ELSEVIER

Mechanistic insights into the beneficial effects of curcumin on insulin resistance: Opportunities and challenges

Pitchai Balakumar [1,*], Kumar Venkatesan [2], Noohu Abdulla Khan [3], N.M. Raghavendra [4], Vijayan Venugopal [5], D.R. Bharathi [6], Neeraj K Fuloria [7]

[1] The Office of Research and Development, Periyar Maniammai Institute of Science & Technology (Deemed to be University), Vallam, Thanjavur 613 403, Tamil Nadu, India
[2] Department of Pharmaceutical Chemistry, College of Pharmacy, King Khalid University, Al-Qara, Abha 61421, Saudi Arabia
[3] Department of Clinical Pharmacy, College of Pharmacy, King Khalid University, Al-Qara, Abha 61421, Saudi Arabia
[4] Department of Pharmaceutical Chemistry, College of Pharmaceutical Sciences, Dayananda Sagar University, Bengaluru 560 111, India
[5] School of Pharmacy, Sri Balaji Vidyapeeth Deemed-to-be University, Puducherry 607 402, India
[6] Department of Pharmacology, Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University, B G Nagara, Nagamangala 571 448, India
[7] Pharmaceutical Chemistry Unit, Faculty of Pharmacy, AIMST University, Semeling, 08100 Bedong, Malaysia

The past couple of decades in particular have seen a rapid increase in the prevalence of type 2 diabetes mellitus (T2DM), a debilitating metabolic disorder characterised by insulin resistance. The insufficient efficacy of current management strategies for insulin resistance calls for additional therapeutic options. The preponderance of evidence suggests potential beneficial effects of curcumin on insulin resistance, while modern science provides a scientific basis for its potential applications against the disease. Curcumin combats insulin resistance by increasing the levels of circulating irisin and adiponectin, activating PPARγ, suppressing Notch1 signalling, and regulating SREBP target genes, among others. In this review, we bring together the diverse areas pertaining to our current understanding of the potential benefits of curcumin on insulin resistance, associated mechanistic insights, and new therapeutic possibilities.

Keywords: curcumin; insulin resistance; PPARγ; irisin; adiponectin

Introduction

DM is a chronic disease caused by the body being unable to either produce a sufficient amount of, or effectually utilise, insulin. The global prevalence of DM has been suggested to have almost doubled since 1980.[1] In addition, its global prevalence has been projected to be ~700 million by the year 2045, with 90–95% of all DM cases being type 2 in nature.[2] DM is a heterogeneous and complex metabolic disorder characterised by hyperglycaemia secondary to either insulin resistance, inadequate insulin secretion, or both. The most common categories of DM are type 1 DM (T1DM), T2DM, and gestational DM. Of these, T1DM is caused by an absolute or near-absolute insulin deficiency, whereas T2DM is largely associated with insulin resistance with an inadequate compensatory increase in insulin secretion, and a relative deficiency of insulin with T2DM.[3] Gestational DM is defined as the glucose intolerance that is recognised in pregnancy, with onset generally during the third trimester of pregnancy. Patients with gestational DM can have a risk of developing T2DM later in life.[3].

The pathophysiology of T2DM and associated secondary complications have been largely investigated in biomedical research; nevertheless, the effective prevention, management, and treatment of this insidious disease remain inadequate. T2DM is often characterised by insulin resistance and chronic hyperglycaemia[4,5]

* *Corresponding author. Balakumar, P. (pbala2006@gmail.com), Balakumar, P. (directorcr@pmu.edu).*

https://doi.org/10.1016/j.drudis.2023.103627

and the former has been suggested to affect a quarter of the adult population worldwide.[6] Despite advances in medicine and pharmacotherapy, T2DM with insulin resistance remains an overwhelming health problem. Curcumin [(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], a natural bioactive polyphenol found in turmeric (*Curcuma longa* Linn), has been suggested to be useful in the management of diabetic complications.[7,8] Turmeric is 'generally recognised as safe' (GRAS) as a food ingredient by the US Food and Drug Administration (FDA), and curcumin is available as a dietary supplement.

Evidence from experimental and clinical studies suggests that curcumin could offer beneficial effects in the management of insulin resistance by virtue of its potential to improve insulin sensitivity via various mechanisms.[8–18] Curcumin has wide-ranging beneficial pharmacological activities, including anti-inflammatory, antioxidative, antifibrogenic, antiproliferative, antiviral, and antidiabetic potential.[19–23] In clinical practice, it has been suggested that curcumin may be recommended as an adjunct to the treatment of patients with T2DM to improve insulin resistance and glycaemic management.[12] In this review, we highlight the most promising findings with regard to the therapeutic potential of curcumin in the management of insulin resistance as well as underlying mechanistic insights, which may provide details for the development of targeted therapy for endocrine diseases, such as insulin resistance, a hallmark of T2DM.

Diabetes-associated insulin resistance: A succinct look

If managed inadequately for a considerable amount of time, DM leads to serious long-term health complications, such as impaired renal function, blindness, neuropathy, vasculopathy, stroke, myocardial infarction, dermatopathy, and lower limb amputation, among others.[24–29] Furthermore, DM and coexisting dyslipidaemia, often referred to as 'diabetic dyslipidaemia', have a key pathogenic role in cardiovascular illness. Moreover, diabetic dyslipidaemia is associated with insulin resistance, elevated plasma triglyceride levels, reduced high-density lipoprotein (HDL)–cholesterol concentration and increased numbers of small, dense low-density lipoprotein (LDL)-cholesterol particles.[30] Together, chronic DM and its complications are major causes of mortality worldwide. The prevalence of DM has increased significantly in recent years, with T2DM comprising ~90% of cases of DM.[31] Individuals with a family history of T2DM can have an increased risk of developing T2DM themselves.[32] Thus, T2DM has become an urgent global health challenge.[33] In general, T2DM is considered a metabolic disorder of carbohydrates, proteins, and fats caused by insulin deficiency or insulin resistance, mediating high oxidative stress, inflammation, and macro- or microvascular dysfunctions, and eventually developing into diverse complications.[20]

Insulin resistance is a complex metabolic disorder characterised by the inability of cells to efficiently utilise glucose. This might occur because of a reduction in the ability of cells to respond to insulin, which in turn causes elevated blood glucose concentration in the midst of hyperinsulinaemia, which is considered the basal state of origin of insulin resistance. Hyperinsulinaemia is characterised by unusually high blood insulin levels, and is an important contributing factor in insulin resistance, obesity, and metabolic syndrome. Consequently, patients with insulin resistance are predisposed to a cluster of risk factors, such as T2DM, obesity, hypertension, and dyslipidaemia, among others.[34] Evidence supports that T2DM is largely associated with insulin resistance,[35,36] defined as a normal or elevated level of insulin producing an attenuated biological response, denoting impaired sensitivity to insulin-mediated disposal of glucose.[37]

