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Oxidative Stress, IR, and Plant Antioxidants in Diabetes

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Abstract: Type 2 Diabetes Mellitus (T2DM) is a major global health concern characterised by insulin resistance and progressive β-cell dysfunction. Emerging evidence indicates that oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) generation and the body's antioxidant defences, plays a central role in its pathogenesis. Chronic hyperglycemia and lipid overload promote excessive mitochondrial ROS formation, which activates stress-sensitive signalling pathways such as JNK, p38 MAPK, and NF-κB. These pathways impair insulin signalling by inducing serine phosphorylation of insulin receptor substrate (IRS) proteins, leading to diminished insulin responsiveness. Concurrently, pancreatic β-cells, possessing limited antioxidant capacity, are highly susceptible to oxidative injury, resulting in reduced insulin secretion and apoptosis over time.

This review explores the molecular interplay between oxidative stress, insulin resistance, and β-cell dysfunction in T2DM. It further evaluates the therapeutic potential of plant-derived antioxidants, including polyphenols, carotenoids, and vitamins, in mitigating oxidative damage. Evidence from in vitro studies, animal models, and clinical trials is critically examined to assess the translational relevance. While experimental studies demonstrate strong antioxidant and insulin-sensitising effects, clinical outcomes remain inconsistent, largely due to issues such as poor bioavailability and loss of synergistic activity outside whole-food matrices. Diets naturally rich in antioxidants, such as Mediterranean and plant-forward patterns, consistently show beneficial metabolic effects. Future research should emphasise delivery systems, synergistic phytochemical formulations, and personalised nutritional approaches to enhance the clinical utility of plant-based antioxidants in T2DM management.

Keywords: Insulin Resistance, Oxidative Stress, Personalized Nutrition, Plant-Based Antioxidants, Reactive Oxygen Species.

INTRODUCTION

The Pathophysiological Link Between Diabetes and Oxidative Stress

1.1. A Global Perspective on the Burden of Type 2 Diabetes Mellitus: A Growing Public Health Concern

The 21st century has witnessed a remarkable rise in Type 2 Diabetes Mellitus (T2DM), marking it as a major contributor to the worldwide epidemic of non-communicable diseases. As per the most recent statistics reported by the International Diabetes Federation (IDF) Diabetes Atlas, an estimated 589 million adults aged 20-79 were living with diabetes in 2024, corresponding to one in every nine adults globally [1]. This figure represents a dramatic escalation over the past three decades, and projections indicate a continued, alarming progression, with the number of affected individuals predicted to reach 853 million by 2050, or one in every eight adults ("Facts & Figures," n.d.). The burden of this disease is not distributed equally. An astounding 81% of adults with diabetes reside in low- and middle-income countries (LMICs), where healthcare systems are often least equipped to manage the complexities of chronic disease care ("Facts & Figures," n.d.). This geographic disparity points toward a powerful nexus between socioeconomic development and metabolic disease. The rising incidence of Type 2 Diabetes Mellitus

(T2DM) is strongly associated with rapid urbanisation, population ageing, increasing sedentary lifestyle, and the growing prevalence of excess body weight and obesity, which accompany the transition from traditional to modern ways of living ("Facts & Figures," n.d.). These trends reveal that diabetes is not merely a medical disorder but a broader societal issue, shaped by economic growth, environmental transitions, and lifestyle changes that surpass our biological capacity to adapt and place pressure on public health systems. Consequently, unless efforts also address the underlying social and economic drivers of the disease, medical treatments alone are unlikely to suffice. The large number of undiagnosed cases further intensifies the challenge. An estimated 252 million adults, roughly 43% of all people with diabetes, remain unaware of their condition ("Facts & Figures," n.d.). This silent epidemic is particularly pronounced in low- and middle-income countries, where limited healthcare access and inadequate screening programmes delay diagnosis and early intervention, ultimately heightening the risk of severe, long-term complications. The economic consequences are just as profound. In 2024, diabetes-related global health expenditure surpassed USD 1 trillion for the first time, a 338% increase over the last 17 years, imposing an immense strain on national economies and healthcare systems ("Facts & Figures," n.d.). This escalating human and economic cost draws attention to the immediate need for more impactful and accessible strategies for the prevention and management of T2DM.

MATERIAL AND METHODS

1.2. Search Methodology:

A comprehensive literature search was conducted to identify relevant studies on oxidative stress, insulin resistance, and the role of plant-based antioxidants in type 2 Diabetes Mellitus (T2DM). Electronic databases, including PubMed, Scopus, ScienceDirect, Google Scholar, and Web of Science, were searched from January 2000 to September 2025 using MeSH terms and Boolean operators. Key terms included: "type 2 diabetes mellitus", "insulin resistance", "oxidative stress", "reactive oxygen species", "plant antioxidants", "polyphenols", "carotenoids", "vitamin C", "vitamin E", "phytochemicals", "nanotechnology delivery systems", "microbiome", and "nutrigenomics". Relevant peer-reviewed articles, clinical trials, meta-analyses, and reviews were included. Non-English articles were excluded.

1.3. Insulin Resistance: The Core Pathophysiological Defect

The pathophysiology of T2DM is primarily driven by insulin resistance (IR). Insulin resistance is a metabolic condition in which target tissues, primarily skeletal muscle, adipose tissue, and the liver, exhibit a reduced responsiveness to the physiological effects of insulin (Freeman et al., 2025). Under physiological conditions, insulin facilitates the uptake, utilisation, and storage of glucose, thereby maintaining glucose homeostasis. In an insulin-resistant state, a given concentration of insulin produces a subnormal biological response, leading to impaired glucose disposal (Mir et al., 2025). It is well established that insulin resistance is the core event that precedes T2DM, often developing silently for years or even decades before a diagnosis is ever made (Reaven, 1995). During the early phases of insulin resistance, the pancreatic β-cells compensate by increasing insulin secretion, a state known as compensatory hyperinsulinemia, which successfully maintains normal blood glucose levels (Freeman et al., 2025). However, this compensatory mechanism cannot be sustained indefinitely. Eventually, an individual's genetic background, combined with the damaging effects of chronically high blood sugar and fat levels (glucolipotoxicity), causes the progressive decline and ultimate failure of β-cells (Freeman et al., 2025). When pancreatic insulin production is insufficient to overcome the resistance in peripheral tissues, profound hyperglycemia develops, marking the transition from prediabetes to clinical T2DM (Reaven, 1995). The impact of insulin resistance is much more than the disordered glucose metabolism. It forms the core of a group of interconnected cardiometabolic conditions collectively referred to as metabolic syndrome or "Syndrome X" (Reaven, 1995). This condition is characterized not only by impaired glucose tolerance but also by high blood pressure, abnormal lipid profiles (typically elevated triglycerides and reduced high-density.

lipoproteins and cholesterol), elevated uric acid levels, endothelial dysfunction, and a persistent, low-grade inflammatory state that promotes clot formation(Freeman et al., 2025). Collectively, these overlapping abnormalities make insulin resistance a central pathogenic factor, substantially increasing the likelihood of multiple chronic diseases, with cardiovascular complications being among the most significant.

1.4. Oxidative Stress: A Fundamental Pathogenic Contributor to Diabetes

Growing evidence indicates that oxidative stress serves as a central link in the pathogenesis of both insulin resistance and long-term complications of diabetes. Oxidative stress is defined as "a state of imbalance between the cellular production of highly reactive molecules, known as reactive oxygen species (ROS) and reactive nitrogen species (RNS), and the capacity of the endogenous antioxidant defence state to neutralise them" (Panic et al., 2022).

In the context of diabetes, chronic hyperglycaemia is the principal driver of this imbalance (*Oxidative Stress in Type 2 Diabetes*, n.d.).

