjunction with GLP-1 mimetics for the treatment of T2DM and its related disorders.(Pathak, 2018)
HONEY	**INSULIN**	The study found that honey treatment for six weeks reduced dyslipidemia and oxidative stress. Wistar rats with experimental diabetic neuropathy exhibited improved sensory nerve conduction velocity after receiving honey and insulin for six weeks.(Sirisha et al., 2021)

FERULIC ACID	**INSULIN**	Combination therapy demonstrated neuroprotective effects against diabetic neuropathy in STZ-induced diabetic rats.(Dhaliwal et al., 2020)

Figure 1

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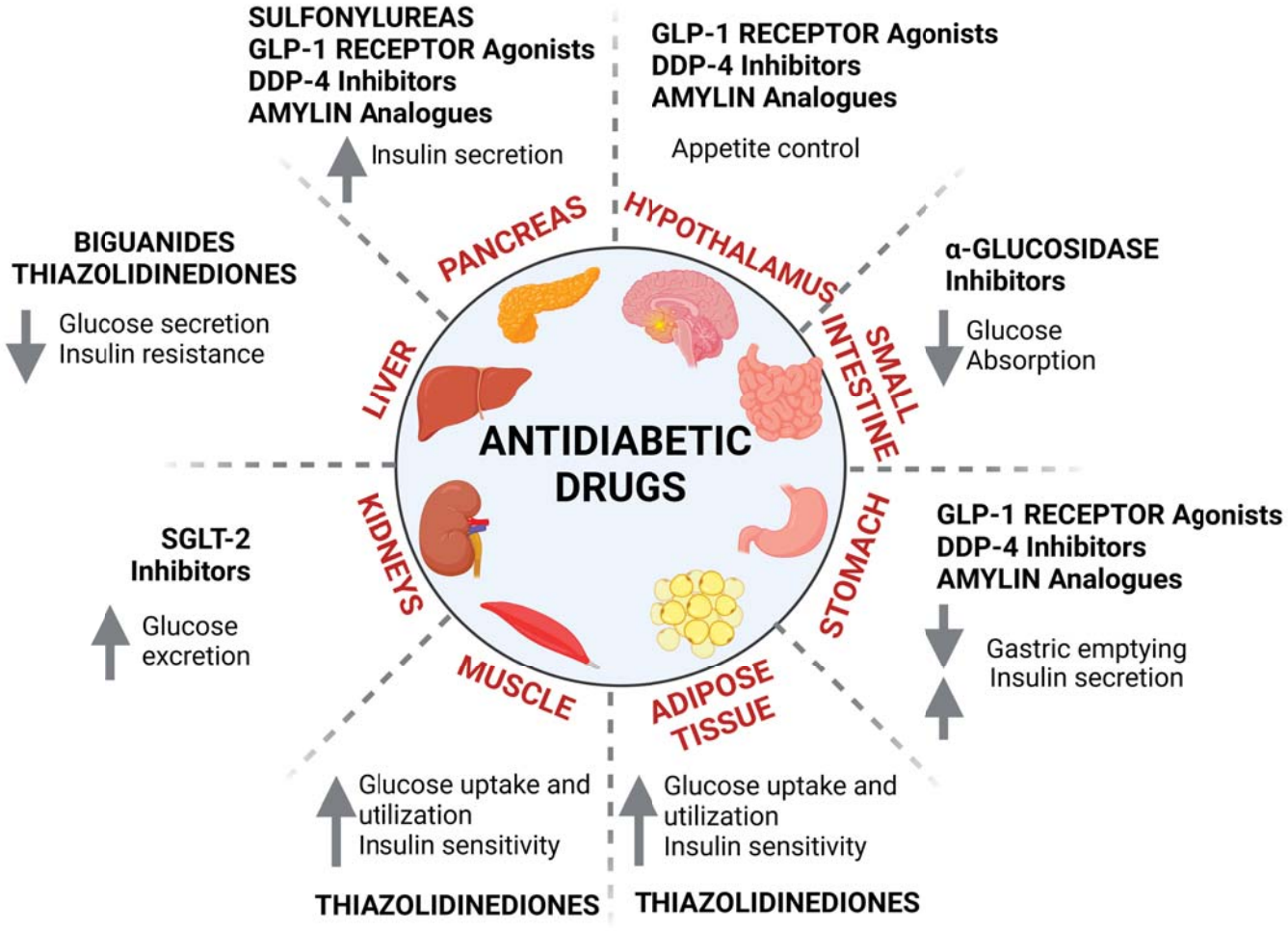

