

Impact of Lipids on Insulin Resistance: Insights from Human and Animal Studies

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Abstract: Insulin resistance (IR) is a complex pathological condition central to metabolic diseases such as type 2 diabetes mellitus (T2DM), cardiovascular disease, non-alcoholic fatty liver disease, and polycystic ovary syndrome (PCOS). This review evaluates the impact of lipids on insulin resistance (IR) by analyzing findings from human and animal studies. The articles were searched on the PubMed database using two keywords: (1) “Role of Lipids AND Insulin Resistance AND Humans” and (2) “Role of Lipids AND Insulin Resistance AND Animal Models”. Studies in humans revealed that elevated levels of free fatty acids (FFAs) and triglycerides (TGs) are closely associated with reduced insulin sensitivity, and interventions like metformin and omega-3 fatty acids show potential benefits. In animal models, high-fat diets disrupt insulin signaling and increase inflammation, with lipid mediators such as diacylglycerol (DAG) and ceramides playing significant roles. DAG activates protein kinase C, which eventually impairs insulin signaling, while ceramides inhibit Akt/PKB, further contributing to IR. Understanding these mechanisms is crucial for developing effective prevention and treatment strategies for IR-related diseases.

Keywords: high-fat diet, insulin resistance, lipid profile, type 2 diabetes mellitus

Introduction

Insulin resistance (IR) is a complex pathological condition that has become a focal point in studies related to metabolic diseases such as type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), non-alcoholic fatty liver disease (NAFLD), and polycystic ovary syndrome (PCOS).¹ IR is characterized by the unresponsiveness of cells to insulin, which has a significant impact on global public health due to increasing obesity and unhealthy lifestyles.^{2,3} Lipids, such as diacylglycerol (DAG) and sphingolipids, are key mediators of impaired insulin sensitivity.⁴ DAG, for example, activates protein kinase C (PKC) which in turn inhibits the insulin signaling pathway through serine/threonine phosphorylation of insulin receptor substrate 1 and insulin receptor substrate 2 (IRS-1 and IRS-2).⁵ Sphingolipids such as ceramide cause stress on the endoplasmic reticulum (ER) and mitochondrial dysfunction, both of which contribute to IR. Ceramide inhibits the Akt signaling pathway by activating protein phosphatase 2A (PP2A), ultimately impairing glucose absorption and nutrient storage. In addition, the accumulation of ceramide in insulin-responsive tissues, such as muscle and liver, impairs insulin sensitivity and contributes to the development of obesity.⁶

As dietary patterns change, for example, the consumption of high-fat foods and carbohydrates increases, the necessity for an in-depth study of the mechanisms of lipid-IR interaction in metabolic diseases is crucial. Human studies, in the form of observational research and clinical trials, may provide important insights into the relationship between lipids and IR. Many studies in humans consistently show that increased levels of circulating free fatty acids (FFAs) and triglycerides (TGs) correlate with decreased insulin sensitivity,⁷⁻⁹ leading to fat accumulation in non-adipose tissues like muscle and liver, thus further inhibiting insulin action.¹⁰ Nevertheless, to understand the molecular mechanisms underlying this relationship, animal models have become a valuable research platform.

Animal models, such as rats and mice, offer deeper insights into the impact of lipids in IR. Dietary manipulations with high-fat diet (HFD) in these models reveal complex interactions between lipids and insulin pathways, proving that lipids directly influence insulin sensitivity, accelerate hepatic lipid deposition, and eventually lead to IR in a relatively short time.^{11–15} Additionally, animal models allow researchers to investigate the long-term effects of lipid exposure on IR, which is difficult to do in human studies.

In this context, this review aims to evaluate the impact of lipids in causing IR, focusing on findings from studies in humans and animal models. The ways that lipids and IR are connected will be discussed, along with what these results mean for creating ways to prevent and treat conditions that are linked to IR. By bringing together findings on both models, it is anticipated that this review may provide deeper insights into the complexity of interactions between lipid and insulin pathways, as well as identify promising future research directions in this area.

Methods

To collect relevant information about the role of lipids in inducing IR in humans and animal models, a literature search was conducted in the PubMed database, limited to articles published from 2014 to 2024 to ensure that this review captures recent developments in understanding the impact of lipids in IR. The search was carried out using two keywords: (1) “Role of Lipids AND Insulin Resistance AND Humans”, which resulted in a total of 145 articles; (2) “Role of Lipids AND Insulin Resistance AND Animal Models”, which resulted in a total of 456 articles. Following the initial search, articles were screened based on title and abstract to exclude articles that were not directly relevant to the topic. The full texts of the remaining articles were retrieved and evaluated according to the inclusion criteria (free full-text articles written in English, studies related to lipid-induced IR, and studies directly related to the topic of the role of lipids in IR in humans and animal models). Finally, 62 articles met the criteria and were selected for review, as depicted in Figure 1. Additional searches were conducted as needed to ensure comprehensive coverage of the mechanisms underlying the relationship between lipids and IR.

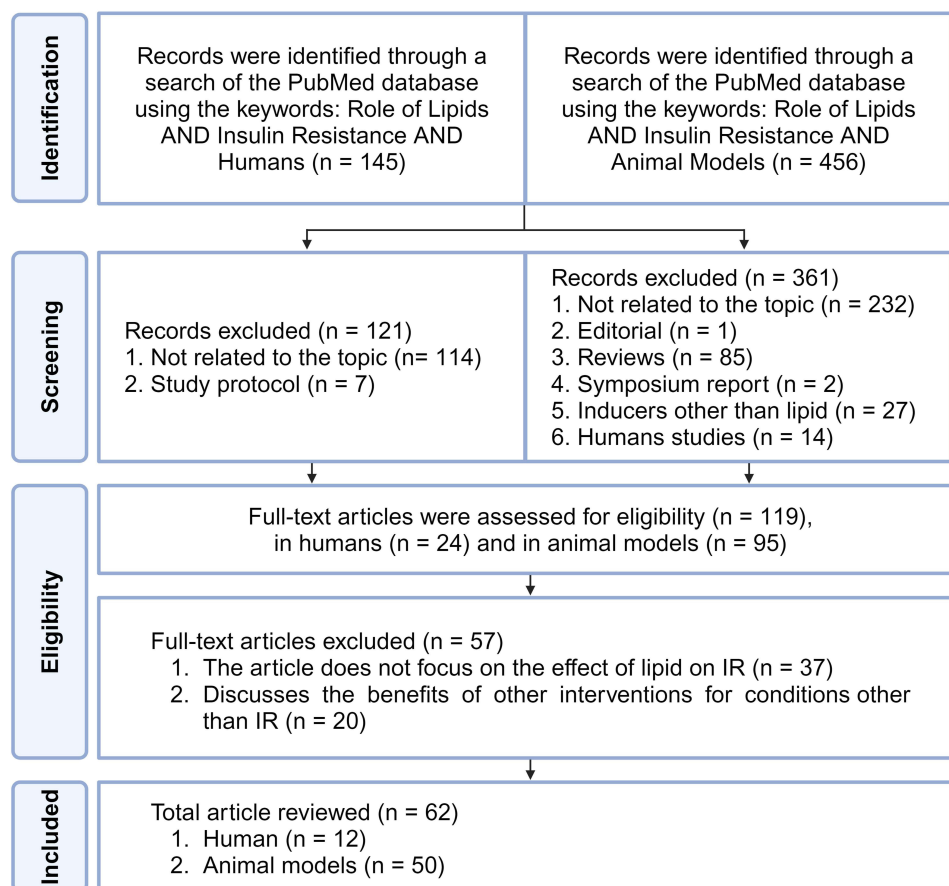


Figure 1 Literature review search method.

Results

Of the 62 articles, 12 articles described studies in humans (Table 1), and 50 articles confirmed studies in animal models (Table 2).

The total participants and/or patients included in the 12 articles were 952 males (933 of those were with T2DM) and 799 females (597 of those were with T2DM). Only 6 of the 12 articles delineate ethnicity, with Chinese being the largest group in the studies. Studies that have been conducted regarding IR involve the participation of two main groups of patients, namely diabetic patients (5 studies), PCOS patients (2 studies), and others (5 studies). Of the five studies conducted on T2DM patients, various aspects related to the management of IR and changes in lipid metabolism were reported. However, the variations in ethnicity and gender diversity in human studies may contribute to the limitation of this review. Furthermore, various types of design studies used, such as RCT (randomized controlled trial), double-blind or single-blind, cross-over, and open-label or placebo-controlled, duration of the study, and the interventions used (synthetic drugs or plant-derived drugs), have also contributed to the limitations of this review.

Of the 50 articles on animal studies, only 3 included the use of extracts from plants as part of their research, including the extraction method and solvent used for extraction. In animal models, a high-fat diet is given to create an animal model of IR. The duration of HFD induction in the study ranged from 4 to 30 weeks. Various types of experimental animals were used, with various characteristics, such as varying ages and different genders, with the majority of male mice, and some were mice with special conditions such as diabetes or obesity. Certain demographic data, such as age, body weight, and sample size, are also included in the results of this review, which can provide information about the animal population used in the experiments. A total of 24 articles mentioned the use of C57BL/6J mice, which is the most widely used type of mouse. The C57BL/6J mouse strain is widely used in metabolic research as an animal model for diet-induced obesity (DIO).⁷¹

This study used standard care drugs; for example, 4 articles mentioned metformin (biguanide class, for treating T2DM),^{11,12,26,27} 2 articles mentioned pioglitazone (thiazolidinedione class, for treating T2DM),^{28,29} and 1 article each mentioned amitriptyline (tricyclic antidepressant)³⁰ and orlistat (weight loss medication).³¹ Based on the research carried out, the results show that exposure to lipids in humans and experimental animals can contribute to IR, and IR is the main trigger factor related to the development of T2DM.