The insulin signalling pathway is initiated when insulin binds to its receptor. Once formed, the insulin-receptor complex triggers tyrosine phosphorylation of second messengers, such as insulin receptor substrate 1 and 2 (IRS1 and 2). In turn, this activates phosphoinositide-3-kinase (PI3K), which stimulates the serine phosphorylation of Akt (PKB/protein kinase B), which then stimulates glucose transport in muscle and adipose tissue by translocation of glucose transporter-4 (GLUT4) from the cytoplasm to plasma membrane.[34] GLUT4 is a high-affinity insulin-responsive glucose transporter predominantly expressed in adipocytes and myocytes; failure of its translocation to the cell membrane in response to insulin action is recognised as an early event in the development of insulin resistance.[38] Importantly, IRS1/2 tyrosine phosphorylation has been suggested to activate IRS proteins to bind to signalling molecules in the insulin signalling pathway.[34] By contrast, serine phosphorylation of IRS proteins has been suggested to attenuate insulin signalling, adding an additional mechanism of insulin resistance as demonstrated in rodents.[34]

Insulin resistance is a pathological condition mainly characterised by tissues showing resistance or less responsiveness to the action of insulin.[38] T2DM can result from insulin resistance in skeletal muscle, adipose tissue, and the liver, involving several risk factors, such inflammation, hyperlipidaemia, obesity, and physical inactivity.[38] Globally obesity is considered one of the major health problems, contributing to the increasing prevalence of insulin resistance and T2DM.[39] Chronic inflammation in adipose tissue has been suggested to be a key pathological condition for insulin resistance development in obese individuals.[39] Macrophages, immune cells abundantly present in adipose tissue, have a key role in the inflammation of adipose tissue, and macrophage mitochondrial dysfunction has been suggested to be a key mediator of obesity-associated macrophage inflammatory response and insulin resistance.[39] In this context, mitochondrial dysfunction is documented to drive NLRP3 inflammasome activation, inducing the release of IL-1β, which leads to decreased insulin sensitivity of insulin target cells.[39] In addition, the hypertrophied adipocytes and infiltration of macrophage-associated local inflammation can lead to insulin resistance.[40]

Therapeutic potential of curcumin in insulin resistance and associated mechanistic insights: Experimental and clinical evidence

Insulin sensitisers, such as thiazolidinediones and biguanides, are the mainstay of treatment of T2DM with insulin resistance.[35] Yet, the long-term clinical application of these agents is associated with several harmful adverse effects, emphasising the need to investigate natural therapeutic products that might avoid such effects.[35] A growing body of evidence suggests that curcumin modulates glucose homeostasis and improves insulin resistance.

Despite its well-known efficacies against several pathological conditions, the limited systemic bioavailability of curcumin is a continuing concern, while its poor bioavailability might have curtailed its clinical development as a potential therapeutic agent. Nevertheless, there have been numerous studies investigating the potential reasons for the reduced bioavailability of curcumin and, as a result, various therapeutic approaches have been developed to improve its bioavailability.[41] Below we summarize the therapeutic potentials of curcumin in combating insulin resistance and accompanying mechanistic insights.

Various experimental and clinical studies have demonstrated the efficacy of curcumin in the management of insulin resistance, and it has long been used in traditional medicine to improve the symptoms of DM and its comorbidities.[9] Curcumin could act as a regulator of protein homeostasis and has potential to modulate various intracellular pathways.[9] Curcumin supplementation is proposed to improve insulin resistance via the activation of the insulin receptor and its downstream pathways, as seen in experimental models.[9]

In high-fat diet (HFD)-fed male Wistar rats, the beneficial effects of curcumin on oxidative stress, inflammation and insulin resistance were evaluated.[10] Rats fed a HFD showed elevated levels of insulin, Homeostasis Model Assessment for Insulin Resistance (HOMA-IR), fasting plasma glucose, total cholesterol (TC), very LDL (VLDL) and triacylglycerol (TAG), and decreased levels of HDL cholesterol.[10] In addition, the rats showed an increase in plasma inflammatory markers, such as tumor necrosis factor (TNF)-α, and skeletal muscle oxidative stress parameters, such as malondialdehyde (MDA) and total oxidant status.[10] Curcumin treatment was noted to significantly reduce these parameters, the levels of glucose, insulin, and HOMA-IR, and also liver fat deposition.[10] These results indicate that curcumin supplementation has the potential to improve HFD-induced dyslipidaemia, inflammation, oxidative stress, and insulin resistance.[10]

A growing body of evidence suggests high fructose consumption as a potentially important risk factor for the increasing incidence of insulin resistance and DM globally. In this context, a study by Maithilikarpagaselvi *et al.*[11], in high fructose-fed male Wistar rats, investigated the potential preventive effects of curcumin on oxidative stress, inflammation, and insulin resistance at the molecular level. In this study, feeding of fructose for 10 weeks induced oxidative stress, inflammation, and insulin resistance in rats.[11] Curcumin treatment attenuated insulin resistance by diminishing IRS-1 serine phosphorylation and increasing IRS-1 tyrosine phosphorylation in the skeletal muscle of high fructose-fed rats.[11] In addition, curcumin attenuated hyperinsulinaemia, glucose intolerance and HOMA-IR level, and reduced TNF-α and C-reactive protein (CRP) levels.[11] Moreover, curcumin treatment inhibited the increase in MDA and total oxidant status, and suppressed the expression of extracellular kinase 1/2 (ERK 1/2) and p38 in the skeletal muscle of the fructose-fed rats.[11] Furthermore, at the molecular level, curcumin has the potential to inhibit the activation of stress-sensitive kinases and inflammatory cascades.[11] This study highlights the potential therapeutic abilities of curcumin in attenuating glucose intolerance and insulin resistance by virtue of its marked antioxidant and anti-inflammatory properties, suggesting the use of curcumin as an adjuvant in the management of insulin resistance and diabetes-associated complications.[11]

Macrophages activated by stressed cells can induce nuclear factor kappa-B (NFκB), resulting in the production of proinflammatory cytokines, such as TNF and interleukin (IL)-6, while these inflammatory macrophages in adipose tissue and liver can promote insulin resistance.[42] Curcumin has been recognised as an antioxidant and an inhibitor of NFκB.[42] In addition to acting as a scavenger of intracellular small oxidative molecules, such as hydrogen peroxide, superoxide anions, hydroxyl radicals, and peroxyl radicals, curcumin also activates downstream antioxidant genes and Nrf2, a master regulator of the endogenous antioxidant response.[9] Interestingly, curcumin has the potential to reduce inflammation and prevent or delay obesity-induced insulin resistance and associated complications.[42] Yekollu *et al.*[43] investigated the mechanism by which systemic delivery of curcumin-containing liposomes (curcusomes) improves insulin resistance in a leptin-deficient (ob/ob) mouse model of insulin resistance. This study suggested that both hepatic TNF/inducible nitric oxide synthase-producing dendritic cells (Tip-DCs) and adipose tissue macrophages (ATMs) contribute to insulin resistance in ob/ob mice.[43] Interestingly, curcusomes inhibited proinflammatory pathways in hepatic Tip-DCs and ATMs, and subsequently reversed the insulin resistance,[43] suggesting targeting inflammatory DCs as an additional approach for the management of insulin resistance-associated T2DM.[43]

Curcumin has been suggested to interact with specific proteins in adipocytes, hepatic stellate cells, pancreatic cells, macrophages, and muscle cells, where it can suppress several cellular proteins, such as NFκB and STAT3, and can activate peroxisome proliferator-activated receptor gamma (PPARγ) signalling pathways.[44] Moreover, curcumin has the potential to downregulate inflammatory cytokines and upregulate adiponectin and other associated proteins.[44] Thus, the interactions of curcumin with several signalling pathways could reverse insulin resistance, hyperlipidaemia, and other inflammatory symptoms allied with obesity and metabolic diseases.[44].

