Mechanism and Basis of Traditional Chinese Medicine Against Obesity: Prevention and Treatment Strategies

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In the last few decades, the incidences of obesity and related metabolic disorders worldwide have increased dramatically. Major pathophysiology of obesity is termed “lipotoxicity” in modern western medicine (MWM) or “dampness-heat” in traditional Chinese medicine (TCM). “Dampness-heat” is a very common and critically important syndrome to guild clinical treatment in TCM. However, the pathogenesis of obesity in TCM is not fully clarified, especially by MWM theories compared to TCM. In this review, the mechanism underlying the action of TCM in the treatment of obesity and related metabolic disorders was thoroughly discussed, and prevention and treatment strategies were proposed accordingly. Hypoxia and inflammation caused by lipotoxicity exist in obesity and are key pathophysiological characteristics of “dampness-heat” syndrome in TCM. “Dampness-heat” is prevalent in chronic low-grade systemic inflammation, prone to insulin resistance (IR), and causes variant metabolic disorders. In particular, the MWM theories of hypoxia and inflammation were applied to explain the “dampness-heat” syndrome of TCM, and we summarized and proposed the pathological path of obesity: lipotoxicity, hypoxia or chronic low-grade inflammation, IR, and metabolic disorders. This provides significant enrichment to the scientific connotation of TCM theories and promotes the modernization of TCM.

Keywords: traditional Chinese medicine, metabolic disorders, inflammation, dampness-heat syndrome, hypoxia, obesity

Abbreviations: AP-1, activator protein-1; DHS, dampness-heat syndrome; FFA, free fatty acid; FXR, farnesoid X receptor; GGQLD, Gegen Qinlian Decoction; HIF, hypoxia inducible factor; HRE, hypoxia response element; IR, insulin resistance; JNK, Jun N-terminal kinase; KC, Kupffer cells; LPS, lipopolysaccharide; MWM, modern western medicine; NAFLD, Non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NF-κB, nuclear factor-κB; NLRP3, NOD-like receptor family protein 3; PHD, prolyl hydroxylase domain; RHM, recruited liver macrophages; SC, Scutellaria-coptis herb couple; SCFAs, short-chain fatty acids; T2DM, type 2 diabetes; TCM, traditional Chinese medicine; TLR, Toll-like receptor; UPR, unfolded protein reaction.
INTRODUCTION

In the last few decades, the number of cases of obesity and related diseases has significantly increased globally, with more than 1.9 billion overweight adults and 650 million obese adults by 2019 (Ahirwar and Mondal, 2019). The increased prevalence of obesity is related to the increased incidence of metabolic disorders. Obesity is defined as excessive body weight, which is caused by the excessive and unproportioned amount of energy storage as adipose tissues (González-Muniesa et al., 2017; Blüher, 2019; San-Cristobal et al., 2020). Obesity is therefore characterized more particularly by an increase in the quantity of adipose tissue. Such an increase in fat progressively promotes the imbalance of energy storage and expenditure, showing glucose, lipid, and protein metabolic disorders (Charakida et al., 2014). Obesity leads to chronic low-grade inflammation (Bell et al., 2018). In terms of TCM, obese patients have internal “heat” or specifically “dampness-heat” (Shi Re in Chinese) with special signs of hot and wet appearance in patients, which is a very important TCM syndrome often observed in obese patients. The development of obesity is closely related to severe metabolic disorders, such as insulin resistance (IR), type 2 diabetes (T2DM), and liver steatosis. These pathological changes cause severe morbidity and mortality in patients (Saltiel and Olefsky, 2017; Ghaben and Scherer, 2019; Yu et al., 2019) and create a significant burden for individuals, families, and society. Today, eating habits and lifestyles have markedly changed in the population (Malik et al., 2013), and a sedentary lifestyle reduces energy consumption (Guthold et al., 2018; San-Cristobal et al., 2020). In TCM, the diagnosis and treatment of diseases are based on a method of differentiation of signs and symptoms known as “syndrome” differentiation or “ZHENG”, which relies on the gathering of clinical information through inspection, auscultation and olfaction, inquiry, and palpation (Chen et al., 2012). One of the most common “ZHENG” in TCM is “dampness-heat syndrome” (DHS) (Shi Re Zheng) (Dai et al., 2013; Yao et al., 2017), which is thought to be caused by a combination of “dampness” and “heat”. DHS can be caused by either external or internal sources (Dai et al., 2013). In addition, hypoxia is also an important feature occurring in this DHS (Lu, 2010).

DHS is prevalent in obesity with chronic low-grade systemic inflammation, is prone to IR, and eventually leads to severe obese metabolic disorders. In the following parts of this review, we focus on the mechanisms underlying obesity with DHS in TCM and propose potential prevention and treatment strategies using TCM theory. To fulfill the purpose, the current knowledge of modern western medicine (MWM) is applied to explain clearly DHS identified by the classic theories of TCM. Hopefully, it may enrich the scientific connotation of TCM theories and promote the modernization of TCM.

THE RELATIONSHIP BETWEEN ADIPOSE TISSUE, DHS AND METABOLIC DISORDERS

The TCM description of obesity was first seen in the ancient book “Nei Jing”. An unhealthy diet was considered an important cause of obesity. “Su Wen • Qi Bing Lun” described how “The people enjoyed rich food and became fat, experiencing internal heat and dampness. Fat made people hot, sweet made people full.” Sitting for a long period and lack of exercise were also important causes of obesity (Mao, 2005). It was clearly pointed out that partial edible fat and thick oily or sweet taste food with obesity were the causes of the DHS, while internal heat due to fat accumulation and unhealthy food was generated to account for the pathogenesis of DHS (Guo et al., 2020).

