New insights of active constituents from herbs and nutraceuticals and their mechanisms in obesity-induced insulin resistance

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Abstract

Insulin resistance (IR) is a main etiology of various metabolic diseases such as type 2 diabetes mellitus (T2DM), hypertension, hyperlipidemia and coronary heart disease. IR is a multi-factorial etiology disease regulated by various mechanisms. Obesity, a significant public health problem worldwide, is considered as a high-risk factor to induce IR and T2DM. Thus, inhibiting obesity-induced IR is one of the key therapeutic strategies to improve T2DM. Natural products from herbs and nutraceuticals have shown promising efficacy on obesity-induced IR and T2DM owing to its multi-component and multi-target characteristics. However, the active constituents and the action mechanisms are still not yet well elucidated. In this review, the natural constituents with protective capacities against IR were summarized. The active constituents include crude extracts such as polyphenols, saponins, alkaloids, terpenoids, phenylpropanoids, as well as monomeric compounds such as curcumin, berberine, capsaicin, naringenin, quercetin, betaine and isoliquiritigenin. The action mechanisms of these active constituents could be mainly divided into 4 categories: ameliorating metabolic abnormality, inhibiting inflammation, reversing gut microbiota dysbiosis, regulating micro RNAs (miRNAs). Their precise roles in regulating PI3K/AKT, AMPK, PPARs, SIRT1 and NF-ϰB pathways, brown adipose tissue activity and white adipose tissue browning, NLRP3 inflammasome activity, gut microbiota structure and composition and miRNA expression were discussed. The sources, chemical structures, experimental models, pharmacological effects and action targets of these active constituents were also summarized. This review provides new active constituents, therapeutic targets and reasoning for the clinical application of herbs and nutraceuticals in the treatment of IR and T2DM.

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11**Abbreviations:** AKT, protein kinase B; AMPK, adenosine 5'-monophosphate-activated protein kinase; β3-AR, β3 adrenergic receptor; BAT, brown adipose tissue; CoA, Coenzyme A; DIO, diet-induced obese; DM, diabetes mellitus; ERK, extracellular regulated protein kinases; ERS, endoplasmic reticulum stress; FBG, fasting blood glucose; FOXO1, Forkhead box 1 protein; GLUT4, glucose transporter 4; GSK-3β, glycogen

synthase kinase-3 beta; HFD, high fat diet; HG, high glucose; HOMA-IR, homeostatic model assessment of insulin resistance; IKK, inhibitor of NF-κB; IL-6, interleukin-6; IR, insulin resistance; IRS, insulin receptor substrate; JNK, c-Jun N-terminal kinase; miRNA, micro RNA; NAD, nicotinamide adenine dinucleotide; NF-κB, nuclear factor kappa-B; NLRP3, NOD-like receptor thermal protein domain associated protein 3; PGC-1α, peroxisome proliferator activated receptor γ coactivator 1α· PI3K, phosphatidylinositol-3-kinase; PPARs, peroxisome proliferator activated receptor; ROS, reactive oxygen species; SCFAs, short chain fatty acid; SIRT1, silent information regulator 1; STZ, streptozotocin; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TCM, traditional Chinese medicine; TG, triglyceride; TNF-α, tumor necrosis factor-α· WAT, white adipose tissue.

ABSTRACT

Insulin resistance (IR) is a main etiology of various metabolic diseases such as type 2 diabetes mellitus (T2DM), hypertension, hyperlipidemia and coronary heart disease. IR is a multi-factorial etiology disease regulated by various mechanisms. Obesity, a significant public health problem worldwide, is considered as a high-risk factor to induce IR and T2DM. Thus, inhibiting obesity-induced IR is one of the key therapeutic strategies to improve T2DM. Natural products from herbs and nutraceuticals have shown promising efficacy on obesity-induced IR and T2DM owing to its multi-component and multi-target characteristics. However, the active constituents and the action mechanisms are still not yet well elucidated. In this review, the natural constituents with protective capacities against IR were summarized. The active constituents include crude extracts such as polyphenols, saponins, alkaloids, terpenoids, phenylpropanoids, as well as monomeric compounds such as curcumin, berberine, capsaicin, naringenin, quercetin, betaine and isoliquiritigenin. The action mechanisms of these active constituents could be mainly divided into 4 categories: ameliorating metabolic abnormality, inhibiting inflammation, reversing gut microbiota dysbiosis, regulating micro RNAs (miRNAs). Their precise roles in regulating PI3K/AKT, AMPK, PPARs, SIRT1 and NF-κB pathways, brown adipose tissue activity and white adipose tissue browning, NLRP3 inflammasome activity, gut microbiota structure and composition and miRNA expression were discussed. The sources, chemical structures, experimental models, pharmacological effects and action targets of these active constituents were also summarized. This review provides new active constituents, therapeutic targets and reasoning for the clinical application of herbs and nutraceuticals in the treatment of IR and T2DM.

Keywords: insulin resistance, obesity, type 2 diabetes mellitus, traditional Chinese medicine

1. Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is increasing rapidly worldwide (Rosengren & Dikaiou, 2023). International Diabetes Federation reported that the number of T2DM patients will probably rise to 700 million by 2045 (Cucinotta et al., 2021). Obesity is a high-risk factor for T2DM, and there is a close link between the two conditions (Kojta, Chacinska & Blachnio-Zabielska, 2020). In support, the epidemiological survey has demonstrated that obese patients are more likely to develop T2DM (Lee, Park & Choi, 2022).

Insulin is a hypoglycemic hormone secreted under endogenous or exogenous stimulation, which helps to store energy as the form of lipid (Najjar, Caprio & Gastaldelli, 2023). Nowadays, insulin is losing its physiological significance in energy storage with abundant nutritional sources. Conversely, over-nutrition triggers insulin resistance (IR). Accumulating facts have evidenced that IR plays a pivotal role in obesity-induced T2DM (Samuel & Shulman, 2012). It has been recognized that obesity could weakens the metabolic functions of insulin in the liver, skeletal muscle and adipose tissues, induce triglyceride (TG) accumulation and β-cells failure, thereby leading to IR and finally T2DM (Kojta, Chacinska & Blachnio-Zabielska, 2020). Obese patients could deliver the risk of IR to the next generation as early as pregnant (Nicholas, Morrison, Rattanatray, Zhang, Ozanne & McMillen, 2016). Hence, relieving obesity-induced IR is one of the key therapeutic strategies to improve T2DM.