Recognised as a member of the nuclear receptor superfamily, PPARγ regulates the gene expression of proteins involved in the metabolism of glucose. PPARγ activation has an important role in glucose metabolism by means of enhancing insulin sensitisation, and PPARγ is a primary target for thiazolidinedione-like insulin sensitisers, such as rosiglitazone and pioglitazone, used for the management of insulin resistance and T2DM.[45] PPARγ is considered a key regulator of insulin sensitisation, and is an important pharmacological target to combat insulin resistance.[46] Moreover, PPARγ activation inhibits vascular inflammatory events and adhesion cascades.[45] A growing body of evidence suggests that curcumin has the potential to upregulate or activate PPARγ.[44,47,48] This is supported by results obtained in a randomised, double-blind, placebo-controlled trial that evaluated the effect of curcumin on glycaemic control and the associated mechanisms involved in women with polycystic ovary syndrome (PCOS).[48] In this study, compared with placebo, curcumin significantly reduced fasting glucose, serum insulin, and insulin resistance, and significantly increased insulin sensitivity. In addition, curcumin administration has been observed to

upregulate the expression of *PPARγ*,[48] implying that a beneficial effect of curcumin in combating insulin resistance could involve PPARγ upregulation and activation (Figure 1). Another randomised placebo-controlled clinical trial evaluated the efficacy of curcumin supplementation on PPARγ coactivator 1α (*PGC1α*) gene expression in patients with PCOS,[49] wherein curcumin supplementation significantly increased the expression of this gene.[49]

A recent randomised controlled study suggested that curcumin has a synergistic effect with metformin in improving insulin resistance in patients with PCOS.[50] Abuelezz *et al.*[51] investigated the pancreatic levels of PI3K/AKT/mTOR in a PCOS animal model and explored the impact of nanocurcumin against pancreatic pathologies. Western blots revealed a significant reduction in the levels of PI3K/AKT/mTOR, leading to impaired insulin sensitivity and decreased β cell mass and function.[51] However, nanocurcumin significantly improved oxidative markers and glucose indices, as well as being shown to reinstate the levels of PI3K/AKT/mTOR, alleviate insulin resistance, and retain the integrity of islets.[51] Thus, this study suggests that nanocurcumin has the potential to alleviate insulin resistance and pancreatic deficits in rats with PCOS.[51]

Curcumin has been suggested to stimulate insulin-mediated glucose uptake via the PI3K/Akt pathway, which in turn can cause the translocation of GLUT4 to the membrane of skeletal muscle and adipocytes, resulting in an increase in glucose uptake.[52] In addition, curcumin has the potential to activate AMP-activated protein kinase (AMPK), which has been suggested to not only suppress gluconeogenesis in hepatocytes, but also enhance GLUT4 translocation and subsequent glucose uptake in adipocytes.[52] Moreover, curcumin improves glucose homeostasis by activating glucose transporter 2 and glucokinases in the liver by increasing PPARγ transcription.[52] The Notch pathway is a signal transduction pathway that has been suggested to be involved in energy metabolism.[53] Interestingly, an experimental study in rats fed a HFD suggested that the hepatic Notch 1 pathway can be suppressed by curcumin, which could have a role in the amelioration of fatty liver and insulin resistance.[53]

Sterol regulatory element-binding proteins (SREBPs) are considered major transcription factors regulating the expression of genes involved in the synthesis of fatty acids, cholesterol, and triglyceride.[54] Inhibition of the SREBP pathway has been suggested as a strategy to treat obesity with T2DM.[54] Ding *et al.*[54] reported that curcumin can inhibit the expression of SREBP *in vitro*, which decreased the synthesis of fatty acids and cholesterol. In HFD-induced obese mice, curcumin ameliorated HFD-induced body weight gain and accumulation of fat in the liver or adipose tissues, and improved serum lipids and insulin sensitivity.[54] Subsequently, it has been suggested that curcumin could regulate SREBP target genes and metabolism-associated genes in the liver or adipose tissues, which might contribute directly to lowering lipid levels and improving experimental insulin resistance.[54]

These findings might support the possible translation of curcumin to clinical practice for the prevention and management

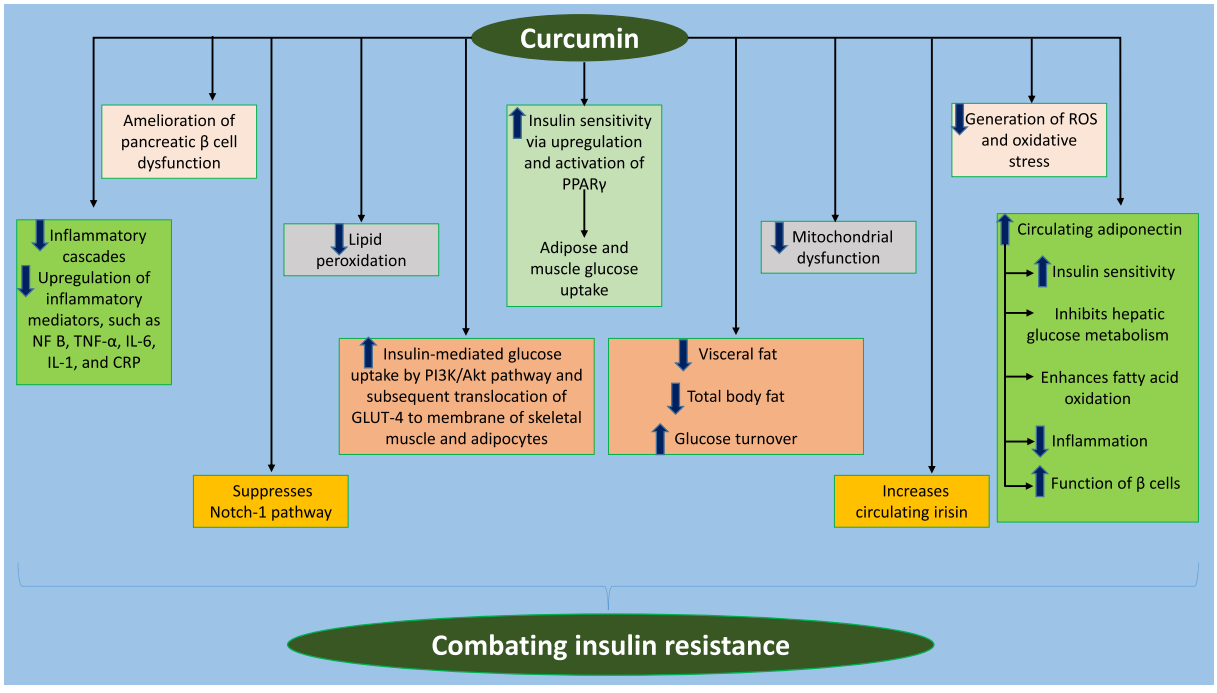

FIGURE 1

Possible involvement of multifaceted mechanisms in curcumin-mediated improvement of insulin resistance. Curcumin combats insulin resistance by increasing the levels of circulating adiponectin and irisin, activating peroxisome proliferator-activated receptor gamma (PPARγ), suppressing Notch1 signalling, and reducing inflammation and oxidative stress, among other mechanisms. Abbreviations: CRP, C-reactive protein; IL, interleukin; NFκB, nuclear factor kappa-B; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α. (See main text for more details.)

of insulin resistance. Moreover, the comparatively low cost of curcumin, and its safety margin and therapeutic efficacy could recommend it to be a part of healthy diet for patients with T2DM and insulin resistance. The possible mechanisms involved in curcumin-mediated improvement of insulin resistance are depicted in Figure 1. Key preclinical and clinical studies demonstrating the potential actions of curcumin in combating insulin resistance are summarised in Table 1.

