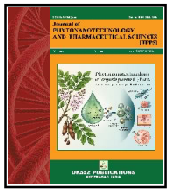
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Inflammatory markers in diabetes: Biomarkers, pathophysiology, and phytochemical interventions

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Abstract

Diabetes mellitus, particularly type 2 diabetes (T2D), is characterised by chronic low-grade inflammation that drives insulin resistance, β-cell dysfunction, and microvascular and macrovascular complications. This review examines inflammatory biomarkers including interleukin-6 (IL-6), C-reactive protein (CRP), tumour necrosis factor-α (TNF-α), and transforming growth factor-β1 (TGF-β1), alongside emerging candidates including immunoglobulin free light chains (FLCs), EN-RAGE/S100A12, and the neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios (NLR/PLR), detailing their cellular sources, signalling mechanisms, and associations with diabetic complications. Inflammatory activation escalates progressively from normoglycaemia through prediabetes to T2D, with hyperglycaemia amplifying cytokine production via NF-κB, MAPK, and JNK pathways. TGF-β1 links hyperglycaemia to renal fibrosis; EN-RAGE correlates with insulin resistance; FLC λ and κ/λ ratios offer urine-based inflammatory readouts; NLR and PLR show utility in diabetic retinopathy risk stratification. The review further evaluates phytochemicals, including berberine, resveratrol, curcumin, EGCG, quercetin, and related polyphenols, that attenuate these inflammatory pathways and improve metabolic outcomes in preclinical models. Collectively, the evidence supports biomarker-guided prediction of diabetic complications and positions anti-inflammatory phytochemicals as candidate adjunct therapies warranting clinical investigation.

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder with an increasing global burden and substantial medical and economic consequences, partly because of its associated complications (Pickering *et al.,* 2018; Siddiqui *et al.,* 2022). People with type 2 diabetes (T2D) are particularly susceptible to chronic kidney disease (CKD), which is associated with increased morbidity and mortality (Waheed and Manik, 2024). Diabetic retinopathy (DR) is a major microvascular complication and an important cause of vision loss in working-age adults (Gong and Su, 2017; Stitt *et al.,* 2016). Increased formation of advanced glycation end products (AGEs) contributes to the development and complexity of atherosclerotic plaques and the cardiovascular risk associated with diabetes (Nabi *et al.,* 2019). Inflammation is also closely associated with the development and progression of T2D, with interleukin-6 (IL-6) and C-reactive protein (CRP) among the most extensively studied markers (Doi *et al.,* 2005; Wannametheet *al.,* 2007). IL-6 is released by activated leukocytes, endothelial cells and adipocytes, whereas CRP is an acute-phase protein produced mainly in the liver (Donath and Shoelson, 2011; Gabay, 2006). The availability of sensitive assays and the stability of CRP during storage facilitate its use in epidemiological research (Donath and Shoelson, 2011). This review examines inflammatory biomarkers alongside plant-derived compounds investigated for diabetes and its complications (Quratul-ain *et al.,* 2024; Siddiqui *et al.,* 2022).

2. Inflammatory markers

Numerous inflammatory illnesses, includinginflammatory bowel disease, psoriasis, SLE, and rheumatoid arthritis (RA), are associated with elevated levels of the C5a protein, a powerful inflammatory mediator. Crucially, C5a promotes tissue factor activity and adhesion molecule production in endothelial cells, which contributes to coagulation. A recent study discovered that prediabetic individuals consistently had higher levels of inflammatory markers like CRP, IL-6, and C5a (Maschirow *et al.,* 2015)**.** In the prediabetic condition, this results in elevated coagulation activity, exacerbating subsequent cardiovascular problems.A recent study, the Women's health study, initiated in 1992, discovered a link between higher initial blood levels of IL-6 and CRP and the onset of T2D.

Measurements of inflammatory markers, such as white blood cell count, granulocytes, monocytes, CRP, IL-18, and IL-1 receptor antagonist (IL-1RA), as well as neopterin, showed a significant increase in the inflammatory reaction among individuals with prediabetes and diabetes (Grossmann *et al.,* 2015)**.** The profile of inflammatory and immunological biomarkers changed as the glycemic state changed from normoglycemic to prediabetes to T2D. Being able to differentiate between the initial preclinical and clinical stages, as well as the illness's effects and progression, could be beneficial. Acute-moderate hyperglycemia was associated with elevated levels of pro-thrombotic factors (plasminogen activator inhibitor-1 and P-selectin), atherogenic vascular adhesion molecules (VCAM, ICAM, and E-selectin), and IL-6 response(Perkins *et al.,* 2015)**.** This indicates that in non-diabetic overweight and obese people, there is an increase

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in proinflammatory and proatherogenic indicators as well as the activation of strong systemic cytokines. In contrast, these benefits were reversed upon exposure to acutely elevated physiological insulin levels, which is consistent with findings from a prior investigation.

2.1 Cytokines

Cytokines in prediabetes: Organs that emit the proinflammatory cytokine IL-6 include adipocytes, endothelial cells, and activated leukocytes (Jansen *et al.,* 2018)**.** In both human and mouse models, it has been demonstrated to cause hyperglycemia and compensatory hyperinsulinemia. On the other hand, hyperglycemia can directly promote the upregulation of adhesion molecules, cytokines, and chemokines, altering several pathways that lead to NF-κB signalling (Nishida and Otsu, 2017). Significant elevations in high-mobility group box 1 (HMGB1) protein levels were observed in both isolated heart cells and immune cells that had been subjected to elevated blood sugar concentrations. Tshe overactivation of the MAPK and NF-κB signaling pathways resulted in an increase in the release of TNF-α and IL-6 (Wang *et al.,* 2014). TNF-α is a cytokine that causes inflammation, which makes it harder for the body to use insulin by affecting how the GLUT 4 transports glucose and by altering the IRS-1 signaling pathway. TNF-α has a crucial role in lipid metabolism, and was previously referred to as cachectin due to its association with cachexia, a condition linked to several diseases (Akash *et al.,* 2018)**.** Individuals undergoing treatment with a TNF-α inhibitor for psoriasis or rheumatoid arthritis (RA) commonly experience weight gain.

Etanercept treatment has been found to alleviate oxidative stress and lipid peroxidation in patients with psoriasis.Throughout the treatment period, a significant improvement in plasma total antioxidant capacity was observed, accompanied by a rise in paraoxonase-1 (PON-1) activity, an anti-inflammatory enzyme associated with high-density lipoproteins (HDL).TNF-α controlled signaling pathways exhibit a dual nature, encompassing both pro-inflammatory and anti-inflammatory characteristics, with the CKII-SIRT1-SM22a pathway being upregulated in response to TNF-α (Shu *et al.,* 2017)**.**Studies have shown that the expression of SM22a can suppress the inflammatory response in vascular smooth muscle cells, with both laboratory-based and animal-based experiments demonstrating this phenomenon (Shu *et al.,* 2017)**.**

Insulin resistance and prediabetes are significantly influenced by immune cell infiltration of adipose tissue. M1-like phenotypic macrophages exhibit proinflammatory characteristics, whereas M2-like phenotypic macrophages are responsible for the secretion of anti-inflammatory cytokines, including TGF-β and IL-10, which function to mitigate inflammation and enhance insulin sensitivity within adipose tissue (Guzik and Cosentino, 2018)**.** In mouse studies, more macrophages were found in the fat tissue of animals with insulin resistance compared to those without the condition.

Macrophages that invade visceral adipose tissue have been observed to increase serum insulin levels. T regulatory cells, known for their anti-inflammatory properties, are also found in normal adipose tissue. Studies indicate that these cells could potentially possess an insulin receptor and secrete TGF-beta and IL-10 (Guzik and Cosentino, 2018). Excessive insulin levels impair the ability of T regulatory cells to suppress inflammatory responses. In this region, Th2 cells release anti-inflammatory cytokines such as IL-4, IL-10, IL-13, and IL-5 (Guzik *et al.,* 2017).