Diabetes Mellitus (DM)

DM is prevalent worldwide and increasing annually. The International Diabetes Federation (IDF) ranks Indonesia 5th globally, after China, India, Pakistan, and America, for the highest number of adults (20–79 years) with DM in 2021 and 2045.⁷² According to WHO, DM is marked by increased blood glucose levels, known as hyperglycemia,⁷³ occurring when the body cannot produce or effectively use insulin.⁷⁴ Insulin, synthesized by pancreatic beta-cells, controls blood glucose levels, facilitates cell respiration, and is crucial for protein and fat metabolism.⁷²

IR, the main trigger for T2DM, occurs when insulin cannot effectively stimulate glucose uptake or when target cells (muscle, adipose tissue, liver) respond poorly to insulin.^{75,76} This leads to hyperinsulinemia, and over time, pancreatic exhaustion results in elevated blood glucose and T2DM.⁷⁷ IR also contributes to complications, such as heart disease, stroke, high blood pressure, and other metabolic problems.^{78–80}

Obesity is a major risk factor for IR and T2DM.^{81,82} Obesity is the excessive accumulation of fat due to an imbalance in food intake and expenditure and can cause various health problems.⁷⁷ The main cause of obesity is an unhealthy lifestyle and a poor diet, such as one high in fat and sugar, followed by a lack of physical activity.^{83,84} HFD can increase the number of small adipocytes, leading to fat accumulation in the liver and decreased insulin sensitivity.⁸⁵ In obese individuals, there is increased production of FFAs, reactive oxygen species (ROS), and proinflammatory cytokines, which may contribute to the development of IR.⁸⁶ An increase in FFAs concentration occurs for several reasons, such as greater FFA release due to increased adipose tissue mass, and FFA clearance may also be impaired.⁷⁷ Consequently, high concentrations of FFA inhibit the antilipolytic activity of insulin and increase the rate of FFA release into the circulation.⁸⁷ Therefore, it is important to adopt a healthy lifestyle, such as partaking in healthy foods, avoiding excessive calorie consumption, exercising regularly, and maintaining an ideal body weight.^{88,89} A vegan diet, which excludes

Table 1 Relationship Between Lipids and Insulin Resistance in Humans

Gender (n)	Ethnicity	Type of Study	Intervention Groups (n)	Duration	Result	Ref
Studies in T2DM Patients						
Males (n = 466); females (n = 273)	Chinese, aged 18–70 years with a BMI range of 18.5–35.0 kg/m ² , and HbA1c ≥7.5% and ≤10.0%	Randomized, double-blind, Phase 3 trial	Chiglitazar 32 mg (n = 245), Chiglitazar 48 mg (n = 246), and Sitagliptin 100 mg (n = 248)	2-week, single-blind, placebo run-in period, and a 24-week double-blind treatment period	Increased FFA, TG, LDL levels, and decreased HDL levels, may lead to IR. Both chiglitazar 32 and 48 mg treatment resulted in a greater reduction in fasting and 2-h postprandial plasma glucose and fasting insulin compared with sitagliptin.	[7]
Males (n = 330); females (n = 205)	Chinese, aged 18–70 years with a BMI range of 18.5–35.0 kg/m ² , and HbA1c ≥7.5% and ≤10.0%	Randomized, double-blind, placebo-controlled, phase 3 trial	Placebo (n = 202); Chiglitazar 32 mg (n = 167); Chiglitazar 48 mg (n = 166)	52 weeks	IR, a common feature of T2DM, characterized by abnormal blood lipid levels, can be effectively managed through lipid management. Both chiglitazar 32 and 48 mg resulted in significant clinical reductions in HbA1c.	[8]
Males (n = 98); females (n = 75)	Korean, aged 18–80 years with a BMI range of 21–40 kg/m ² , HbA1c 6.5–9% or HbA1c 7–10%	Multicenter, randomized, double-blind, parallel-group, placebo-controlled trial	Lobeglitazone 0.5 mg (n = 110) Placebo (n=58)	24 weeks	Increased waist circumference, TG, and low HDL cholesterol, as well as fatty liver disease, are characteristics of IR. Lobeglitazone 0.5 mg is a well-tolerated therapy for T2DM.	[16]
Males (n = 5); females (n = 20)	Ethnicity was not described. Inclusion criteria were elevated waist circumference (>89 cm for women or >102 cm for men), established and stable diabetes for at least 5 years but not on insulin therapy.	Randomized crossover design	High-fat breakfast with cranberries (n=12) and high-fat breakfast without cranberries (n=13)	The duration of the study was 2 weeks, with a 1-week washout period between the two conditions	T2DM patients who were given a high-fat breakfast experienced an increase in postprandial serum glucose. Cranberry treatment did not significantly improve the serum insulin, and HOMA-IR, total cholesterol, LDL, and HDL levels, compared to control.	[17]
Males (n = 34); females (n = 24)	Not described	Double-blind placebo-controlled trial	Placebo (n = 29) and anthocyanin 80 mg twice daily (n = 29)	24 weeks	Patients with IR, T2DM, and obesity showed a decrease in serum adiponectin levels, while serum TG levels increased. Administration of anthocyanins increased serum adiponectin concentrations and reduced serum TG after 24 weeks of intervention.	[18]

Studies in PCOS Patients						
Females (n = 21)	Caucasian (21)	Controlled intervention	The healthy volunteer (n=10) and the PCOS (n=11) were given intralipid and insulin infusions	Intralipid infusion is given over 5 hours	Fetuin-A levels were higher, and FGF19 levels were found to be lower in women with insulin-resistant PCOS.	[19]
Females (n = 19)	Not described	Controlled intervention	The healthy volunteer (n=9) and the PCOS (n=10) were given intralipid and insulin infusions	Intralipid infusion is given over 5 hours	Elevated plasma levels of CTRP-2 and GDF-8 likely play a physiological role in lipid metabolism and insulin sensitivity.	[20]
Another study in humans						
Males (n = 8); females (n = 67)	Ethnicity: Non-Hispanic (n=64), Hispanic (n=6), did not disclose (n=5)	Single-center, randomized, open parallel study	The vegan group follows a low-fat vegan diet (n=38) and control group (n=37)	16 weeks	Decreased intake of stearic acid (C18:0) and CLA-trans-10-cis12, as well as increased intake of linoleic acid (C18:2) and alpha-linolenic acid (C18:3), were associated with reduced insulin resistance. A low-fat vegan diet is associated with reduced fat mass and IR, as well as increased insulin secretion.	[21]
Females (n = 71)	Not described	Analytical observational with a cross-sectional approach	No intervention. The study group was divided into females with lipodystrophy (n=16), female healthy controls (n=41), and female athletes (n=14)	N/A	Intramuscular lipid composition (IMCL) is higher in female subjects with lipodystrophy (LD) and higher IMCL is associated with early-stage IR.	[22]
Males (n = 11); females (n = 1)	Not described	Cross-over, RCT, single-blinded	Participants underwent one of two randomized interventions: they received an infusion of intralipid (20%) or normal saline, along with a glucose infusion (n=12)	Intralipid infusion is given over 5 hours	Increased TG and FFAs cause increased blood sugar levels and decreased insulin sensitivity.	[23]
Females (n = 11)	Not described	Experimental	The intervention involved palmitate treatment on myotubes cultured from premenopausal (n=6) and postmenopausal (n=5) female	N/A	Increased ceramide accumulation due to palmitate intervention causes inflammation and reduces insulin signaling in postmenopausal women. Female hormones may protect against lipid-mediated inflammation.	[24]
Females (n = 12)	Not described	One-group pretest–post-test explanatory study	Supplementation with 550 mg berberine tablets with 2 daily oral doses (one before lunch and one at dinner)	60 days	Increased TG, LDL, TC, and decreased HDL associated with IR cause atherogenic dyslipidemia. Berberine supplementation significantly reduced VLDL and TG levels, indicating an association between improved lipid profile and decreased IR, as measured using HOMA.	[25]