High glucose levels drive the excessive generation of ROS by activating a series of interconnected biochemical pathways. These mechanisms involve excessive superoxide radicals through the mitochondrial electron transport chain, enhanced activity of the polyol and hexosamine pathways, activation of protein kinase C (PKC), and the non-enzymatic glycation of proteins leading to the formation of advanced glycation end products (AGEs) (*Oxidative Stress in Type 2 Diabetes*, n.d.). This persistent pro-oxidant state causes oxidative injury to vital cellular constituents, notably lipids, proteins, and DNA (Evans et al., 2003).

More importantly, oxidative stress isn't simply a consequence of established diabetes; it is a primary pathogenic event that initiates and fuels the acceleration of the development of insulin resistance as well as the long-term complications associated with diabetes (Evans et al., 2003). This shifts the therapeutic focus from merely controlling glucose to actively addressing the underlying oxidative burden. In Type 2 Diabetes Mellitus, oxidative stress and the chronic, low-grade inflammation characteristic of the disease form a self-reinforcing cycle, with each process amplifying the other and driving widespread cellular dysfunction (*Oxidative Stress in Type 2 Diabetes*, n.d.). This ongoing oxidative damage is increasingly recognised as a key link between elevated blood glucose, insulin resistance, and progressive failure of pancreatic β-cells, ultimately contributing to both microvascular complications such as retinopathy, nephropathy, neuropathy and microvascular complications including cardiovascular disease (Yaribeygi et al., 2020). Given its central role in the disease process, oxidative stress has become a primary focus for exploring plant-derived antioxidants as potential therapeutic agents in diabetes management.

2. The Molecular Pathophysiology of Insulin Resistance

Insulin resistance stems from disturbances at both the cellular and molecular levels in critical metabolic tissues. A central factor in this process is the cells' reduced capacity to manage a prolonged excess of nutrients, which causes lipid byproducts to accumulate in tissues that are not meant for fat storage, a phenomenon referred to as lipotoxicity.

2.1. Impaired Insulin Signalling in Skeletal Muscle and Adipose Tissues

Skeletal muscle is the main tissue responsible for postprandial glucose uptake, handling up to 70% of glucose absorbed from the circulation (Freeman et al., 2025). Therefore, impaired insulin action in this tissue has profound consequences for whole-body glucose homeostasis. Insulin resistance in skeletal muscle is closely associated with chronic excess calorie intake, which causes the buildup of lipids within the muscle cells. A key lipid intermediate involved in this process is diacylglycerol (DAG). Elevated intracellular DAG levels act as a signal of energy excess, activating a specific isoform of protein kinase C, PKC-theta (PKC-θ) (Freeman et al., 2025). Activated PKC-θ interferes with the insulin signalling pathway, which reduces the amount of GLUT4 that can reach the cell membrane. As a result, glucose uptake by the muscle decreases, leading to excess glucose being redirected to other tissues, particularly the liver (Freeman et al., 2025).

Even though they account for a smaller amount of glucose uptake than muscle, adipose tissues play a vital part in the body's metabolic regulation (Samuel & Shulman, 2016). A major characteristic of insulin resistance in adipose tissue is the inability of insulin to effectively suppress lipolysis (breakdown of stored triglycerides) (Freeman et al., 2025). Due to this dysfunction, non-esterified free fatty acids (FFAs) and glycerol are released into the bloodstream in excessive amounts. The prolonged elevation of circulating FFAs contributes significantly to insulin resistance, as these lipids accumulate in organs such as the liver and skeletal muscle, leading to ectopic fat deposition and further disruption of insulin signalling, a process referred to as lipotoxicity (Freeman et al., 2025). This highlights the essential role of adipose tissue as a "metabolic buffer"; when it cannot safely store surplus lipids, it triggers a chain reaction that promotes systemic insulin resistance. In addition to storing fat, adipose tissue functions as an endocrine organ, releasing signalling molecules known as adipokines. During insulin resistance, the balance of adipokines is altered, with decreased levels of the insulin-sensitising hormone adiponectin and increased levels of hormones that exacerbate insulin resistance, such as leptin and resistin (Samuel & Shulman, 2016).

2.2. Hepatic Insulin Resistance and Dysregulated Glucose Production

The liver is a central metabolic hub, responsible for processing, storing and producing glucose and fatty acids to meet the body's energy demands (Freeman et al., 2025). When the skeletal muscle becomes insulin-resistant, the resulting excess circulating glucose is diverted to the liver. This excess substrate promotes de novo lipogenesis (DNL), the metabolic pathway that converts carbohydrates into fatty acids (Freeman et al., 2025). Similar to skeletal muscle, this results in the buildup of DAG in the liver.

However, hepatic DAG activates a different isoform of protein kinase C, PKC-epsilon (PKC-ε) (Freeman et al., 2025). The activation of PKC-ε by the same lipid second messenger (DAG) that activates PKC-θ in muscle highlights a highly conserved, fundamental mechanism. This process senses an energy surplus and, despite using tissue-specific components, leads to the same pathological outcome, i.e., insulin resistance.

A key consequence of hepatic insulin resistance is the inability of insulin to suppress hepatic glucose production (HGP). In a healthy state, insulin signalling effectively shuts down gluconeogenesis (the synthesis of new glucose) and glycogenolysis (the process of glycogen breakdown) after a meal. In the insulin-resistant liver, this suppression is defective. Hepatic glucose production persists, leading to continued release of glucose into the bloodstream even when the circulating glucose levels are already high, which is a key contributor to the fasting hyperglycemia characteristic of T2DM (Freeman et al., 2025).

2.3. The Role of Lipotoxicity and Ectopic Lipid Accumulation

The concept of lipotoxicity synthesises the dysfunctions observed in muscle, adipose tissues, and the liver into a unified pathological framework. Lipotoxicity refers to the cellular damage caused by the accumulation of lipids in non-adipose tissues that are not designed for significant lipid storage (Freeman et al., 2025). This process is driven by a vicious cycle initiated by adipose tissue insulin resistance. The failure of insulin-resistant adipocytes to suppress lipolysis leads to a chronic elevation of circulating FFAs. These FFAs are then transported to the liver and skeletal muscle, leading to the deposition of intracellular lipid metabolites like DAG and ceramides. When fat accumulates in the tissues not designed for fat storage (a process called ectopic lipid deposition), it directly interferes with insulin signalling in these organs, further worsening systemic insulin resistance (Freeman et al., 2025). Genetics can also influence this process; for instance, certain variants of the apolipoprotein C3 (APOC3) gene have been associated with increased lipid accumulation in the liver, which can contribute to insulin resistance (Samuel & Shulman, 2016). This ongoing cycle of lipid overload and tissue dysfunction plays a central role in the progression from simple obesity to full-blown T2DM.

3. Oxidative Stress-Activated Signalling Cascades in Insulin Resistance

In diabetes, the heightened pro-oxidant state promotes insulin resistance not just by causing broad cellular damage. Rather, reactive oxygen species (ROS) serve as signalling agents that trigger distinct stress-responsive pathways within the cell. These pathways interfere with the key elements of the insulin signalling network, compromising its function and establishing the molecular basis for insulin resistance.

3.1. c-Jun N-Terminal Kinase (JNK) Pathway: A Major Stress-Responsive Kinase

c-Jun N-terminal kinase (JNK), part of the mitogen-activated protein kinase (MAPK) superfamily, serves as a crucial member of cellular responses to stress (Feng et al., 2020). In T2DM, JNK activity is elevated by factocrs commonly present in the disease, including reactive oxygen species (ROS), elevated free fatty acids, and pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) (Yung & Giacca, 2020).

3.1.1. Reactive Oxygen Species (ROS)-Mediated Activation of JNK

JNK becomes active through a defined phosphorylation process. Under conditions of oxidative stress, upstream kinases, primarily MAPK kinase 4 (MKK4) and MKK7, are stimulated. These kinases then modify the JNK by adding phosphate groups to specific tyrosine (Tyr-185) and threonine (Thr-183) residues in its activation loop which fully triggers its enzymatic activity (Feng et al., 2020). Once activated, JNK can translocate to the nucleus, where it regulates transcription factors such as c-Jun and activator protein-1 (AP-1). Its more direct and critical role during the development of insulin resistance occurs within the cytoplasm (Feng et al., 2020).