The most natural and successful approaches to cure IR and T2DM are changing unhealthy lifestyles, taking more exercise and keeping on a healthy diet, however, it is hard to maintain a healthy routine. Gastric bypass surgery or bariatric surgery could also reduce the blood glucose levels in diabetic patients, but it

sacrifices caloric intake and bodyweight artificially (Sylow, Tokarz, Richter & Klip, 2021). Insulin sensitizers (biguanides and thiazolidinediones), nutrient absorption adjustment medicine (α-glucosidase inhibitors), insulin secretion-promoting medicine (sulfonylurea) and glucagon-like peptide-1 (GLP-1) agonists medicine are frequently used to improve T2DM. However, these medicines have limited efficacy and unsatisfied side effects (Bellary, Kyrou, Brown & Bailey, 2021; Perreault, Skyler & Rosenstock, 2021). For example, metformin, a first-line drug of biguanides, is forbidden to use in patients with advanced chronic kidney disease and liver disease. Sulfonylurea administration might cause hypoglycemia, weight gain, and cardiovascular disease exacerbation. Therefore, screening for natural medicines with potent efficacy and few side effects on obesity-induced T2DM are attracting great attention.

Diabetes mellitus (DM) is named "Xiao Ke" in traditional Chinese medicine (TCM), it is mandarin, for a general term of a series of symptoms including polydipsia, polyphagia, polyuria, emaciation, and sweet urine (Su, Hu, Tang, Tang & Huang, 2023). "Xiao Ke" was mentioned in the book "*Su Wen * Tong Ping Xv Shi Lun*(*Plain Questions & General Comments*)", which explained that obesity was a major pathogenic factor in DM and guided the principles of medication in TCM for diabetes. As TCM, herbs, and nutraceuticals share a lot of similarities in their original materials, it makes sense to look for neoteric cures for diabetes-related disorders in these natural herbs and nutraceuticals (Fang et al., 2021).

As IR is a multi-factorial etiology disease with complex pathomechanism, single target therapy is limited for its prevention and treatment. Recently, natural products from herbs and nutraceuticals have shown unique characteristics as multi-component and multi-target in improving IR and T2DM efficiently, which attracts wide attention and favor (Law et al., 2022). An increasing number of researches have indicated that active constituents from herbs and nutraceuticals might ameliorate DM and its complications by improving metabolic abnormalities, inhibiting inflammation, reversing intestinal flora disorder and regulating miRNAs. For instance, resveratrol, berberine and curcumin have been proved to exert anti-diabetic effects through various mechanisms simultaneously (Kim, Chung & Song, 2019; Kunnumakkara et al., 2017; Xu et al., 2021).

The aim of the present review was to summary the effects of natural active constituents on IR (especially obesity-induced IR), as well as to explain and discuss the action mechanisms. This review will provide potential perspectives for the clinical treatment of IR and T2DM.

2. Method

Distilled key points and stablished basic article structure after investigating sufficient quantity perspectives and reviews involved IR, then searched for experimental articles based on animals, cells and humans with the keywords: IR, obesity, T2DM, TCM, herbs, finally collated the articles into different categories according to the highlights. All the references have been published since 2000 and could be found on Web of Science.

3. Mechanisms of natural active constituents in alleviating IR

The mechanisms of active constituents from herbs and nutraceuticals in alleviating IR were divided into different categories as below: ameliorating metabolic abnormality, inhibiting inflammation, reversing gut microbiota dysbiosis, regulating miRNAs and others (Fig 1). The categories listed below, however, should only be used as a guide since the signaling pathways and other factors almost always work in concert.

3.1 Ameliorating metabolic abnormality

Insulin is a major regulator of carbohydrate, fat and protein metabolism. Lipid overflow hypothesis suggests that systematic IR and T2DM are mainly caused by abnormal increased lipid levels. The impaired storage capacity in adipose tissues could cause lipid overflow, that lipid would enter into the circulation and accumulated ectopically in other tissues such as skeletal muscle, liver and heart. Microscopically, ectopic lipid accumulation is caused by lipid intermediates, such as diacylglycerols, long chain fatty acyl- coenzyme A (CoAs) and acylcarnitines (Bosma, Kersten, Hesselink & Schrauwen, 2012). The mechanisms by which lipid intermediates affect insulin sensitivity include regulating phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT) pathway, protein phosphatase-2A (PP2A), fatty acid transporter CD36 and nucleotide-binding oligomerization domain (NOD)-like receptor thermal protein domain associated protein 3 (NLRP3)

inflammasome (Petersen & Shulman, 2017; Tsatsoulis, Mantzaris, Bellou & Andrikoula, 2013). Generally, lipid accumulation in local organs leads to partial IR, or worse, secondary systemic IR (Kojta, Chacinska & Blachnio-Zabielska, 2020). For illustration, ectopic lipid accumulation in skeletal muscle and liver might inhibit the insulin signal transduction, leading to impaired muscle glucose uptake and hepatic glycogen synthesis. IR caused by ectopic lipid accumulation occurs earlier in muscle than that in liver, which contributes to glucose transference from muscle to liver and hepatic adipogenesis. Subsequently, macrophages infiltrate into white adipose tissue (WAT), which ultimately aggravates inflammation, hyperlipidemia and postprandial hyperglycemia (Samuel & Shulman, 2016). Also, excess lipid accumulation inhibits the capacity of mitochondria in catabolizing fatty acid substrate, leads to incomplete β-oxidation, thereby causing oxidized lipid byproducts accumulation and IR (Johnson, Milner & Makowski, 2012).

3.1.1 Activating PI3K/AKT pathway

PI3K/AKT pathway plays an important role in multitudinous physiological functions, and insulin is its main ligand to regulate metabolism. PI3K/AKT pathway participates the cellular metabolism through directly regulating nutrient transporters, metabolic enzymes and transcriptional factors involved in lipid metabolism (Hoxhaj & Manning, 2020). PI3K, AKT, insulin receptor substrate (IRS), glucose transporter 4 (GLUT4) are the key effector molecules of PI3K/AKT pathway in maintaining glucose homeostasis. Also, PI3K/AKT pathway regulates lipid metabolism by mediating the inhibition of insulin on very low-density lipoprotein secretion (Mazibuko-Mbeje et al., 2019; Sharma, Kim & Rhyu, 2015). Presently, it is generally accepted that early growth response protein 1 (EGR-1) is one of the inhibitors of PI3K/AKT pathway (Yu et al., 2011).