Does curcumin-mediated effects in the improvement of insulin resistance involve irisin?

Irisin is a novel myokine secreted in response to activation of PGC1α.[55] It is an exercise-induced myokine, secreted by skeletal muscles, that induces browning of white adipose tissue to increase energy expenditure, reduce insulin resistance, and improve glucose tolerance.[56–59] Increased levels of circulating irisin have been suggested to be associated with improved glucose homeostasis by reducing insulin resistance.[57] The active involvement of irisin in energy homeostasis created much interest in understanding its key role in cellular metabolism and glucose homeostasis.

Irisin might have a modulatory role in many inflammatory pathways, via mechanisms including reducing the production of proinflammatory cytokines, increased production of anti-inflammatory cytokines, and reduced macrophage proliferation, in addition to interfering with vascular permeability and preventing inflammasome formation.[58] Treatment with irisin of cells exposed to inflammatory stimuli ameliorated the inflammatory response and promoted cellular viability.[58] Zhang *et al.*[60] demonstrated that irisin significantly reduced atherosclerosis in apolipoprotein E-deficient mice by suppressing oxidised LDL (ox-LDL)-induced cell inflammation and apoptosis, which could have a therapeutic role against atherosclerotic diseases.[60] Moreover, various studies have reported diminished levels of irisin in patients with T2DM.[58,61–63]

Irisin and diabetes mellitus

An observational study showed that circulating irisin was lower in patients with T2DM compared with nondiabetic controls.[55] Xuan *et al.* evaluated the role and levels of serum irisin in older patients with T2DM in a case-control study,[64] finding that the serum irisin level in patients with T2DM was significantly lower relative to the control group, suggesting irisin as a protective factor against T2DM.[64] Even in patients with newly diagnosed T2DM, circulating irisin concentrations were significantly lower compared with healthy controls.[65] A systematic review and meta-analysis study revealed that, compared with nondiabetic controls, circulating irisin concentrations were significantly lower in patients with insulin-resistant conditions, such as T2DM and gestational DM, but 30% higher in patients with T1DM, suggesting that circulating irisin levels are decreased only in patients with T2DM and GDM.[66].

A recent meta-analysis suggested a strong association between low serum irisin concentration and diabetic nephropathy in patients with T2DM.[67] Compared with patients with T2DM and normoalbuminuria, patients with microalbuminuria and macroalbuminuria showed significantly lower levels of serum irisin,[67] particularly in patients with T2DM and macroalbuminuria compared with those with microalbuminuria.[67] Therefore, diabetic nephropathy could be significantly related to decreased serum irisin concentrations in patients with T2DM in a concentration–response manner.[68] Given that the progression of diabetic nephropathy reflects an advanced state of DM, the change in serum irisin concentration might reflect glucose intolerance via insulin resistance.[68] In line with these reports, Hu *et al.*[69] demonstrated that patients with T2DM and macroalbuminuria had a significantly lower serum irisin concentration relative to control subjects and patients with T2DM and normal albuminuria and microalbuminuria. Using regression analysis, the serum irisin concentration in patients with T2DM was revealed to be negatively correlated with age, HOMA-IR, fasting plasma glucose, creatinine, and blood urea nitrogen.[69] Likewise,

TABLE 1

Key preclinical and clinical studies demonstrating the potential actions of curcumin in combating insulin resistance.

Type of study	Key outcomes	Refs
Preclinical	Rats fed a HFD showed elevated levels of insulin, HOMA-IR, and fasting plasma glucose, lipid abnormalities, and increase in plasma inflammatory markers, such as TNF-α and skeletal muscle oxidative stress. Curcumin treatment reduced these abnormalities and the levels of glucose, insulin and HOMA-IR in HFD-fed male rats, indicating the potential ability of curcumin supplementation to improve HFD-induced dyslipidaemia, inflammation, oxidative stress, and insulin resistance	10
	In high fructose-fed male rats, curcumin showed the potential to attenuate glucose intolerance and insulin resistance by virtue of its potent antioxidant and anti-inflammatory properties	11
	In C57 BL/6 mice fed a HFD, curcumin increased plasma irisin concentrations and improved insulin sensitivity	13
	In leptin-deficient (ob/ob) mouse model of insulin resistance, systemic delivery of curcumin-containing liposomes (curcusomes) improved insulin resistance	43
	In rats with PCOS, nanocurcumin showed potential to alleviate insulin resistance and pancreatic deficits	51
	In HFD-induced obese mice, curcumin ameliorated HFD-induced body weight gain and accumulation of fat in the liver or adipose tissues, and enhanced insulin sensitivity	54
Clinical	In a randomised, double-blind, placebo-controlled trial in women with PCOS, curcumin significantly reduced fasting glucose, serum insulin, and insulin resistance, and markedly increased insulin sensitivity compared with placebo	48
	In a randomised controlled study, curcumin had a synergistic effect with metformin in improving insulin resistance in patients with PCOS	50

Shelbaya *et al.*[59] reported lower irisin concentrations in patients with DM and diabetic nephropathy relative to those without complications. In addition, a statistically significant negative correlation was shown between irisin and systolic and diastolic blood pressure, body mass index, serum creatinine, albumin/creatinine ratio, and HbA_{1c} in all patients with T2DM studied.[59].

Irisin and insulin resistance

A growing body of evidence reveals the relationship between irisin concentration and insulin signalling. Decreased irisin secretion contributes to muscle insulin resistance in HFD-fed mice.[70] Circulating irisin concentration is suggested to be negatively associated with obesity and insulin resistance.[71] An experimental study using human liver-derived HepG2 cells indicated that irisin can ameliorate the dysregulation of hepatic lipid/glucose metabolism and cell death in insulin resistance through AMPK activation, revealing a novel irisin-mediated protective mechanism in hepatic metabolism.[72] This might provide a scientific basis to consider irisin as a potential therapeutic target in the management of T2DM and insulin resistance.[72] In another experimental study, irisin was shown to ameliorate glucolipotoxicity-associated β cell dysfunction and apoptosis through AMPK signaling and anti-inflammatory activities.[73].

In type 2 diabetic mice and hepatocytes, irisin inhibited hepatic gluconeogenesis and increased glycogen synthesis via the PI3K/Akt pathway.[74] Additionally, in diabetic mice, persistent subcutaneous perfusion of irisin improved insulin sensitivity, reduced fasting blood glucose levels, increased the phosphorylation of GSK3 and Akt, and the irisin and glycogen content, and suppressed glycogen synthase (GS) phosphorylation and phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) expression in the liver.[74] This study suggested that irisin could improve glucose homoeostasis by reducing gluconeogenesis through PI3K/Akt/FOXO1-mediated downregulation of PEPCK and G6Pase, and by increasing glycogenesis through PI3K/Akt/GSK3-mediated activation of GS.[74] In addition, the authors suggested that irisin could be regarded as a novel therapeutic strategy for the management of insulin resistance and T2DM.[74].