3.1.2. Phosphorylation-mediated Inhibition of Insulin Receptor Substrate (IRS) Proteins

The primary mechanism by which JNK induces resistance is through the direct inhibitory phosphorylation of IRS proteins, mainly IRS-1 and IRS-2 (Solinas & Becattini, 2016). These IRS proteins function as essential bridges that take the signal from the activated insulin receptor and pass it along to the rest of the cell's metabolic pathways. Normal insulin signalling requires the phosphorylation of IRS proteins on multiple tyrosine residues. However, activated JNK phosphorylates IRS-1 on several inhibitory serine residues, with serine-307 (Ser307) being one of the most well-characterised sites (Feng et al., 2020). This serine phosphorylation acts as a molecular brake; it creates a conformational change in the IRS-1 protein that sterically hinders its ability to bind to and be phosphorylated by the insulin receptor kinase (Solinas & Becattini, 2016). This effectively uncouples the insulin receptor from its downstream signalling cascade, representing a direct and potent

mechanism of stress-induced insulin desensitisation (Solinas & Becattini, 2016).

3.2. The IKKβ/NF-κB Pathway: Linking Inflammation and Metabolism

The inhibitor of κB (IκB) kinase β (IKKβ)/nuclear factor-κB (NF-κB) pathway is the master regulator of the innate immune and inflammatory responses (Hernandez & Zhou, 2021). Groundbreaking research has revealed that this pathway is the critical molecular connection between the sustained inflammatory state linked to obesity and its contribution to insulin resistance (Shoelson et al., 2003).

3.2.1. Oxidant-Mediated Activation of the IKKβ Complex

Similar to JNK, the IKK complex is activated by a range of metabolic and inflammatory stressors, including ROS, FFAs and cytokines (Yaribeygi et al., 2020). IKKβ is a key catalytic subunit responsible for mediating the standard pro-inflammatory signal (Hernandez & Zhou, 2021). In this inactive state, the transcription factor NF-κB remains dormant in the cytoplasm by its inhibitory binding partner, IκBα. Once activated by upstream signals, IKKβ phosphorylates IκBα on specific serine residues, which marks it for ubiquitination (degradation by proteosomes), thus leading to its degradation (Hernandez & Zhou, 2021).

3.2.2. NF-κB Driven Pro-inflammatory Cytokine Production and Insulin Desensitization

The degradation of IκBα releases NF-κB, enabling its movement into the nucleus. There, NF-κB binds to the promoter sequences of a vast array of effector genes, leading to the activation of genes encoding pro-inflammatory mediators, mainly cytokines (e.g., TNF-α, interleukin-6 [IL-6], chemokines, and adhesion molecules) (Feng et al., 2020). These secreted cytokines then act in an autocrine and paracrine fashion to further amplify the inflammatory state. This establishes a powerful positive feedback loop, with TNF-α serving as a potent activator of the JNK and IKKβ/NF κB signalling cascades, thus intensifying the insulin-resistant state (Feng et al., 2020). Beyond its indirect effects, activated IKKβ can directly disrupt insulin signalling. Much like JNK, it promotes phosphorylation of IRS-1 at certain serine sites, an action that hampers the protein's ability to transmit insulin's signal effectively, thereby contributing to the development of insulin resistance (Yaribeygi et al., 2020).

3.3. Attenuation of the PI3K/Akt Survival Pathway

Phosphoinositide 3-kinase (PI3K)/Akt serves as the main downstream signalling pathway responsible for most of the metabolic actions of insulin, including the stimulation of glucose uptake and glycogen production (Deepa Rajendiran et al., 2025).

3.3.1. The Central Role of PI3K/Akt in Insulin-Mediated Glucose Uptake

The insulin signalling process begins when insulin binds to its receptor located on the cell membrane. This binding activates the receptor's built-in tyrosine kinase function, which in turn phosphorylates the insulin receptor substrate (IRS) proteins at specific tyrosine residues (Styskal et al., 2012). These phosphorylated IRS proteins then act as docking points for the regulatory subunit of phosphoinositide 3-kinase (PI3K), bringing it to the plasma membrane and activating it. Once active, PI3K converts phosphatidylinositol (4,5)-bisphosphate (PIP2) into phosphatidylinositol (3,4,5)-triphosphate (PIP3), a key step in propagating the insulin signal within the cell (Li et al., 2024).

PIP3 acts as a second messenger, recruiting and facilitating the stimulation of the serine/threonine kinase Akt (protein kinase B) (Miao et al., 2022). Akt is a key protein that, once activated, adds phosphate groups to many other proteins. This action is what ultimately allows the cell to execute insulin's metabolic commands. A key target is the protein AS160 (Akt Substrate of 160 kDa), whose phosphorylation is the critical signal that triggers the translocation of intracellular vesicles containing the GLUT4 glucose transporter to the plasma membrane, thereby facilitating the entry of glucose into muscle and adipose cells (Deepa Rajendiran et al., 2025).

3.3.2. ROS-Mediated Inhibition of Key Components and Impaired GLUT4 Translocation

The PI3K/Akt pathway is the ultimate downstream pathway target and victim of the oxidative stress-activated JNK and IKKβ pathways. The inhibitory serine phosphorylation of IRS proteins by JNK and IKKβ prevents the recruitment and activation of PI3K, effectively breaking the signalling chain at one of its earliest steps (Deepa Rajendiran et al., 2025). This impairment of GLUT4 translocation is the direct cellular manifestation of insulin resistance in peripheral tissues. In addition to this signalling blockade, a high level of ROS may also cause direct oxidative damage to components of the pathway, such as PI3K itself, further contributing to its inactivation (Styskal et al., 2012).

The molecular events described reveal a highly integrated and pathological network. The stress kinases JNK and IKKβ are not independent; they are co-activated by the same upstream stressors (ROS, FFAs) and converge on the same critical signalling node: the inhibitory phosphorylation of IRS proteins. This convergence highlights that IRS

proteins act as a crucial meeting point where insulin's anabolic "grow and store" signal from insulin (mediated by tyrosine phosphorylation) directly competes with the catabolic "danger/stress" signal from the cellular environment (mediated by serine phosphorylation) (Solinas & Becattini, 2016). At a molecular level, insulin resistance is characterised as a condition where the stress-induced serine phosphorylation signal persistently dominates the insulin-induced tyrosine phosphorylation signal, effectively diminishing insulin's metabolic signals.

Figure 1:
Schematic Representation of insulin signalling and its disruption by free fatty acids (FFAs) and reactive oxygen species (ROS), Stress kinase activation (JNK1, p38 MAPK, CK-2) impairs IRS-1 signalling and redirects GLUT4 from the plasma membrane to lysosomes, leading to insulin resistance (Hurrle & Hsu, 2017).

4. Phytochemical Antioxidants as Potential Therapeutic Agents

In response to the central role of oxidative stress in insulin resistance, there is growing interest in the therapeutic use of antioxidants, especially those obtained from edible plants. These phytochemicals represent a vast and structurally diverse group of compounds that may offer a way to counteract the pro-oxidant state associated with T2DM.

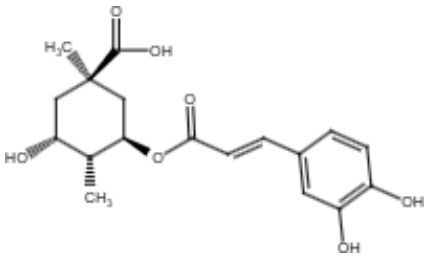
4.1. Major Classes of Phytochemical Antioxidants

Based on chemical structure and biological origin, plant-based antioxidants are generally classified into several main categories. A nutrient-rich diet including a variety of fruits, vegetables, whole grains, nuts and spices provides a complex mixture of these compounds (Lourenço et al., 2019).