In a state of overnutrition, excessive calories need to be stored in adipose tissue. Adipose tissue maintains proper blood vessel formation, insulin sensitivity, and the levels of the anti-inflammatory hormone adiponectin and other metabolic regulatory adipokines. However, progressive adipocyte hypertrophy leads to increased hypoxia with relatively insufficient blood circulation in adipose tissue, which leads to tissue fibrosis with insufficient blood vessel formation. Moreover, hypoxic fat cells are apoptotic and necrotic, leading to immune cell infiltration and tissue inflammation. These factors together lead to a decrease in adipose tissue function, an increase in blood glucose and lipid levels, and lipid deposition in non-fat tissues such as muscle and liver tissues (Ghaben and Scherer, 2019), which is termed “lipid-toxicity (Fei Du in TCM)”.

Nowadays, people generally have more than enough food supply. A normal day-to-day diet is usually above the threshold of required nutrition with excessive fatty and greasy food. The amount of exercise decreases with reduced energy expenditure. Accumulated excessive energy causes an increase in fat tissues, showing a symptom of internal humid or “dampness” and internal hot or “heat” in TCM (Tian et al., 2018). The word “dampness-heat (Shi Re)” first appeared in the “Huang Di Nei Jing”, which was considered to be the collective name of “wet evil” (Shi Xie) and “hot evil” (Re Xie). The book “Zheng Yin Mai Zhi” argues as follows: "Or the order of hot and humid ... The moisture stays for a long period, and becomes hot”. DHS refers to the syndrome related to “dampness-heat” in various clinical diseases (Guo et al., 2020). DHS exhibits the main pathological features of body internal retention of excess water or moisture without “polymerization” and internal accumulation of dampness-heat without “transpiration” (Zhang et al., 2011). The clinical manifestations are chest distress, accumulated internal heat without volatilization, tiredness, heavy and soft limbs, dripping and burning yellow urine, dry stool, and a thick yellow tongue coating (Li et al., 2020). DHS is often a chronic disease that is difficult to cure. In MWM, such chronic disease may include metabolic disorders, type 2 diabetes, obesity, etc. (Tian et al.,
2018). DHS was often observed in diabetes, fatty liver, obesity (Xiang et al., 2018), and usually severe IR (Yin and Wei, 2012). The fatty liver was caused by excessive fatty food and the accumulation of evil energy "Qi" in the liver (Liu, 2019). Diabetes belongs to the category of weight-loss and thirsty or "Xiao Ke" in TCM. The most obvious feature is thirsty but no-intention to drink or thirsty without drinking much water. In TCM, it may be caused by the combination of dampness and heat as "dampness-heat" (Huang, 2014). Releasing the heat and removing dampness are the principles in the treatment of DHS (Tian et al., 2018; Li et al., 2020).

THE RELATIONSHIP BETWEEN HYPOXIA AND OBESITY

In TCM, obesity belongs to the "dampness-heat syndrome". "Dampness" causes disturbance of circulation and hypoxia in adipose tissue and small intestine. Hypoxia is an important feature of "dampness" (Lu, 2010). Chronic low-grade inflammation is common in obese patients. In MWM, inflammation causes temperature raise or "heat". Hypoxia increases the production of hypoxia-inducible factors (HIFs), leading to an increase in inflammatory factors, a decrease in adiponectin, a disturbance of glucose metabolism, imbalance of intestinal flora, and an increase in lipopolysaccharide (LPS); all factors together cause chronic inflammation, IR, and obese metabolic diseases (Figure 1).

Obesity triggers hypoxia in adipose tissue and small intestine, leading to adverse metabolic effects, including IR and non-alcoholic fatty liver disease (NAFLD) (Gonzalez et al., 2018). With the increase in adipose tissue, inflammation and hypoxia occur in adipose tissue to cause insulin resistance (Ichiki and Sunagawa, 2014; Lin and Yun, 2015). When adipocyte size increases, the oxygen supply decreases due to the decrease in capillary density. The increased consumption of oxygen by fat cells in obesity triggers the expression of HIF-1α, leading to inflammation and IR (Ban et al., 2014; Lee et al., 2014). Hypoxia stimulates the secretion of many inflammation-related adipokines (Wood et al., 2009; Trayhurn, 2013) and inhibits adiponectin release from fat tissues of obese people (Ye et al., 2007). Due to a combination of accumulated saturated fatty acids and expression of ADP/ATP translocase 2 (ANT2) in the mitochondria, adipose tissue becomes hypoxic with an increase in uncoupled respiration in the mitochondria (Gonzalez et al., 2018). This decoupling leads to the stabilization of HIF1α. HIF1α induces the expression of cytokine signaling inhibitor 3 (SOCS3), activates Janus kinase (JAK) to phosphorylate SOCS3, activates transcription 3 (STAT3), and inhibits the expression of adiponectin (Gonzalez et al., 2018). Here,
Hypoxia also increases the instability of adiponectin mRNA (Hosogai et al., 2007). In addition, hypoxia inhibits the differentiation of adipocytes; such inhibition is conducive to the expansion of adipose tissue (Arias-Loste et al., 2015). Moreover, hypoxia increases the expression of genes related to fat formation (Piguet et al., 2009), induces IR in adipose tissue, and promotes fibrosis of adipose tissue (Wood et al., 2009; Trayhurn, 2013).