Interestingly, irisin has been suggested to improve insulin resistance and T2DM by increasing the sensitivity of insulin receptors in the skeletal muscle and heart, improving hepatic lipid and glucose metabolism, and promoting the functions of pancreatic β cells, and browning of white adipose tissue.[75] Skeletal muscle is a major site of insulin resistance because it takes up most of its glucose via insulin. Thus, irisin could facilitate glucose uptake by skeletal muscles, having a favourable effect on hyperglycaemia, and, hence, could act as an insulin-sensitising hormone.[75] Metformin, an antihyperglycaemic agent, improves insulin sensitivity by augmenting insulin-mediated insulin receptor tyrosine kinase activity, which in turn activates post-receptor insulin signalling pathways.[76] Intriguingly, in diabetic obese db/db mice, metformin, but not glibenclamide, increased the expression of intramuscular fibronectin type III domain-containing protein 5 (FNDC5) mRNA/protein and blood irisin levels.[77] Metformin-mediated promotion of irisin release suggests irisin stimulation as an additional mechanism involved in the insulin-sensitising action of metformin, highlighting the key role of irisin in therapeutics against insulin resistance.

Physical exercise has been suggested to induce the expression of *PGC1a* in skeletal muscle and downstream membrane proteins, such as FNDC5, which is proteolytically cleaved to form irisin.[75] Thus, adipose tissue and muscle might produce irisin during exercise, with irisin acting as a thermogenic adipomyokine that can improve glucose and lipid metabolism, and ameliorate the consequences of obesity-driven inflammation, DM, and metabolic syndrome.[78] Furthermore, exercise-induced irisin can activate anti-inflammatory pathways that might have an important role in the improvement of inflammatory conditions and their outcomes.[78] Moreover, irisin has potentially protective properties against the development of obesity-related pathological conditions, such as insulin resistance, T2DM, and arteriosclerosis.[79]

Effect of curcumin on irisin concentration

Zou *et al*. evaluated the metabolic effects of curcumin in association with the regulation of energy metabolism and activation of FNDC5/irisin.[13] In C57 BL/6 mice fed a HFD, curcumin administration increased the plasma irisin concentration and notably improved insulin sensitivity of the mice.[13] In addition, curcumin increased the oxygen consumption and heat production in HFD mice, accompanied by enhancement of metabolic activity in brown fat and inguinal white adipose tissue.[13] Moreover, curcumin-mediated improvement of basal metabolic rate might be regulated, in part, by the FNDC5/p38 mitogen-activated protein kinase (p38 MAPK)/ERK1/2 signal transduction pathway.[13] The authors suggested that dietary curcumin could alleviate diet-induced adiposity through improving insulin sensitivity and whole-body energy metabolism via impacting the FNDC5/p38 MAPK/ERK pathway.[13] Thus, this study demonstrates the efficacy of curcumin in improving insulin sensitivity and increasing energy expenditure in experimental HFD-induced obese condition by triggering the activation of FNDC5/irisin.[13] The possible mechanisms by which curcumin-mediated increases in irisin concentration could contribute to improvement of insulin resistance are shown in Figure 2.

Does curcumin improve insulin resistance through an effect on adiponectin?

Adipose tissue produces pro- and anti-inflammatory mediators, which influence both local and systemic inflammation. Adiponectin is an adipokine secreted by adipocytes, and it regulates insulin sensitivity, glucose levels, and lipid metabolism through its anti-inflammatory, antifibrotic, and antioxidant actions.[87] Adiponectin appears to promote insulin sensitivity by enhancing glucose and lipid metabolisms.[87] Its level is reduced in association with T2DM and insulin resistance.[80] Here, we provide a brief overview of the key role of adiponectin in the improvement of insulin resistance, and effects of curcumin on circulating adiponectin.

Adiponectin and insulin resistance: an overview

Adiponectin is an adipocyte-specific protein with a modulatory role in insulin resistance.[80] The potential mechanism by which

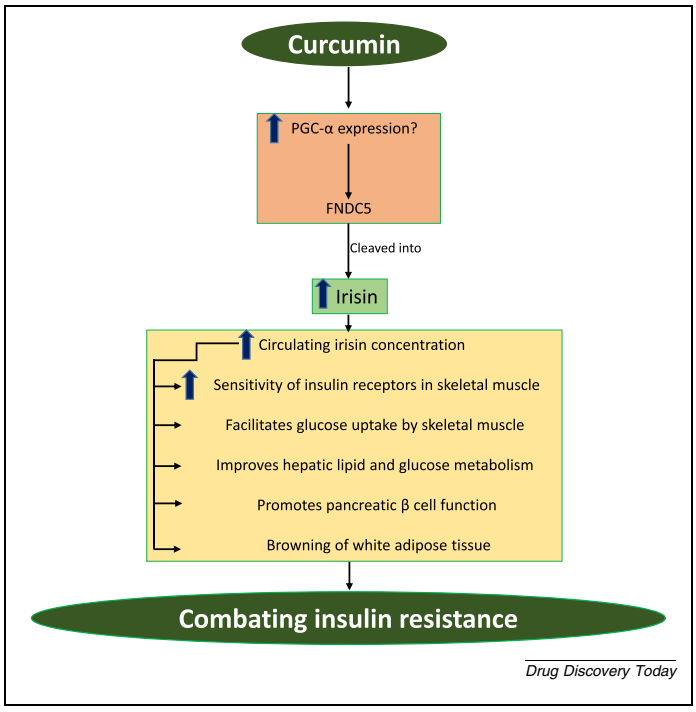

FIGURE 2

Possible mechanisms by which curcumin-mediated increases in irisin concentration might contribute to the improvement of insulin resistance. Administration of curcumin can result in increases in plasma irisin concentration, which, through a variety of mechanistic events, helps to combat insulin resistance. Abbreviations: FNDC5, fibronectin type III domain-containing protein 5; PGC1α, peroxisome proliferator activated receptor γ coactivator 1α. (See main text for more details.)

adiponectin enhances insulin sensitivity is mediated through inhibition of hepatic glucose production and increases in fatty acid oxidation.[80] Adiponectin levels are increased by treatment with thiazolidinediones, a well-known class of insulin-sensitising drugs,[81] suggesting the key role of adiponectin in ameliorating insulin resistance. Adiponectin is an insulin-sensitising and anti-inflammatory fat-cell hormone and an important pharmacological target site for obesity-associated disorders, including insulin resistance, T2DM, and atherosclerosis.[82,83] Its interaction with its receptor results in the activation of various signalling pathways, such as IRS1/2, AMPK, and p38 MAPK, whereas adiponectin signalling-mediated activation of IRS1/2 is suggested to be a major mechanism by which adiponectin sensitises the action of insulin in insulin-responsive tissues.[84] Administration of adiponectin in humans and rodents has insulin-sensitising, anti-inflammatory, and antiatherogenic effects, among others,[84] and, consequently, pharmacological interventions that can increase the levels of adiponectin under certain pathological conditions could be considered as a mainstay for the management of obesity, T2DM/insulin resistance, and atherosclerosis.