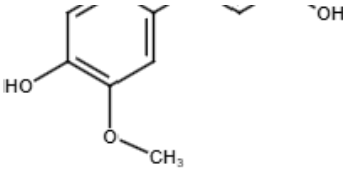
4.1.1. Polyphenols

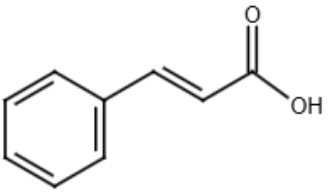
Polyphenols are a vast and heterogeneous class of plant secondary metabolites distinguished by having multiple phenolic groups within their structure. They are among the most abundant antioxidants in the human diet and are divided into several major subclasses (Lourenço et al., 2019):

- **Flavonoids:** This represents the largest class of polyphenols and comprises compounds such as quercetin (present in vegetables like onions and fruits like apples and berries), catechins (commonly found in green tea) and anthocyanins (which impart red, blue and purple colours to the berries, grapes and eggplant) (Lafay & Gil-Izquierdo, 2008).
- **Phenolic Acids:** These consist of compounds derived from benzoic acid, such as gallic acid found in tea and nuts, and from cinnamic acid, including chlorogenic acid present in coffee and ferulic acid in whole grains (Lafay & Gil-Izquierdo, 2008).
- **Stilbenes:** Predominantly present in grapes, red wine and peanuts, with resveratrol the best-characterised member of this class (Truong et al., 2018).
- **Lignans:** These compounds are present in significant amounts in seeds, notably flax and sesame, as well as in whole grains and a variety of vegetables (Soleymani et al., 2020; Touré & Xueming, 2010).



Chlorogenic acid





Ferulic acid

4.1.2. Carotenoids

Lipid-soluble carotenoids are responsible for the characteristic yellow, orange and red hues of fruits and vegetables. More than 600 different carotenoids have been characterised, which are classified into two main groups (Irwandi Jaswir, 2011):

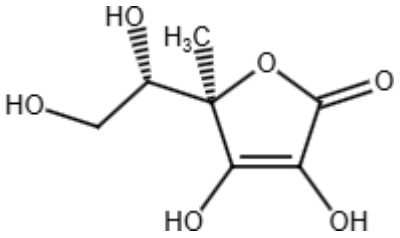
- **Carotenes:** These are pure hydrocarbons and include compounds like β-carotene (abundant in carrots, sweet potatoes and kale) and lycopene (abundant in tomatoes, watermelon and pink grapefruit) (Irwandi Jaswir, 2011). Certain carotenes, such as β-carotene, serve as precursors for vitamin A.
- **Xanthophylls:** Xanthophylls are the oxygenated derivatives and include lutein and zeaxanthin, which are predominantly present in green leafy produce like spinach and kale (Irwandi Jaswir, 2011).

4.1.3. Antioxidant Vitamins and Minerals

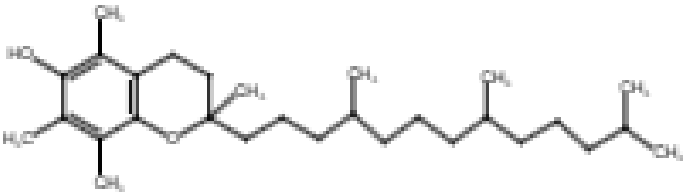
Several essential micronutrients either possess their own antioxidant properties (intrinsic) or serve as critical cofactors for the body's endogenous

antioxidant enzymes:

- **Vitamin C (Ascorbic acid)**: It serves as a highly effective water-soluble antioxidant present in citrus fruits, berries, kiwis and green peppers (Doseděl et al., 2021).
- **Vitamin E (Tocopherol and Tocotrienols):** A group of lipid-soluble antioxidants that protect cell membranes from damage. Key dietary sources include seeds, nuts, vegetable oils and green leafy vegetables (Shahidi et al., 2021).
- **Selenium, Zinc and Manganese:** These trace minerals do not act as direct antioxidants but are essential cofactors for key enzymatic antioxidants, such as glutathione peroxidase (selenium), superoxide dismutase (zinc, manganese) and catalase (Services, n.d.).



Ascorbic acid



α- Tocopherol

4.2. Mechanisms of Antioxidants Action: Beyond Radical Scavenging

While the term "antioxidants" often evokes the simple image of a molecule directly neutralising a free radical, the biological activity of many phytochemicals is far more complex and nuanced. While direct radical scavenging is a valid mechanism, many of their most significant effects are indirect, involving the modulation of cellular signalling pathways (Clemente-Suárez et al., 2025). This distinction is critical, as the often-low bioavailability of these compounds means they may not reach concentrations high enough for effective stoichiometric scavenging. Instead, they seem to function as signalling molecules that amplify the body's own defence systems.

Key indirect mechanisms include:

- **Upregulation of Endogenous Antioxidant Defences:** Several phytochemicals, including quercetin and curcumin, can stimulate the activation of transcription factor nuclear factor erythroid 2-related factor 2 (k). Nrf2 acts as a primary regulator of the antioxidant defence mechanism. Its activation results in upregulation of a range of protective genes, including those encoding endogenous antioxidant enzymes like catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx), as well as enzymes involved in glutathione synthesis (Szkudelski et al., 2025). This mechanism allows a single molecule of a phytochemical to trigger the production of thousands of enzyme molecules, providing a powerful and sustained protective effect.
- **Modulation of Pro-inflammatory Signalling:** As will be discussed in detail, compounds like resveratrol and quercetin can directly interfere with pro-inflammatory pathways by inhibiting key kinases like IKKβ and JNK, thereby suppressing the NF-κB activation and decreasing the release of pro-inflammatory cytokines (Szkudelski et al., 2025).
- **Chelation of Pro-oxidant Metal Ions:** Certain polyphenols are capable of chelating transition metal ions, including iron (Fe^{2+}) and copper (Cu^{+}). By chelating these metals, polyphenols prevent their involvement in Fenton and Haber-Weiss reactions that produce highly reactive hydroxyl radicals (·OH), one of the most reactive ROS (Shahidi & Danielski, 2024).

The physiochemical properties of these antioxidants also dictate their biological roles.

Lipid-soluble compounds like vitamin E and carotenoids are primarily incorporated into cell membranes and lipoproteins, where they are strategically positioned to inhibit oxidative degradation of lipids, which is a major type of oxidative stress-induced damage (Styskal et al., 2012). In contrast, water-soluble antioxidants like vitamin C function in the aqueous environments of the cytosol and extracellular fluid (Rajendiran et al., 2018). This compartmentalization highlights the need for a diverse dietary intake of various antioxidants to ensure the protection of all cellular domains, which may explain why clinical trials using high doses of a single antioxidant often fail to match the benefits seen with antioxidant-rich diets.

5. Efficacy of Specific Plant Antioxidants in Modulating Insulin Sensitivity

While a wide range of plant compounds exhibit antioxidant properties, several have been extensively studied for their specific effects on the molecular pathways underlying insulin resistance. The evidence for these compounds comes from a wide range of studies, from in vitro and animal models to human clinical trials. Although the findings are complex, they still offer a promising outlook for the therapeutic potential of these compounds. Table 1 provides a summary of key clinical trials, while Table 2 outlines the primary molecular targets and mechanisms of action for the major antioxidant classes discussed.