2.2 Interleukin-6 (IL-6)

IL-6 is a cytokine that drives the transition from acute to chronic inflammation by changing the composition of white blood cells that infiltrate tissues, shifting from neutrophils to monocytes/ macrophages, and also enhances T- and B-cell activity, which leads to increased antibody production, ultimately contributing to a chronic inflammatory response (Rehman *et al.,* 2017)**.**

IL-6 functions in conjunction with IL-1β and TNF-α to influence the immune system, the acute phase response, inflammation, and the proliferation and development of hematopoietic cells and embryonic stem cells. IL-6 has been linked to diabetic retinopathy in several studies. Although, we did observe some indications of a positive link between PDR and IL-6 in this investigation, there were not enough samples above the IL-6 detection level to support additional statistical analysis. Patients with macrovascular disease or nephropathy also had greater levels of IL-6, suggesting that more research on this molecule's role in vascular consequences in diabetes may be necessary (Yao *et al.,* 2019)**.**

In terms of probable additional sources of cytokine production, plasma IL-6 levels were shown to be associated with BMI in diabetic participants, indicating that adipose tissue may be a source of production. Previous research also suggests that complicated regulatory mechanisms reduce cytokine production in the blood. Research indicates that specific acute-phase proteins, such as CRP, serum amyloid A, and IL-6, which we have previously found to be elevated in T2D, exhibit anti-inflammatory and immunosuppressive capabilities, aiding in the resolution of inflammation (Bowker *et al.,* 2020)**.**

2.3 TGF-β1

Studies have discovered a link between hyperglycemia and increased TGF-β1 expression *via* various routes (Heydarpour *et al.,* 2020). TGF-β1 is also important for immunological function. TGF-1β is involved in the processes of differentiation, chemotaxis, cell survival, and lymphocyte proliferation. It also governs leukocyte activity, and the disruption of this regulatory function can result in autoimmune conditions such as type 1 diabetes mellitus (T1DM). TGF-β1 targets T lymphocytes, which destroy insulin-producing β cells in type 1 Diabetes. Blocking TGF-β1 signalling in mice resulted in an autoimmune phenotype, including T cell activation and differentiation. TGF-β1 prevents the development of T1DM in β cells by regulating insulin promoter expression (Lee *et al.,* 2020)**.**

Several diabetic complications, including diabetic neuropathy and impaired wound healing, have been associated with disruptions in the TGF-β1 signalling pathway. Several key features of diabetic neuropathy include glomerular sclerosis, tubulointerstitial fibrosis, alterations to the extracellular matrix (ECM), and mesangial expansion. TGF-β1 plays a crucial role in the development of fibrosis in diabetic nephropathy, as evident from the increased expression of TGF-β1 in the kidneys of individuals with prolonged exposure to high blood sugar levels, both in humans and animal studies (Wu *et al.,* 2015)**.** Researchers Braga Gomes *et al*. have identified TGF-β1 as a traditionally anti-inflammatory immune mediator. In the presence of IL-6, a cytokine that frequently appears before the onset of T2D, TGF-β1 modifies its function, promoting the formation of T helper 17 (Th17) cells, a specific type of immune cell linked to pro-inflammatory conditions. Studies by Hydarpoor*et al.* found that

high levels of pro-inflammatory cytokines in PBMCs play a significant role in causing damage to the blood vessels of people with T2DM, leading to insulin resistance and β cell dysfunction.A number of previous studies have identified a correlation between the duration of type 1 diabetes in children and adolescents and the subsequent occurrence of vascular complications, which can be associated with their TGF-β1 serum levels (Zorena *et al.,* 2013)**.** Researchers led by El-Sherbini discovered that high blood sugar levels trigger the activation of glucose transporter-1. The kidneys' cells, especially mesangial tubular cells or invading renal cells, produce more TGF-β1 in patients with T2D.

2.4 Tumor necrosis factor-α (TNF-α)

TNF-α is a pro-inflammatory cytokine produced mainly by monocytes and macrophages, with adipocytes also contributing. It disrupts insulin signalling and glucose metabolism and has been implicated in obesity-related insulin resistance and T2D (Akash *et al.,* 2018; Liu *et al.,* 2016). Experimental models also implicate TNF-α in diabetic renal injury. In streptozotocin-induced diabetic rats, glomerular TNF-α mRNA increased during disease progression and reached 4.2-fold the control level at 24 weeks (Nakamura *et al.,* 1993). In patients with T2D and cardiac autonomic neuropathy, α-lipoic acid treatment was associated with reductions in circulating TNF-α and other inflammatory indices (Serhiyenko*et al.,* 2020). In rats with experimental diabetes, citral treatment reduced inflammatory factors and downregulated hepatic TNF-α and IL-6 expression (Zarandi *et al.,* 2021). These observations do not establish a uniform relationship between circulating TNF-α, BMI and diabetes duration.

2.5 C-reactive protein (CRP)

The primary mediator of the acute phase response in downstream processes is CRP, which is produced in the liver and relies on IL-6 for its production. This marker is among the most thoroughly researched indicators of inflammation associated with prediabetes, diabetes, and the cardiovascular conditions linked to them (Luc *et al.,* 2019)**.** Its primary functions include regulating platelet activation, increasing leukocyte activity, and fixing complement. CRP levels were observed to be much higher in prediabetics than in normoglycemic individuals. However, when diabetic and prediabetic patients were compared, CRP increased just slightly. This shows that even in cases of prediabetes, initial low-grade inflammation is common, which can be detected by a rise in CRP levels.

Polymorphisms in the promoter's noncoding and untranslated regions have a significant impact on baseline CRP levels. Variations in the IL-6 and IL-1 genes, which lead to increased CRP production, also affect baseline CRP concentrations. Many single-nucleotide polymorphisms (SNPs) in the CRP gene are frequently co-inherited, resulting in the formation of five primary haplotypes. Two of these conditions are linked to higher baseline CRP levels, whereas two others are associated with lower baseline levels.These haplotypes also impact CRP levels during acute-phase responses and are associated with an increased risk of various diseases (Luc *et al.,* 2019)**.**

In humans, the CRPis crucial in the acute-phase response to inflammation, infection, or tissue damage, with plasma levels rising as much as 1,000-fold within a time frame of 24 to 72 h. Several types of cells, including neurons, epithelial cells, monocytes, lymphocytes, and smooth muscle cells, exhibit CRP expression; however, the gene responsible for CRP is primarily activated in hepatocytes in response to elevated levels of pro-inflammatory cytokines, mainly IL-6.Notably, CRP produced in extrahepatic tissues does not significantly contribute to circulating plasma levels. CRP has an approximate half-life of 19 h, and its concentration is typically reported in mg/l or mg/dl. However, laboratory results may vary due to the absence of a universally standardized reference range. Typically, CRP values under 0.3 mg/dl are deemed normal, whereas levels above 10 mg/dl suggest bacterial or viral infections or substantial tissue damage (Stanimirovic *et al.,* 2022)**.**

CRP can be detected and quantified through several methods. The most employed method in clinical settings is immunoturbidimetry. ELISA and FLISA, which are conventional measurement methods, are also commonly employed for quantifying CRP levels. These methods frequently incorporate intricate protocols and are not economically viable. New advancements have led to the development of quantum dot-based FLISA and His-tag-HRP functionalized nanoconjugate-based immunoassays incorporating CdSe/ZnS, resulting in significant improvements. The latest techniques exhibit increased sensitivity, faster processing times, and a wider range of detection in serum samples. Additionally, they achieve lower limits of detection (LOD), enabling earlier identification of CRP-a key factor in timely diagnosis. Innovative platforms such as electro chemical biosensors and microfluidic sensor systems further support these diagnostic needs (Rhodes *et al.,* 2011)**.**

CRP levels closely reflect the presence and resolution of inflammatory stimuli. It has a well-established function as a biomarker for diagnosis and prognosis, both in acute infections and chronic diseases such as hepatitis C, T2D, atherosclerosis, and several types of cancer. Additionally, there is mounting evidence linking the underlying processes of T2D to complement system activation (Siddiqui *et al.,* 2022)