Effect of curcumin on adiponectin concentration

A growing body of evidence suggests that curcumin could improve insulin resistance through beneficial effects on adiponectin levels. In this context, a randomised double-blind, placebo-controlled trial in patients with metabolic syndrome evaluated the effect of curcumin supplementation on serum adipokine concentrations.[85] An 8-week curcumin supplementation was associated with a significant increase in the levels of serum adiponectin,[85] suggesting that curcumin improves serum adiponectin levels in patients with metabolic syndrome.[85] Likewise, a randomised, double-blind, placebo-controlled trial analysing the effect of 10-week curcumin supplementation on serum adiponectin concentration in patients with T2DM showed an increase in the mean serum adiponectin concentration compared with placebo.[8] Moreover, a systematic review and meta-analysis of randomised controlled trials evaluating the modulatory effect of curcumin supplementation on circulating adiponectin levels reported that curcumin supplementation significantly increased the concentration of adiponectin compared with placebo, with a greater effect on adiponectin concentration observed in study trials lasting ≤10 weeks.[86] Thus, curcumin could be used as an adjunct or complementary pharmacological agent to increase plasma adiponectin, the action of which could ameliorate insulin resistance and T2DM.

Concluding remarks

This review provides mechanistic insights related to the current understanding of the potential benefits of curcumin on insulin resistance. T2DM is characterised by defective insulin secretion, which might result from insufficient compensatory increases in β cell mass and deficient glucose-dependent insulin release. T2DM is an intricate metabolic disease characterised by chronic hyperglycaemia, which occurs as a result of either defective insulin secretion or inadequate insulin signalling because of insulin resistance, inducing major complications and premature death. Insulin resistance is associated with many pathological conditions, such as T2DM, carbohydrate intolerance, cardiovascular disease, and metabolic syndrome. It is imperative to identify safe therapeutic interventions aimed to efficiently combat insulin resistance and reduce its pathogenic outcomes. Several preclinical and clinical investigations showed beneficial effects of curcumin in improving insulin sensitivity, involving multifaceted molecular and cellular mechanisms. Mitigation of insulin resistance might be associated with an improvement of diabetic complications by curcumin because it has wide-ranging beneficial pharmacological activities, including anti-inflammatory, antioxidative, antifibrogenic, antiproliferative, and antidiabetic potential. In addition, curcumin could combat insulin resistance through various key mechanisms, such as improvements in circulating irisin and adiponectin levels, upregulation and activation of PPARγ, and suppression of Notch 1 signaling, among others. Polyphenols, such as curcumin, occur naturally in the diet and might not cause significant adverse effects; thus, they could be used efficiently for the prevention and treatment of insulin resistance, particularly as an adjunct or complementary therapeutic agent. Based on existing evidence, the application of curcumin could be an appropriate strategy to improve insulin resistance-related diseases, with the dose, time of treatment, and type of formulation determining its therapeutic outcomes.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

The authors express their gratitude to the Deanship of Scientific Research at King Khalid University, Saudi Arabia for supporting this work through Large Groups Project under grant number (RGP2/125/44). The authors convey their sincere gratitude to Drs. P.K. Srividhya and S. Kumaran (Periyar Maniammai Institute of Science & Technology) for their inspiration.