In obesity, the small intestine becomes hypoxic, resulting in the accumulation of hypoxia HIF2α in the intestine epithelial cells. HIF2α stimulates the expression of gene encoding sialidase 3 (NEU3), which hydrolyzes gangliosides to form ceramides. Elevated ceramide levels lead to obesity due to decreased fat browning, increased fatty acid synthesis, and IR (Gonzalez et al., 2018). Chronic activation of HIF2α leads to increased inflammation and fibrosis and decreased fatty acid β-oxidation. These changes adversely affect liver physiology, leading to NAFLD and non-alcoholic steatohepatitis (NASH) (Gonzalez et al., 2018). Stable liver HIF-2β improves insulin sensitivity (Taniguchi et al., 2013).

Under the hypoxic condition, a rapid increase in the expression of pro-inflammatory cytokines and fibro-genic genes is observed (Qu et al., 2011). Hypoxia induces inflammation in adipose tissue by regulating gene expression in adipocytes and macrophages. The inflammation-related genes include genes encoding TNF-α, IL-1, IL-6, etc. (Semenza et al., 2000; Ye, 2009).

HIFs are the main regulators of hypoxia adaptation and inflammation. HIFs contribute to inflammation through action on cells involved in innate immunity (Imtiyaz and Simon, 2010). HIFs are a family of transcription factors activated by hypoxia and consist of one α subunit (HIF1α, HIF2α or HIF3α) and one β subunit (HIF1β) (Zhang et al., 2010; Klöting and Blüher, 2014).

Under normoxia, the proline residues on the α subunit of HIF are hydroxylated by HIF prolyl hydroxylase, so that HIF is recognized and ubiquitinated by VHL E3 ubiquitin ligase. It is then rapidly degraded by the proteasome. Asparagine hydroxylation inhibits the interaction of HIFα with the co-activator cAMP response element binding (CREB)-binding protein (CBP) and histone acetyltransferase p300 (p300). During hypoxia (B), the enzyme activities of PHD and FIH are inhibited, resulting in the stabilization of HIFα subunit. After being transported to the nucleus, HIFα complexes with the β subunit, recruits p300 and CBP, and then binds to the hypoxia response element (HRE) in the target gene promoter to initiate transcription. Hypoxia and inflammation (C). On the one hand, inflammation is usually characterized by tissue hypoxia or the stabilization of hypoxia-dependent transcription factors such as hypoxia-inducible factor (HIF). On the other hand, hypoxia is characterized by secondary inflammatory changes. In order to meet the challenge of hypoxia and ensure cell survival, the regulation of HIF and nuclear factor-κB (NF-κB) occurs through oxygen-sensitive prolyl hydroxylase (PHD). Hypoxia activates NF-κB through a pathway involving IκB kinase–β (IKKβ) activation, which leads to phosphorylation-dependent degradation of IκBα and the release of NF-κB. PHD and FIH regulate the activation of NF-κB by regulating the activity of IKKβ.

**FIGURE 2** The relationship between hypoxia and inflammation. Under normal oxygen (A), the proline residues on the α subunit of HIF are hydroxylated by HIF prolyl hydroxylase, so that HIF is recognized and ubiquitinated by VHL E3 ubiquitin ligase. It is then rapidly degraded by the proteasome. Asparagine hydroxylation inhibits the interaction of HIFα with the co-activator cAMP response element binding (CREB)-binding protein (CBP) and histone acetyltransferase p300 (p300). During hypoxia (B), the enzyme activities of PHD and FIH are inhibited, resulting in the stabilization of HIFα subunit. After being transported to the nucleus, HIFα complexes with the β subunit, recruits p300 and CBP, and then binds to the hypoxia response element (HRE) in the target gene promoter to initiate transcription. Hypoxia and inflammation (C). On the one hand, inflammation is usually characterized by tissue hypoxia or the stabilization of hypoxia-dependent transcription factors such as hypoxia-inducible factor (HIF). On the other hand, hypoxia is characterized by secondary inflammatory changes. In order to meet the challenge of hypoxia and ensure cell survival, the regulation of HIF and nuclear factor-κB (NF-κB) occurs through oxygen-sensitive prolyl hydroxylase (PHD). Hypoxia activates NF-κB through a pathway involving IκB kinase–β (IKKβ) activation, which leads to phosphorylation-dependent degradation of IκBα and the release of NF-κB. PHD and FIH regulate the activation of NF-κB by regulating the activity of IKKβ.
Hypoxia and inflammation are related and interact with each other. On the one hand, inflammatory diseases are usually characterized by tissue hypoxia or the stabilization of hypoxia-dependent transcription factors such as HIF. On the other hand, hypoxia-caused diseases are characterized by secondary inflammatory changes (Bartels et al., 2013). In order to meet the challenge of hypoxia and to ensure cell survival, the HIF and nuclear factor-κB (NF-κB) are activated; both are regulated by oxygen-sensitive prolyl hydroxylase (PHD) (Van Welden et al., 2017). In addition to HIF-1α, NF-κB is also activated by hypoxia (Ye et al., 2007). Hypoxia activates NF-κB through a pathway involving IκB kinase-β (IKKβ) activation, which leads to phosphorylation-dependent degradation of IκBα and the release of NF-κB (Michiels et al., 2002; Bartels et al., 2013). PHD and FIH regulate the activation of NF-κB by controlling the activity of IKKβ (Eltzschig and Carmeliet, 2011). Hypoxia induces IKKβ activation by inhibiting PHD activities (Devraj et al., 2017). PHD2 hydroxylates IKKβ, while PHD3 prevents the interactions between IKKβ and heat shock protein 90 (HSP90) and between IKKγ and apoptosis inhibitor (cIAP1). PHD1 may hydroxylate IKKβ, but it has not been fully established (Van Welden et al., 2017) (Figure 2).