Curcumin (Fig 2) is a diketone compound mainly extracted from Zingiberaceae or Araceae plants, such as the rhizomes of *Curcuma longa* . Li et al. verified that curcumin and its intracorporal degradation products (hexahydrocurcumin, octahydrocurcumin) alleviated IR, oxidative stress, inflammation and endoplasmic reticulum stress (ERS) in high glucose (HG)-induced HepG2 cells by increasing glucose uptake and inhibiting extracellular regulated protein kinases (ERK)/c-Jun N-terminal kinase (JNK) phosphorylation (Li et al., 2020).

Dendrobium officinale polysaccharide (Supporting Information Table S1) ameliorated T2DM and IR in high fat diet (HFD) combined with streptozotocin (STZ)-induced male BALB/c mice via PI3K/AKT-mediated glycogen synthesis and glucose metabolism. In brief, the polysaccharide promoted glycogen synthase kinase-3 beta (GSK-3β), glycogen synthase and GLUT4 expression, increased pyruvate kinase, hexokinase (HK) and phosphoenolpyruvate carboxykinase activity, reduced fasting blood glucose (FBG) and hepatic steatosis (Wang et al., 2018).

Mogroside is a triterpenoid compound extracted from *Siraitia grosvenorii* . Mogroside III, Mogroside IV and Mogroside V all positively improved glucose metabolism, with Mogroside V being the most effective, according to Liu et al (Liu et al., 2019). Mogroside V-treated rats exhibited reduced FBG levels, attenuated liver damages and increased insulin sensitivity through modulating PI3K/AKT pathway.

3.1.2 Activating AMPK pathway

Adenosine 5'-monophosphate-activated protein kinase (AMPK) is a heterotrimer composed of three subunits, including α, β and γ, each of which is encoded by multiple genes such as α1, α2, β1, β2, γ1, γ2, γ3. AMPK integrates nutritional and hormonal signals in peripheral tissues and hypothalamus, thus regulating adipokines-mediated food intake, body weight, glucose and lipid homeostasis (Kahn, Alquier, Carling & Hardie, 2005). One of the widely accepted theories is that AMPK can be used as an energy sensor to adjust metabolic adaptation capability and energy metabolism when the ATP/AMP ratio is reduced under an IR state (Lin & Hardie, 2018). Inhibiting lipid synthesis, boosting fat oxidation, and increasing skeletal muscle glucose absorption are the three main ways that AMPK reduces IR (Hardie, 2013; Lindegaard et al., 2013). Specifically, accelerating fatty acid oxidation is considered as a main mechanism by which AMPK alleviates IR in peripheral tissue. In this process, AMPK primarily phosphorylates acetyl CoA carboxylase, attenuates palmitoyl-CoA transferase-1 (CPT1), promotes long-chain fatty acyl-CoA to enter the mitochondria, eventually stimulating fatty acid oxidation (Kahn, Alquier, Carling & Hardie, 2005). AMPK activity can also

be inhibited by chronic low-grade inflammation; however, this effect is bidirectional (Day, Ford & Steinberg, 2017; Liong & Lappas, 2015). It is noted that AMPK and silent information regulator 1 (SIRT1) share many common signal factors and exert synergistic actions in alleviating IR. By deacetylating liver kinase B1 (LKB1), which is located upstream of AMPK, SIRT1 can activate AMPK. AMPK can also regulate SIRT1 by increasing nicotinamide adenine dinucleotide (NAD)/ reduced form of nicotinamide-adenine dinucleotide (NADH) ratio or nicotinamide phosphoribosyltransferase (NAMPT) expression (Rogacka et al., 2018).

Soy isoflavones (Supporting Information Table S2), a flavonoid compound, is a class of secondary metabolite produced in the soybean growth, also known as a phytoestrogen. Soy isoflavones regulated lipid metabolism in adipocytes via AMPK/sterol regulatory element binding protein-1 (SREBP-1) pathway. Soy isoflavones treatment significantly reduced body weight, adipocyte hypertrophy and excessive lipid accumulation in diet-induced obese (DIO) male rats (Tanet al., 2019).

Myricanol, a diarylheptane compound, is one of the active ingredients from *Myrica rubra* . It was proved to modulate skeletal muscle–adipose tissue crosstalk, reducing lipid accumulation, increasing WAT browning, and leading to improved mitochondrial function and insulin sensitivity (Shen, Liao, Zhang, Pan & Lin, 2019). The mechanisms were probably involved in AMPK/peroxisome proliferator activated receptor γ coactivator 1α (PGC-1α) pathway.

p-Coumaric acid is a ubiquitous flavonoid metabolite of plants. An*in vitro* study indicated that p-coumaric acid promoted fatty acid β-oxidation, inhibited TG accumulation and enhanced 2-NBDG uptake in differentiated L6 skeletal muscle cells (Yoonet al., 2013). The data suggested that p-coumaric acid inhibited lipid accumulation and improved glucose uptake to exert health-promoting effects by activating AMPK expression.

3.1.3 Promoting BAT activity and WAT browning

Adipose tissue is critical in regulating insulin sensitivity due to its lipid storage capacity, thermogenic function, and endocrine regulation capacity. Generally, adipose tissue can be roughly classified into three types: WAT, brown adipose tissue (BAT), beige adipose tissue. WAT is mostly located in the subcutaneous and visceral/omental regions and is used for lipid storage. BAT plays a significant role in energy expenditure and is primarily found in the interscapular space, supraclavicular regions, paravertebral and perirenal areas. Beige adipose tissue is defined as a transitional adipose tissue, which has properties of both WAT and BAT (Gustafson, Hedjazifar, Gogg, Hammarstedt & Smith, 2015).

Brown adipocytes have small lipid droplets, great mitochondrial number, brown exterior, and excellent capacity in energy expenditure. BAT generates heat by absorbing fatty acid from the circulation and uncoupling chemical energy production (such as ATP) via oxidative phosphorylation into non-shivering thermogenesis, leading to ectopic lipid accumulation. BAT activation also plays a critical role in glycemic control by increasing systemic glucose disposal (Chait & den Hartigh, 2020; Chondronikola et al., 2014). Numerous variables, including as cold stimulation, gut microbiota composition, PFG-1α, PPARγ, SIRT1 expression and β3 adrenergic receptor (β3-AR), contribute to WAT browning (Li et al., 2017; Ma et al., 2022). It was established that BAT transplantation potently alleviated IR in a dose-dependent manner on the BAT-recipient mice (Stanford et al., 2013). When exposed to cold, BAT-positive men could increase resting energy expenditure, glucose oxidation, whole-body glucose disposal and insulin sensitivity (Chondronikolaet al., 2014). Besides, BAT might have a greater impact on women than on males (Keuper & Jastroch, 2021). Thus, it might be a feasible way to improve IR and T2DM by promoting BAT activity and WAT browning.