2.6 Immunoglobulin-free light chain (FLC) (Novel biomarkers)

Preliminary examination of urine samples showed a connection between FLC λ values and the κ/λ ratio in sera, suggesting that urinary FLC levels could serve as an effective and non-invasive biomarker for diabetes. Because HbA1c cannot be tested through urine samples, FLCs may be a more practical option for diabetes biomarkers than HbA1c. The presence of FLCs in diabetes patients indicates their condition is characterized by inflammation and immune activation, implying that urine FLCs could serve as a practical non-invasive marker for diabetes. Because HbA1c levels cannot be measured in urine samples, FLCs may be more valuable for identifying diabetes biomarkers than HbA1c. The presence of FLCs in diabetes is significant, as they are a marker of inflammation and immune system activation, indicating the disease's inflammatory and immune-related characteristics. FLC λ and the κ/λ ratio have emerged as more specific and sensitive biomarkers for diagnosing T2D mellitus (T2DM) compared to HbA1c, which is associated with NF-κB activation in the inflammatory cascade. FLCs appear to be promising indicators of inflammation and may reflect NF-κB pathway activation. Study revealed that patients with T1DM exhibit elevated FLC λ levels and a reduced κ/λ ratio compared to those with T2DM. The mechanism underlying FLC λ activation remains unclear. One possibility is that diabetes stimulates the activation of β lymphocytes and plasma cells responsible for FLC λ production. Alternatively, the regulation of FLC κ and λ may differ in T1DM due to a lack of

NF-κB-mediated control, unlike in T2DM.These results imply that several regulatory pathways might control the synthesis of FLCs. If confirmed, altered FLC profiles could provide insight into disease-specific immune responses in diabetes. Furthermore, NF-κB targeting, especially FLC regulation, may present a unique therapeutic approach for anti-inflammatory therapies and function as a stand-in endpoint in the treatment of diabetes (El-Sherbini *et al.,* 2013).

2.7 EN-RAGE (Extracellular newly identified receptor for advancedglycation end-products binding protein)

S100A12, also known as Calgranulin C and EN-RAGE, is primarily produced by granulocytes and is a calcium-binding pro-inflammatory protein. Its primary targets include RAGE (the Receptor for Advanced Glycation End Products) and TLR4 (Toll-like receptor 4) (Foell *et al.,* 2013). Activation of innate immune receptors including EN-RAGE, TLR4, triggers inflammatory responses through pathways such as NF-κB and the c-Jun NH2-terminal kinase (JNK). JNKand NF-κBsignalling pathways contribute to insulin resistance and T2D. Studies have found a positive correlation between EN-RAGE and chronic inflammatory conditions, including inflammatory bowel disease, chronic kidney disease, subclinical atherosclerosis, and coronary artery disease. A cross-sectional study conducted in the Italian population found that both prediabetic and diabetic individuals had elevated levels of proinflammatory S100A12 and decreased levels of RAGE in their plasma (Di Pino *et al.,* 2016). The Rotterdam Study, which found increased EN-RAGE plasma levels in people with T2D, had previously shown a link between EN-RAGE and the occurrence of coronary heart disease. A significant association exists between EN-RAGE and both HOMA-IR and HOMA-B indices, implying that proinflammatory EN-RAGE contributes to the development of T2D by promoting insulin resistance and pancreatic beta-cell dysfunction.

2.8 Neutrophil-to-lymphocyte ratio (NLR) andplatelet-to-lymphocyte ratio (PLR)

The NLR and PLR have demonstrated potential as indicators of inflammatory condition in DR. Notably, PLR is a relatively new biomarker linked to cardiovascular disease and increased risk of death from any cause (Jaaban *et al.,* 2021). Research suggests that examining fluctuations in NLR and PLR as ongoing metrics may be more beneficial than categorizing them based on random threshold values (Chen *et al.,* 2021; Li *et al.,* 2022). Individuals with T2D mellitus commonly exhibit a complex mix of various risk factors, co-existing health conditions, and complications, which may develop over time due to a poor lifestyle (Chou *et al.,* 2018). A larger non-proliferative or proliferative diabetic retinopathy may be linked to a greater risk of developing diabetic retinopathy or experiencing more severe diabetic retinopathy; the precise risk of this outcome is likely to be affected by several other factors such as glycemic control, the length of time the individual has been living with diabetes, and the presence of additional microvascular or macrovascular complications (Dascalu *et al.,* 2023). The principal inflammatory markers implicated in diabetes mellitus, their cellular sources, mechanisms of action, associations with T2D and its complications, and clinical utility are summarised in Table 1.

Table 1: Inflammatory markers in diabetes: Cellular source, mechanism, clinical association, and utility

Inflammatory marker	Cellular source	Mechanism of action	Association with T2D/complications	Clinical utility	References
Interleukin-6 (IL-6)	Adipocytes, endothelial cells, activated leukocytes	Drives acute-to-chronic inflammation; shifts infiltrating leukocytes from neutrophils to monocytes/macrophages; enhances T- and B-cell activity; upregulates CRP *via* hepatocytes; promotes NF-κB signalling; in combination with TGF-β1, promotes Th17 cell formation	Elevated in prediabetes and T2D; associated with hyperglycaemia and compensatory hyperinsulinaemia; linked to diabetic retinopathy, nephropathy, and macrovascular disease; plasma levels correlate with BMI in diabetic patients	Predictor of T2D onset (Women's health study); potential marker for vascular complications; elevated levels support diagnosis of inflammatory state in dysglycaemia	(Bowker *et al.,* 2020; Doi *et al.,* 2005; Gabay, 2006; Rehman *et al.,* 2017; Wannamethee *et al.,* 2007; Yao *et al.,* 2019)
C-reactive protein (CRP)	Hepatocytes (primary); also neurons, epithelial cells, monocytes, lymphocytes, smooth muscle cells	Acute-phase protein induced by IL-6; regulates platelet activation, leukocyte activity, and complement fixation; half-life ~19 h; can rise up to 1,000-fold within 24–72 h of inflammatory stimulus	Elevated in prediabetes vs normoglycaemia; rises further in T2D; linked to T2D-associated cardiovascular disease, atherosclerosis, and hepatitis C; genetic polymorphisms (SNPs, haplotypes) influence baseline and acute-phase CRP levels	Among the most validated inflammatory biomarkers for prediabetes/diabetes screening; detectable by immunoturbidimetry, ELISA, FLISA, electrochemical biosensors; normal <0.3 mg/dl; bacterial infection/tissue damage >10 mg/dl	(Donath and Shoelson, 2011; Luc *et al.,* 2019; Rhodes *et al.,* 2011; Siddiqui *et al.,* 2022; Stanimirovic *et al.,* 2022)
Tumour necrosis factor-α	Macrophages (primary), monocytes, adipocytes	Pro-inflammatory adipocytokine; suppresses insulin signalling *via*	Elevated in obesity and insulin resistance; associated with T2D onset and	Marker of insulin resistance and T2D progression; cor-	(Akash *et al.,* 2018; Liu *et al.,* 2016; Nakamura *et al.,* 1993;