Hypoxia promotes changes in mitochondrial structure and genome stability, resulting in reduced mitochondrial respiration, reduced ATP production, and accumulated mtDNA mutation (Vega et al., 2015). MtDNA-mediated inflammation is driven by the activation of inflammasomes (McGarry et al., 2018). The NOD-like receptor family protein 3 (NLRP3) inflammasome is a target of mtDNA; activation of NLRP3 leads to the subsequent activation of caspase-1 and the secretion of IL-1β and IL-18 (Nakahira et al., 2011). IL-1β belongs to the family of interleukin-1 cytokines and is activated by NF-kB-mediated HIF-1α (Jung et al., 2003). Hypoxic conditions increase levels of reactive oxygen species (ROS) and oxidative stress (McGarry et al., 2018); here, mitochondrial ROS may induce the activation of NLRP3 inflammasome (Zhou et al., 2011).

In addition to being induced by hypoxia, other non-hypoxic stimuli, such as lipopolysaccharide (LPS) and pro-inflammatory cytokines, may induce NF-κB-dependent increase in HIF1 mRNA levels. HIF promotes the activation of NF-κB (Van Welden et al., 2017). LPS is the main component of Gram-negative bacterial membranes and activates HIF-1 in macrophages or monocytes (Devraj et al., 2017). In macrophages, LPS regulates the activation of hypoxia-regulated genes through the HIF-1 pathway (Blouin et al., 2004). LPS is recognized by Toll-like receptors (TLR) expressed on myeloid cells. The downstream signal transduction of TLR involves NF-κB, which increases the expression of HIF-1 and key inflammatory cytokines such as tumor necrosis factor α (Arias-Loste et al., 2015). In addition, certain types of intestinal flora are responsible for the production of short-chain fatty acids (SCFA) (acetic acid, propionic acid, and butyric acid). The intestinal epithelial cells at the top of the villi are the main users of butyric acid. Peroxisome proliferation PPARγ (inducible by butyrate) in the cells activates β-oxidation and oxidative phosphorylation. In this process, a large amount of oxygen is consumed, which makes the top of the intestinal crypts physiologically hypoxic (Masłowski, 2019).

THE RELATIONSHIP BETWEEN CHRONIC LOW-GRADe INFLAMMATION, INSULIN RESISTANCE, AND METABOLIC DISORDERS

“Dampness-heat” is closely related to inflammatory factors (Guo et al., 2020). DHS is mostly reflected by the changes in inflammatory factors and abnormal immune function. It is also closely related to oxidative damage, energy metabolism, endotoxin, blood lipid metabolism, etc. (Tian et al., 2018).

The inflammatory response plays an important role in the pathogenesis of obesity and related chronic diseases (Rodriguez-Hernández et al., 2013). There is strong evidence that obesity is closely associated with chronic low-grade systemic inflammation, which is a key element to the occurrence and development of obese metabolic diseases (Crunkhorn, 2013; Laselín and Capuron, 2014; Yu et al., 2019). Obesity- and inflammation-related metabolic disorders usually show clear IR (Sun and Karin, 2012).

Chronic low-grade inflammation has no signs of concomitant infection or autoimmunity and no large-scale tissue damage. In addition, the inflammation activation is often limited and referred to as “low-grade” chronic inflammation (Monteiro and Azevedo, 2010). Obesity-related chronic low-grade inflammation has the activation of various inflammatory signaling cascades leading to the activation of NF-κB, Jun N-terminal kinase (JNK), and inflammatory bodies (Catrysse and van Loo, 2017). Chronic inflammation with metabolic syndrome is the inflammation in multiple organs and tissues, including adipose tissue, pancreas, liver, muscle, hypothalamus, and gastrointestinal tract (Yu et al., 2019).

Adipose tissue inflammation is considered a key event leading to metabolic diseases (Yu et al., 2019). In dysfunctional hypertrophic adipose tissue, lipolysis increases to cause excessive free fatty acid (FFA) production. This leads to mitochondrial dysfunction and oxidative stress in adipose tissue and activates the inflammatory response through NF-κB. FFAs indirectly bind to Toll-like receptor (TLR) 4 and TLR2 through the adaptor protein fetuin A, thereby promoting inflammation and activation of NF-κB and JNK. Once activated, NF-κB and JNK pathways increase the synthesis and secretion of inflammatory factors and chemokines in adipocytes and hepatocytes (Shi et al., 2006; Calle and Fernandez, 2012; Saltiel and Olefsky, 2017). In addition, excessive nutrients may overload the function of the endoplasmic reticulum, and lead to more protein misfolding by activating the unfolded protein reaction (UPR). UPR induces activation of NF-κB through transcription factor 6 and other factors to promote the pro-inflammatory response and
Obesity and related metabolic disorders are a global epidemic, leading to increased mortality and medical costs. No effective treatment options have been established (Dai et al., 2013; Saltiel and Olefsky, 2017; Ghaben and Scherer, 2019). The best way nowadays is to change eating habits and lifestyle and to treat obesity and its complications with various strategies. One of the strategies that has been shown to be effective is the use of traditional Chinese medicine (TCM) for the treatment of metabolic disorders. TCM is an ancient system of medicine that has been used for thousands of years in China. It is based on the belief that the body is a complex system of interconnected organs and systems, and that health is achieved through the balance of these systems.

Obesity is a major health concern that affects millions of people worldwide. It is characterized by an excess of body fat, which can lead to a number of health problems, including diabetes, heart disease, and certain cancers. The prevalence of obesity is increasing rapidly, and it is estimated that by 2040, more than 2.2 billion adults will be overweight or obese. This poses a significant challenge for healthcare systems and public health authorities around the world.