Table 2 Relationship Between Lipids and Insulin Resistance in Animal Models

Medicinal Plants (Family)	Plant Part and Extraction Method (Solvent Used)	Animal Used	Induction Method	Experimental Group	Result	Ref
N/A	N/A	Male C57BL/6J mice, 6 weeks old, weight 21–23 g (n = 40)	HFD for 8 weeks	Control (0.9% sodium solution containing 0.1% DMSO); HFD control (0.9% sodium solution containing 0.1% DMSO); HFD+RSV 100 mg/kg/day; HFD+MET 250 mg/kg/day (n = 10/group)	IPGTT revealed that HFD feeding to mice increased blood glucose levels, indicating IR, while RSV and MET attenuated this by regulating lncRNAs.	[11]
N/A	N/A	Male Wistar rats, 5–6 months old, weighing 180 ± 20 g (n = 30)	HFD for 8 weeks	Control group; control group + stevioside (20 mg/kg/day); T2DM group; T2DM + metformin (50 mg/kg/day); and T2DM + stevioside (20 mg/kg/day) (for 45 days, n = 6/group)	Rats fed HFD showed increased FBG, insulin, and oxidative stress, indicating IR. Stevioside positively manages IR and glycemic control in T2DM rats.	[12]
N/A	N/A	Male C57BL/6N mice, 5 weeks old (n = N/A)	HFD for 10 weeks	HFD; HFD + berberine 300 mg/kg/day for 4 weeks; and NCD group	HFD-feeding mice increased body weight, FBG, lipid accumulation, and IR. BBR reduced HIF-2 α accumulation, and ceramide production, and improved lipid and glucose metabolism.	[13]
N/A	N/A	Male C57BL/6J mice, 4 weeks old (n = 40)	HFD for 12 weeks	SD group and HFD group (n = 20/group)	Hyperinsulinemia, a condition induced by HFD, can lead to obesity, impaired glucose and lipid metabolism, and impaired microglial activation, resulting in the production of pro-inflammatory cytokines and energy metabolism dysfunction.	[14]
N/A	N/A	Male Wistar rats, 4 weeks old, weight 60–100 g (n = 40)	HFD for 7 weeks	Control (standard chow); HFD; CBD; and HFD + CBD (10 mg/kg BW/day i.p for 14 days) (n = 10/group)	HFD affects sphingolipid metabolism, potentially leading to IR. CBD administration to mice reduces ceramide concentrations and improves sphingolipid metabolism, potentially preventing metabolic disorders.	[15]

<i>Polygonatum sibiricum</i> (Liliaceae)	Rhizome; Ultrasonication (ethanol)	Male Kunming mice, 4 weeks old, weight 18–25 g (n = 48)	HFD for 4 weeks and STZ at a dose of 60 mg/kg for 2 days	NC (normal saline); T2DM/TC control (normal saline); HDC (PSS of 1600 mg/kg); MDC (PSS of 800 mg/kg); LDC (PSS of 400 mg/kg), and PC (metformin 250 mg/kg) (n = 8/group)	HFD in mice leads to obesity and abnormal lipid metabolism, resulting in increased TCHO, TG, and LDL contents. IR develops in the TC group, with a higher HOMA-IR index. PSS can reduce blood lipids, improve glucose tolerance, and combat IR.	[26]
<i>Momordica charantia</i> (Cucurbitaceae); Ginseng (Araliaceae); <i>Salviae miltiorrhiae</i> (Lamiaceae); <i>Puerariae</i> (Fabaceae); <i>Polygoni multiflori</i> (Polygonaceae)	Radix; Reflux	Male Sprague-Dawley rats, 13 months old, weight 500 ± 50 g (n = 70)	HFD for 8 weeks and STZ 20 mg/kg i.p	Normal control (n = 10); model/T2DM (distilled water, n = 12); positive control (metformin 0.14 g/kg/day, n = 10); PRD-L (3.375 g/kg/day, n = 10); PRD-M (6.75 g/kg/day, n = 10); PRD-H (13.5 g/kg/day, n = 10)	Administering an HFD to mice increased blood glucose levels, indicating IR and DM. It also improves lipid metabolism parameters. PRD, a component of Chinese medicine, can treat NAFLD disease in T2DM mice.	[27]
N/A	N/A	Male Wistar rats, weight 180–220 g (n = 110)	HFD for 12 weeks and STZ 28 mg/kg for 3 days	Normal (n = 10); model group (distilled water); low-dose TDQ (1.5 g/kg daily); middle dose group TDQ (3.0 g/kg daily); TDQ group high-dose (6.0 g/kg daily), and Pioglitazone (3.0 mg/kg daily) (for 5 weeks, n = 14/group)	Rats fed with an HFD had increases in HOMA-IR values, body weight, FBG, and poor glucose tolerance. TDQ can effectively lower blood glucose and improve IR in diabetic rats.	[28]
N/A	N/A	Female C57BL/6J mice and male ZDF fa/fa rats, 12 weeks old (n = 31)	HFD for 16 weeks	Lean group (n = 8); fa/fa group (n = 11); and fa/fa + PIO group (pioglitazone 30 mg/kg/day, for 4 weeks, n = 6) all groups were given a standard chow diet	Blood glucose levels and miR-29 levels in the liver were significantly increased in HFD-fed mice and ZDF mice. Increased miR-29 is associated with IR. Pioglitazone can correct the level of miR-29 in the liver, indicating a link between miR-29 and IR.	[29]
N/A	N/A	Adult male Sprague-Dawley rats, weight 130–150 g (n = N/A)	HFD for 6 weeks and STZ 40 mg/kg a single time i.p	Control group, untreated diabetic, and diabetic treated with amitriptyline (10 mg/kg, i.p. for 14 days)	The administration of HFD with STZ increased FBG and FFA levels, and ASM expression, contributing to IR and endothelial dysfunction, while treatment with amitriptyline improved insulin sensitivity.	[30]

(Continued)

Table 2 (Continued).

Medicinal Plants (Family)	Plant Part and Extraction Method (Solvent Used)	Animal Used	Induction Method	Experimental Group	Result	Ref
N/A	N/A	C57BL/6 male mice (n = 50–60)	HFD for 8 weeks	SD (CMC 0.5%); HFD; HFD + CuE (LD 0.25mg/kg/day); HFD + CuE (HD 0.5 mg/kg/day); and HFD + orlistat group (50 mg/kg/day) (over 10 weeks, n = 10–12)	HFD-MetS mice showed increased FFA, TG, LDL, and cholesterol concentrations, but reduced after CuE treatment. CuE improved glucose intolerance and decreased basal insulin levels in HFD-MetS mice.	[31]
N/A	N/A	Male and female C57BL/6J mice, 8 weeks old (n = 24)	HFD for 16 weeks	Male LFD; Male HFD; Female LFD; and Female HFD (n = 6 per sex and per treatment)	HFD causes IR in male mice, but not in female mice. Both male and female mice experienced similar increases in plasma FFA and cholesterol concentrations, suggesting that the role of lipids in IR differs by sex.	[32]
N/A	N/A	Male WT C57BL/6J and B6.BKS(D)-Lepr ^{db} /J (db/db) T2DM mice, 16 weeks old (n = 156)	N/A	C57BL/6J WT (n = 35); db-Veh (equivalent dose of DMSO dissolved in 10% Kolliphor oil, n = 50); and db-P7C3 (treated with Namp1 activator P7C3 10 mg/kg BW for 4 weeks, n = 51)	IR in db-Veh mice led to increased LDL/VLDL levels and low HDL. Namp1 P7C3 treatment decreased HOMA-IR, improved insulin sensitivity, rescued T2DM, and improved skeletal muscle function.	[33]
N/A	N/A	Male C57BLKS/J db/m and db/db mice, 6 weeks old (n = 32)	N/A	db/db; db/m; db/db + AdipoR 30 mg/kg; and db/m + AdipoR 30 mg/kg (for 4 weeks, n = 8/group)	IR in diabetic mice is linked to increased ceramide biosynthesis, facilitated by TLR4 expression, and treatment with AdipoRon can improve this condition.	[34]
N/A	N/A	Male and female Wistar rats, weight 120–150 g (n = 28)	HFD for 12 weeks and STZ 35 mg/kg	NDC; DC (HFD); Ins (HFD + 2.5 U/kg insulin twice daily i.p.); and GABA (HFD + GABA 1.5 g/kg i.p) (n = 7/group)	TG, LDL, and VLDL levels in the DC group were higher, indicating dyslipidemia and IR. GABA administration potentially reduces IR in the DC group.	[35]
N/A	N/A	Male and female C57BL/6J mice, 4 weeks old (n = N/A)	HFD for 15 and 31 weeks	SD and HFD group	The study found that mice fed an HFD exhibited increased body weight, glycemic control changes, and IR, with male mice experiencing poor IR and female mice experiencing delayed development.	[36]
N/A	N/A	Male C57BL/6J mice, 8 weeks old (n = N/A)	HFD for 10 weeks	Chow; HFD + vehicle; and HFD + peptide 7 (n = 4–5/group)	HFD feeding to mice caused increased insulin levels, hepatic fat accumulation, and renal SGLT2 expression, indicating IR. Peptide 7, derived from TNFSF14, reduced this problem in mice.	[37]