Table 1:
Summary of Key Clinical Trials on Plant-based Antioxidants and Glycemic Control (Abbreviations: RCT, Randomized Controlled Trial, T2DM, Type 2 Diabetes Mellitus; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; FBG, Fasting Blood Glucose; HbA1c, Glycated Hemoglobin; CRP, C-Reactive Protein; LPO, Lipid Peroxidase; GPx, [redacted]Peroxidase; CVD, Cardiovascular Disease)

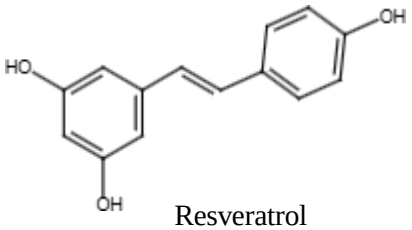
Table 2:
The diverse classes, sources, mechanisms, primarily molecular targets, significant drawbacks and scope of use of these compounds are summarised in this table.

5.1. Polyphenols: Multi-Target Agents in Diabetes Management

Polyphenols have attracted significant attention for their capacity to simultaneously modulate multiple cellular signalling networks. This multi-target approach is well suited for a complex, multifactorial disease like T2DM, potentially explaining why its effects are so robust in preclinical models compared to single-target antioxidants (Shahidi & Danielski, 2024).

5.1.1. Resveratrol

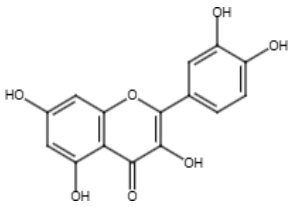
The antidiabetic properties of resveratrol are largely attributed to its potent activation of two key metabolic regulators: Sirtuin-1 (SIRT1) and AMP-activated protein kinase (AMPK) (Su et al., 2022). The SIRT1/AMPK signalling pathways play a central role in maintaining cellular energy homeostasis. Resveratrol-mediated activation of this pathway enhances mitochondrial biogenesis and function, promotes fatty acid oxidation and directly improves insulin sensitivity (Su et al., 2022). Additionally, it facilitates glucose uptake in peripheral tissues by upregulating and promoting the translocation of GLUT4 (Su et al., 2022). Although numerous animal studies support these effects, evidence from human clinical trials remains less consistent. Meta-analysis suggests that resveratrol supplementation may improve oxidative stress and inflammatory markers in patients with T2DM, yet its impact on direct measures of glycaemic control, such as HbA1c, has been variable, underscoring the need for larger, rigorously designed clinical trials (Zhu et al., 2025).



Resveratrol

5.1.2. Quercetin

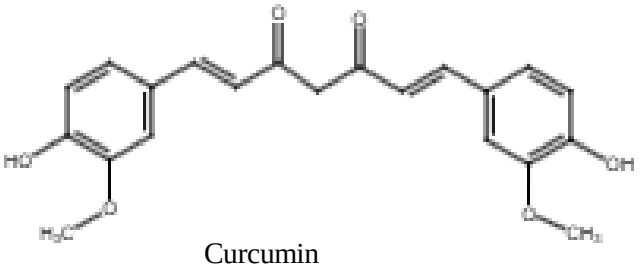
Quercetin demonstrates notable pleiotropy, exhibiting a broad spectrum of biological actions. One of the key benefits is the protection of pancreatic β-cells, where it enhances glucose-stimulated insulin secretion and shields these cells from oxidative damage, partly through activation of the ERK1/2 signalling pathway (Szkudelski et al., 2025). In peripheral tissues, quercetin addresses factors contributing to insulin resistance by inhibiting the IKK/NF-κB inflammatory pathway and activating the Nrf2 antioxidant defences (Szkudelski et al., 2025). Furthermore, quercetin can improve glucose utilisation by activating AMPK, which facilitates the translocation of GLUT4 to the muscle surface (Kuppusamy et al., 2024). Evidence from rodent diabetes consistently indicates that quercetin supplementation lowers blood glucose levels, preserves β-cell mass, and mitigates oxidative and inflammatory stress markers (Szkudelski et al., 2025).
Even though human intervention studies are less numerous, and their results obtained are mixed, the strong understanding of its mechanistic basis makes quercetin a highly promising candidate for further clinical investigations (Williamson & Sheedy, 2020).



Quercetin

5.1.3. Curcumin

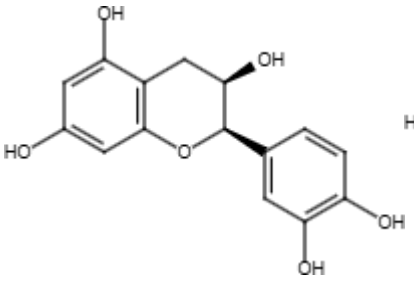
Curcumin, the principle curcuminoid in turmeric, exhibits potent antidiabetic properties through multiple mechanisms. Like other polyphenols, it acts as a powerful anti-inflammatory and antioxidant agent, capable of inhibiting the JNK and NF-κB pathways to protect pancreatic β-cells from glucotoxicity-induced apoptosis (Qihui et al., 2020). In peripheral tissues, curcumin enhances insulin sensitivity by upregulating glucose transporters and activating AMPK (GHorbani et al., 2014). Uniquely, curcumin has also been identified as a direct inhibitor of the 26S proteosome (Weisberg et al., 2016). The proteasome plays a key role in protein degradation, and its inhibition by curcumin may represent a novel mechanism for enhancing β-cell function and insulin sensitivity. In vivo studies in diabetic mice have demonstrated that dietary curcumin prevents hyperglycaemia, promotes insulin secretion and preserves β-cell mass (Weisberg et al., 2016). Collectively, extensive in vitro and animal research provides strong support for the therapeutic potential of curcumin in diabetes management (Den Hartogh et al., 2020).



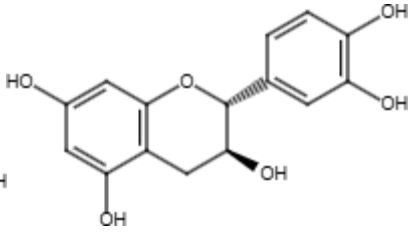
Curcumin

5.1.4 Green Tea Catechins

Green tea and its principle catechin, epigallocatechin (EGCG), have been widely investigated for their effects on glycaemic control, yet the findings remain inconsistent (Liu et al., 2014). Several meta-analyses of randomised controlled trials (RCTs) suggest that green tea supplementation can result in statistically significant reductions in fasting blood glucose, HbA1c and markers of insulin resistance (Toolsee et al., 2013). Conversely, other systematic reviews and meta-analyses report no significant impact on these parameters. This inconsistency is also evident in individual clinical trials; for instance, one study observed improvements in insulin resistance and GLP-1 levels following green tea extract supplementation, but these effects were not statistically significant compared to the placebo group. Such variability may arise from differences in study population, intervention durations, and the dose or formulation of green tea extract administered (Liu et al., 2014).



(-)-Epicatechin



(+)-Catechin

5.2. Carotenoids: Evidence from Epidemiological and Intervention Studies

The primary antidiabetic mechanism attributed to carotenoids is their powerful antioxidant activity. Due to their lipophilic nature, these molecules are able to embed themselves within cellular membranes and lipoproteins. In these locations, they are particularly effective at neutralising singlet oxygen and scavenging peroxyl radicals, thereby providing crucial protection against lipid peroxidation (Wu et al., 2022). Some preclinical studies also indicate that specific carotenoids, such as β-carotene, may directly enhance insulin signalling by promoting Akt phosphorylation and increasing GLUT4 expression (Wu et al., 2022).