Allicin, an organic sulfur compound rich in *Allium sativum* L., is a potential medicine for the treatment of obesity and other metabolic diseases. Allicin addition increased expression of brown adipocyte-specific genes (such as UCP1) by activating ERK1/2 and Krüppel-like factors 15 (KFL-15), thus inducing the formation of brown-like adipocytes in differentiated 3T3-L1 and inguinal WAT in mice and accelerating lipid oxidation and energy expenditure (Lee, Rhee, Kim, Um & Pyo, 2019).

Diphyllin is a common aryl naphthalene lignan. Duan et al. found that diphyllin intervention improved the glucolipid metabolism and insulin sensitivity, as evidenced by the increased thermogenesis in BAT and

beige adipose tissues, as well as the enhanced BAT generation and WAT browning. It was speculated that diphyllin acted through inhibiting V-ATPase and intracellular autophagy (Duan et al., 2020). Besides, it is worth mentioning that aryl naphthalene lignans are widely found in various dietary or medicinal plants and have multiple biological activities. For example, some of them were used as folk medicine for adjuvant therapy of DM (Jin et al., 2010; Sun et al., 2016).

3.1.4 Regulating PPARs

Peroxisome proliferator activated receptors (PPARs) are members of the nuclear receptor superfamily of ligand-inducible transcription factors and associated with metabolic homeostasis in the organism. There are three subtypes in the PPARs: PPARα, PPARβ and PPARγ, each of which has different functions and locations *in vivo* . PPARα is mainly expressed in the liver, and promotes adaptive responses to fasting by controlling fatty acid transport, fatty acid oxidation and ketogenesis. PPARδ is highly expressed in skeletal muscle, regulates lipid and glucose metabolism, and participates motor rection by regulating the switch from glycolytic to oxidative muscle fibers. PPARγ is a main regulator of lipogenesis, increasing lipid storage, glucose metabolism and insulin sensitivity via lipid-steal action (Ahmadian et al., 2013; Montaigne, Butruille & Staels, 2021).

PPARα and PPARγ play critical roles in enhancing insulin sensitivity (Gustafson, Hedjazifar, Gogg, Hammarstedt & Smith, 2015; Montaigne, Butruille & Staels, 2021). Adiponectin-stimulated PPARα expression could increase fatty-acid combustion and energy consumption, decrease TG content in the liver and skeletal muscle, thus improving insulin sensitivity. Meanwhile, lipolysis-derived fatty acid ligands-mediated PPARα activation could promote mitochondrial activity and adipose tissue energy metabolism. PPARγ, predominantly expressed in WAT and BAT, mainly regulates IR through promoting adipose denaturation. It was found that after deacetylation by SIRT1 in a NAD-dependent manner, PPARγ in WAT promoted WAT browning, balanced energy storage and expenditure, thus improving IR (Qiang et al., 2012). PPARγ agonists are prospective medicines for alleviating IR. However, activated PPARγ might exhibit contrary effects in different tissues. For example, short-chain fatty acids (SCFAs) from dietary fiber fermentation prevented obesity and enhanced insulin sensitivity by inhibiting PPARγ expression in the liver and adipose tissues (den Besten et al., 2015).

Capsaicin (Supporting Information Table S3) is an effective alkaloid from *Capsicum annuum* . Jiang et al. demonstrated that capsaicin treatment could decrease body weight, adipose tissue weight, tumor necrosis factor-α (TNF-α), MCP-1 and interleukin-6 (IL-6) expression and improve glucose tolerance in DIO mice. Further studies suggested that capsaicin might act through dual action on PPARγ/PPARα and transient receptor potential vanilloid type-1 (TRPV-1) expression (Kang, Tsuyoshi, Han, Kawada, Kim & Yu, 2010).

Naringenin is a *Citrus* flavonoid with remarkable therapeutic effects on hyperlipemia, obesity and IR. A previous study demonstrated that naringenin restored the grip strength, increased the insulin sensitivity, and inhibited inflammation in C-26 tumor-bearing mice (Snoke et al., 2021). As shown in a case study on a diabetic woman, naringenin supplementation could reduce body weight, insulin content and HOMA-IR, and further *in vitro* experiment demonstrated that naringenin might act via regulating PPARα and PPARγ expression in human subcutaneous adipose-derived stem cells (Murugesan, Woodard, Ramaraju, Greenway, Coulter & Rebello, 2020).

Cinnamaldehyde, an aldehyde organic compound, is a yellow viscous liquid mainly extracted from *cinnamomum cassia* . It was demonstrated that cinnamaldehyde administration significantly reduced body weight gain, attenuated adipocyte hypertrophy and hyperplasia in epididymal WAT and promoted metabolic activity in interscapular BAT, thus leading to IR improvement in a time-dependent manner. Cinnamaldehyde exposure also modulated the blood lipid profiles and lowered free fatty acids (FFAs), leptin, TG, total cholesterol (TC) and low-density lipoprotein cholesterol levels. The mechanisms were partially related to up-regulation of PPARγ expression (Zuo et al., 2017).

Luteolin is a flavonoid compound widely found in herbs, such as*Thymus mongolicus* and *Mentha hyplocalyx* . The ways that luteolin enhances IR and T2DM are numerous. For example, it was reported that luteolin

enhanced hepatic insulin sensitivity by regulating the interaction between the liver and adipose tissue (Kwon, Jung, Park, Yun & Choi, 2015). Likewise, luteolin was able to prevent hepatic and adipocyte fibrosis and IR via the toll-like receptor (TLR) signaling pathway (Kwon & Choi, 2018). By directly stimulating the PPARγ pathway or regulating the insulin signaling cascades, luteolin may also improve the function of insulin in adipocytes (Ding, Jin & Chen, 2010).