N/A	N/A	Male C57BL/6 mice, 5 weeks old; NGBR ^{fl/fl} mice; NGBR ^{hepKO} mice; db/db mice (B6.BKS(D)-Lepr ^{db/J}) (n = 27)	HFD for 4 weeks and STZ 50 mg/kg BW for 7 days	NC (citrate buffer + fed normal chow, n = 5); T2D (HFD diet + AAV9-GFP, n = 7); and T2D+NGBR (HFD diet + AAV9-NGBR, n = 7)	HFD and STZ induction in mice increased lipid accumulation, NEFA and TG, and influenced IR, while NGBR regulates lipid metabolism and insulin sensitivity.	[38]
N/A	N/A	Male Wistar rats, weight 170–200 g (n = 24)	HFD for 12 weeks	CTL (diet and distilled water); MLT (melatonin 4 mg/kg BW); OBS (HFD 40%); and OBS+MLT (HFD and melatonin combination) (n = 6/group)	HFD feeding leads to weight gain, hyperinsulinemia, oxidative stress, and inflammation in adipose tissue, triggering IR and T2DM risk. Melatonin may offer therapeutic benefits for managing obesity-related metabolic disorders.	[39]
N/A	N/A	Male Fat Aussie mice (FA/FA/oz/foz), 6 months old, average weight 45 g, and WT mice, 6 months old, average weight 26 g. Young female FA mice, weight 22.2 ± 1.0 g, and female WT, weight 21.2 ± 0.8 (n = 63)	HFD	FA and WT group	Lipid accumulation in hepatocytes disrupts calcium signaling, potentially leading to IR and metabolic disorders like obesity and steatohepatitis. GLP-1 analogs like exenatide can be effective in treating and preventing these metabolic disorders.	[40]
N/A	N/A	KO (Zfp217 ^{+/-}) and WT (Zfp217 ^{+/+}) male mice (n = 12)	HFD for 16 weeks	Zfp217 ^{+/-} NC; Zfp217 ^{+/-} HFD; Zfp217 ^{+/+} NC; and Zfp217 ^{+/+} HFD	HFD causes glucose metabolism disturbances in mice, indicating IR. Zfp217-deficient mice show increased glucose clearance and better insulin sensitivity, suggesting loss of Zfp217 expression may reduce HFD-induced obesity-related metabolic syndrome.	[41]
N/A	N/A	Male Wistar rat, weight 180 ± 20 g	HFD for 4 weeks and STZ 30 mg/kg	Control group; DM group; and PUE group (puerarin 300 mg/kg/day for 4 weeks)	Puerarin improves glucose tolerance in T2DM mice, lowering blood glucose levels and inhibiting hepatic gluconeogenesis, suggesting that HFD administration induces IR.	[42]
N/A	N/A	C57BL/6 male mice, 5–6 weeks old, weight 15–18 g (n = 60)	HFD for 8 weeks	SCD group; HFD group; HFD+ad-KD-NC; HFD + ad-KD miR-130b-5p; HFD+ad-oe-NC; HFD + ad-oe IGFBP2; and HFD + ad-KD miR-130b-5p + ad-KD IGFBP2 (HFD-fed mice were given an intraperitoneal injection of 1×10 ⁹ pfu/100 µL adenovirus, n = 15/group)	HFD-fed mice exhibited increased body weight, FBG, FINS, HOMA-IR, and liver triglyceride levels, while decreased miR-130b-5p expression prevented lipid accumulation and IR in NAFLD mice.	[43]

(Continued)

Table 2 (Continued).

Medicinal Plants (Family)	Plant Part and Extraction Method (Solvent Used)	Animal Used	Induction Method	Experimental Group	Result	Ref
N/A	N/A	Male AMPK $\alpha 2$ -KO mice and WT mice on a C57BL/6J background (n = N/A)	HFD for 12 weeks	Genotype groups (WT and AMPK $\alpha 2$ -KO); and diabetes status groups (control, T2D, and T2D treated with crocin)	Mice fed HFD showed increased body weight, FBG levels, TG, NEFA, and TC levels, all of which are indicators of IR. Crocin has the potential as a therapeutic agent for diabetes and obesity-related conditions.	[44]
N/A	N/A	Male C57BL/6 mice, 6 weeks old (n = 18)	HFD for 4 weeks	Normal (0.25 mL distilled water); RRK LD (12.5 mg/kg BW); and RRK HD (50 mg/kg BW) (For 10 days, n = 6/group)	HFD induces IR in mice, increasing HOMA-IR values. Red rice koji extract decreases blood glucose and insulin levels, indicating improved insulin sensitivity.	[45]
N/A	N/A	WT male C57BL/6 J mice, 8 to 10 weeks old and GRX2-KO mice (n = 64)	HFD for 16 weeks	Ctrl/WT; HFD/WT; Ctrl/KO; and HFD/KO. (n = 16/group)	HFD in mice leads to weight gain, IR, and fat accumulation, affecting brain health, particularly in mice lacking GRX2, a protective protein that suppresses inflammation, oxidative stress, and mitochondrial dysfunction through GSK-3 β signaling.	[46]
N/A	N/A	ANXA1 ^{-/-} mice and WT C57BL/6 mice, 10 weeks old (n = N/A)	HFD for 10 weeks	WT mice were divided into chow, HFD + vehicle (Hepes 50 mM, NaCl 140 mM i.p.), and HFD + hrANXA1 (40 μ g/kg, i.p); ANXA1 ^{-/-} mice were divided into chow, HFD + vehicle (Hepes 50 mM, NaCl 140 mM i.p.), and HFD + hrANXA1 (40 μ g/kg, i.p)	Animal studies indicate that ANXA1 can mitigate HFD-induced IR, suggesting potential as a therapeutic target for treating T2DM and related complications.	[47]
N/A	N/A	WT and Spred2 KO mice, 4 weeks old (n = N/A)	HFD for 16 weeks	WT HFD; KO HFD; WT SD; and KO SD	The study found that Spred2 KO mice showed worse glucose and insulin tolerance, increased abdominal adiposity, and elevated cholesterol, indicating that loss of Spred2 function worsens obesity and IR conditions induced by HFD.	[48]
N/A	N/A	Kindlin-2 ^{fl/fl} Adipoq-Cre male mice, namely adipocyte selective mice Kindlin-2 – KO mice, 6 weeks old (n = N/A)	HFD for 18 weeks	WT HFD; KO HFD; WT NCD; and KO NCD	Kindlin-2-deficient (KO) mice fed with an HFD show increased fasting glucose levels, glucose intolerance, and peripheral IR. This suggests that Kindlin-2 is essential for healthy adipogenesis, balanced lipid metabolism, and bone homeostasis.	[49]
N/A	N/A	Male CD40 ^{fl/fl} CD11c ^{cre} and WT, 6–8 weeks old (n = N/A)	HFD for 18 weeks	CD40 ^{fl/fl} SFD; CD40 ^{fl/fl} CD11c ^{cre} SFD; CD40 ^{fl/fl} HFD; and CD40 ^{fl/fl} CD11c ^{cre} HFD	HFD CD40 ^{fl/fl} CD11c ^{cre} mice showed a 1.7-fold increase in fasting plasma insulin levels compared to WT mice, and worsening IR was observed in HOMA-IR assessments.	[50]

<i>Citrus aurantium</i> (Rutaceae)	Fructus; N/A (etanol/air)	C57BL/6J male mice, 8 weeks old (n = 36)	HFD for 12 weeks	Chow; HFD; TFQ (HFD and daily dose of 300 mg/kg TFQ for 12 weeks) (n = 12/group)	TFQ positively impacts obesity, liver inflammation, and IR in mice on an HFD, while also modifying gut microbiota composition, suggesting potential therapeutic benefits against obesity-related metabolic disorders.	[51]
N/A	N/A	Male C57BL/6 mice (n = N/A)	HFD for 16 weeks	Control group (normal chow diet); and the HFD group	HFD causes lipotoxicity, increased COPI and TRB3, and decreased SIRT1, leading to IR. Test animals show decreased glucose metabolism and increased serum levels of NEFA, TG, and TC compared to normal diets.	[52]
N/A	N/A	Male NSY mice, 4 weeks old, weight ± 14 g (n = 16)	HFD for 12 weeks	ND (control and 2 mg Se/L SeMet treatment); and HFD (control and 2 mg Se/L SeMet treatment) (n = 8/group)	HFD in mice causes increased liver weight, lipid peroxidation, and IR. Coadministration of SeMet increases blood glucose and plasma FFA levels, exacerbating IR.	[53]
N/A	N/A	Multiparous dairy cows, average age 4.3 ± 0.3 years, weight 683 ± 21 kg (n = 6)	TG emulsion for 17 hours	Control group (saline infusion); and TG group (soybean oil and egg yolk phospholipids)	TG emulsion in cattle may impair insulin sensitivity and cause ceramide accumulation, leading to impaired peripheral insulin action.	[54]
N/A	N/A	C57BL/6J WT mice and JAZF1-OX mice, 4 weeks old, weight 10–18 g (n = 32–40)	HFD for 12 weeks	NC (RD fed); HF (HFD fed); NJ (RD-fed JAZF1-OX mice); and HJ (HFD-fed JAZF1-OX mice) (n = 8–10/group)	Overexpression of JAZF1 reduced blood lipids, glucose levels, body weight, inflammatory markers, and adipose tissue macrophages in mice fed an HFD, indicating that HFD causes IR.	[55]
N/A	N/A	Male C57BL/6 mice, 8–10 weeks old, weight 15–20 g; and male db/db mice, 10–12 weeks old, weighing 45–50 g (n = N/A)	HFD, HFrD for 10–12 weeks and STZ 100 mg/kg i.p	Control group (saline); and treated group (acute PSTi8 treatment 5 mg/kg and chronic 2 mg/kg for 10 days)	Mice fed an HFD exhibited increased blood glucose levels, indicating IR, and PSTi8 effectively mitigated this resistance.	[56]
N/A	N/A	Male Sprague-Dawley rats, 7 weeks old, weight ± 160 g (n = 20–30)	HFD, EtOH, Fr 8 weeks	LFD; HFD; HFD+30% kcal ethanol; HFD+ 30% fructose; HFD+ 30% EtOH+ 30% Fr (n = 4–6 mice/group)	Rats on an HFD experienced increased body weight, hepatic steatosis, hyperleptinemia, and higher HOMA-IR values. Additionally, serum C-peptide and TG levels increased, and the glucose-to-insulin ratio decreased, indicating IR.	[57]
N/A	N/A	Male C57BL/6 mice (n = 30)	HFD for 12 weeks	Control (standard rodent chow, n = 10); HFD (normal saline, n = 10); HFDG (given subcutaneous treatment with GLP-1 at 200 μ g/kg twice daily for 4 weeks, n = 10)	HFD administration in mice increases FBG and insulin, podocyte damage, lipid accumulation, and autophagy, indicating IR. PI3K expression is lowered and GLUT4 translocation is blocked. GLP-1 treatment lessens IR caused by HFD.	[58]

(Continued)

Table 2 (Continued).