The evidence from human research reveals a clear contradiction. Several extensive observational studies have consistently shown that individuals who consume diets rich in carotenoids exhibit a lower likelihood of developing type 2 diabetes mellitus (T2DM) and metabolic syndrome (*A Diet Rich in Carotenoids May Help Improve Insulin Sensitivity - American Society for Nutrition*, 2020). These findings imply a possible protective effect of carotenoid-containing foods. In contrast, results from randomised controlled trials (RCTs) using isolated carotenoid supplements have been largely

disappointing and, at times, worrisome. A recent meta-analysis indicated that carotenoid supplementation led to only modest reductions in fasting blood glucose and HbA1c, with the reliability of evidence considered very low (Shokri-Mashhadi et al., 2025). Additionally, major studies such as the Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study and the Carotene and Retinol Efficacy Trial (CARET) reported that high-dose β-Carotene supplementation failed to deliver cardiovascular benefits and, alarmingly, increased the risk of lung cancer and mortality among smokers (Corbi et al., 2022). This divergence suggests that the favourable associations seen in population studies may arise from synergistic interactions among various nutrients within whole foods or from other beneficial lifestyle patterns common in individuals consuming more fruits and vegetables, rather than from the effects of a single antioxidant compound administered at high doses.

5.3. Antioxidant Vitamins (C and E): A critical Re-evaluation of Clinical Evidence

Vitamins C and E serve as well-known examples of antioxidants that interrupt free radical chain reactions. Vitamin E, being lipid-soluble, plays a key role in defending cell membranes from lipid peroxidation, whereas the water-soluble Vitamin C neutralises radicals in the aqueous environment and helps restore Vitamin E to its active reduced form (Rajendiran et al., 2018). Because individuals with diabetes often exhibit reduced vitamin levels and elevated oxidative stress, supplementation with these antioxidants has been strongly suggested as a beneficial strategy (Tuell et al., 2023).

Despite this, the results from extensive randomised controlled trials (RCTs) have been mostly unsatisfactory. The majority of these studies have shown that supplementation with vitamin E or C does not produce significant improvements in blood glucose control or reduce cardiovascular complications in diabetic individuals (Chehade et al., 2009). Although certain smaller meta-analyses have noted minor reductions in fasting blood glucose and Hb1Ac following vitamin C intake, the reliability of this evidence is low, and its clinical relevance remains uncertain (Fong et al., 2022). This phenomenon, often termed the *antioxidant paradox*, highlights an important concern that excessive, non-physiological doses of single antioxidants may upset the body's redox balance and, under some conditions, even behave as pro-oxidants (Miller et al., 2005). Consequently, it is increasingly recognised that the health-promoting effects of an antioxidant-rich diet arise from the coordinated and synergistic activity of multiple phytochemicals present in whole foods, rather than from isolated, high-dose supplementation of individual vitamins.

6. Translational Challenges in Advancing Plant-Based Antioxidants for Diabetes Management

Despite the compelling scientific rationale and promising preclinical data for many plant-based antioxidants, their use in standard clinical practice for diabetes management has progressed exceptionally slowly. This gap between lab research and clinical use is a result of three major interconnected problems: poor bioavailability, a lack of consistent products and the risk of dangerous herb-drug interactions.

6.1. The Bioavailability Challenge: Absorption, Metabolism and Excretion

Bioavailability refers to the proportion of an administered compound that enters the systemic circulation in an active form capable of exerting a biological effect (Abourashed, 2013). A major challenge for most plant polyphenols is the low or extremely low oral bioavailability that is often estimated to be less than 10% and sometimes below 1% (Abourashed, 2013). This presents a major challenge, as it creates a significant disconnect between the high concentration often shown to be effective in in vitro cell culture experiments and the low nanomolar concentration typically achieved in human plasma after dietary intake (Stromsnes et al., 2021).

Several factors contribute to this poor bioavailability (Abourashed, 2013):

- **Poor Solubility and Stability:** Many polyphenols are poorly soluble (one part of solute to 1000 parts of solvent) in water and can be unstable in the harsh chemical environment of the gastrointestinal (GI) tract.
- **Limited Absorption:** The molecular structure and size of many polyphenols limit their ability to passively diffuse across the intestinal epithelium.
- **Extensive First-Pass Metabolism:** Once absorbed into intestinal enterocytes, and subsequently in the liver, polyphenols undergo extensive phase II metabolism. They are rapidly conjugated with glucuronic acid, sulphate or methyl groups, which facilitates their rapid excretion in urine and bile (Abourashed, 2013).

Due to this rapid metabolism and excretion, the parent compound, typically the form tested in vitro, exhibits a very short half-life and low circulating levels. This raises a critical scientific question: are the in vivo effects observed a result of these low concentrations of the parent compound, or are they predominantly driven by the metabolites produced by the host and the gut microbiota? Emerging evidence indicates that the key biological effects may be carried out by these metabolites, which can differ from the parent compound in both pharmacokinetics and molecular targets. This "metabolite versus parent compound challenge" implies that much of the current in vitro research may not accurately

reflect in vivo conditions, highlighting the need for a re-evaluation of how these compounds are investigated.

6.2. Standardization of Herbal Extracts: A Critical Hurdle in Clinical Research

Achieving consistent quality and reproducible effects is essential for both reliable therapeutic use and high-quality clinical studies. While this is easily accomplished with synthetic drugs, herbal extracts present a far greater challenge, which remains a significant obstacle to their widespread acceptance in evidence-based medicine (Kunle, 2012).

The key difficulties in standardisation include:

- **Inherent Chemical Complexity:** A single plant extract is not a single molecule but a complex mixture of hundreds or even thousands of different phytochemicals. In many cases, the specific compound or combination of compounds responsible for the therapeutic effect is unknown (Kunle, 2012).
- **Profound Natural Variability:** The chemical fingerprint of a plant is not static. It varies dramatically depending on the plant's genetics (species and cultivar), its growing conditions (soil composition, climate, altitude), the time of harvest and the specific part of the plant used (Kunle, 2012).
- **Lack of Universal Standards**: For most of the herbal products, there are no universally accepted pharmacopoeial monographs or reference standards that define their identity, purity, and potency. This makes it nearly impossible to ensure batch-to-batch consistency, rendering the comparison of results between different clinical trials exceptionally difficult (Patel, n.d.).

Addressing these challenges requires a comprehensive strategy that combines advanced analytical methods, such as High Performance Liquid Chromatography (HPLC) and Mass Spectroscopy (MS) for detailed chemical profiling, with strict compliance to Good Agricultural and Collection Practices (GACP) and Good Manufacturing Practices (GMP), ensuring the production of reliable and safe products appropriate for clinical research (Patel, n.d.).

6.3. Herb-Drug Interactions: Safety Considerations on Polypharmacy

Patients with T2DM are often managing multiple comorbidities and are typically prescribed several medications, such as oral hyperglycaemic agents (e.g., metformin), statins and antihypertensives. The concurrent use of herbal supplements in this population is common and raises significant safety concerns due to the potential for herb-drug interaction (Aluefua, 2017):

- **Pharmacokinetic Interactions:** These interactions occur when an herbal compound modifies the absorption, distribution, metabolism or excretion (ADME) of a conventional drug. A primary mechanism of concern is the modulation of cytochrome P450 (CYP) enzymes in the liver and intestine. Many phytochemicals can either inhibit or induce specific CYP enzymes (e.g., CYP3A4, CYP2C9). Inhibition can lead to dangerously elevated levels of a co-administered drug, increasing the risk of toxicity, while induction can accelerate a drug's metabolism, reducing its concentration and rendering it ineffective (Aluefua, 2017).
- **Pharmacodynamic Interactions:** These occur when an herb and a drug have additive, synergistic, or antagonistic effects at the site of action. For example, an herb with intrinsic hypoglycaemic properties, when taken with a sulfonylurea or insulin, could potentiate the drug's effect and lead to a severe hypoglycaemic event. Conversely, some herbs may antagonise the action of antidiabetic drugs, compromising glycaemic control (Aluefua, 2017).

Given the prevalence of polypharmacy in the diabetic population, the risk of these interactions is a major barrier to the safe integration of herbal antioxidants into clinical care. Clinicians must be vigilant in questioning patients about their use of supplements, and further research is desperately needed to characterise these potential interactions.