In the case of obesity, traditional Chinese medicine (TCM) offers a number of potential treatment options. TCM recognizes that obesity is not just a physical condition, but also a condition of the mind and spirit. TCM therefore focuses on treating the whole person, rather than just treating the symptoms of obesity. TCM treatments for obesity may include acupuncture, herbal medicine, nutritional counseling, and physical therapy.

One of the key concepts in TCM is the idea of Qi, which is a life force energy that is believed to flow through the body. Qi is associated with the body's organs and systems, and is thought to be responsible for maintaining health and well-being. When Qi is imbalanced, it is believed to contribute to the development of disease. In the case of obesity, it is believed that the imbalance of Qi may lead to an excess of fat in the body.

TCM also recognizes the importance of nutrition in the prevention and treatment of obesity. The Chinese believe that food is medicine, and that the right food can help to balance Qi and maintain good health. TCM dietary advice may include the consumption of foods that are high in fiber, low in fat, and rich in nutrients, such as vegetables, fruits, and whole grains. It may also advise against the consumption of processed foods and sugary drinks, which are believed to contribute to the development of obesity.

Finally, TCM also recognizes the importance of exercise in the prevention and treatment of obesity. It is believed that regular physical activity can help to balance Qi and promote good health. TCM may advise individuals to engage in regular exercise, such as walking, yoga, or tai chi, to help to maintain a healthy body weight.

In conclusion, traditional Chinese medicine offers a number of potential treatment options for obesity. These may include acupuncture, herbal medicine, nutritional counseling, and physical therapy. Additionally, TCM recognizes the importance of nutrition and exercise in the prevention and treatment of obesity. Overall, TCM provides a holistic approach to the prevention and treatment of obesity, and may offer a promising alternative to traditional Western treatments.
participate actively in physical exercise. The incidence of T2DM is equally increasing, and Asia populations are particularly prevalent in T2DM globally, especially in China and India (Zheng et al., 2018). NAFLD is currently a common metabolic disease. Recently, NAFLD has also been named metabolic-related fatty liver disease (MAFLD) (Eslam et al., 2020), which is characterized by excessive deposition of lipids in the liver. The high incidence of NAFLD affects approximately 25% of the adult population worldwide (Diehl and Day, 2017; Friedman et al., 2018; Paul and Davis, 2018; Eslam et al., 2020). NAFLD may further develop into NASH and eventually liver cancer. These diseases are closely related to obesity and obese metabolic disorders and are often accompanied by chronic low-grade systemic inflammation, identified as obese metabolic disorders in MWM or “dampness-heat” in TCM. Dampness-heat is well established TCM syndrome for obese metabolic disorders.

Obesity has the symptoms of “dampness-heat”, with disturbance of glucose and lipid metabolism. Hypoxia is often occurring in adipose tissue and small intestine with chronic low-grade inflammation. These hypoxia and inflammation are prone to IR and eventually lead to obese metabolic diseases. The TCM mainly uses “heat-releasing” and “dampness-cleaning” drugs to prevent and treat obese metabolic diseases or to improve glucose and lipid metabolism, to reduce inflammation, to inhibit HIF, and to reverse IR in MWM (Figure 4).

FIGURE 3 | Pathological pathway of “Lipid-toxicity Inflammation” or “Dampness-heat Syndrome” —Insulin Resistance—Metabolic disease. We try to explain the classic theory of TCM by using modern western medicine (MWM). In obese patients with dampness heat syndrome, a large amount of free fatty acid (FFA) is produced in the body, causing lipotoxicity, called “lipid toxicity or Fei Du”. A large amount of FFA may cause chronic low-grade systemic inflammation, which causes “heat” as one symptom of inflammation. These may be the modern medical interpretation of “fat makes people hot” in dampness heat syndrome. The severity of obesity-type metabolic disorders (diabetes, fatty liver, obesity) reflects the degree of inflammatory injury. The activation of various inflammatory signaling cascades in chronic low-grade systemic inflammation leads to the activation of NF-κB, Jun N-terminal kinase (JNK), and inflammatory bodies, thereby causing insulin resistance. The common pathological feature of obese metabolic disorders is chronic low-grade inflammation and insulin resistance. IR, insulin receptor; IRS, insulin receptor substrate; FFA, free fatty acids. The signal pathway map here was generated by Adobe Illustrator software.
In MWM, chemical drugs used to prevent obese metabolic diseases mainly include drugs improving metabolism (such as PPARα/δ agonists, PPARγ agonists), anti-inflammation, antioxidants, anti-FXR, regulating intestinal flora, inhibiting DAG and ceramide production, and reducing gluconeogenesis and glycogenolysis (such as metformin), etc. (Zhang et al., 2020). Obesity patients generally have excessive adipose tissue and/or small intestine hypoxia, chronic low-grade inflammation, and IR, which eventually leads to obese metabolic diseases. Therefore, HIF inhibitors may be used to prevent and treat obese metabolic diseases. Based on the HIF1α-SOCS3-STAT3-adiponectin pathway in adipose tissue, the HIF inhibitor pyridine prevents obesity and IR caused by a high-fat diet (HFD) (Jiang et al., 2013). PX-478 selectively inhibits fat HIF1α, thereby partially improves metabolic dysfunction by reducing fat fibrosis (Sun et al., 2013). In addition, the HIF inhibitor PT2385 reduces the level of ceramide in the intestine and serum, which thereby improves metabolism (Gonzalez et al., 2018).

TCM may act on multiple targets of the pathological pathway of “lipid toxicity (Fei Du)-Inflammation-DHS-IR-Metabolic disease”. TCM drugs, such as medicines for clearing away heat and dampness, medicines for improving glycolipid metabolism, medicines for anti-inflammation, and medicines for improving IR, may be used to prevent and treat obese metabolic disorders (Figure 4).