References

1. Duffy S et al. Using community health workers and a smartphone application to improve diabetes control in rural Guatemala. *Glob Health Sci Pract*. 2020;8:699–720.
2. Ng JY, Nayeni M, Gilotra K. Quality of complementary and alternative medicine information for type 2 diabetes: a cross-sectional survey and quality assessment of websites. *BMC Complement Med Ther*. 2021;21:233.
3. Solis-Herrera C, Triplitt C, Reasner C, DeFronzo RA, Cersosimo E. Classification of diabetes mellitus. In: Feingold KR, ed. *Endotext*. South Dartmouth (MA): MDText; 2018.
4. Chansela P, Potip B, Weerachayaphorn J, Kangwanrangsan N, Chukijrungroat N, Saengsirisuwan V. Morphological alteration of the pancreatic islet in ovariectomized rats fed a high-fat high-fructose diet. *Histochem Cell Biol*. 2022;157:427–442.
5. Sajadimajd S, Deravi N, Forouhar K, Rahimi R, Kheirandish A, Bahramsoltani R. Endoplasmic reticulum as a therapeutic target in type 2 diabetes: role of phytochemicals. *Int Immunopharmacol*. 2023;114 109508.
6. Khan MS, Cuda S, Karere GM, Cox LA, Bishop AC. Breath biomarkers of insulin resistance in pre-diabetic Hispanic adolescents with obesity. *Sci Rep*. 2022;12:339.
7. Chiu YJ, Lo YH, Yang JS, Kuo SC, Tsai SC. Curcumin derivative MTH-3 regulates palmitate-induced insulin resistance in mouse myoblast C2C12 cells. *In Vivo*. 2021;35:3181–3191.
8. Adibian M, Hodaei H, Nikpayam O, Sohrab G, Hekmatdoost A, Hedayati M. The effects of curcumin supplementation on high-sensitivity C-reactive protein, serum adiponectin, and lipid profile in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. *Phytother Res*. 2019;33:1374–1383.
9. Jiménez-Osorio AS, Monroy A, Alavez S. Curcumin and insulin resistance-Molecular targets and clinical evidences. *Biofactors*. 2016;42:561–580.
10. Maithilikarpagaselvi N, Sridhar MG, Swaminathan RP, Sripradha R. Preventive effect of curcumin on inflammation, oxidative stress and insulin resistance in high-fat fed obese rats. *J Complement Integr Med*. 2016;13:137–143.
11. Maithilikarpagaselvi N, Sridhar MG, Swaminathan RP, Zachariah B. Curcumin prevents inflammatory response, oxidative stress and insulin resistance in high fructose fed male Wistar rats: potential role of serine kinases. *Chem Biol Interact*. 2016;244:187–194.
12. Zhang T, He Q, Liu Y, Chen Z, Hu H. Efficacy and safety of curcumin supplement on improvement of insulin resistance in people with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *Evid Based Complement Alternat Med*. 2021;2021:4471944.
13. Zou T, Li S, Wang B, Wang Z, Liu Y, You J. Curcumin improves insulin sensitivity and increases energy expenditure in high-fat-diet-induced obese mice associated with activation of FNDC5/irisin. *Nutrition*. 2021;90 111263.
14. Huang J, Guan B, Lin L, Wang Y. Improvement of intestinal barrier function, gut microbiota, and metabolic endotoxemia in type 2 diabetes rats by curcumin. *Bioengineered*. 2021;12:11947–11958.
15. Atazadegan MA, Bagherniya M, Fakheran O, Sathyapalan T, Sahebkar A. The effect of herbal medicine and natural bioactive compounds on plasma adiponectin: a clinical review. *Adv Exp Med Biol*. 2021;1328:37–57.
16. Brimson JM et al. Plant polyphenols for aging health: Implication from their autophagy modulating properties in age-associated diseases. *Pharmaceuticals (Basel)*. 2021;14:982.
17. Sayeli VK, Shenoy AK. Antidiabetic effect of bio-enhanced preparation of turmeric in streptozotocin-nicotinamide induced type 2 diabetic Wistar rats. *J Ayurveda Integr Med*. 2021;12:474–479.
18. Kapar FS, Ciftci G. The effects of curcumin and Lactobacillus acidophilus on certain hormones and insulin resistance in rats with metabolic syndrome. *J Diabetes Metab Disord*. 2020;19:907–914.
19. Balakumar P et al. The potential modulatory role of curcumin on renal epithelial-to-mesenchymal transition in renal diseases. *Pharmacol Res*. 2021;169 105646.
20. Tang C et al. Curcumin and its analogs as potential epigenetic modulators: prevention of diabetes and its complications. *Pharmacology*. 2022;107:1–13.
21. Vaiserman AM, Lushchak OV, Zayachkivska A, Koliada A. Curcumin. In: Koltover VK, ed. *Anti-Aging Pharmacology*. Cambridge; Academic Press; 2023:153–176.
22. Ezati M et al. Design, synthesis, spectroscopic characterizations, antidiabetic, in silico and kinetic evaluation of novel curcumin-fused aldohexoses. *Spectrochim Acta A Mol Biomol Spectrosc*. 2023;285 121806.
23. Mahboob A, Senevirathne DKL, Paul P, Nabi F, Khan RH, Chaari A. An investigation into the potential action of polyphenols against human islet amyloid polypeptide aggregation in type 2 diabetes. *Int J Biol Macromol*. 2023;225:318–350.
24. Balakumar P, Arora MK, Ganti SS, Reddy J, Singh M. Recent advances in pharmacotherapy for diabetic nephropathy: current perspectives and future directions. *Pharmacol Res*. 2009;60:24–32.
25. Balakumar P, Arora MK, Singh M. Emerging role of PPAR ligands in the management of diabetic nephropathy. *Pharmacol Res*. 2009;60:170–173.
26. Balakumar P, Kadian S, Mahadevan N. Are PPAR alpha agonists a rational therapeutic strategy for preventing abnormalities of the diabetic kidney? *Pharmacol Res*. 2012;65:430–436.
27. Balakumar P, Maung-U K, Jagadeesh G. Prevalence and prevention of cardiovascular disease and diabetes mellitus. *Pharmacol Res*. 2016;113:600–609.
28. Balakumar P. Implications of fundamental signalling alterations in diabetes mellitus-associated cardiovascular disease. *Indian J Biochem Biophys*. 2014;51:441–448.
29. Iatcu CO, Steen A, Covasa M. Gut microbiota and complications of type-2 diabetes. *Nutrients*. 2021;14:166.
30. Balakumar P, Mahadevan N, Sambathkumar R. A contemporary overview of PPARα/γ dual agonists for the management of diabetic dyslipidemia. *Curr Mol Pharmacol*. 2019;12:195–201.
31. Shang H, Liu ZP. Prioritizing type 2 diabetes genes by weighted pagerank on bilayer heterogeneous networks. *IEEE/ACM Trans Comput Biol Bioinform*. 2021;18:336–346.
32. Meza CA, Amador M, McAinch AJ, Begum K, Roy S, Bajpeyi S. Eight weeks of combined exercise training do not alter circulating microRNAs-29a, -133a, -133b, and -155 in young, healthy men. *Eur J Appl Physiol*. 2022;122:921–933.
33. Wang Z et al. Comparative analysis of the therapeutic effects of amniotic membrane and umbilical cord derived mesenchymal stem cells for the treatment of type 2 diabetes. *Stem Cell Rev Rep*. 2022;18:1193–1206.
34. Shehata MF. Role of the IRS-1 and/or -2 in the pathogenesis of insulin resistance in Dahl salt–sensitive (S) rats. *Heart Int*. 2009;4:e6.
35. Blahova J, Martiniakova M, Babikova M, Kovacova V, Mondockova V, Omelka R. Pharmaceutical drugs and natural therapeutic products for the treatment of type 2 diabetes mellitus. *Pharmaceuticals (Basel)*. 2021;14:806.
36. Xu B, Li S, Kang B, Zhou J. The current role of sodium–glucose cotransporter 2 inhibitors in type 2 diabetes mellitus management. *Cardiovasc Diabetol*. 2022;21:83.
37. Wilcox G. Insulin and insulin resistance. *Clin Biochem Rev*. 2005;26:19–39.
38. Lin J et al. Molecular basis of irisin regulating the effects of exercise on insulin resistance. *Appl Sci*. 2022;12:5837.
39. Xu L et al. Macrophage polarization mediated by mitochondrial dysfunction induces adipose tissue inflammation in obesity. *Int J Mol Sci*. 2022;23:9252.
40. Gołacki J, Matuszek M, Matyjaszek-Matuszek B. Link between insulin resistance and obesity–from diagnosis to treatment. *Diagnostics (Basel)*. 2022;12:1681.
41. Balakumar P et al. A unifying perspective in blunting the limited oral bioavailability of curcumin: a succinct look. *Curr Drug Metab*. 2022;23:897–904.