3.1.5 Activating SIRT1

SIRT1, a member of Sirtuins, is the major nuclear NAD-dependent deacetylase *in vivo* . SIRT1 is involved in the regulation of many processes in the organism, such as mitochondrial biogenesis, inflammation, intracellular metabolism, stress resistance, apoptosis and glucose homeostasis (Szkudelski & Szkudelska, 2015). The mechanisms by which SIRT1 alleviates IR include attenuating mitochondrial dysfunction via the SIRT1–SIRT3–mitochondrial complex I pathway (Zhang et al., 2015), inhibiting protein tyrosine phosphatase 1b (PTP1B, a negative regulator of the insulin signaling pathway) (Sun et al., 2007), regulating macrophages infiltration and polarization (Hui et al., 2017), suppressing inflammatory responses in macrophages (Yoshizaki et al., 2010). In addition, SIRT1 is connected to BAT activity and WAT browning. In support, Xu et al. found that SIRT1 deficiency significantly promoted BAT degeneration in HFD-challenged mice, resulting in IR aggravation (Xu et al., 2016). Another study that demonstrated how SIRT1 significantly increased WAT browning by deacetylating PPAR on Lys268 and Lys293 further confirmed this finding (Li Qiang & Yingming Zhao, 2012). In addition to PPARγ, there are numerous additional substrates for SIRT1 deacetylation, including FOXO1, nuclear factor kappa-B (NF-κB) P65, PGC-1α, which are all closely associated with IR. Hence, activation of SIRT1 might be a prospective target for selecting medicine to improve IR.

Resveratrol (Supporting Information Table S4), a non-flavonoid polyphenolic organic compound, is an antitoxin produced by plants being irritated. Cote et al. demonstrated that resveratrol improved hypothalamic insulin sensitivity by activating SIRT1 and AMPK in duodenum to initiate a gut–brain–liver neuronal axis in rats (Cote et al., 2015).

Berberine, a quaternary ammonium alkaloid, is a main effective constituent of *Coptis chinensis* . It was evidenced that berberine alleviated HG-induced IR by stimulating liver kinase B1/AMPK/PGC1α pathway in the liver of mice (Li, Wang, Shen, Bai & Xu, 2020). By targeting the MEKK1/MEK/ERK pathway, Berberine could alleviate TNF-α-induced IR in hepatocyte (Li et al., 2022). Berberine also potently promoted adipose tissue remodeling and thermogenesis by regulating PPARγ deacetylation via AMPK/SIRT1 pathway (Xu et al., 2021). Furthermore, a previous study suggested that berberine could improve insulin signaling transduction by reducing ERS (Wang, Lu, Xu & Dong, 2010).

Patchouli alcohol, a tricyclic sesquiterpene, naturally exists in*Pogostemon cablin* Benth. Patchouli alcohol could ameliorate inflammation, skeletal muscle IR and hepatic steatosis, and improve systematic glucose tolerance and insulin sensitivity in HFD-induced mice by up-regulating fatty acid oxidation via liver kinase B1/AMPK/SIRT1-dependent pathway (Pyun et al., 2021).

3.2 Inhibiting inflammation

Inflammation, characterized by swelling, redness, pain and fever, is helpful for dealing with external injuries and enhancing immune system aggressiveness and tissue repair and remodeling. However, long-term chronic low-grade inflammation could lead to significant adverse consequences (Gustafson, Hedjazifar, Gogg, Hammarstedt & Smith, 2015). Obesity-induced IR, mainly triggered by macrophages infiltration in WAT, is characterized by chronic low-grade tissue inflammation in the organism. Stimulated adipocytes could secrete cytokines, which would travel to peripheral tissue and result in localized inflammation and IR in the liver, skeletal muscle, etc. (Johnson & Olefsky, 2013). Thus, inhibiting the inflammatory cytokines and signaling pathways, such as IL-6, TNF-α, JNK and NF-κB might contribute to alleviation of IR and its associated disorders.

3.2.1 Inhibiting NF- κB πατηωαψ

NF-κB family transcription factors are the major regulators of immune and inflammatory processes in

response to injuries and infections in the organism. NF-κB pathway is one of the classical inflammation-related signaling pathways, which plays an important role in IR-related inflammation and exhibits different effects in different tissues. For example, the activated NF-κB pathway in hypothalamus mediated leptin resistance (Osborn & Olefsky, 2012), promoted pancreatic fibrosis via NF-κB-TGF-β1 crosstalk (Yan, Ren, Kou, Meng & Li, 2012), and induced muscle atrophy by inhibitor of kappa B kinase (IKK)/NF-κB activation (Samuel & Shulman, 2012). In most cases for obesity-induced IR, NF-κB activation is mainly caused by excessive lipid accumulation and fatty acid extravasation in adipocytes (Chen, Chen, Wang & Liang, 2015). Usually, NF-κB is packaged by its inhibitor IκB and formed into a complex stored in cytoplasm. NF-κB complex is a classic IKK target, in which IKK phosphorylates IκBα subunit and leads to proteasomal degradation, eventually resulting in NF-κB nuclear translocation (including p50 and p65 subunits) and pro-inflammatory gene expression (Samuel & Shulman, 2012). Various studies have revealed that blocking NF-κB pathway is a prospective strategy to suppress inflammation and consequently alleviate IR. In support, aspirin was found to improve IR by blunting NF-κB activation (Amy Fleischman, Steven E. Shoelson, Raquel Bernier & Allison B. Goldfine, 2008).

β-sitosterol (Fig 3) is a bioactive constituent rich in vegetable oils or seeds. A published study showed that β-sitosterol treatment for 30 days significantly prevented body weight gain, decreased SREBP-1c and PPAR-γ contents in serum and inhibited TNF-α and IL-6 expression in adipose tissues of T2DM rats (Jayaraman et al., 2021). Further study suggested that the effects of β-sitosterol were probably achieved by inhibiting IKKβ/NF-κB and JNK pathways.

Stevioside (Supporting Information Table S5), a tetracyclic diterpenoid compound derived from *Stevia rebaudiana* Bertoni., has numerous beneficial effects on diabetic patients. For example, Wang et al. found that stevioside was able to improve glucose tolerance and whole-body insulin sensitivity, decrease pro-inflammatory cytokines production and macrophages infiltration in HFD-induced IR mice by inhibiting NF-κB pathway (Wang et al., 2012).

Troxerutin (also named vitamin P4), one of the derivatives of rutin, is a flavonoid compound from *Sophora japonica* . By inhibiting ROS generation and ERS-mediated NOD activation, troxerutin showed excellent antioxidant effects. A published study demonstrated that troxerutin administration improved hyperglycemia in diabetic rats, which was at least partially achieved by its antioxidant capacities (Xing, Xiang & Li, 2020).