7. Future Perspectives and Emerging Therapeutic Strategies

Overcoming the formidable translational hurdles facing plant-based antioxidants will require innovative scientific approaches. Three emerging fields – nanotechnology, microbiome science, and nutrigenomics – hold particular promise for unlocking the therapeutic potential of these natural compounds and moving towards a new paradigm of evidence-based, personalised nutritional medicine for diabetes.

7.1. Nanotechnology-based Delivery Systems for Enhanced Bioavailability

Nanotechnology offers a revolutionary platform to directly address the critical challenge of poor bioavailability that plagues many promising phytochemicals (Kılınç & Açar Kuru, 2025). By encapsulating antioxidant compounds within nano-carriers (typically between 1 and 100 nm in size), it is possible to dramatically improve their pharmacokinetic properties (Kathole et al., 2025).

Several types of nano-delivery systems are being actively investigated (Kathole et al., 2025):

- **Liposomes**: Liposomal vesicles are nanoscale or microscale, spherical carriers formed by one or more concentric lipid bilayers, capable of entrapping hydrophilic agents within their aqueous core while simultaneously

incorporating lipophilic molecules into the lipid phase.

- **Polymeric nanoparticles:** Solid colloidal particles made from biodegradable polymers that can entrap or adsorb the active compound.
- **Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLC):** Lipid-based
- carriers that are solid at room temperature, offering better stability than emulsions or liposomes.
- **Nanoemulsions:** Finely dispersed oil-in-water or water-in-oil systems at the nanometre scale, promoting greater surface area and improved absorption efficiency.

These nanoscale delivery systems have the potential to improve the effectiveness of plant-derived antioxidants by (Silva et al., 2013):

- **Improving solubility:** Encapsulation of compounds with low water solubility within a carrier can substantially improve their distribution in aqueous solutions.
- **Protecting from Degradation:** The carrier can shield the antioxidant from the harsh acidic and enzymatic environment of the gastrointestinal tract.
- **Enhancing absorption:** Intestinal uptake of nanoparticles is enhanced through different endocytosis pathways.
- **Enhancing Targeted Delivery:** Nanocarrier surfaces can be modified with ligands that specifically recognise and bind to receptors on target cells, enabling tissue-specific delivery while minimising off-target effects.

Through improved bioavailability and precise targeted delivery, nanotechnology has the potential to boost the efficacy of plant antioxidants, permitting lower effective doses and reducing the likelihood of adverse effects (Kılınç & Açar Kuru, 2025).

7.2. The Gut Microbiome: A Key Mediator of Polyphenol Bioactivity

Comprising trillions of microorganisms, the human gut microbiome is increasingly regarded as a critical organ with profound effects on host metabolism and health (Jang & Lee, 2021). Dietary polyphenols and the gut microbiota engage in a dynamic, two-way interaction that is central to mediating their biological effects (Corrêa et al., 2019).

- **Metabolism of Polyphenols by the Microbiota:** The majority of dietary polyphenols (>90%) are poorly absorbed in the small intestine due to their structural complexity or glycosylation. Consequently, they reach the colon largely unaltered, where they are extensively metabolised by the gut microbiota (Corrêa et al., 2019). Gut bacteria harbour a diverse set of enzymes capable of degrading complex polyphenols into simpler phenolic compounds, such as phenolic acids and urolithins. These microbial metabolites are often more readily absorbed into systemic circulation and may be more biologically active than their parent compounds (Corrêa et al., 2019). This reframes the gut microbiome as a personalised "bioreactor" or "drug factory". The health benefit derived from a particular polyphenol-rich food may depend less on the food itself and more on the interaction between the food and an individual's unique microbial composition. This helps explain the high inter-individual variability observed in the clinical studies and suggests the future interventions may require a symbiotic approach, co-administering a polyphenol with a specific probiotic strain to ensure the desired metabolic conversion occurs.
- **Modulation of the Microbiota by Polyphenols:** Polyphenols and their metabolites can exert prebiotic effects, influencing both the composition and function of the gut microbiota. They have been reported to selectively enhance the growth of beneficial bacteria, such as Bifidobacterium and Lactobacillus, while suppressing potentially pathogenic strains (Corrêa et al., 2019). By alleviating gut dysbiosis commonly observed in T2DM, polyphenols may help restore gut barrier integrity, reduce the translocation of pro-inflammatory bacterial components like lipopolysaccharide (LPS), and mitigate chronic low-grade inflammation associated with insulin resistance (Corrêa et al., 2019).

7.3. Nutrigenomics and Personalized Nutrition: Precision Approaches to Antioxidant Therapy

The conventional 'one-size-fits-all' model for dietary guidance is being increasingly questioned by nutrigenomics and personalised nutrition. Nutrigenomics focuses on how nutrients and bioactive food components interact with an individual's genome to regulate gene expression, thereby affecting phenotype and altering disease risk (Felisbino et al., 2021).

It is now recognised that plant-derived antioxidants, especially polyphenols, can function as epigenetic modulators. They are capable of affecting DNA methylation and histone modifications, thereby regulating the expression of critical genes involved in glucose transport, insulin signalling, lipid metabolism, and endogenous antioxidant and inflammatory pathways (Felisbino et al., 2021).

This gene-nutrition interaction forms the basis for personalised nutrition, an approach that aims to provide dietary recommendations tailored to an individual's unique biological makeup (Munawaroh et al., 2025). Individual responses to dietary

interventions are highly variable, largely due to differences in genetic factors (e.g. single nucleotide polymorphisms in metabolic genes), metabolic profiles, and the composition of the gut microbiome (Munawaroh et al., 2025). By integrating data from these "omics" platforms – genomics, transcriptomics, and metagenomics – it may become possible to predict an individual's response to specific foods and nutrients (Munawaroh et al., 2025).

This leads to a future vision for a truly synergistic and personalised therapeutic pipeline. First, nutrigenomic and microbiome analyses could identify which specific antioxidant or, more likely, which microbial metabolite is more effective for a given individual's unique biological profile. Then, nanotechnology could be employed to create a targeted delivery system for that specific, personalised compound, ensuring it reaches its target tissue at a therapeutic concentration. Such an integrated approach surpasses conventional dietary guidelines, moving toward a precision medicine model that maximises the preventive and therapeutic benefits of plant-based antioxidants in managing T2DM (Chehade et al., 2009).

8. CONCLUSION

The worldwide increase in type 2 diabetes mellitus constitutes a complex public health challenge, necessitating novel and effective management approaches. At the core of its pathophysiology lies insulin resistance, a complex metabolic state driven by a vicious cycle of hyperglycemia, lipotoxicity and chronic inflammation. This review has established oxidative stress as a central and unifying pathogenic principle, activating specific stress-sensitive signalling cascades – notably the JNK and IKKβ/NF-κB pathways – that converge to directly impair the insulin signalling machinery at the levels of IRS proteins.

Plant-derived antioxidants, especially polyphenols such as resveratrol, quercetin, and curcumin, demonstrate significant preclinical potential not merely as free radical scavengers but as complex modulators of cellular networks that can mitigate pathological pathways, protect pancreatic β-cells, and improve insulin sensitivity. However, this promise is currently tempered by a triad of formidable translational hurdles: poor bioavailability, a profound lack of standardisation for herbal extracts, and significant risk of herb-drug interactions. These interconnected challenges largely explain the frequent failure to translate compelling benchtop findings into successful bedside therapies and underscore the limitations of using high-dose, single-agent vitamin supplements, which have consistently failed to deliver on their initial promise.

The path forward, however, is not barred. The integration of emerging scientific fields offers a clear and synergistic strategy to overcome these obstacles. Nanotechnology-based delivery systems provide a powerful tool to enhance the bioavailability and targeted delivery of these natural compounds. A deeper understanding of the gut microbiome as a personalised "bioreactor" is revolutionising our view of polyphenol metabolism, highlighting the critical role of microbial metabolites in mediating bioactivity. Finally, the advent of nutrigenomics and personalised nutrition provides a framework for tailoring antioxidant interventions to an individual's unique genetic and microbial profile. By integrating these advanced approaches together, researchers and clinicians can advance beyond conventional dietary advice toward targeted, evidence-driven nutritional interventions, maximising the benefits of plant-derived antioxidants for the prevention and management of type 2 diabetes mellitus.