Medicinal Plants (Family)	Plant Part and Extraction Method (Solvent Used)	Animal Used	Induction Method	Experimental Group	Result	Ref
N/A	N/A	Bama mini-pigs, 8 months old, weight 25–26 kg (n = 8)	HFHSD for 30 weeks	Obese (n = 3, body weight ≥ 55 kg); and thin (n = 5, body weight < 55 kg)	Pigs with HFHSD experienced obesity, hyperglycemia, high TG, decreased adiponectin levels, and increased IL-6, resulting in IR and hyperglycemia.	[59]
N/A	N/A	Male DGK ϵ KO and WT mice, 5 weeks old (n = 40–54)	HFD	WT HFD (n = 14–20); HFD KO (n = 11–16); WT chow (n = 8–10); and KO chow (n = 7–8)	DGK ϵ deficiency in HFD-fed mice leads to increased whole-body lipid oxidation, indicating that DGK ϵ may play a role in the regulation of lipid metabolism affected by HFD.	[60]
N/A	N/A	CD-1 mice, 4 weeks old (n = 20)	HFD for 24 weeks	Chow (chow and regular drinking water); chow+butyrate (chow and 1% Sodium Butyrate in drinking water); HFD (HFD and regular drinking water); and HFD+Butyrate (HFD and 1% Sodium Butyrate in drinking water) (administration of sodium butyrate for 12 weeks, n = 5/group)	Sodium butyrate may be a potential therapeutic strategy for heart problems and metabolic disorders in T2DM and obesity because mice fed an HFD develop glucose intolerance and hyperinsulinemia which are indicators of IR.	[61]
N/A	N/A	TRIB3 MKO mice (n = 8–12) and TRIB3 MOE mice (n = 8–12), 20 weeks old	HFD for 16 weeks and STZ 50 mg/kg BW for 5 days	Control group; TRIB3 MKO group; and TRIB3 MOE group.	HFD-induced IR was observed in TRIB3 MOE mice, resulting in increased body weight, FBG, plasma insulin, total cholesterol, and triglyceride levels, while TRIB3 MKO mice showed protection against this resistance.	[62]
N/A	N/A	Golden Syrian hamsters, females (n = 18) and males (n = 17), 5 month old, weight 125.1 ± 10.5 g (n = 35)	HFD for 6 weeks and STZ 40 mg/kg twice i.p	Control group; insulin-resistant group; and T2DM group (n=10/group).	HFD feeding to hamsters leads to increased body weight, visceral obesity, IR, and adverse serum lipid levels. Important genes like SREBP and LXR show increased activity in these groups.	[63]
N/A	N/A	Male C57Bl/6 mice, 8 weeks old (n = N/A)	HFD for 10 weeks	Immunoneutralization experimental group: HFD Ab (HFD and eNAMPT Ab); HFD IgG (HFD and IgG); mCON Ab (standard diet and eNAMPT Ab); CON IgG (standard diet and IgG) (n = 24/group) For eNAMPT experimental: control (saline); eNAMPT (5 ng/mL) for 14 days (n = 8/group)	HFD consumption increases IR and eNAMPT-monomer levels, potentially leading to T2DM. Neutralizing the eNAMPT monomer can help control blood sugar, IR, pancreatic islet function, hepatic insulin sensitivity, and inflammation in mice, suggesting a potential therapeutic strategy for diabetes.	[64]

N/A	N/A	Male C57BL/6J mice, 8 weeks old (n = 21)	HFD for 8 weeks and STZ 120 mg/kg	Control (vehicle i.p and were fed with normal diet); STZ/HFD (normal drinking water); and STZ/HFD-BAIBA (BAIBA 150 mg/kg/day) (for 4 weeks, n = 7/group)	STZ/HFD-induced mice experience increased blood glucose levels, IR, and impaired lipid metabolism. BAIBA administration reduces these, improves IR, and improves lipid metabolism disorders.	[65]
N/A	N/A	Male and WT vanin-1 ^{-/-} mice, 12–14 weeks old; male thin Wistar rats and ZDF rats, 8 weeks old (n = N/A)	HFD for 16 weeks	WT HFD (n = 7–9); Vnn-1 ^{-/-} HFD (n = 7–9); WT LFD (n = 7–9); Vnn-1 ^{-/-} LFD (n = 7–9); control (n = 5); and RR6 group (given the pantetheinase inhibitor vanin, RR6 3 mg/mL, for 8 days, n = 5).	Administering HFD to mice can induce obesity and IR, with increased vanin activity observed in the plasma and liver of obese and ZDF-diabetic mice. However, vanin-1 ablation slightly improved glucose tolerance and insulin sensitivity.	[66]
N/A	N/A	GGPPS knock-out male mice, 8 weeks old (n = N/A)	HFD for 12 weeks	MCK- GGPPS ^{+/-} ; MCK- GGPPS ^{+/-} ; and MCK- GGPPS ^{+/+}	Heterozygous knockout mice of GGPPS in skeletal muscle protect against HFD-induced IR by increasing glucose tolerance and insulin sensitivity, confirming that HFD can trigger IR.	[67]
N/A	N/A	Male LDLR ^{-/-} mice, 8 weeks old (n = 40)	HFD for 24 weeks	Normal (RC and PBS); RC + Rs-LPS; HFD (HFD and PBS); HFD + Rs-LPS (Rs-LPS 1 µg/mouse in PBS solution twice a week for 10 weeks)	HFD administration in mice increased body weight, FBG, plasma lipids, insulin, and HOMA-IR, indicating IR in LDLR ^{-/-} mice. TLR4 antagonists attenuated vascular inflammation and atherogenesis in HFD-T2DM.	[68]
N/A	N/A	Male C57BL/6 mice, 6 weeks old (n = 28)	HFD for 16 weeks	No MetS, PBS-treated (fed regular mouse chow and injected with PBS); MetS, PBS-treated (fed with HFD and injected with PBS); No MetS, LPS-treated (fed regular mouse chow and injected with LPS); and MetS, LPS-treated (given HFD and injected with LPS) (LPS given for 4 weeks, n = 7/group)	Mice fed HFD showed increased fasting insulin levels and HOMA-IR, indicating IR, leading to MetS, a condition linked to increased periodontal inflammation and alveolar bone loss.	[69]
N/A	N/A	Male C57BL/6 mice, 9–12 weeks old (n = N/A)	HFD for 2 weeks	Groups given apoA-I WT, apoA-I Milano, and NaCl solution as controls	HFD administration to mice increased fasting serum glucose and insulin levels, indicating IR. Treatment with apoA-I may improve glucose management and ameliorate IR in these mice.	[70]

animal products, may help in reducing body weight, fat mass, and visceral fat volume, as well as improve insulin sensitivity.²¹

Metformin is a commonly used antihyperglycemic agent in the management of T2DM, working by increasing insulin sensitivity and reducing glucose production by the liver.⁹⁰ Omega-3 fatty acids, found in fatty fish, also play an important role in improving insulin function by increasing insulin sensitivity, reducing ceramide content, and increasing adiponectin expression in animal models,⁹¹ while reducing inflammation and IR.⁹²

With a better understanding of the link between DM and IR, as well as appropriate prevention efforts, it is hoped that we can reduce the burden of this disease on individuals and society as a whole. Prevention and appropriate management can help reduce the risk of serious complications and improve the quality of life for those living with diabetes.

Studies in Humans

Studies in humans reveal that lipid accumulation, particularly saturated fats, triggers the occurrence of IR.^{21,22,93} These lipids, including FFAs and TGs, disrupt insulin signal transduction, produce pro-inflammatory cytokines, and oxidative stress, and inhibit intracellular signaling pathways.⁷⁷ Ceramide is also a key mediator of IR.⁹⁴ Understanding these lipids could lead to more effective prevention and treatment strategies for IR and related diseases.