Figure 2

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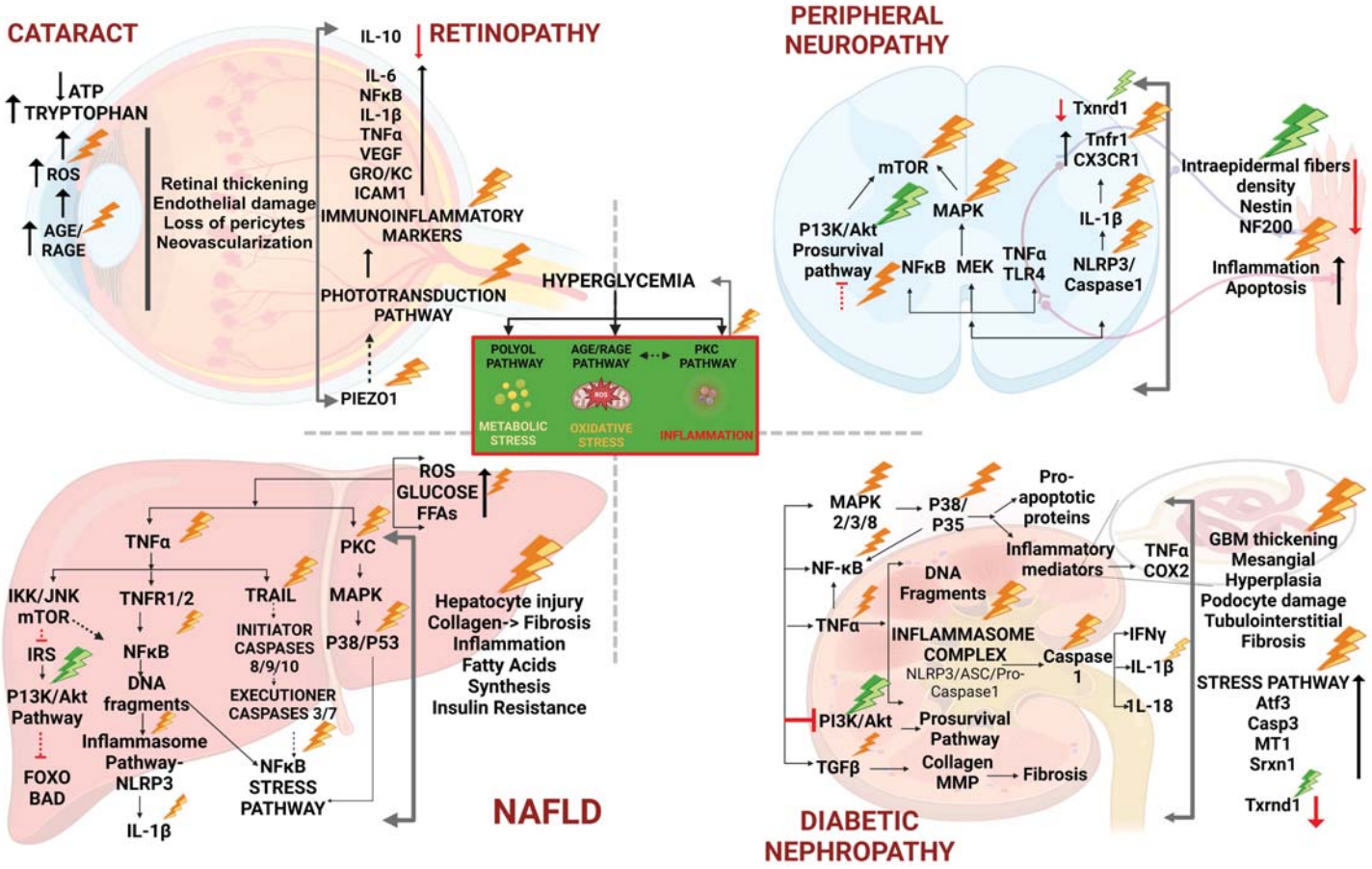

Figure 3