3.2.2 SuppressingNLRP3 inflammasome activity

NLRP3 inflammasome, a group of protein complex composed of NLRP3, apoptosis-associated spot-like protein containing CARD and pro-caspase-1, plays a central role in the progression and development of obesity and IR (Wan, Xu, Lu, Zhu, Yu & Li, 2015). Various factors including hypoxia, β-cell products islet amyloid polypeptide, uric acid, glucose, FFAs, ceramide, palmitate, NF-κB and AMPK were involved in NLRP3 inflammasome activity (Rohm, Meier, Olefsky & Donath, 2022; Strowig, Henao-Mejia, Elinav & Flavell, 2012; Wan, Xu, Lu, Zhu, Yu & Li, 2015). Especially, NLRP3 inflammasome was reported to act by regulating the pro-inflammatory cytokines (Strowig, Henao-Mejia, Elinav & Flavell, 2012). For instance, NLRP3 inflammasome-induced IL-1β accumulation could induce β-cells death or dysfunction and promote chemokines production in a(n) autocrine or paracrine manner (Rohm, Meier, Olefsky & Donath, 2022; Strowig, Henao-Mejia, Elinav & Flavell, 2012). IL-18 levels in serum of insulin resistant patients were also significantly up-regulated, which was attributed to the activation of NLRP3 inflammasome (Donath, Dinarello & Mandrup-Poulsen, 2019; Lee, Kim, Kim, Shong, Ku & Jo, 2013). These evidences indicated that NLRP3 inflammasome might be a reasonable target in regulating the initiation and development of various autoinflammatory and autoimmune diseases, providing a feasible direction to develop novel drugs for IR treatment. Numerous studies have confirmed this perspective. For example, glibenclamide improved glucose levels and β-cells functions in T2DM patients by suppressing NLRP3 inflammasome-mediated IL-1β release (Lee, Kim, Kim, Shong, Ku & Jo, 2013; Strowig, Henao-Mejia, Elinav & Flavell, 2012).

Isoliquiritigenin (Supporting Information Table S6), a flavonoid compound exacted from *Glycyrrhiza uralensis* Fisch., is a potential candidate for inflammatory disease by targeting NLRP3 inflammasome. It was found

that isoliquiritigenin intervention potently alleviated HFD-induced obesity, hepatic steatosis, lipid metabolic disorder and IR in mice by preventing NLRP inflammasome activation (Honda et al., 2014).

Betaine, a quaternary ammonium base alkaloid, is a metabolite of choline in animals, and also an active ingredient of *Lycium chinense*Miller. and most leguminous plants. Betaine could reduce NLRP3 inflammasome activity by activating PI3K/AKT pathway and suppressing FOXO1 phosphorylation, thus leading to the inhibition of the inflammatory responses and improvement of IR in diabetes (Kim et al., 2017).

Quercetin is a natural flavonoid compound widely extracted from the stems, barks, flowers, leaves, buds, seeds and fruits of many plants. It has been demonstrated that quercetin has central nervous system activity, which leads to reduced AMPK activation, thioredoxin-interacting protein overexpression, and glutamine-glutamate cycle dysfunction in the hypothalamus of high fructose-fed rats (Zhang et al., 2014). Simultaneously, quercetin could ameliorate high fructose-caused hypothalamic inflammatory lesions by inhibiting NF-$\varkappa$B pathway, NLRP3 inflammasome activation and IL-1β maturation. Given these, quercetin might have potential for improving IR and hyperlipidaemia.

3.3 Reversinggut microbiota dysbiosis

Human gut microbiota comprises trillions of bacteria that constitutes the largest intestinal microecosystem in the organism. A growing number of evidences have proven that the gut microbiota compositions in lean and obese populations are significantly different (Tsukumo, Carvalho, Carvalho & Saad, 2015). The changes in gut microbiota composition and structure, such as the Firmicutes/Bacteroides ratio alteration, could affect intestinal function, host metabolism and signal transduction pathways, resulting in obesity, IR and eventually diabetes (He et al., 2022; Xie, Zhao & Chen, 2021).

Effects of the gut microbiota on the organism function are mainly achieved by two aspects. The gut microbiota can increase the energy intake from indigestible polysaccharides (Tsukumo, Carvalho, Carvalho & Saad, 2015). Meanwhile, the gut microbiota-derived metabolites could act on the organism. For example, the endogenous endotoxin (such as lipopolysaccharide) secreted by gram-negative bacteria in gut microbiota could lead to metabolic inflammation, obesity and IR through activating TLR4 (Saad, Santos & Prada, 2016). The gut microbiota could also release SCFAs, amino acids derivatives and secondary bile acids, which positively regulates the lipid and glucose metabolism of the host (Heet al., 2022). Growing evidences have suggested that the pathways by which the gut microbiota alleviates the metabolic syndromes include regulation of TMAO pathway, mammalian target of rapamycin (mTOR) pathway and miRNAs expression (Heet al., 2022; Xie, Zhao & Chen, 2021). Hence, adjusting the gut microbiota is a potential way to alleviate IR. Yang et al. showed that exercise improved glucose metabolism and insulin sensitivity, partially by modulating gut microbiota compositions in patients (Yang, Lin, Lin & Xu, 2020).

Curcumin was proved to ameliorate hepatic steatosis and IR in HFD-fed obese mice by decreasing Firmicutes/Bacteroidetes ratio and endotoxin-producing Desulfovibrio bacteria abundance, increasing Akkermansia abundance and SCFAs-producing bacteria abundance and reversing gut microbiota dysbiosis (Li et al., 2021).

Astragaloside IV (Fig 4), a triterpenoid saponin compound, is one of the major active components of *Astragalus membranaceus* . Gong et al. hypothesized that astragaloside IV probably improved IR by modulating the gut microbiota compositions (Gong et al., 2021). It was considered that HG and HFD feeding could lead to excess ROS generation by inducing oxidative stress and resulting in significant gut microbiota disorders. Then, the signaling pathways related to insulin transduction were inhibited and subsequently IR occurred. Astragaloside IV exhibited the ability to scavenge ROS, balance the gut microbiota structures and activate the insulin signaling pathways, thus ameliorating IR symptoms. Additionally, astragaloside IV could be metabolized into astragalus alcohol by gut microbiota, further contributing to sodium-dependent glucose transporters 2 expression reduction and T2DM improvement.