(TNF-α)		impaired GLUT4 transport and IRS-1 pathway alteration; activates MAPK and NF-κB pathways; dual role - pro- and anti-inflammatory *via* CKII-SIRT1-SM22α pathway; involved in lipid metabolism and cachexia	progression; TNF-α mRNA levels in diabetic rat glomeruli increase progressively (2-fold at 4 wks → 4.2-fold at 24 wks); linked to diabetic nephropathy and metabolic dysfunction; often undetectable in plasma by standard assays requiring high-sensitivity immunoassay	relation with BMI not consistently established; TNF-α inhibitor therapy (*e.g.,* etanercept) associated with improved oxidative stress and lipid peroxidation in psoriasis/RA patients	Serhiyenko *et al.,* 2020; Shu *et al.,* 2017; Wang *et al.,* 2014; Zarandi *et al.,* 2021)
Transforming growth factor-β1 (TGF-β1)	Mesangial and tubular renal cells, infiltrating renal cells; broadly expressed in response to hyperglycaemia	Regulates lymphocyte proliferation, chemotaxis, differentiation, and survival; governs leukocyte activity; normally anti-inflammatory, but in presence of IL-6 promotes pro-inflammatory Th17 cell forma tion; activates glucose transporter-1 in renal cells under high-glucose conditions; drives fibrosis *via* ECM remodelling	Disrupted TGF-β1 signneuropathy, nephropathy (glomerular sclerosis, tubulointerstitial fibrosis, mesangial expansion), and impaired wound healing; TGF-β1 expression elevated in kidneys of T2D patients; serum levels correlate with duration of T1DM and vascular complication onset in children /adolescents	Potential prognostic marker for fibrotic complications of diabetic nephropathy; serum TGF-β1 levels correlate with vascular complication timeline in paediatric T1DM; therapeutic target *via* Smad3 signalling inhibition	Heydarpour *et al.,* 2020; Lee *et al.,* 2020; Wu *et al.,* 2015; Zorena *et al.,* 2013
Immunoglobulin free light chains (FLC λ, κ/λ ratio)	β lymphocytes and plasma cells	Markers of B-lymphocyte and plasma cell activation; reflect NF-κB pathway activation; FLC λ elevated and κ/λ ratio reduced in T1DM vs T2DM, suggesting disease-specific regulatory differences; possible differential regulation of κ and λ chains in T1DM due to altered NF-κB-	FLC λ and κ/λ ratio show higher specificity and sensitivity for T2DM diagnosis than HbA1c in some studies; FLC λ elevated in T1DM; urinary FLC levels correlate with sera κ/λ ratio, offering a non-invasive readout; elevated FLCs indicate immune activation and inflammation in diabetes mediated control	Potential urine-based non-invasive biomarker - advantage over HbA1c which cannot be measured in urine; may serve as surrogate endpoint in anti-inflammatory diabetes therapy targeting NF-κB	(El-Sherbini *et al.,* 2013)
EN-RAGE / S100A12 (cal granulin C)	Granulocytes (primary)	Calcium-binding pro-inflammatory protein; activates innate immune receptors RAGE and TLR4; triggers NF-κB and JNK signalling pathways, contributing to insulin resistance; reduced plasma RAGE alongside elevated S100A12 observed in prediabetes and T2D	Elevated in T2D (Rotterdam Study); associated with coronary heart disease incidence; significant positive correlation with HOMA-IR and HOMA-B indices, implicating EN-RAGE in insulin resistance and pancreatic β-cell dysfunction; elevated in prediabetic and diabetic subjects in Italian cross-sectional study	Marker of subclinical inflammation; risk stratification for coronary heart disease and chronic kidney disease in T2D; potential therapeutic target *via* TLR4/NF-κB/JNK pathway inhibition	(Di Pino *et al.,* 2016; Foell *et al.,* 2013)
Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte	Derived from complete blood count; reflects systemic immune and inflammatory	NLR and PLR are haematological ratios reflecting the balance between pro-inflammatory (neutrophil/	Both markers elevated in T2D; associated with severity of diabetic retinopathy (non-proliferative and proliferative DR);	Risk stratification tool for diabetic retinopathy; PLR is a relatively novel marker for cardio-	Chen *et al.,* 2021; Chou *et al.,* 2018; Dascalu *et al.,* 2023; Jaaban*et al.,* 2021; Li *et al.,* 2022

ratio (PLR)	balance	platelet) and regulatory (lymphocyte) immune components; continuous tracking proposed as more informative than threshold-based categorisation	influenced by glycaemic control, diabetes duration, and presence of micro/ macrovascular complications; PLR linked to cardiovascular disease risk and all-cause mortality	vascular risk and mortality prediction in T2D; low cost and widely available from routine CBC; serial monitoring more valuable than single threshold classification	
Complement component C5a	Complement system activation; endothelial cells (downstream)	Potent complement-derived inflammatory mediator; promotes tissue factor activity and adhesion molecule production in endothelial cells, contributing to coagulation activation; involved in amplifying proatherogenic vascular responses	Elevated in prediabetes alongside CRP and IL-6 (Maschirow *et al.*); elevated coagulation activity in prediabetes contributes to subsequent cardiovascular complications; complement system activation linked to T2D pathogenesis	Emerging marker for prediabetes-associated coagulation and cardiovascular risk; supports complement pathway as therapeutic target in early T2D; currently less clinically established than CRP or IL-6	Maschirow *et al.*, 2015

3. Phytochemical modulation of inflammatory pathways in diabetes

3.1 Alkaloids

3.1.1 Berberine

Berberine, a derivative of the alkaloid isoquinoline, is chemically denoted as 2,3-methylenedioxy-9,10-dimethoxyprotoberberine chloride. The substance was initially derived from *Cortex phellodendri* (Huangbai) and *Rhizomacopitidis* (Huanglian). This condition has been frequently used to treat gastroenteritis and diarrhoea. Berberine exhibits a range of advantageous effects, comprising the prevention of fat cell creation, decrease in blood levels of repression of inflammation, as well as low-density lipoprotein (LDL) cholesterol. In models of diabetes created using streptozotocin (STZ), berberine substantially decreased levels of chronic inflammatory indicators such as C-reactive protein, free fatty acids, cholesterol, and triglycerides in the bloodstream. The primary cause of this effect is its inhibition of protein tyrosine phosphatase-1B (PTP-1B) and dipeptidyl peptidase-4. Berberine also boosts insulin sensitivity, which in turn reduces insulin resistance and decreases fasting blood glucose levels (Habtemariam, 2020). Berberine has shown significant anti-inflammatory properties in diabetic nephropathy models, achieved by blocking the RhoA/ROCK signalling pathway and reducing NF-κB transcriptional activity. The inhibition leads to a reduction in the expression of fibronectin, intercellular adhesion molecule-1 (ICAM-1), and transforming growth factor beta-1 (TGF-β1). The administration of berberine resulted in a significant decrease in the expression of multiple pro-inflammatory genes within the adipose tissue of diabetic db/db mice, specifically iNOS, IL-1β, IL-6, MCP-1, TNF-α, and COX-2.

Research has demonstrated that berberine is capable of reducing oxidative stress through a decrease in reactive oxygen species (ROS) levels generated in glomerular mesangial cells under conditions of high glucose in laboratory experiments (Kong *et al.,* 2021). Research has shown that berberine can prevent ongoing chronic inflammation in the organs of non-obese diabetic mice with type 1 diabetes-like symptoms, specifically the spleen, liver, and kidneys, by controlling the balance between pro-inflammatory and anti-inflammatory cytokines and affecting the immune response involving Th1/Th2 cells. Research is increasingly pointing to the gut microbiome as a pivotal element in the progression of diabetes and associated health issues, and also as a potential area for developing effective treatments for diabetes (Canfora *et al.,* 2019). Research indicates that berberine's benefits in relation to diabetes are largely due to its influence on the gut microbiota. Studies using mouse models of obesity induced by a high-fat diet showed that berberine reduced both blood glucose and lipid levels, and this decrease was correlated with significant changes in the gut microbiota composition. The metabolites produced by gut microbes play a vital role in determining how the gut microbiota impacts the development of metabolic diseases. In a rat study on insulin resistance, berberine altered the composition of the gut microbial community, substantially boosting the numbers of bacteria that synthesise short-chain fatty acids, notably *Blautia* and *Allobaculum*, thereby elevating levels of these SCFAs in faeces. Fermentation of branched-chain amino acids also yields branched-chain fatty acids, a key factor in the development of metabolic disorder. Giving berberine to mice that ate a high-fat diet resulted in a significant reduction in insulin resistance and liver inflammation associated with metabolism, which was accompanied by a notable decrease in bacteria that produce BCAAs, including those within the Clostridiales orderand the Streptococcaceae, Clostridiaceae, and Prevotellaceae families, as well as the *Streptococcus* and *Prevotella* genera (Yue *et al.,* 2019).