42. Maradana MR, Thomas R, O'Sullivan BJ. Targeted delivery of curcumin for treating type 2 diabetes. *Mol Nutr Food Res*. 2013;57:1550–1556.
43. Yekollu SK, Thomas R, O'Sullivan B. Targeting curcusomes to inflammatory dendritic cells inhibits NF-κB and improves insulin resistance in obese mice. *Diabetes*. 2011;60:2928–2938.
44. Shehzad A, Ha T, Subhan F, Lee YS. New mechanisms and the anti-inflammatory role of curcumin in obesity and obesity-related metabolic diseases. *Eur J Nutr*. 2011;50:151–161.
45. Balakumar P, Kathuria S. Submaximal PPARγ activation and endothelial dysfunction: new perspectives for the management of cardiovascular disorders. *Br J Pharmacol*. 2012;166:1981–1992.
46. Chigurupati S, Dhanaraj SA, Balakumar P. A step ahead of PPARγ full agonists to PPARγ partial agonists: therapeutic perspectives in the management of diabetic insulin resistance. *Eur J Pharmacol*. 2015;755:50–57.
47. Agrawal R, Nath V, Kumar H, Kumar V. Deciphering PPARγ activation in cardiometabolic syndrome: studies by in silico and *in vivo* experimental assessment. *J Recept Signal Transduct Res*. 2018;38:122–132.
48. Jamilian M et al. Effects of curcumin on body weight, glycemic control and serum lipids in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. *Clin Nutr ESPEN*. 2020;36:128–133.
49. Heshmati J et al. The effects of curcumin supplementation on oxidative stress, Sirtuin-1 and peroxisome proliferator activated receptor γ coactivator 1α gene expression in polycystic ovarian syndrome (PCOS) patients: a randomized placebo-controlled clinical trial. *Diabetes Metab Syndr*. 2020;14:77–82.
50. Sohrevardi SM et al. Therapeutic effect of curcumin in women with polycystic ovary syndrome receiving metformin: a randomized controlled trial. *Adv Exp Med Biol*. 2021;1308:109–117.
51. Abuelezz NZ, Shabana ME, Abdel-Mageed HM, Rashed L, Morcos GNB. Nanocurcumin alleviates insulin resistance and pancreatic deficits in polycystic ovary syndrome rats: insights on PI3K/AKT/mTOR and TNF-α modulations. *Life Sci*. 2020;256 118003.
52. Chien YJ, Chang CY, Wu MY, Chen CH, Horng YS, Wu HC. Effects of curcumin on glycemic control and lipid profile in polycystic ovary syndrome: systematic review with meta-analysis and trial sequential analysis. *Nutrients*. 2021;13:684.
53. Zhao NJ, Liao MJ, Wu JJ, Chu KX. Curcumin suppresses Notch-1 signaling: Improvements in fatty liver and insulin resistance in rats. *Mol Med Rep*. 2018;17:819–826.
54. Ding L et al. Curcumin rescues high fat diet-induced obesity and insulin sensitivity in mice through regulating SREBP pathway. *Toxicol Appl Pharmacol*. 2016;304:99–109.
55. Liu JJ et al. Lower circulating irisin is associated with type 2 diabetes mellitus. *J Diabetes Complications*. 2013;27:365–369.
56. Boström P et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature*. 2012;481:463–468.
57. Perakakis N et al. Physiology and role of irisin in glucose homeostasis. *Nat Rev Endocrinol*. 2017;13:324–337.
58. Slate-Romano JJ, Yano N, Zhao TC. Irisin reduces inflammatory signaling pathways in inflammation-mediated metabolic syndrome. *Mol Cell Endocrinol*. 2022;552 111676.
59. Shelbaya S, Abu Shady MM, Nasr MS, Bekhet MM, Mageed YA, Abbas M. Study of irisin hormone level in type 2 diabetic patients and patients with diabetic nephropathy. *Curr Diabetes Rev*. 2018;14:481–486.
60. Zhang Y et al. Protective effect of irisin on atherosclerosis via suppressing oxidized low density lipoprotein induced vascular inflammation and endothelial dysfunction. *PLoS ONE*. 2016;11:e0158038.
61. Akgul Balaban Y, Yilmaz N, Kalayci M, Unal M, Turhan T. Irisin and chemerin levels in patients with type 2 diabetes mellitus. *Acta Endocrinol (Buchar)*. 2019;15:442–446.
62. Shoukry A, Shalaby SM, El-Arabi Bdeer S, Mahmoud AA, Mousa MM, Khalifa A. Circulating serum irisin levels in obesity and type 2 diabetes mellitus. *IUBMB Life*. 2016;68:544–556.
63. Khidr EG, Ali SS, Elshafey MM, Fawzy OA. Association of irisin and FNDC5 rs16835198 G.T gene polymorphism with type 2 diabetes mellitus and diabetic nephropathy. An Egyptian pilot study. *Gene*. 2017;626:26–31.
64. Xuan X et al. Serum irisin levels and clinical implication in elderly patients with type 2 diabetes mellitus. *J Clin Med Res*. 2020;12:612–617.
65. Zhang C, Ding Z, Lv G, Li J, Zhou P, Zhang J. Lower irisin level in patients with type 2 diabetes mellitus: a case-control study and meta-analysis. *J Diabetes*. 2016;8:56–62.
66. Du XL, Jiang WX, Lv ZT. Lower circulating irisin level in patients with diabetes mellitus: A systematic review and meta-analysis. *Horm Metab Res*. 2016;48:644–652.
67. Wang R, Liu H. Association between serum irisin and diabetic nephropathy in patients with type 2 diabetes mellitus: a meta-analysis. *Horm Metab Res*. 2021;53:293–300.
68. Kawada T. Serum irisin and diabetic nephropathy in patients with diabetes mellitus. *Horm Metab Res*. 2021;53:825.
69. Hu W, Wang R, Li J, Zhang J, Wang W. Association of irisin concentrations with the presence of diabetic nephropathy and retinopathy. *Ann Clin Biochem*. 2016;53:67–74.
70. Yang Z, Chen X, Chen Y, Zhao Q. Decreased irisin secretion contributes to muscle insulin resistance in high-fat diet mice. *Int J Clin Exp Pathol*. 2015;8:6490–6497.
71. Moreno-Navarrete JM et al. Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance. *J Clin Endocrinol Metab*. 2013;98:E769–E778.
72. So WY, Leung PS. Irisin ameliorates hepatic glucose/lipid metabolism and enhances cell survival in insulin-resistant human HepG2 cells through adenosine monophosphate-activated protein kinase signaling. *Int J Biochem Cell Biol*. 2016;78:237–247.
73. Zhang D, Xie T, Leung PS. Irisin ameliorates glucolipotoxicity-associated β-cell dysfunction and apoptosis via AMPK signaling and anti-inflammatory actions. *Cell Physiol Biochem*. 2018;51:924–937.
74. Liu TY et al. Irisin inhibits hepatic gluconeogenesis and increases glycogen synthesis via the PI3K/Akt pathway in type 2 diabetic mice and hepatocytes. *Clin Sci (Lond)*. 2015;129:839–850.
75. Arhire LI, Mihalache L, Covasa M. Irisin: a hope in understanding and managing obesity and metabolic syndrome. *Front Endocrinol (Lausanne)*. 2019;10:524.
76. Wiernsperger NF, Bailey CJ. The antihyperglycaemic effect of metformin: therapeutic and cellular mechanisms. *Drugs*. 1999;58:31–39. discussion 75–82.
77. Li DJ, Huang F, Lu WJ, Jiang GJ, Deng YP, Shen FM. Metformin promotes irisin release from murine skeletal muscle independently of AMP-activated protein kinase activation. *Acta Physiol (Oxf)*. 2015;213:711–721.
78. Alves HR, Lomba GSB, Gonçalves-de-Albuquerque CF, Burth P. Irisin, exercise, and COVID-19. *Front Endocrinol (Lausanne)*. 2022;13 879066.
79. Mazur-Bialy AI, Pocheć E, Zarawski M. Anti-inflammatory properties of irisin, mediator of physical activity, are connected with TLR4/MyD88 signaling pathway activation. *Int J Mol Sci*. 2017;18:701.
80. Lihn AS, Pedersen SB, Richelsen B. Adiponectin: action, regulation and association to insulin sensitivity. *Obes Rev*. 2005;6:13–21.
81. Riera-Guardia N, Rothenbacher D. The effect of thiazolidinediones on adiponectin serum level: a meta-analysis. *Diabetes Obes Metab*. 2008;10:367–375.
82. Phillips SA, Kung JT. Mechanisms of adiponectin regulation and use as a pharmacological target. *Curr Opin Pharmacol*. 2010;10:676–683.
83. Hossain MM, Mukheem A, Kamarul T. The prevention and treatment of hypoadiponectinemia-associated human diseases by up-regulation of plasma adiponectin. *Life Sci*. 2015;135:55–67.
84. Achari AE, Jain SK. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. *Int J Mol Sci*. 2017;18:1321.
85. Panahi Y et al. Effects of supplementation with curcumin on serum adipokine concentrations: a randomized controlled trial. *Nutrition*. 2016;32:1116–1122.
86. Clark CCT, Ghaedi E, Arab A, Pourmasoumi M, Hadi A. The effect of curcumin supplementation on circulating adiponectin: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Metab Syndr*. 2019;13:2819–2825.
87. Nguyen TMD. Adiponectin: Role in physiology and pathophysiology. *Int J Prev Med*. 2020;11:136.