Qiao et al. found that resveratrol treatment showed anti-obesity effects by improving HFD-induced gut microbiota disorders, as evidenced by the reduced Firmicutes/Bacteroidetes ratio (Qiao, Sun, Xia, Tang, Shi

& Le, 2014). Further assays demonstrated resveratrol administration significantly increased fasting-induced adipocyte factor expression (*Fiaf* , a key gene negatively regulated by the intestinal microflora), thereby decreasing the expression levels of genes associated with fatty acid synthesis and lipogenesis.

Oleanolic acid (Supporting Information Table S7), a natural pentacyclic triterpenoid consisting in various plants in a free or ligand form, is rich in the fruits of *Ligustrum lucidum* . Effects of oleanolic acid on gut microbiota disorders were confirmed by a previous study (Xue et al., 2021). Briefly, oleanolic acid supplementation markedly restored HFD-induced metabolic disturbances, IR and hepatic steatosis in rats. HFD-induced intestinal barrier dysfunction and endotoxin-mediated TLR4-related pathways were modulated by oleanolic acid addition, thus inhibiting endotoxemia and systemic inflammation and balancing the gut-liver axis homeostasis. Besides, oleanolic acid treatment effectively reduced Firmicutes/Bacteroidetes ratio and increased butyrate-producing bacteria abundance, implying that the gut microbiota compositions in HFD-fed rats were significantly remodeled by oleanolic acid intervention.

3.4 Regulating miRNAs

miRNA, a single-stranded, small and non-coding RNA molecule, is the biomarker of multiple diseases by targeting at mRNAs transcribed from gene clusters rather than the single genes. miRNAs from different tissues can enter the internal circulation in the form of exosomes to affect the metabolic profiles of distant organs, thus promoting the crosstalk among various organs (Ji & Guo, 2019). Specifically, the exosomes from the liver, adipose tissue and macrophages-derived play a critical role in regulating glucose homeostasis and insulin sensitivity. In particular, the adipose tissue-derived miRNAs are one of the key sources of all circulating miRNAs, which are recognized as novel adipokines (Ying et al., 2021; Ying et al., 2017). Reportedly, miRNAs primarily regulated the metabolism by modulating adipocytes differentiation, cytokines secretion and inflammatory genes and proteins expression (Arner & Kulyte, 2015).

It has been discovered that miRNA-141 expression was considered as an important biomarker of IR (Faheem, Rehman, Jabeen & Akash, 2020). miRNA-690 from lean adipose tissue macrophages was confirmed as an insulin-sensitizing miRNA (Yinget al., 2021). Ying et al. demonstrated that glucose intolerance and IR occurred in the recipient lean mice when treated with adipose tissue macrophage-derived exosomal miRNAs from obese mice (Yinget al., 2017). On the contrary, adipose tissue macrophage-derived exosomal miRNAs from lean mice could enhance the glucose tolerance and insulin sensitivity of obese mice. Many miRNAs related biomolecules, such as miRNA mimics, anti-miRNA oligonucleotides and exosome containing miRNAs, are potential therapeutic targets for the treatment of IR (Ji & Guo, 2019).

Curcumin (Supporting Information Table S8) administration significantly restored fructose-induced body weight gain in rats without affecting the food and water intake (Ding et al., 2015). The serum insulin, TG, TC and uric acid levels, as well as the glucose and insulin intolerance of rats were also significantly modulated by curcumin treatment. These effects were probably achieved by activating miR-206 expression to downregulate PTP1B and then improving insulin signaling to prevent fructose-induced glomerular foot cell injury and proteinuria.

Emodin is an anthraquinone compound, mainly derived from the rhizomes of*Rheum officinale* Baill. The anti-diabetic capacities of emodin were demonstrated by Xiao et al. in a published study (Xiao et al., 2019). It was revealed that emodin supplementation markedly reversed hyperglycemia, dyslipidemia and glucose metabolic disorders in T2DM rats in a dose- and time-dependent manner. Further assays elucidated that emodin addition probably decreased glucose consumption by down-regulating miR-20b-mediated SMAD7 expression.

δ-Tocotrienol, a subtype of vitamin E, is a lipid-soluble vitamin with benzo-monohydropyran carbon frame structure and unique antioxidant and anti-inflammatory properties. δ-Tocotrienol intervention significantly alleviated the blood glucose, inflammation and oxidative stress of T2DM patients, contributing to the inhibition of diabetes development and its complications. Recently, the research based on 304 T2DM patients have suggested that δ-tocotrienol treatment improved IR and T2DM through up-regulating miRNA-126 and miRNA-132 expression (Mahjabeen, Khan, Mirza & Pervez, 2021).

3.5 Others

As a multifactorial metabolic disease, IR is probably associated with various signal pathways and targets that acts simultaneously. As a result, not all of the mechanisms by which naturally occurring herbal and nutraceutical active constituents modulate insulin resistance could be generalized to the above pathways and factors. For example, emodin not only acted by regulating miRNAs, but also achieved the effects by inhibiting 11 beta-Hydroxysteroid dehydrogenase type 1 (11β-HSD1, an enzyme highly expressed in liver, brain and adipose tissues) (Feng et al., 2010). In brief, emodin administration significantly improved insulin sensitivity and lipid metabolism on prednisone- or dexamethasone-induced IR mice by inhibiting 11β-HSD1 mRNA expression. Moreover, bitter gourd, the fruit of *Momordica charantia* L., is an herb that is utilized in TCM as a heat-clearing medicament and is regarded as a remedy for "Xiao Ke". A recent study has shown that the soluble and insoluble fractions of bitter gourd could restore metabolic disturbance, hyperlipidemia, hyperglycemia and improve glucose tolerance by suppressing inflammation and SREBP-1c/FAS pathway (Xu, Cao, Feng & Liu, 2018).

Some naturally occurring active ingredients' processes, however, have not been fully explained. For example, mulberry fruit polysaccharide was found to reduce blood glucose levels and body weight gain in STZ-induced mice, possibly due to its antioxidant and hypoglycemic properties, however, further studies are still needed to clarify the precise targets (Chen, Huang, Li & Fu, 2017). The mechanisms by which theaflavins treatment protected against palmitic acid-induced HepG2 cells were also unclear (Tong et al., 2018).