Several studies highlight the impact of lipid infusions on glucose and insulin metabolism in the context of IR. Lipid infusions can significantly affect glucose and insulin metabolism, leading to IR. It increases the levels of TG and FFAs in the blood, worsening glucose tolerance and insulin sensitivity. Lipids affect pancreatic beta-cell function, causing insulin hypersecretion. However, decreased insulin clearance also contributes to hyperinsulinemia.²³ Research has identified proteins that respond to intralipid and insulin infusions in healthy women and women with PCOS. Intralipid infusion reduces the ability of insulin to stimulate glucose utilization, indicating increased IR. In addition, intralipid infusion decreased fibroblast growth factor 19 (FGF19) levels, indicating impaired regulation of glucose and lipid metabolism.¹⁹

Lipid excess can lead to the accumulation of intramyocellular lipid metabolites (IMCL), which coincides with impaired insulin response. The fat composition in IMCL, especially saturated fat, has an important role in mediating IR.²² Palmitic acid, a saturated fat found in muscle TG, is associated with IR through increased concentrations of ceramide, which interferes with insulin activation of cell receptors and downstream signaling molecules such as IRS-1 and Akt/protein kinase B (PKB).^{95,96}

Female sex hormones also play a role in protecting against lipid-mediated IR. Postmenopausal women, who naturally have increased levels of saturated fat, tend to accumulate more ceramides in response to high lipid loads, thereby increasing the risk of IR. This suggests that premenopausal women's hormones may have a protective effect against ceramide accumulation and associated IR.^{24,32} Understanding the lipid composition in IMCL and the influence of female sex hormones may provide new insights into the management of IR and diabetes risk.

Ceramide, a type of fat in cells, has been linked to lipid-mediated skeletal muscle IR.^{97–99} Research has shown that individuals with T2DM have higher blood levels of ceramide,¹⁰⁰ which is associated with IR, insulin sensitivity, and cardiovascular risk.¹⁰¹ This is consistent with a previous study showing obese and diabetic patients have higher levels of ceramide in their muscles.¹⁰² These findings support the role of ceramide in skeletal muscle IR.

Chiglitazar and lobeglitazone show potential for managing T2DM. Chiglitazar, a PPAR agonist (peroxisome proliferator-activated receptor), activates all three PPAR types (-alpha, -gamma, -delta), controlling glucose and fat levels, decreasing TG, increasing HDL-cholesterol, and enhancing insulin sensitivity.^{7,8} Lobeglitazone, a PPAR-gamma agonist, improves insulin sensitivity, reducing IR. Both drugs improve glycemic control, lipid regulation, and IR in T2DM patients, reducing disease complications.¹⁶

Natural substances can improve IR in T2DM and PCOS. Berberine, an alkaloid in Chinese herbal medicine, increases glucose consumption and absorption in cells, inhibits alpha-glucosidase, and improves insulin sensitivity.²⁵ Cranberries, rich in polyphenols such as proanthocyanidins, inhibit carbohydrate digestive enzymes, decrease intestinal glucose absorption, and modulate inflammatory biomarkers, all of which contribute to improved insulin sensitivity.¹⁷ Anthocyanins in colored fruits and vegetables improve insulin sensitivity by increasing adiponectin expression and fatty acid oxidation.¹⁸ Overall, these three natural substances have a complementary role in improving IR, demonstrating their potential as therapeutic agents in managing T2DM and related metabolic conditions.

Studies in Animal Models

Various studies show that mice treated with an HFD experience increased glucose intolerance and IR,³⁷ characterized by increased fasting blood glucose (FBG), insulin,⁵¹ total cholesterol, TG,⁶⁸ and FFA levels, as well as decreased adiponectin levels.⁵³ The underlying mechanisms involve complex biological pathways.

One of the main mechanisms is changes in insulin signaling in the liver and skeletal muscle. Signaling cascades such as IRS-1/Akt/GSK-3 β (Glycogen Synthase Kinase-3 beta) have a major role in the regulation of glucose transport, glycogen synthesis, and energy metabolism.¹⁰³ Increased Ser307 phosphorylation of IRS-1 characterizes peripheral IR, inhibits Glucose Transporter Type 4 (GLUT4) translocation to the cell surface, and causes hyperglycemia.¹⁰⁴

In addition, HFD elevates the concentration of sphingolipids, such as ceramide, which interfere with the insulin signaling pathway by inhibiting insulin-induced phosphorylation of Akt/PKB in skeletal muscle and liver. This inhibition of Akt/PKB leads to the inhibition of GSK-3 α/β phosphorylation at Ser21/Ser9, resulting in impaired insulin sensitivity.^{13,15}

HFD also triggers low-grade inflammation in adipose tissue, which in turn leads to the recruitment of immune cells and the production of proinflammatory cytokines, leading to IR.⁵⁵ Studies in mice show that increased plasma FFA could activate muscle NF-kappaB signaling,¹⁰⁵ which eventually leads to higher levels of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF- α), interleukin-1 beta (IL-1 β), IL-6, and Monocyte Chemoattractant Protein-1 (MCP-1).¹⁰⁶ This increase in plasma MCP-1 can promote the migration of monocytes from the blood to adipose tissue. When macrophages settle in adipose tissue, they differentiate into inflammatory macrophages, which can release a large number of inflammatory factors.¹⁰⁷ Additionally, HFD-induced increases in FFA also increase Toll Like Receptor-4 (TLR-4) activity, which may trigger inflammatory signaling pathways that contribute to the development of IR and atherosclerosis.⁶⁸

Overall, this review shows that HFD significantly escalates the risk of developing IR in mice. The multiple mechanisms involved highlight the complexity of the role of HFDs in the development of IR, which has significant implications for metabolic health and the development of diseases such as T2DM. Therefore, a better understanding of these mechanisms is important for the development of appropriate prevention and treatment strategies.

This review discusses the unique role of proteins such as TNFSF14 (Tumor Necrosis Factor Superfamily Member 14) and NGBR (Nogo-B Receptor) in influencing glucose metabolism and IR. TNFSF14, specifically Peptide 7, increases insulin signaling and fatty acid oxidation in skeletal muscle cells, improving glucose management and IR in mice fed with HFD.³⁷ Overexpression of NGBR suggests that this protein functions in the improvement of insulin sensitivity and the reduction of endoplasmic reticulum stress in the liver and skeletal muscle.³⁸

Bioactive compounds have also been identified as potential treatments for DM. *Polygonatum sibiricum* saponin (PSS) has demonstrated its ability to reduce IR, improve pancreatic beta-cell function, and facilitate the normal biological role of insulin. The mechanism of action of PSS involves increasing Akt which triggers GLUT4, thereby helping control blood glucose and improving glucose tolerance.²⁶ Berberine, a bioactive compound from *Rhizoma coptidis*, shows potential in improving IR by reducing the accumulation of ceramide, which interferes with insulin signaling and activates AMP-activated protein kinase (AMPK) signaling.¹³ Cannabidiol (CBD) from *Cannabis sativa* lessens the accumulation of sphingolipids and exhibits anti-inflammatory and antioxidant effects that help improve the condition of IR and other diabetic complications.¹⁵ Stevioside, found in *Stevia rebaudiana* leaves, increases glucose uptake and oxidation in muscles by activating the IR/IRS-1/Akt/GLUT4 pathway and inhibiting oxidative stress.¹² Not only that, resveratrol and cucurbitacin E also indicate the potential to overcome IR. Resveratrol increases glucose uptake via the PI3K/Akt signaling pathway to attenuate IR,¹¹ while cucurbitacin E affects several pathways, including the inhibition of Janus Kinase/Signal Transducers and Activators of Transcription (JAK-STAT5), influences adipokines, decreases lipogenesis, activates AMPK, and regulates insulin signaling.³¹

Glucagon-like Peptide-1 (GLP-1) analogs, synthetic versions of the GLP-1 hormone, regulate glucose levels with a prolonged effect.^{108,109} They increase insulin release, reduce glucagon release, and slow gastric emptying.¹¹⁰ GLP-1 analogs maintain healthy blood glucose by modulating calcium signals in hepatocytes and reducing lipid accumulation.⁴⁰ They restore insulin sensitivity by promoting GLUT4 translocation, facilitating glucose uptake, and reducing blood glucose. In HFD-fed mice, GLP-1 restored reduced phosphoinositide 3-kinase (PI3K) expression, improving the insulin signaling pathway.⁵⁸

High levels of pancreastatin can cause IR in T2DM. PST inhibitor peptide-8 (PSTi8) improves insulin sensitivity in mice with IR by increasing glucose clearance, glycogenesis, glycolysis, and gluconeogenesis. PSTi8 targets the IRS1/2-PI3K-Akt signaling pathway, making it a promising therapeutic agent for metabolic diseases, particularly DM.⁸⁰

The intricate interplay of lipid accumulation, inflammatory responses, and disrupted insulin signaling pathways underscores the multifaceted mechanisms through which an HFD-induced IR, highlighting the critical need for targeted prevention and therapeutic strategies to mitigate metabolic diseases such as T2DM.