3.2 Non-flavonoid polyphenols

3.2.1 Resveratrol

Resveratrol compound, classified as 3,42 ,5-trihydroxystilbene, is a type of polyphenolic phytoalexin found in several plant species such as grapes, plums, peanuts, and nuts. Extensive research has been conducted into its diverse pharmacological properties, encompassing antidiabetic, anti-obesity, anticancer, neuroprotective, and cardioprotective benefits (Cao *et al.,* 2019; Novelle *et al.,* 2015). Research on rats with diabetes caused by STZ has demonstrated

that extended administration of resveratrol can inhibit NF-κB activation and decrease the levels of pro-inflammatory compounds such as TNF-α, IL-6, and COX-2 (Ghadiri Soufi *et al.,* 2015). Specifically, resveratrol reduced retinal inflammation and consequently improved diabetic retinopathy. In cells of the retina exposed to high glucose levels, the expression of TGF-β, VEGF, IL-6, and IL-8 – critical factors associated with diabetic retinopathy progression – decreased in a dose-dependent manner. Resveratrol significantly decreased retinal damage in diabetic rats treated with STZ primarily through upregulation of paraoxonase-1, inhibition of oxidized DLD activity, and suppression of AGEs, IL-1β, TNF-α, IL-6, MCP-1,VEGF and IFN-λ in the retina(Chen *et al.,* 2019). It led to increased levels of phosphorylated AMP-activated protein kinase (AMPK), reactivated sirtuin 1 (SIRT1), and reduced NF-κB phosphorylation within the retinas of diabetic mice. The compound also decreased leukocyte adhesion in the retinas of individuals with diabetes, coupled with a decrease in the expression of ICAM-1 and VEGF. In addition to protecting the retina, resveratrol also provided protection against cerebral ischemia/reperfusion injury occurs primarily *via* reduced oxidative stress and inflammation.

Experimental studies have demonstrated the therapeutic potential of Resveratrol in diabetic kidney disease (DKD) models, mainly because of its anti-inflammatory effects. The improvement in kidney function in diabetic rats, observed was associated with a decrease in levels of the pro-inflammatory cytokine IL-1β in the kidneys. Resveratrol supplementation taken orally effectively suppressed the heightened activity of TNF-α, IL-6, NF-κBand IL-1β p65 subunits within the kidneys, ultimately reducing inflammation-related kidney damage in diabetic kidney disease. In addition to its protective effects on the kidneys, resveratrol has also been demonstrated to provide a safeguard against vascular complications that are induced by diabetes. Supplementation with resveratrol in diabetic db/db mice resulted in a substantial decrease in blood glucose and lipid levels. These metabolic benefits were accompanied by vascular protective effects, as shown by reduced expression of ICAM-1, monocyte chemoattractant protein-1 (MCP-1) and vascular cell adhesion molecule-1 (VCAM-1), in aortic tissues (Guo *et al.,* 2014). Notably, the beneficial outcomes observed in rodent models have also been corroborated in higher primates. In rhesus monkeys fed a diet high in fat and sugar, two years of resveratrol supplementation led to substantial improvements in metabolic function, encompassing the normalisation of fat cell size, increased levels of SIRT1 expression, and enhanced insulin sensitivity within visceral white fat tissue (Kong *et al.,* 2021). The research highlights several advantages of resveratrol in controlling diabetes and its associated microvascular issues, especially those affecting the eyes and kidneys, mainly because of its effect on inflammatory processes.

3.2.2 Emodin

Emodin, a polyphenolic compound primarily isolated from *Polygonum multiflorum*, *Rheum palmatum*, *Cassia obtusifolia*, and *Polygonum cuspidatum*, is well known as an active compound in herbal laxatives. In addition to its established properties as a laxative, emodin also displays significant anti-inflammatory effects and anti-tumor. Recent studies indicate that it could be an effective treatment option for managing diabetes and its associated problems. Research has found that emodin influences glucose metabolism, and this effect was confirmed in laboratory tests which showed that it increased glucose absorption and activation of the AMPK signalling pathway leads to utilisation in C_2C_{12} myotubes and 3T3-L1 adipocytes. Emodin triggered an increase in glycolysis and a decrease in lipolysis in 3T3-L1 adipocytes, with corresponding drops in the levels of phosphorylated perilipin. This compound mechanistically blocked the activation of the NF-κB and ERK pathways in both cell types (Zhang *et al.,* 2015). Research has demonstrated that emodin has protective effects against vascular inflammation and endothelial dysfunction caused by diabetes. In diabetes, elevated glucose levels trigger an overproduction of the ligand 5 (CCL5) and chemokine (C-C motif), a compound that promotes the movement of inflammatory cells to blood vessels and plays a role in the initial damage to the endothelial lining. Emodin inhibited apoptosis in endothelial cells and vascular inflammation triggered by high glucose levels by downregulating CCL5 expression and lowering the phosphorylation of ERK1/2 and p38 MAPK.Emodin possesses potential as an effective therapeutic agent for diabetes treatment and associated vascular complications.

3.2.3 Ellagic acid

Ellagic acid (2,3,7,8-tetrahydroxychromeno[5,4,3-cde]chromene-5,10-dione), a compound derived from the breakdown of tannins, is found in berries, pomegranates and dried fruits (Ceci *et al.,* 2018). It has been investigated for its therapeutic potential in various chronic conditions, including cardiovascular (Jordão *et al.,* 2017)and neurodegenerative diseases (Firdaus *et al.,* 2018), due to its diverse biological properties, including anti-inflammatory, anticancer and antioxidant actions. (Baradaran Rahimi *et al.,* 2020). New research suggests that ellagic acid may be a promising agent for treating diabetes. Using a rat model that simulates T2D accompanied by kidney damage, ellagic acid demonstrated significant improvements in elevated blood sugar levels, insulin sensitivity, and diabetic kidney disease, mainly by blocking the activation of NF-κB. A significant decline in inflammatory response was closely linked to the protective effect observed, characterised by reduced serum levels of pro-inflammatory cytokines IL-1β, TNF-α, and IL-6 (Gratas-Delamarche *et al.,* 2014). More recent findings indicate that chronic ellagic acid treatment alleviated anxiety and depression-like behaviours, enhanced locomotor and exploratory activity, and restored cognitive function in diabetic rats. These neuroprotective effects were linked to enhanced blood sugar regulation, the regulation of inflammatory processes, and a decrease in neuronal cell death (Farboodet *al.,* 2019). Furthermore, hyperglycaemia-induced renal damage by suppressing the high mobility group box 1 (HMGB1)-toll-like receptor 4 (TLR4)-NF-κB signalling pathway (Zhou *et al.,* 2019), reinforcing the idea that its anti-inflammatory action plays a central role in its protective effects against diabetes and its complications.

3.3 Flavonoid polyphenols

3.3.1 Epigallocatechin gallate

A naturally occurring compound called epigallocatechin gallate is predominantly found in green tea, but it also appears in a variety of foods such as blackberries, apples, cherries, peaches, cranberries, pistachios, pears, avocados, strawberries, kiwis,pecans, and hazelnuts. Thorough research it demonstrated its repeated health advantages, encompassing anti-inflammatory properties, weight reduction, decreased blood cholesterol levels, and cardiovascular safeguarding (Legeay *et al.,* 2015). In recent years, EGCG has gained attention as a promising anti-diabetic compound. In STZ-induced diabetic mice, EGCG treatment significantly enhanced wound healing,

an effect closely linked to lower levels of pro-inflammatory cytokines, including IL-1β, TNF-α, and IL-6, as well as suppression of Notch signalling and macrophage infiltration at the wound site (Huang *et al.,* 2019). On a mechanistic level, EGCG was shown to counteract high glucose-induced upregulation of intercellular adhesion molecule-1 (ICAM-1) andvascular cell adhesion molecule-1 (VCAM-1)in the kidneys of diabetic mice and high glucose-exposed mesangial cells. The protective action was facilitated by the activation of nuclear factor E2-related factor 2 (NRF2), a crucial transcription factor which plays a significant role in regulating oxidative stress and inflammation (Sun *et al.,* 2017).