4. Discussion

In this present review, the active constituents from herbs and nutraceuticals with anti-diabetic effects, as well as the underlying action mechanisms, were comparatively summarized and discussed. Generally, the active constituents mainly acted through ameliorating metabolic abnormalities, inhibiting chronic low-grade inflammation and reversing gut microbiota dysbiosis, all of which were further regulated by different signaling pathways or factors. For example, herbs and nutraceuticals could reduce WAT accumulation, increase BAT activity or promote WAT browning to ameliorate lipid metabolism disorders. Also, it was also reported to relieve IR by inhibiting inflammatory infiltration and cytokines secretion via suppressing NF-ϰB, TLR4 and NLRP3 activities. Although the mechanism by which natural herbal and nutraceutical active constituents reverses gut microbiota dysbiosis is still largely unclear, it has been confirmed that they could regulate gut microbiota abundance and metabolite emission, thereby alleviating the impairments from detrimental metabolite. In addition, herbs and nutraceuticals could also achieve the improvement of IR by regulating miRNA expression.

Current studies usually distinguish the contributions of different factors involved with IR, which exaggerates the individual role of a single factor. The pathogenic underpinnings of IR, however, resemble the chicken-and-egg cycle, making it challenging to pinpoint the initial event that triggers IR. For example, the lipid metabolism disorder in an obese and insulin resistant patient could trigger systemic chronic low-grade inflammation of the whole body, further regulate the gut microbiota abundance and affect the gastrointestinal absorption, eventually causing the aggravation of obesity and IR. Another theory suggests that the emergence of IR may come before obesity. One possible explanation is that HG and HFD could affect the gut microbiota abundance before the development of obesity. When the gut microbiota abundance changed, the gut microbiota metabolites are able to enter the systemic circulation and regulate the functions of the body. In other words, IR is probably derived from hyperglycemia and hyperinsulinemia, which subsequently induce IR of the liver and eventually the entire body (Tang, Le-Tien, Goldstein, Shin, Lai & Fantus, 2001; Yuet al., 2011). This process probably skips the step of obesity, which explains the facts that some patients with IR or T2DM are not obese.

Meanwhile, a therapeutic target, such as PPARγ, might exhibit converse functions in different tissues. PPARγ activity is directly proportional to the fat mass which is a pathogenic factor to induce chronic inflammation and exacerbate IR. However, PPARγ could also improve the insulin sensitivity of the organism (Gijs Den Besten, Rick Havinga & Albert K. Groen, 2015). Therefore, PPARγ has a dual role in IR, and

studies on PPARγ should focus on its regulation rather than activation.

Metabolic diseases including IR and T2DM are regulated by multi-mechanisms, multi-targets and multi-pathways. Herein, it is hard for single-target drugs to achieve satisfying therapeutic effects. Alternatively, natural herbal constituents have showed great potential and significance to develop anti-diabetic medicines with multi-targets. For illustration, resveratrol (Fig 5) has been proved to alleviate IR by several mechanisms acted simultaneously as below: (1) Regulating NAD/NADH ratio and SIRT1 expression to relieve ethanol-induced IR (Luoet al., 2017); (2) Inhibiting PTP1B in a SIRT1-independent manner to restore peripheral insulin transduction (Gonzalez-Rodriguez et al., 2015); (3) Reducing liver ERS to improve insulin sensitivity (Zhao, Zhang, Shu, Song & Ma, 2019); (4) Targeting duodenal SIRT1 and AMPK to activate the gut-brain-liver neuronal axis, improve insulin sensitivity and reduce blood glucose level (Cote et al., 2015).

Meanwhile, TCM holds that the organs harmony keeps the body in shape, which also has guiding significance for further researches on metabolic diseases. Traditional research methodology on IR is also limited. Due to the various mechanisms and organs involved in metabolic diseases, it is finite to study the impact of a single target. A growing number of studies have been performed from a multi-organ linkage perspective. Supporting this view, Shen et al. focused on the skeletal muscle–adipose tissue crosstalk to investigate the protective effects and mechanisms of myricanol against IR (Shen, Liao, Zhang, Pan & Lin, 2019). It was shown that the gut-brain-liver axis played a critical role in glucose production (Wang et al., 2008). The subcutaneous adipose tissue-liver axis was also found to control hepatic gluconeogenesis (Reilly et al., 2015).

Active constituents from natural products may have few side effects, however this does not make them completely non-toxic. For instance, resveratrol inhibited normal insulin signaling pathway by suppressing p-AKT/AKT level in ethanol-induced IR rats (Luoet al., 2017). Besides, it was reported that resveratrol showed negative effects on cells at higher concentrations, which encouraged ERS and IR (Zhao, Zhang, Shu, Song & Ma, 2019). Holistically, the doses of natural active ingredients should be taken into consideration to avoid side effects. The therapeutic effects of natural active ingredients on IR are a function of both their positive and negative effects, as well as their concentrations.

Numerous constituents from herbs and nutraceuticals effectively against IR, such as artemisinin, green tea polyphenols and berberine have been extensively employed in clinical trials. Nevertheless, most studies still stayed at the early stage of cell or animal studies. There is still lack of the clinical drugs with great efficacy, few side effects and precise action mechanisms. Here, this review also demonstrated that most active constituents against obesity-induced IR were flavonoids or alkaloids from herbs and nutraceuticals, which provided clues for developing new medicines. Further studies on natural medicine resources are moving forward to develop novel anti-diabetic drugs and clarify the connection between obesity and T2DM.

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Conflict of interest

None.

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Figure legends

Fig 1. The mechanism of metabolic disorder, inflammation, miRNAs and gut microbiota affecting IR. HFD-induced obesity promotes fat accumulation, leading to macrophage recruitment, lipid overflow and ectopic accumulation. Macrophages infiltrate into WAT, causing long-term chronic low-grade inflammation and increasing inflammatory factor secretion. Gut microbiota disorder cause lipopolysaccharide, secondary bile acids, SCFAs secretion maladjusted, leading to IR. miRNA transcribed from DNA transfer to the liver, WAT, skeletal muscle in the form of exosome, regulating IR in variety way. The active constituents might affect miRNA function by blocking miRNAs transcription or transport. Each of these has the potential to directly or indirectly alter IR.

Fig 2. The chemical structures of compounds from herbs and nutraceuticals that improves IR by ameliorating metabolic abnormalities.

Fig 3. The chemical structures of compounds from herbs and nutraceuticals that improves IR by inhibiting inflammation.

Fig 4. The chemical structures of compounds that improves IR by reversing gut microbiota dysbiosis, regulating miRNAs and others.

Fig 5. The mechanisms by which resveratrol prevents IR. Resveratrol alleviates IR via regulating NAD/NADH ratio, SIRT1 expression, PTP1B, ERS and gut-brain-liver neuronal axis.

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