Lipid-Induced Insulin Resistance

Adipose tissue, composed of adipocytes, can expand and store lipids through hypertrophy (enlargement of the cell size of the adipocyte) or hyperplasia (proliferation). When fat absorption increases, hypertrophic adipocytes stimulate hyperplastic adipocytes, which then attract more macrophages to enter and release inflammatory substances called adipokines. Over time, these hypertrophic adipocytes become dysfunctional and highly lipolytic, producing excessive FFA and contributing to the development of IR. This process is facilitated by the elastic properties of the tissue.¹¹¹ Excess FFA will accumulate ectopically, thereby exceeding the rate of fatty acid oxidation and intracellular storage. Ectopic lipid accumulation is the buildup of fat outside normal adipose tissue, such as in the liver and skeletal muscle, which can cause severe IR.¹¹¹ Ectopic fat produces toxic lipids, for example, ceramide and DAG.¹¹²

Lipid-induced IR may occur due to the aggregation of specific lipid mediators. Lipid mediators are lipid molecules that function as intermediaries in cellular signals.¹¹³ DAG and ceramide have been widely studied as mediators of lipid-induced IR in the liver and skeletal muscle, able to interfere with insulin signaling pathways.^{114,115} DAG can accumulate in IR individuals due to an imbalance between its production and the addition of triacylglycerol (TAG) or triglyceride hydrolysis pathways. Ceramide coordinates cellular responses to cytokines or nutritional signals, such as saturated fatty acids.¹¹³

DAG is a signal intermediate that activates members of the PKC family. There are three groups in the PKC family: conventional (α , β I, β II, γ), novel (δ , ϵ , η , θ), and atypical (ζ and λ), and novel PKCs (nPKCs) have a greater affinity for DAG. DAG is known to mediate the role of DAG in IR.¹¹⁶ PKC- ϵ is mainly involved in tissues such as liver and adipose tissue.¹¹⁷ PKC- δ may also be increased in the liver of obese individuals, causing IR through a significant decrease in insulin-stimulated IRS-1 phosphorylation at Tyr612 and a decrease in Akt phosphorylation at Ser473.¹¹⁸ DAG activates PKC- θ in skeletal muscle, leading to IR through increased IRS-1 serine 1101 phosphorylation and inhibition of insulin-stimulated IRS-1 tyrosine phosphorylation and Akt2 phosphorylation.¹¹⁹ Through PKC activation, *sn*-1,2-DAG mediates lipid-induced insulin resistance in the liver, skeletal muscle, and white adipose tissue (WAT).^{120,121}

Figure 2 illustrates the mechanism of IR in skeletal muscle. Cells take up fatty acids (FA) via a specific transport protein in the cell membrane (CD36).¹²² Esterification of fatty acids with coenzyme A forms Long Chain Fatty Acid-CoA (LCFA-CoA). When there are too many FAs and/or mitochondrial problems that prevent β -oxidation from occurring, LCFA-CoA builds up and is broken down into DAG and ceramide. DAG induces sustained activation of serine/threonine kinases such as PKC- θ , which facilitates serine phosphorylation of IRS-1. The serine-phosphorylated form of IRS-1 is unable to associate with and activate PI3K, resulting in decreased PI3K and Akt2 activity. GLUT4 regulates glucose transport through cell membranes, which in turn reduces glucose intake and glycogen synthesis due to this decrease in Akt2 activity. The liver's IR mechanism bears similarities to that of skeletal muscle. When there is more DAG in liver cells, PKC- ϵ gets activated. This lowers the activity of insulin receptor kinase, which in turn lowers the tyrosine phosphorylation of IRS-2 by insulin. This, in turn, lowers the activation of PI3K and Akt2. When Akt2 activation is minimal, there is a decrease in hepatic glucose uptake. Furthermore, reduced Akt2 activity leads to decreased phosphorylation of the transcription factor forkhead box O (FOXO), allowing it to enter the nucleus and activate transcription of gluconeogenesis rate-controlling enzymes. The result is an increase in liver glucose production. This allows glucose to escape via GLUT2, contributing to increased plasma glucose levels.^{111,113,123,124}

The role of ceramide in inducing IR is still controversial. However, the accumulation of hepatic ceramides and certain dihydroceramides (eg, C16:0) is increased in insulin-resistant humans with non-alcoholic steatohepatitis (NASH) and is positively correlated with oxidative stress and hepatic inflammation.¹²⁵ Ceramide is a bioactive sphingolipid produced from intracellular fatty acids and sphingosine.^{111,113} Ceramide disrupts insulin action by activating PP2A, which dephosphorylates Akt2, thereby reducing insulin signaling, but not due to issues in upstream signaling steps like IR or

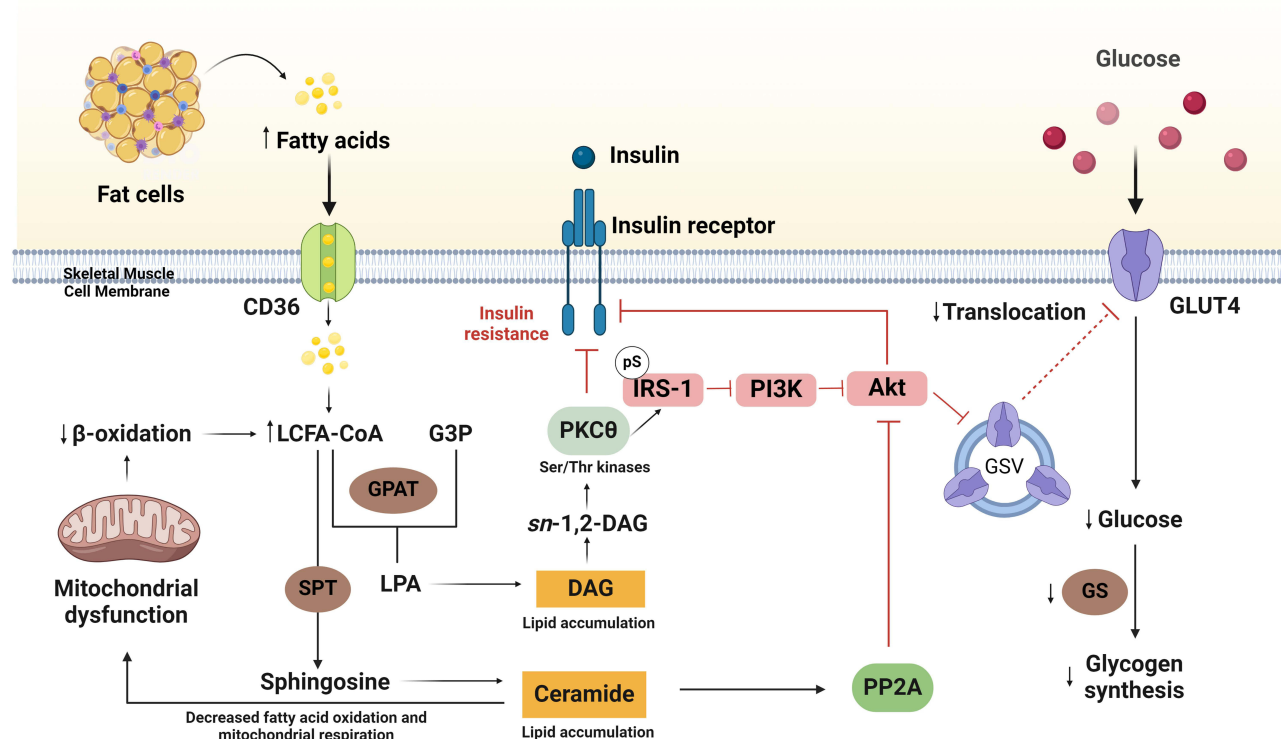


Figure 2 The mechanism of insulin resistance (IR) in skeletal muscle. Insulin induces activation of the insulin receptor, resulting in autophosphorylation and activation of the insulin receptor intrinsic tyrosine kinases and subsequently associates with phosphoinositide 3-kinase (PI3K). Activated PI3K will induce protein kinase B (Akt) which contributes a main role in glucose metabolism by regulating the translocation of the cytosolic glucose transporter type 4 (GLUT4), to the skeletal muscle membrane cell. Inhibition of PI3K and/or PKB/Akt attenuates the translocation of GLUT4. Insulin also increases LCFA uptake via a cluster of differentiation 36 (CD36), which leads to the increase of DAG and/or ceramide levels, thus activating PKC and subsequently the occurrence of IR. Created with BioRender.com.

Abbreviations: LCFA-CoA, long-chain fatty acid-CoA; DAG, diacylglycerol; PKC, protein kinase C; IR, insulin receptor; IRS, insulin receptor substrate; PI3K, phosphatidylinositol 3-kinase; GLUT4, glucose transport protein 4; G3P, glycerol 3-phosphate; GPAT, glycerol-3-phosphate acyltransferase; LPA, lysophosphatidic acid; SPT, serine palmitoyl transferase; PP2A, protein phosphatase 2A.

PI3K activation.¹¹³ Research shows that liver-specific deletion of *Cers6* can reduce ceramide levels in the liver, protect against high-fat diet-induced obesity, and improve glucose tolerance.¹²⁶

In summary, lipid accumulation and the resulting metabolic disturbances in adipose tissue, liver, and skeletal muscle play an important role in inducing IR through multiple pathways, including activation of inflammatory responses, impaired insulin signaling, and alteration of mitochondrial function.