Research has shown that epigallocatechin gallate (EGCG) has significant antioxidant capabilities in human liver cancer cells (HepG2) largely by decreasing the production of reactive oxygen species (ROS) and increasing the activity of key antioxidant enzymes, including superoxide dismutase and glutathione peroxidase.These effects serve a protective function in mitigating insulin resistance and inflammation resulting from oxidative stress in HepG2 cells (Zhang *et al.,* 2018). Using a rat model of cardiovascular damage related to diabetes, epigallocatechin gallate showed heart-protective effects by decreasing the levels of circulating inflammatory substances such as TNF-α, IL-6, and IL-1β, as well as molecules involved in cell adhesion, including ICAM-1 and VCAM-1 (Othman *et al.,* 2017). Suppression of vascular inflammation by EGCG has also been shown, through its ability to prevent NF-κB activation, in both human umbilical vein endothelial cells and db/dbmice. It is noteworthy that consuming a low concentration of EGCG (0.1%) has been found to decrease inflammation in the fat tissue of Goto-Kakizaki rats, an animal model used to study early-onset T2D in a non-obese polygenic context. Taken together, these findings support the therapeutic potential of EGCG in diabetes management, largely due to its anti-inflammatory and antioxidant activities.

3.3.2 Curcumin

The primary bioactive component in turmeric is curcumin, which features the chemical formula [1,7-bis(4-hydroxy-3-methoxyphenyl) -1,6-heptadiene-3,5-dione], and is predominantly found in the rhizome of *Curcuma longa*. It has shown a variety of therapeutic benefits, such as lowering cholesterol, protecting the liver, and reducing inflammation (Noureddin *et al.,* 2019). Research is increasingly showing that it could be an effective treatment for diabetes and its related health issues. Studies of metabolic disorders in mice, particularly those lacking leptin (ob/ob mice) and those made obese by high-fat diets, have demonstrated that curcumin supplementation improves insulin responsiveness and glucose metabolism. These beneficial metabolic effects were associated with decreased macrophage infiltration in white adipose tissue, increased adiponectin production, and lowered NF-κB activity in the liver (Kong *et al.,* 2021).

Curcumin has been studied in genetically diabetic db/db mice and significantly modulated inflammatory and metabolic pathways by coordinating the activity of NF-κB, AMP-activated protein kinase (AMPK) andperoxisome proliferator-activated receptor gamma (PPAR-γ) (Jiménez-Flores *et al.,* 2014). In a rat model of diabetic nephropathy caused by streptozotocin, administering curcumin for 12 weeks resulted in reduced kidney tissue damage and fibrosis, as well as decreased expression of pro-inflammatory genes. Notably, it reduced caveolin-1 Tyr14 phosphorylation and inhibited toll-like receptor 4 (TLR4) expression in both diabetic kidneys and high glucose-exposed podocytes, suggesting these actions play a central role in curcumin's anti-inflammatory effects in diabetic nephropathy (Sun, 2014).

Curcumin has been demonstrated to offer protection to pancreatic β-cells by reducing inflammatory reactions and inhibiting stress signalling within the endoplasmic reticulum and mitochondria, thereby preventing cellular apoptosis (Rashid and Sil, 2015). It also attenuated diabetes-induced vascular inflammation by reducing reactive oxygen species (ROS) production and limiting leukocyte-endothelium interactions (Wongeakin *et al.,* 2014). These collective findings underscore the potential of curcumin as a novel therapeutic approach for T2D mellitus (T2DM) and its associated complications, hence underscoring the need for additional clinical studies.

3.3.3 Baicalein

Baicalein, a significant bioactive flavonoid, is primarily sourced from the *Scutellaria* root and characterised by its chemical structure of 5,6,7-trihydroxy-2-phenyl-4H-1-benzopyran-4-one (Kong *et al.,* 2021). Its diverse biological properties have attracted increasing attention, particularly regarding its metabolic benefits. Rats with diabetes were created using a combination of a high-fat diet and the toxin streptozotocin (STZ) exhibited a significant decrease in blood glucose levels and an increased response to insulin after a 16-week treatment with baicalein.The therapy was found to be effective in revitalizing glucose metabolism and reducing insulin resistance.

Baicalein significantly enhanced renal tissue health by reducing the production of TGF-β1 and iNOS, along with stifling the inflammatory response mediated by NF-κB (Ahad *et al.,* 2014). Baicalein has been found to alleviate multiple metabolic issues in mice with encompassing glucose intolerance, diet-induced metabolic syndrome, insulin resistance, weight increase, lipid disorders, and accumulation of fat in the liver. These benefits were largely due to the compound's dual mechanism of action, which involved both reducing inflammation and insulin resistance by blocking the MAPK pathway and improving insulin signalling through the IRS1/PI3K/Akt pathway. (Kong *et al.,* 2021). When considered as a whole, baicalein appears to have significant potential as an antidiabetic medication, combining its broader antioxidant, anti-inflammatory, and anticancer properties, which makes it a promising choice for further drug research.

3.3.4 Naringenin

Naringenin is a naturally occurring compound with the chemical structure [5,7-Dihydroxy-2-(4-hydroxyphenyl)chroman-4-one] that is predominantly found in citrus fruits and grapefruit (Den Hartogh and Tsiani, 2019). A growing body of research highlights its therapeutic potential as an antidiabetic agent. In a rat model of T2D mellitus (T2DM), naringenin showed that it improves hyperglycaemia, insulin resistance, and lipid abnormalities (Ren *et al.,* 2016). Additionally, in a murine model of gestational glucose intolerance, naringenin reduced blood glucose levels, primarily through enhanced GLUT4 translocation and glucose uptake mediated by the activation of AMP-activated protein kinase (AMPK) in skeletal muscle cells (Li *et al.,* 2019b). It also suppressed the liver's ability to produce glucose through gluconeogenesis *via* the activation of AMPK, similar to the action of metformin, and displayed anti-inflammatory and anti-proliferative properties (Nyane *et al.,* 2017).

Naringenin has also exhibited a strong capacity to mitigate diabetic vascular complications. This compound reduced kidney damage and corrected lipid imbalances in a diabetic nephropathy model, primarily through enhanced expression of peroxisome proliferator-activated receptors (PPARs) and suppressed expression of pro-inflammatory cytokines TNF-α and IL-6 (Chtouroue*t al.,* 2016; Ding *et al.,* 2019)**.** In T2DM rats, it lowered levels of endothelial adhesion molecules such as ICAM-1, and improved vascular function, as evidenced by restored vascular contractility and relaxation responses. *In vitro* studies supported these findings, showing that naringenin suppressed NF-κB activation and downregulated ICAM-1 mRNA in endothelial cells exposed to palmitic acid, shedding light on its cardiovascular protective mechanisms (Ren *et al.,* 2016)**.**

Naringenin's antidiabetic properties have identified inflammation as a key focus area. Treatment with naringenin in diabetic rats reduced inflammation in both liver and pancreas tissues (Burke *et al.,* 2018) and substantial decreases in the levels of inflammatory cytokines, such as TNF-α, IL-6, TGF-β, and ICAM-1, were observed in the systemic circulation of diabetic pregnant rats (Zhao *et al.,* 2020)**.** Naringenin suppressed the expression of pro-inflammatory cytokines and chemokines in human placental and visceral adipose tissues induced by TNF-α *in vitro* (Nguyen Ngo *et al.,* 2019). This treatment also reduced inflammatory activity in macrophages and neutrophils, key components of the innate immune system within adipose and other metabolically active tissues (Tsuhako *et al.,* 2020)**.** These results strongly suggest that naringenin holds promise as a potential treatment for diabetes and related issues, primarily due to its potent anti-inflammatory and metabolic control properties.