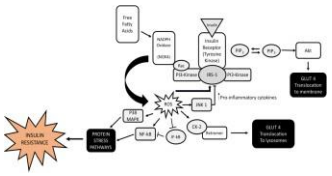


Figure 1:
Schematic Representation of insulin signalling and its disruption by free fatty acids (FFAs) and reactive oxygen species (ROS), Stress kinase activation (JNK1, p38 MAPK, CK-2) impairs IRS-1 signalling and redirects GLUT4 from the plasma membrane to lysosomes, leading to insulin resistance (Hurrle & Hsu, 2017).

Class	Antioxidant/Source	Study design	Population characteristics	Key outcomes	Certainty of evidence	Reference
Polyphenols	Cocoa Flavanols [(-)-Epicatechin]	Meta analysis of RCTs	Healthy and hypertensive	↓ s -IR, ↓ fasting insulin	Moderate	(Williamson & Sheedy, 2020)
	Anthocyanins	Meta analysis of RCTs	T2DM, Overweight/Obese	↓ HOMA-IR, ↓ fasting insulin	Moderate	(Williamson & Sheedy, 2020)
	Resveratrol	Meta analysis	T2DM, Obese	↓CRP, ↓LPO,	Low to	(Zhu et al.,

		of RCTs		↑GPx, ↑catalase; inconsistent effects on glycaemic markers	very low	2025)
Carotenoids	Mixed Carotenoids	Meta-analysis of RCTs	General, T2DM	↓FBG, ↓HbA1c	Very low	(Shokri-Mashhadi et al., 2025)
	β-Carotene	Meta-analysis of RCTs	General, Smokers	No benefit or increased risk of mortality (Lung cancer, CVD)	Moderate (for harm)	(Corbi et al., 2022)
	Lycopene	Meta-analysis of RCTs	T2DM	↓FBG in T2DM patients; inconsistent overall	Low to very low	(Leh et al., 2021)
Vitamins	Vitamin C (Ascorbic acid)	Meta-analysis of RCTs	T2DM	↓FBG, ↓HbA1c, ↓post-prandial glucose	Very low	(Fong et al., 2022)
	Vitamin E (Tocopherol)	Meta analysis of RCTs	T2DM, CVD risk	Generally no significant benefit on glycaemic control; mixed results on complications	Low (for no effect)	(Chehade et al., 2009)

Table 1:
Summary of Key Clinical Trials on Plant-based Antioxidants and Glycemic Control (Abbreviations: RCT, Randomized Controlled Trial, T2DM, Type 2 Diabetes Mellitus; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; FBG, Fasting Blood Glucose; HbA1c, Glycated Hemoglobin; CRP, C-Reactive Protein; LPO, Lipid Peroxidase; GPx, Glutathione Peroxidase; CVD, Cardiovascular Disease)

Antioxidant class	Sub-class/representative compounds	Mechanism of Action	Primary molecular Targets	Significant Drawbacks	Scope of Use	Key Dietary sources
Polyphenols	Flavonoids (Quercetin, Catechins & Anthocyanins), **Phenolic acids** (Ferulic acid, Caffeic acid), **Stillbenes** (Resveratrol)	Increases insulin sensitivity, decreases inflammation, and increases antioxidant defence.	IRS, NF-κB, AMPK, Nrf2	Suboptimal Bioavailability, Metabolism-Linked Outcomes	Personalised dietary interventions as an adjunct Therapy	Onions, apples, green tea, berries, citrus fruits, red wine, dark chocolate

Carotenoids	**Carotenes** (β-Carotene, Lycopene), **Xanthophylls** (Lutein, Zeaxanthin)	Singlet oxygen quenching, light filtering (in macula), Attenuation of Lipid Peroxidation	Nrf2, mitochondrial ROS	Lipophilicity is influenced by the composition and structure of the food matrix.	Ocular-related complications (e.g., diabetic retinopathy), Support for vascular function	Carrots, sweet potatoes, tomatoes, watermelon, Leafy greens (spinach, kale), corn, egg yolk
Vitamins	Vitamin C (Ascorbic Acid), Vitamin E (alpha-tocopherol)	Water-soluble radical scavenger, regenerates oxidised vitamin E, enzyme cofactor	Nrf2, NF-κB, NOS	efficacy of the intervention varies; it is observed once certain threshold levels are reached	Adjunct anti-oxidant therapy	Citrus fruits, bell peppers, berries, kiwi, broccoli, Nuts, seeds, vegetable oils, leafy greens

Table 2:
The diverse classes, sources, mechanisms, primarily molecular targets, significant drawbacks and scope of use of these compounds are summarised in this table.

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Lastly, we are grateful for the cooperation, teamwork, and dedication of all group members, without whom this literature review would not have been possible.

ABBREVIATIONS

AGEs – Advanced Glycation End Products
Akt - Protein Kinase B
AMPK – AMP-Activated Protein Kinase
AP-1 – Activated Protein – 1
AS160 – Akt Substrate of 160 kDA
ATBC – Alpha-Tocopherol Beta-Carotene
CVD – Cardiovascular Disease
CAT – Catalase
CARET – Carotene and Retinol Efficacy Trial
CYP – Cytochrome P450
CRP – C-Reactive Protein
DAG – Diacyl Glycerol
DNL – De Novo Lipogenesis
EGCG – Epigallocatechin galate
ERK 1/2 – Extracellular Signal – Regulated kinase 1/2
FFAs – Free Fatty Acids
FBG – Fasting Blood Glucose
GLP 1 – Glucagon–like peptide 1
GLUT 4 – Glucose Transporter type 4
GI - Gastrointestinal
GACP – Good Agricultural and Collection Practices
GMP – Good Manufacturing Practices
GPx – Glutathione Peroxidase
HbA1C – Glycated Haemoglobin
HGP – Hepatic Glucose Production
HOMA-IR – Homeostatic Model Assessment of Insulin Resistance
HPLC – High Performance Liquid Chromatography
IKK-β – Inhibitor of κB Kinase β
IκBα – Inhibitor of κBα
IL-6 – Interleukin 6
IR – Insulin Resistance
IRS – Insulin Receptor Substrate
JNK – c-Jun N-terminal Kinase
LMIC – Low-and-middle income countries
LPO – Lipid Peroxidation
LPS – Lipopolysaccharide
MAPK – Mitogen-Activated Protein Kinase
MKK-4/7 – MAPK Kinase 4/ MAPK Kinase 7
MS – Mass Spectroscopy
NF-Ƙb – Nuclear Factor Kappa-B
NLC – Nano structured Lipid Carrier
Nrf-2 – Nuclear Factor Erythroid 2 – Related Factor 2

NOS – Nitric Oxide Synthase
PKC – Protein Kinase C
PKC-θ – Protein Kinase C – Theta
PKC-ε – Protein Kinase C – Epsilon
PI3K – Phosphoionosityl-3 Kinase
PIP 2 – Phophotidylionositol (4,5)-bisphosphate
PIP 3 – Phosphotidylionositol (3,4,5)-triphosphate
RCT – Randomized Control Trial
RNS – Reactive Nitrogen Species
ROS – Reactive Oxygen Species
SIRT 1 – Sirtuin -1
SNLs – Solid Lipid Nanoparticles
SOD – Superoxide Dismutase
T2DM – Type 2 Diabetes Mellitus
TNF-α – Tumour Necrosis Factor Alpha
β-cells (Pancreatic)

CONFLICT OF INTEREST

The authors state that there are no conflicts of interest related to this manuscript.

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