The Role of Inflammation in Insulin Resistance

Inflammation is a significant factor in the progression of IR in both humans and animals. Elevated levels of proinflammatory cytokines, such as TNF- α and IL-6, are commonly observed in obese people with IR, suggesting the role of inflammatory mechanisms in this illness.^{127–130} A HFD, in particular, intricately interconnects inflammation and IR. Adipose tissue inflammation in mice that developed obesity due to an HFD begins shortly after the start of the HFD and continues for the duration of the HFD. Nevertheless, the inflammation of adipose tissue decreased promptly following the transition from HFD to a regular diet, suggesting that food significantly influences the regulation of adipose tissue inflammation.¹³¹ The mice in the HFD group had a lot more proinflammatory cytokines in their blood when they were at rest. These included TNF- α , IL-6, leptin, MCP-1, plasminogen activator inhibitor-1 (PAI-1), and resistin.¹³² Research conducted on animal models demonstrates that high-fat diets not only result in elevated levels of proinflammatory cytokines in adipose tissue but also trigger inflammation throughout the entire body. This process entails the activation of the NF-kappaB pathway, which ultimately leads to a decrease in insulin sensitivity. Chiang et al found that giving mice an HFD increased the activation of NF-kappaB. This, in turn, caused higher levels of IKK ϵ in both hepatocytes and adipocytes. Furthermore, when IKK ϵ was removed in mice, they were shielded from obesity and chronic inflammation caused by the HFD.¹³³

Hotamisligil's research revealed that pro-inflammatory cytokines can cause IR.¹³⁴ When there is excess fat, adipose tissue is infiltrated by macrophages and other immune cells, which then produce pro-inflammatory cytokines such as TNF- α , leptin, IL-6, resistin, MCP-1, PAI-1, angiotensinogen, visfatin, retinol binding protein-4, and serum amyloid A. Adipose tissue also produces other substances, such as adiponectin, which decreases as body fat increases.¹³⁵ Consuming high-fat foods and obesity causes fat to accumulate in fat cells (adipocytes). This buildup triggers stress in cells and activates inflammatory signaling pathways, namely IKK β /NF-kappaB and JNK. Proinflammatory cytokines like TNF- α and IL-1 β turn on the JNK and IKK β /NF-kappaB pathways through TNFR and IL-R receptor-mediated mechanisms. Cellular stress, such as oxidative stress and endoplasmic reticulum (ER) stress, also activates JNK and NF-kappaB. Lipid accumulation in adipocytes can increase ROS production, which in turn increases TNF- α , IL-6, and MCP-1 production and reduces adiponectin production. Saturated fats trigger an increase in ceramide synthesis, leading to its accumulation in tissues like muscle and a correlation with IR. Acute lipid infusion activates various PKC isoforms that can also activate IKK β and NF-kappaB.^{135–137}

JNK and IKK β /NF-kappaB are involved in inflammation-induced IR through different mechanisms. JNK makes IR worse by phosphorylating serine residues in IRS-1. This stops the insulin receptor/IRS-1 pathway from working normally, affecting serine-302 (pS302) and serine-307 (pS307). On the other hand, IKK β targets I κ B α for proteasomal degradation, which allows NF- κ B to enter the nucleus and stimulate gene expression. In contrast to JNK, IKK β induces IR by activating NF-kappaB via transcription, thereby increasing target gene expression and thereby increasing IR.¹³⁵ Treatments that inhibit NF-kappaB can increase IR, indicating that the NF- κ B pathway plays an important role in inflammation-associated IR.¹³⁸ Furthermore, studies have demonstrated that inhibiting JNK decreases the release of proinflammatory cytokines associated with IR, including TNF- and MCP-1.^{139,140}

The JAK-STAT pathway, especially through IL-6, plays a part in IR by decreasing the expression of GLUT4 and IRS-1 and increasing the expression of SOCS3.^{141,142} This also stops glycogen synthesis,¹⁴³ leads to the degradation of IRS-1 by proteasomes, and stops insulin signal transduction.¹³⁷ IL-6 plays an important role in regulating metabolism and immunity. Humans have shown visceral fat to be an important site for IL-6 secretion.¹⁴⁴ A very low-calorie diet and weight loss significantly reduced IL-6 levels in adipose tissue and serum, as well as improved insulin sensitivity compared to controls.¹⁴⁵ Additionally, treatment with anti-IL-6 antibodies increased insulin sensitivity in diet-induced obese mice.¹⁴⁶

IL-1 β is a pro-inflammatory mediator that contributes to IR through multiple mechanisms. It binds to the IL-1R1 receptor, activating the JAK protein kinase that stimulates NF- κ B translocation to the nucleus. This triggers the expression of inflammatory genes. IL-1 β also reduces IRS-1 tyrosine phosphorylation and disrupts PI3K and Akt signaling.^{147,148} Experimental studies in animal models indicate that IL-1 β is a proinflammatory mediator that can activate various other proinflammatory cytokines and chemokines.¹⁴⁹

Obesity-induced inflammation and lipid metabolites contribute significantly to IR through multiple inflammatory and metabolic signaling pathways. Because of this, reducing systemic inflammation and targeting inflammatory signaling pathways and proinflammatory cytokines like TNF- α , IL-6, and IL-1 β , may be a good way to fight IR and stop T2DM from happening.

Treatment and Prevention Strategies

It is important to identify gaps in current research regarding the role of lipids in IR. Many studies have linked increased levels of lipids such as DAG and ceramide to IR, but the specific molecular mechanisms of impaired insulin signaling by these lipids remain incompletely understood. For example, Holland et al showed that ceramide synthase inhibitors can increase insulin sensitivity in obese mice.⁹⁹ Li et al confirmed that a Cordyceps extract with myriocin can lower the buildup of ceramide, boost energy use, and improve glucose homeostasis in obese mice. This suggests that it might be useful as a supplement for treating obesity and related metabolic disorders.¹⁵⁰

Dietary intervention for IR is possible. For example, research by Kahleova et al showed that a low-fat plant-based diet significantly reduced body weight, visceral fat, IR, and intramyocellular and hepatocellular lipid levels in overweight adults in 16 weeks.¹⁵¹ Lifestyle interventions and metformin therapy can effectively prevent or delay the disease's onset. According to research, lifestyle interventions are more effective than metformin, with one case of diabetes prevented per seven people treated over three years.¹⁵² It is also important to conduct in-depth investigations into how specific

lipids, such as ceramide and DAG, interact with insulin signaling components such as PKC and PP2A, as well as their impact on mitochondria and oxidative stress.

Getting rid of systemic inflammation and targeting inflammatory signaling pathways and proinflammatory cytokines like TNF- α , IL-1 β , and IL-6 may help beat IR and stop T2DM from happening. Studies have shown that anti-TNF- α antibodies can improve insulin sensitivity in peripheral tissues and increase adiponectin concentrations.¹⁵³ Treatment with shRNA can downregulate TNF- α and increase IRS-1 phosphorylation and insulin response.¹⁵⁴ IL-1 β antibody treatment makes IR, blood sugar control, and β -cell function better in obese mice that were fed a high-fat diet.^{155,156} Tocilizumab is a humanized monoclonal antibody that selectively blocks IL-6 signaling. This lowers HOMA-IR and IR in RA patients who are not diabetic.¹⁵⁷ These studies suggest that inhibiting TNF- α , IL-1 β , and IL-6 can improve IR and T2DM. In addition, salicylates, an important class of anti-inflammatory agents, have been shown to improve insulin sensitivity and glucose tolerance through inhibition of NF- κ B and IKK β .^{158,159}

Omega-3 is a type of polyunsaturated fatty acid that is known to have various health benefits, including positive effects on insulin metabolism and insulin sensitivity. In contrast to saturated fatty acids, which can increase inflammation and contribute to IR, omega-3 reveals anti-inflammatory properties that help reduce the risk of IR. Omega-3 can stimulate the GPR120 receptor, which then inhibits pro-inflammatory signaling pathways in macrophage cells.¹⁶⁰ For this process to function, GPR120 must bind to β -arrestin-2. This stops the activation of TAK1, an important kinase in inflammatory pathways.¹⁶¹ By combining findings from human and animal studies, we can gain a more comprehensive understanding of the molecular mechanisms linking inflammation to IR, as well as identify potential interventions to reduce the negative impact of this condition.

Conclusion

IR, a condition associated with various metabolic disorders, is influenced by lipid metabolism, especially induced by HFD. Furthermore, excessive FFA production may lead to decreased insulin sensitivity, progressive pancreatic beta-cell atrophy, and ectopic fat accumulation, which eventually activate inflammatory mediators in the insulin pathway. Human studies show elevated FFAs and TGs may correlate with reduced insulin sensitivity. Metformin and omega-3 fatty acids, or PPAR agonists such as chiglitazar (a novel non-thiazolidinedione structured PPAR pan-agonist) may be potential interventions to overcome these dysfunctions. Animal studies show that HFDs disrupt insulin signaling and increase inflammation, with lipid mediators like ceramides contributing to IR. Understanding lipid-induced IR interactions is critical to developing effective treatments for metabolic diseases. It is suggested to further investigate the long-term impact of dietary changes and pharmacological interventions on lipid metabolism and IR. Future research needs to focus on several specific areas to address these gaps. It will be a challenge to discover new lipid-lowering therapies, specifically those evaluating the efficacy of new compounds that target ceramide and DAG to reduce IR.

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Disclosure

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