3.3.5 Hesperetin

Hesperetin, the aglycone form of hesperidin, is predominantly a naturally occurring flavanone found mainly in citrus fruits, such as oranges and lemons, with the chemical composition 32 ,5,7-trihydroxy-42 -methoxyflavanone. This compound has a variety of pharmacological properties including lipid-lowering, anti-inflammatory, antioxidant, blood sugar-regulating, blood pressure-lowering, and heart-protecting effects (Iranshahi *et al.,* 2015)**.**In experimental models of streptozotocin (STZ)-induced diabetes, hesperetin has demonstrated significant antidiabetic potential. It significantly reduced high blood sugar levels mainly by suppressing oxidative stress and decreasing the production of inflammatory chemicals including TNF-α and IL-6 (Jayaraman *et al.,* 2018; Mulvihill *et al.,* 2016)**.** These anti-inflammatory effects are pivotal to its broader therapeutic benefits.

Studies have demonstrated that hesperetin also possesses protective properties against microvascular complications associated with diabetes, specifically diabetic nephropathy and retinopathy. Oral administration of hesperetin significantly alleviated kidney damage in diabetic rats, primarily through modulation of the advanced glycation end products (AGEs)/receptor for AGEs (RAGE) axis and suppression of the TGF-β1–ILK–Akt signalling pathway (Chen *et al.,* 2019; Zhang *et al.,* 2018)**.** These mechanisms underscore its role in attenuating inflammation-driven fibrosis and structural renal damage.In diabetic retinopathy models, hesperetin successfully delayed disease progression by reducing the expression of key inflammatory cytokines, such as TNF-α and IL-1β, thereby preventing inflammation-induced retinal degeneration.Collectively, these findings highlight hesperetin notable ability to suppress inflammatory responses and oxidative stress, making it a promising candidate for dietary supplementation or therapeutic development for diabetes and its complications.

3.3.6 Chrysin

A naturally occurring flavonoid, chrysin (5,7-dihydroxyflavone), discovered in medicinal plants, honey, and propolis, is attracting interest due to its potential benefits in managing diabetes and reducing inflammation. Accumulating evidence suggests that chrysin exerts protective effects against both metabolic dysfunction and diabetes-related complications, particularly through its modulation of inflammatory pathways and activation of nuclear receptors (Siddiqui *et al.,* 2018)**.** In athymic nude diabetic mice, chrysin significantly reduced blood glucose levels, an effect closely associated with decreased circulating concentrations of pro-inflammatory cytokines IL-1β and TNF-α (Ramírez-Espinosa *et al.,* 2018)**.** The research highlights the connection between blood sugar regulation and reduced body-wide inflammation.Chrysin's ability to provide metabolic benefits is closely linked to its role as a peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist, a well-documented therapeutic target for the regulation of lipid and glucose homeostasis (Ammazzalorso *et al.,* 2019)**.** Chrysin lowered high systolic blood pressure and reduced blood vessel responsiveness in a rat study of insulin resistance and vascular issues resulting from excessive fructose intake, effects that were attributed to its mechanism involving the PPAR-γ pathway (El-Bassossy *et al.,* 2014)**.**

Chrysin reduced myocardial damage in diabetic rats, resulting in improved heart function through the activation of PPAR-γ and a decrease in oxidative stress and vascular inflammation (Rani *et al.,* 2016). In a commonly used model of T2D, db/db mice, chrysin decreased the presence of kidney fibrosis markers like collagen fibre accumulation and α-smooth muscle actin expression, suggesting a protective effect against diabetic nephropathy. *In vitro*, the observed effect was associated with the suppression of the TGF-β1/Smad2/3 signalling pathway in kidney mesangial cells (Lin *et al.,* 2019)**.** Furthermore, chrysin demonstrated neuroprotective effects in diabetic rats by improving cognitive function and attenuating diabetes-induced neuroinflammation. This was evidenced by reduced activation of NF-κB and decreased expression of IL-6, TNF-α and IL-1β in the hippocampusand cerebral cortex (Li *et al.,* 2019a)**.** Chrysin has the potential to be a versatile treatment option for diabetes and its related issues, due to its robust anti-inflammatory, antioxidant, cardiovascular, renal, and neuroprotective effects, primarily achieved by activating PPAR-γ and regulating inflammatory signalling pathways.

3.3.7 Genistein

Genistein (42 , 5,7-trihydroxy isoflavone), a phytoestrogen isoflavone primarily found in legumes such as soybeans, has attracted attention for its dual role as a metabolic regulator and anti-inflammatory agent, particularly in the context of diabetes and its complications (Jain *et al.,* 2022). Initially characterized as a tyrosine kinase inhibitor, genistein was shown to interfere with insulin signalling *in vitro* by suppressing insulin-stimulated glucose oxidation and blocking GLUT4 translocation in adipocytes. Notably, this inhibitory action did not affect insulin receptor tyrosine autophosphorylation, suggesting that genistein modulates downstream signalling rather than directly blocking receptor activation. This also led to a decrease in glucose uptake in 3T3-L1 adipocytes in response

to insulin and disrupted insulin function in mature adipocytes obtained from mouse MC3T3-G2/PA6 cell lines (Ahmed *et al.,* 2020).

Despite these findings, *in vivo* studies support a net anti-diabetic effect of genistein. In non-obese diabetic (NOD) mice that mimic type 1 diabetes, genistein significantly lowered blood glucose levels. These metabolic improvements were associated with anti-inflammatory responses and beneficial shifts in the gut microbiota, specifically alterations in β-diversity (Huang *et al.,* 2017)**.** Administration of genistein *via* subcutaneous injection to diabetic rat models, either fed a high-fat diet or estragon-deficient, resulted in reduced pancreatic inflammation and tissue damage, thereby demonstrating its ability to protect pancreatic β-cell function under conditions of metabolic stress (Mohammadi *et al.,* 2025). In addition, alloxan-induced diabetic rats that received genistein had a restored histological structure of the pancreas and intestine and decreased systemic inflammation, as evidenced by lower concentrations of IL-6, C-reactive protein (CRP) and TNF-α, (Rehman *et al.,* 2019)**.**

Genistein has also demonstrated a renoprotective role in diabetic conditions. Treatment led to a marked suppression of inflammatory cytokines in the kidney, including monocyte chemoattractant protein-1 (MCP-1), cyclooxygenase-2 (COX-2), and TNF-α, suggesting that the compound mitigates diabetic nephropathy through anti-inflammatory pathways (Danciu *et al.,* 2018). Collectively, genistein's antidiabetic properties appear to stem from a complex interplay between its anti-inflammatory effects, modulation of insulin signalling, and gut microbiota regulation. While it's *in vitro* insulin-antagonistic activity may initially appear paradoxical, its overall *in vivo* benefits support its potential as a therapeutic candidate for diabetes management and the prevention of chronic complications.

3.3.8 Kaempferol

Kaempferol, a compound with the chemical structure 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one, is widely found in nature, often present in a variety of fruits, vegetables, and medicinal plants. Kaempferol, which is present in tea, leeks, onions, broccoli, tomatoes, berries, apples, and various Chinese medicinal plants like aloe vera, *Centella asiatica*, and *Lyciumbar-barum*, has been observed to have antidiabetic, anti-inflammatory, and antioxidant properties (Yang *et al.,* 2022).

In mice consuming a high-fat diet, fractions of kaempferol glycoside led to substantial reductions in body weight gain, decreased levels of blood glucose and triglycerides, and increased insulin sensitivity, thus showing a substantial effect on metabolic balance (Zang *et al.,* 2015)**.**In streptozotocin-induced diabetic rats, kaempferol treatment ameliorated hepatic insulin resistance, largely through suppression of NF-κB-mediated inflammation in the liver, a key player in metabolic inflammation (Luo *et al.,* 2015)**.** Administration of kaempferol in diabetic rats with myocardial ischemia-reperfusion injury reduced oxidative stress and inflammation in the heart, implying a protective effect against diabetic cardiomyopathy (Suchal *et al.,* 2017)**.** Additionally, kaempferol appears to aid in tissue repair and wound healing, an area where diabetes poses a significant clinical challenge:

Application of kaempferol ointment directly to wounds sped up the healing process in both wounds from people with diabetes and those without, likely due to its capacity to decrease inflammation at the wound site and stimulate tissue repair (Özay *et al.,* 2019)**.**Together, these findings support kaempferol as a promising multifunctional agent for diabetes management, addressing hyperglycemia, insulin resistance, cardiovascular complications, and impaired wound healing. Its pleiotropic effects, mediated through NF-κB inhibition, oxidative stress reduction, and improved lipid-glucose metabolism, make it a compelling candidate for further investigation as a nutraceutical or adjuvant therapy in diabetes and its complications.