In this review, Gegen Qinlian Decoction (GGQLD) (prescription), Scutellaria-coptis herb couple (drug pair), Scutellaria baicalensis Georgi or Coptis chinensis Franch (medicinal material), and Baicalin or Berberine (component) have been taken as an example.

First, the influence of traditional Chinese medicine-GGQLD on obesity-related glucose metabolism, lipid metabolism, and microbial metabolism was reported (Zhang et al., 2013; Zhang et al., 2017; Zhang et al., 2020). GGQLD is a classic recipe that originated from Zhang Zhongjing’s “Treatise on Febrile Diseases” to treat DHS (Guo et al., 2020). GGQLD is made up of four herbs: Pueraria montana var. lobata (Gegen), Scutellaria baicalensis Georgi (Huangqin), Coptis chinensis Franch (Huanglian), and Glycyrrhiza uralensis Fisch. ex DC (Gancao) (Zhang et al., 2013; Zhang et al., 2020). Based on the analysis of pathogenesis in MWM, GGQLD prevented and treated obese metabolic disorders and improved T2DM and NASH (Zhang et al., 2013; Wang et al., 2015; Guo et al., 2017; Xu et al., 2020; Zhang et al., 2020). Effects of GGQLD were related to the regulation of glucose and lipid metabolism (Zhang et al., 2013; Sui et al., 2019; Tu et al., 2020), intestinal flora (Zhang et al., 2017; Guo et al., 2018; Liu et al., 2019), levels of SCFAs (Liu et al., 2019), and oxidant stress and inflammatory (Zhang et al., 2020). In TCM, Scutellaria-coptis herb couple (SC) in the “Treatise on Febrile Diseases” had the effect of clearing away heat and dampness, purging fire, and detoxifying. The “Compendium of Materia Medica” recorded that “Scutellaria baicalensis Georgi is tasting bitter and causing internal cold, and cures dampness and heat ... the effect is similar to that of Coptis chinensis” (Tian et al., 2018). SC was reported to improve IR in T2DM (Liu et al., 2013; Zhang et al., 2019). In mice with IR induced by high-fat diet, Scutellaria baicalensis Georgi improved IR by inhibiting macrophage-mediated inflammation (Na and Lee 2019). In addition, the extract of Scutellaria baicalensis Georgi showed strong anti-obesity and anti-triglyceride effects (Song et al., 2013), which prevented FFA-induced lipotoxicity through AMPK-mediated SREBP signaling.

**FIGURE 4 | Strategies for the prevention and treatment of obese metabolic disorders. Obesity has the symptoms of “dampness heat”. Obesity patients exhibit dysfunction of glucose and lipid metabolism. They generally have adipose tissue and/or small intestine hypoxia and chronic low-grade inflammation, and they are prone to insulin resistance (IR) and obese metabolic diseases. Therefore, the TCM drugs to prevent and treat obesity-type metabolic diseases are mainly heat-clearing and anti-dampness, or in MWM anti-inflammation, inhibiting HIF and improving IR.**
pathway, thereby alleviated NAFLD (Chen et al., 2018). Long-term treatment with baicalin improved diet-induced obesity and hepatic steatosis and led to systemic improvements in many metabolic diseases (Dai et al., 2018). The highest reported dose of baicalin at 400 mg/kg/d was safe without significant side effects and significantly reduced obesity and fatty liver disease (Xi et al., 2015). Moreover, baicalin reduced NASH by inhibiting lipid metabolism, inflammation, and fibrosis in mice (Zhang et al., 2018) and reduced diet-induced NASH by inhibiting the activation of the JNK signaling pathway (Zhong and Liu, 2018). Baicalin was effectively used to treat abnormal blood sugar and blood lipid metabolism caused by a long-term high-fat diet by adjusting the abundance of the microbiota and changing the production of a variety of SCFAs (Ju et al., 2019). Berberine regulates liver lipid metabolism by changing the production of a variety of SCFAs (Ju et al., 2018). Baicalin was effectively used to treat abnormal blood sugar and blood lipid metabolism caused by a long-term high-fat diet by adjusting the abundance of the microbiota and changing the production of a variety of SCFAs (Ju et al., 2019). Berberine regulates liver lipid metabolism by changing the production of a variety of SCFAs (Ju et al., 2018). Baicalin was effectively used to treat abnormal blood sugar and blood lipid metabolism caused by a long-term high-fat diet by adjusting the abundance of the microbiota and changing the production of a variety of SCFAs (Ju et al., 2019). Berberine regulates liver lipid metabolism by changing the production of a variety of SCFAs (Ju et al., 2018).

In summary, this article discussed the mechanisms of TCM underlying obesity and related metabolic disorders and proposed accordingly prevention and treatment strategies. In particular, the MWM theories of hypoxia and inflammation were applied to explain the “dampness-heat” syndrome of TCM, and we summarized and proposed the pathological path of obesity, lipotoxicity, hypoxia or chronic low-grade inflammation, IR, and metabolic disorders. Such discussion provides great significance to enrich the scientific connotation of TCM theories and promotes the modernization of TCM.

**DATA AVAILABILITY STATEMENT**

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

**AUTHOR CONTRIBUTIONS**

C-hZ, G-LX, and CC conceived and designed the review; C-hZ, J-qS, W-hX, X-qL, and Y-nX wrote the review; CC read and finalized the review.

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The signal pathway map was generated by Adobe Illustrator software.

### REFERENCES

Ahirwar, R., and Mondal, P. R. (2019). Prevalence of obesity in India: a systematic review. *Diabetes Metab. Syndr.* 13 (1), 318–321. doi:10.1016/j.dsx.2018.08.032

Arias-Lospe, M. T., Fabrega, E., Lopez-Hoyos, M., and Crespo, J. (2015). The crosstalk between hypoxia and innate immunity in the development of obesity-related nonalcoholic fatty liver disease. *Biomed. Res. Int.* 2015, 319745. doi:10.1155/2015/319745

Ban, J. J., Ruttenborg, R. J., Cho, K. W., and Kim, J. W. (2014). Regulation of obesity and insulin resistance by hypoxia-inducible factors. *Hypoxia* 2, 171–183. doi:10.2147/HP.S68771

Bartels, K., Grenz, A., and Eltzschig, H. K. (2013). Hypoxia and inflammation are two sides of the same coin. *Proc. Natl. Acad. Sci. U.S.A.* 110 (46), 18351–18352. doi:10.1073/pnas.1318345110

Bell, J. A., Carslake, D., O’Keeffe, L. M., Frysz, M., Howe, L. D., Hamer, M., et al. (2018). Associations of body mass and fat indexes with cardiometabolic traits. *J. Am. Coll. Cardiol.* 72 (24), 3142–3154. doi:10.1016/j.jacc.2018.09.066

Biegls, V., and Trautwein, C. (2013). The innate immune response during liver inflammation and metabolic disease. *Trends Immunol.* 34 (9), 446–452. doi:10.1016/j.it.2013.04.005

Blouin, C. C., Pagé, E. L., Soucy, G. M., and Richard, D. E. (2004). Hypoxic gene activation by lipopolysaccharide in macrophages: implication of hypoxia-inducible factor 1alpha. *Blood* 103 (3), 1124–1130. doi:10.1182/blood-2003-07-2327
Bücher, M. (2019). Obesity: global epidemiology and pathogenesis. *Nat. Rev. Endocrinol.* 15 (3), 288–298. doi:10.1038/s41574-019-0176-8

Calle, M. C., and Fernandez, M. L. (2012). Inflammation and type 2 diabetes. *Diabetes Metab.* 38 (3), 183–191. doi:10.1016/j.diabmet.2011.11.006

Catryse, L., and van Loo, G. (2017). Inflammation and the metabolic syndrome: the tissue-specific functions of NF-kB. *Trends Cell Biol.* 27 (6), 417–429. doi:10.1016/j.tcb.2017.01.006

Charakida, M., Khan, T., Johnson, W., Finer, N., Woodside, J., Whincup, P. H., et al. (2014). Lifelong patterns of BMI and cardiovascular phenotype in individuals aged 60-64 years in the 1946 British birth cohort study: an epidemiological study. *Lancet Diabetes Endocrinol.* 2 (8), 684–654. doi:10.1016/S2213-8587(14)70103-2

Chassaing, B., Miles-Brown, J., Pellizzon, M., Ulman, E., Ricci, M., Zhang, L., et al. (2014). Gegen Qinlian decoction attenuates high-fat diet-induced steatohepatitis in rats via gut microbiota. *Evid.-Based Complementary Altern. Med.* 2014, 7370891. doi:10.1155/2014/7370891

Guo, Y., Li, J. X., Mao, T. Y., Zhao, W. H., Liu, L. I., and Wang, Y. L. (2017). Targeting Sirt1 in a rat model of high-fat diet-induced non-alcoholic fatty liver disease: comparison of Gegen Qinlian decoction and resveratrol. *Exp. Ther. Med.* 14 (5), 4279–4287. doi:10.3892/etm.2017.5076

Guthold, R., Stevens, G. A., Riley, L. M., and Bull, F. C. (2018). Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1·9 million participants. *Lancet Glob. Health* 6 (10), e1077–e1086. doi:10.1016/S2214-109X(18)30357-7

Hotamisligil, G. S., and Erbay, E. (2008). Nutrient sensing and inflammation in metabolic diseases. *Nat. Rev. Immunol.* 8 (12), 923–934. doi:10.1038/nri2449

Imtyaz, H. Z., and Simon, M. C. (2010). Hypoxia-inducible factors as essential regulators of inflammation. *Carr. Top. Microbiol. Immunol.* 345, 105–120. doi:10.1007/8_2010_74

Jais, A., and Brüning, J. C. (2017). Hypothalamic inflammation in obesity and metabolic disease. *J. Clin. Invest.* 127 (1), 24–32. doi:10.1172/JCI88878

Jiang, C., Kim, J. H., Li, F., Gu, A., Gavrilova, O., Shah, Y. M., et al. (2013). Hypoxia-inducible factor 1α regulates a SOCS3-STAT3-adiponectin signal transduction pathway in adipocytes. *J. Biol. Chem.* 288 (6), 3844–3857. doi:10.1074/jbc.M112426338

Jones, M. L., Marzioni, C. J., Ganopolsky, J. G., Lasselin, J., and Capuron, L. (2014). Chronic low-grade inflammation and diabetes. *Nat. Rev. Drug Discov.* 13 (5), 141. doi:10.1038/nrd3879

Kobayashi, R., and Takahashi, K. (2013). Inflammation as a link between obesity and metabolic syndrome. *Expert Opin. Biol. Ther.* 14 (4), 467–481. doi:10.1517/14712958.2014.880420

Lasselin, J., and Capuron, L. (2014). Chronic low-grade inflammation in metabolic disorders: relevance for behavioral symptoms. *Int. J. Obes. (Lond)* 39 (11), 1607–1618. doi:10.1038/ijo.2015.104

Klöting, N., and Blüher, M. (2014). Adipocyte dysfunction, inflammation and metabolic syndrome. *Rev. Endocr. Metab. Disord.* 15 (4), 277–287. doi:10.1007/s11154-014-9301-0