3.3.9 Eriodictyol

The flavonoid eriodictyol, chemically known as 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-2,3-dihydrochromen-4-one, is abundant in *Eriodictyon californicum* and is characterised by its anti-inflammatory and antioxidant properties. Research indicates that eriodictyol has potential as a therapeutic agent for diabetes and its associated microvascular issues, primarily through the regulation of inflammation, oxidative stress, and glucose metabolism (Guo *et al.,* 2023).

Research findings from both *in vitro* and *in vivo* experiments reveal the multiple pathways through which eriodictyol achieves its antidiabetic outcomes. Eriodictyol enhanced glucose uptake in HepG2 cells and 3T3-L1 cells that had undergone differentiation, this effect being linked to the increased expression of PPARã2 and FABP4, both of which play a crucial role in lipid and glucose metabolism.Treatment with eriodictyol resulted in a marked and dose-related reduction of inflammatory cytokines, adhesion molecules, and nitric oxide synthase levels in diabetic rat retinal tissue, a finding of considerable importance given the prevalence of diabetic retinopathy. Lipid peroxidation, a marker of oxidative damage, was also inhibited (Lv *et al.,* 2019)**.** In rat retinal ganglion cells, eriodictyol is protected against high glucose-induced cytotoxicity, reducing the production of TNF-α and IL-8, both of which are implicated in retinal inflammation and degeneration.In mesangial cells, which play a vital part in both renal function and structure, eriodictyol inhibited high glucose-induced cell growth, reactive oxygen species generation, and the release of inflammatory cytokines, indicating its potential protective effects in diabetic nephropathy (Bai *et al.,* 2019)**.**

These findings collectively point to eriodyctiol's multifaceted benefits in diabetes management, including:

- Improved insulin sensitivity and glucose uptake
- Suppression of inflammatory cytokines (TNF-α, IL-8)
- Reduction of oxidative stress and ROS formation
- Protection of retinal and renal tissues from hyperglycemia-induced damage

Given its potential to mitigate retinal and renal complications, eriodictyol represents an emerging flavonoid worthy of further investigation in preclinical and clinical settings. Its targeting of both inflammation and oxidative stress, two hallmarks of diabetic complications, underscores its promise as a nutraceutical or adjunct therapy in comprehensive diabetes care.

3.3.10 Apigenin

The flavonoid apigenin (42 ,5,7-trihydroxyflavone) is found naturally in a variety of plant-based foods, with notable sources including grapefruit, oranges, onions, parsley, wheat sprouts, tea, and

chamomile (Kong *et al.,* 2024). Apigenin is gaining recognition for its ability to treat diabetes and associated problems due to its antioxidant, anti-inflammatory, antiapoptotic, antifibrotic, and antidiabetic properties.The compound apigenin possesses a distinct method of action, primarily due to its capability to function as a potent pharmacological blocker of the CD38 enzyme, which plays a vital role in regulating NAD + levels outside the cells. In mice that are obese, administering apigenin increased NAD + levels, lowered overall protein acetylation, and re-established balance in glucose and lipid metabolism.The research indicates that apigenin could have antidiabetic properties *via* NAD + dependent pathways, a process with significant implications for metabolic diseases and the aging process.

Studies involving rodents with diabetic cardiomyopathy models showed that apigenin improved endothelial function and lessened cardiac damage. Reduced levels of oxidative stress and inflammation were found to occur mainly as a result of the inhibition of NF-κB activation and the suppression of the pro-inflammatory cytokines IL-1β, TNF-α and IL-6 (Liu *et al.,* 2017)**.** Treatment with apigenin significantly enhanced renal function in a rat model of diabetic nephropathy, also resulting in decreases in glomerulosclerosis, inflammation, and oxidative stress. Research involving rats with diabetic kidney disease demonstrated that administering apigenin led to substantial improvements in kidney functions and reductions in glomeruli scarring, inflammation, and oxidative stress.The protective effects observed on the kidneys were linked to the suppression of the MAPK signalling pathway within the organ (Malik *et al.,* 2017)**.** These multifaceted properties make apigenin a promising nutraceutical and pharmacological candidate for the treatment of T2D and its cardiometabolic complications. Future research is warranted to further elucidate its molecular targets and confirm its efficacy in clinical settings.

3.3.11 Quercetin

The polyphenolic flavonoid, quercetin (3,32 ,42 ,5,7-pentahydroxy-flavone), is abundant in various food items including black tea, apples, berries, capers, red wine, and onions. Extensive scientific research has been conducted on quercetin owing to its highly effective antioxidant and anti-inflammatory properties, which are thought to have substantial potential for preventing and managing diabetes and its related health issues (Shi *et al.,* 2019). Quercetin's well-documented effects include its capacity to reduce oxidative stress and inflammation, both of which play a pivotal role in the development of diabetes.Research has shown that quercetin offers protective effects on pancreatic β cells, safeguarding them against damage caused by cytokines, a crucial function, particularly given that these cells are the only producers of insulin. Studies in animal models have shown that quercetin can decrease liver fat accumulation and inflammation in non-alcoholic fatty liver disease associated with T2D, underscoring its potential benefits in metabolic conditions, including non-alcoholic fatty liver disease caused by T2D (Yang *et al.,* 2019)**.**

Quercetin inhibited the NLRP3 inflammasome in diabetic kidneys, thereby preventing the release of IL-1β and IL-18. The NLRP3 inflammasome is a crucial component in the maturation of pro-inflammatory cytokines. This action hindered the progression of diabetic nephropathy.In diabetic rats, quercetin lowered blood glucose levels and alleviated oxidative stress and inflammation in cardiac tissues, offering protection against diabetes-induced heart injury (Roslan *et al.,* 2017)**.** A significant clinical issue in diabetes is delayed wound healing, largely due to impaired inflammatory resolution. Studies using diabetic rodent models that were given quercetin resulted in a quicker rate of wound healing, as evidenced by the transformation of pro-inflammatory M1 macrophages into anti-inflammatory M2 macrophages, leading to an equilibrium of beneficial inflammation (Ahmed *et al.,* 2018; Fu *et al.,* 2020)**.** Quercetin emerges as a flavonoid with multiple targets, exhibiting significant antidiabetic, anti-inflammatory, organ-protective effects, and antioxidant properties, thereby positioning it as a strong candidate for use in integrative or supplementary therapy in diabetes management.

4. Conclusion

The development and progression of diabetes mellitus, particularly T2D, are significantly impacted by inflammation. Several inflammatory markers, including C-reactive protein (CRP), interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), and transforming growth factor-beta 1 (TGF-β1), have been linked to conditions such as insulin resistance, beta-cell dysfunction, and diabetes-related complications. These markers not only help in understanding the inflammatory processes underlying diabetes but also serve as potential diagnostic and prognostic indicators.The emerging evidence suggests that inflammation-driven pathways contribute to both the early and advanced stages of diabetes. Biomarkers such as free light chains (FLCs) and EN-RAGE have shown promise as novel indicators of inflammation in diabetes, expanding our understanding of immune involvement in the disease. The platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) have shown potential to be useful markers for diabetic complications such as diabetic retinopathy.Further research is needed to explore therapeutic strategies targeting inflammation to prevent and manage diabetes effectively. Understanding the interplay between inflammatory markers and metabolic dysfunction could lead to the development of novel anti-inflammatory interventions, ultimately improving patient outcomes.

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Conflict of interest

The authors declare no conflict of interest relevant to this article.

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