Koh, A., De Vadder, F., Kovatcheva-Datchary, P., and Bäckhed, F. (2016). From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. *Cell* 165 (6), 1332–1345. doi:10.1016/j.cell.2016.05.041

Khan, I. M., Perrard, X. Y., Brunner, G., Sparks, L. M., Smith, S. R., et al. (2012). Inflammation and immunity. *Cell* 150 (2), 141–150. doi:10.1016/j.cell.2014.04.006

Kötting, N., and Blüher, M. (2014). Adipocyte dysfunction, inflammation and metabolic syndrome. *Rev. Endocr. Metab. Disord.* 15 (4), 277–287. doi:10.1007/s11154-014-9301-0

Lee, S. W., Kim, J. W., Osborne, O., Ob, D. Y., Sasik, R., Schenk, S., et al. (2014). Increased adipocyte O2 consumption triggers HIF-1α, causing inflammation
Wood, I. S., de Heredia, F. P., Wang, B., and Trayhurn, P. (2009). Cellular hypoxia and adipose tissue dysfunction in obesity. Proc. Natl. Sci. 68 (4), 370–377. doi:10.1017/S0029665108000206

Xi, Y., Wu, M., Li, H., Dong, S., Luo, E., Gu, M., et al. (2015). Baicalin attenuates high fat diet-induced obesity and liver dysfunction: dose-response and potential role of CaMKKβ/AMPK/ACC pathway. Cell Physiol. Biochem. 35 (6), 2349–2359. doi:10.1159/000374037

Xiang, L., Piao, S., Rong, X., and Guo, J. (2018). Analysis of the distribution of dampness-heat syndrome. J. Ethnopharmacol 202, 265–280. doi:10.1016/j.jep.2017.03.030

Ye, J., Gao, Z., Yin, J., and He, Q. (2007). Hypoxia is a potential risk factor for chronic inflammation and adiponectin reduction in adipose tissue of ob/ob and dietary obese mice. Am. J. Physiol. Endocrinol. Metab. 293 (4), E1118–E1128. doi:10.1152/ajpendo.00435.2007

Ye, J. (2009). Emerging role of adipose tissue hypoxia in obesity and insulin resistance. Int. J. Obes. (Lond) 33 (1), 54–66. doi:10.1038/iibo.2008.229

Yin, C. E., and Wei, H. (2012). Research on the treatment of type 2 diabetes with dietary obese mice. J. Ethnopharmacol 139, 113–120. doi:10.1016/j.jep.2011.07.026

Ye, J., Xiao, X., Pan, C., Wu, J., Wang, L., and Lin, L. (2013). Mediators Inflamm. 2013, 1–9. doi:10.1155/2013/728776

Ye, J. F., Zhang, F., Ma, B. Y., Lu, M. J., and Xiao, Q. Q. (2011). On the etiology, pathogenesis, and treatment of the same disease of damp heat and yin deficiency. Acta Chin. Med. Pharmacol. 39 (6), 4–6.

Zhang, C. H., Wang, M. Y., and Liu, Y. H. (2020). Adipose tissue-specific inhibition of hypoxia-inducible factor 1α induces obesity and glucose intolerance by impeding energy expenditure in mice. J. Biol. Chem. 295 (39), 12442–12454. doi:10.1074/jbc.RA119.013358

Zhang, C., Zhou, B. G., Sheng, J. Q., Chen, Y., Cao, Y. Q., and Chen, C. (2020). Molecular mechanisms of hepatic insulin resistance in nonalcoholic fatty liver disease and potential treatment strategies. Pharmacol. Res. 159, 104984. doi:10.1016/j.phrs.2020.104984

Zhang, C. H., Ma, G. Q., Deng, Y. B., Wang, X. Y., Chen, Y. C., Tu, X. Y., et al. (2017). Effect of Gegen Qinlian Decoction on LPS, TNF-α, IL-6, and intestinal flora in diabetic KK-Ay mice. Chin. Tradit. Herb. Drugs 48 (8), 1611–1616. doi:10.1016/j.chph.2017.08.020

Zhang, J., Zhang, H., Deng, X., Zhang, N., Liu, B., Xin, S., et al. (2018). Baicalin attenuates non-alcoholic steatohepatitis by suppressing key regulators of lipid metabolism, inflammation and fibrosis in mice. Life Sci. 192, 46–54. doi:10.1016/j.lfs.2017.12.026

Zhang, J. F., Zhang, F., Ma, B. Y., Lu, M. J., and Xiao, Q. Q. (2011). On the etiology, pathogenesis, and treatment of the same disease of damp heat and yin deficiency. Acta Chin. Med. Pharmacol. 39 (6), 4–6.

Zhang, X., Lam, K. S., Ye, H., Chung, S. K., Zhou, M., Wang, Y., et al. (2010). Adipose tissue-specific inhibition of hypoxia-inducible factor 1α induces obesity and glucose intolerance by impeding energy expenditure in mice. J. Biol. Chem. 285 (45), 32869–32877. doi:10.1074/jbc.M110.135509

Zhang, Y., Ley, S. H., and Hu, F. B. (2018). Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat. Rev. Endocrinol. 14 (2), 88–98. doi:10.1038/nrendo.2017.151

Zhong, X., and Liu, H. (2018). Baicalin attenuates diet induced nonalcoholic steatohepatitis by inhibiting inflammation and oxidative stress via suppressing JNK signaling pathways. Biomed. Pharmacother. 98, 111–117. doi:10.1016/j.biopha.2017.12.026

Zhou, R., Yazdi, A. S., Menu, P., and Tschopp, J. (2011). A role for mitochondria in NLRP3 inflammasome activation. Nature 469 (7329), 221–225. doi:10.1038/nature09663

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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