

Review

The Significance of Lipoproteins in the Development of Obesity

Alexander Blagov^{1,*}, Konstantin Rufanov², Khokhlova Irina², Vasily Sukhorukov¹,
Andrey Goncharov², Elizaveta Pleshko¹, Alexander Orekhov^{1,*}

¹Laboratory of Angiopathology, Institute of General Pathology and Pathophysiology, 125315 Moscow, Russia

²Immanuel Kant Baltic Federal University, 236016 Kaliningrad, Russia

*Correspondence: al.blagov2014@gmail.com (Alexander Blagov); alexandernikolaevichorekhov@gmail.com (Alexander Orekhov)

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Abstract

Disruption of lipoprotein metabolism plays an important role in the development of several cardiovascular, inflammatory, and metabolic diseases. This review examines the importance of different types of lipoproteins and the role they play in the development of dyslipidemia in obesity. The causes and consequences associated with the disruption of lipid metabolism and its significance in the pathogenesis of obesity are considered. The relationship between such pathological processes, which occur alongside obesity as dyslipidemia and inflammation, is determined. In view of the current efficacy and toxicity limitations of currently approved drugs, natural compounds as potential therapeutic agents in the treatment of obesity are considered in the review. The complex mechanisms of lipid metabolism normalization in obesity found for these compounds can serve as one of the confirmations of their potential efficacy in treating obesity. Nanoparticles can serve as carriers for the considered drugs, which can improve their pharmacokinetic properties.

Keywords: obesity; dyslipidemia; low density lipoproteins (LDL); inflammation

1. Introduction

Obesity is among the most prevalent diseases considered preventable. Moreover, obesity is a significant issue for public health. Obesity has a multifactorial etiology that includes genetic, environmental, socioeconomic, and behavioral or psychological influences. Obesity results from a chronic positive energy balance, which is regulated by a complex interaction between endocrine tissues and the central nervous system [1].

An estimated 500 million adults worldwide are obese, with 1.5 billion classed as overweight or obese. In particular, the prevalence of obesity, or a combination of overweight and obesity, has increased in Brazil, Canada, Mexico, and the United States. Most of the information on obesity in adults relies on using body mass index (BMI) to define obesity [2].

Being obese raises the risk of several illnesses and ailments that are linked to higher death rates. Among these are non-alcoholic fatty liver disease (NAFLD), depression, osteoarthritis, obstructive sleep apnea, coronary artery disease (CAD), a condition called metabolic syndrome (MS), chronic renal failure, hyperlipidemia, and hypertension. Treating these illnesses can put additional strain on the healthcare system: For example, obese patients are thought to have 30% higher medical costs than people with a normal BMI. Since the corresponding total healthcare costs are doubling every decade, treating the consequences of obesity is a costly problem for patients [3].

Obesity has inflammatory components that are directly or indirectly associated with major chronic diseases,

such as diabetes, atherosclerosis, hypertension, and some types of cancer. In overweight and obese individuals, circulating levels of inflammatory cytokines, such as IL-6, TNF- α , C-reactive protein (CRP), IL-18, resistin, and visfatin are altered. Body fat measures have a stronger correlation with inflammatory markers than BMI. It is strongly advised to exercise and follow dietary guidelines to minimize weight gain and its associated problems. It has been demonstrated that calorie restriction effectively lowers inflammation in obese people. However, some research has shown that diet-assisted weight loss lessens the effects of long-term anti-inflammatory interventions. Conversely, regular exercise has a major impact on illnesses linked to obesity, including diabetes, dyslipidemia, hypertension, and chronic inflammation [4].

Obese people frequently have issues related to their lipid metabolism. Between 60 and 70 percent of obese individuals have dyslipidemia. Increased concentrations of oxidized low-density lipoproteins (ox-LDL) result from lipid disorders in obese individuals, which also include raised levels of triglycerides, low high-density lipoproteins (HDL), apolipoprotein B, and very-low-density lipoproteins (VLDL) in the blood [5]. Indeed, ox-LDLs are important pathological mediators in obesity, increasing inflammation and disrupting normal vascular tone [6]. Increased ox-LDL levels result from cellular oxidative stress, which is associated with the development of many chronic diseases [7,8]. Oxidative stress is a key factor that links the pathogenesis of obesity and metabolic syndrome [6,9]. Thus, methods for lowering modified lipids and restoring normal



lipid metabolism may be appealing targets for managing obesity-related inflammatory processes.

2. General Pathogenesis of Obesity

2.1 Food Intake and Energy Balance

There is ongoing debate over the fundamental causes of obesity. The basic physiological principle that fat storage is caused by a difference between calories ingested and expended is the basis of current medical guidelines for preventing obesity. The rise in energy brought on by the increased availability of foods rich in calories and high in nutrition has played a major role in the obesity epidemic. Diet and various social, economic, and environmental factors associated with nutrition significantly impact the patient's ability to achieve balance [10]. In a 13-year follow-up study of 3000 young people, it was found that those who consumed much more fast food weighed an average of about 6 kg more and had a larger waist circumference than those who received less fast food. They were also found to be more likely to experience health problems associated with negative weight, such as elevated triglycerides, and were twice as likely to develop metabolic syndromes. These problems are exacerbated in some individuals who have a genetic predisposition for fat storage, which may be due to the significant interplay between homeostatic circuits and brain reward. Accumulation of lipid metabolites, inflammatory signaling, or other mechanisms of hypothalamic neuronal impairment may also lead to obesity, which may explain the biological defense of increased body fat mass [11].

2.2 Microenvironment and Gut Microbiome

In recent years, there has been a significant increase in our understanding of gut microbiota and its intricate link to illness. For instance, compared to thinner hosts, obesity is linked to alterations in the gut milieu that facilitate a wider variety of viral species. The emergence of pathogenic mutations that might lead to more severe illnesses is more likely in this setting [12]. An increasing amount of data indicates that changes in the gut microbiota impact the weight and metabolism of the host. For instance, sterile male mice (without intestinal microbiota) had 42% less total body fat than mice with normal gut bacteria despite consuming 29% more food daily. Conversely, total body fat increased by 57%, lean body mass decreased by 7%, and daily food consumption reduced by 27% in these mice following the colonization of the caecum by microorganisms [13]. A follow-up investigation revealed that these alterations resulted from a decrease in metabolic rate and an increase in adipose tissue deposition, as the microflora colonization caused a 25% increase in capillary density in the small intestine's distal villi. Comparable outcomes were seen in female mice [14].

2.3 Genetic Factors and Causes

One method to categorize the genetic causes of obesity is monogenic, which is caused by mutations in a single gene, usually found in the leptin–melanocortin pathway. Numerous genes, including melano-cortin-4 receptor (*MC4R*), orexogenic (*PYY*), and agouti-related peptide (*AgRP*), have been linked to monogenic obesity. These genes disrupt the system that regulates appetite and weight, as receptors in the arcuate nucleus of the hypothalamus perceive hormonal signals such as insulin, leptin, and ghrelin [15]. Severe obesity brought on by aberrant nervous system development and associated organ/system abnormalities is known as syndromic obesity. The source may be a broader chromosomal area covering numerous genes or alterations to a single gene [16].

2.4 Epigenetic Modifications

Although several genes linked to monogenic types of obesity have been found by this research, the human genome is changing over too long a period for the genome to be significantly involved in the present obesity epidemic. Nonetheless, without requiring a significant alteration to the DNA, epigenetics can provide a reasonable explanation for the rise in the incidence of obesity during the previous few decades [17]. Each cell type may display the genetic code differently in multicellular animals, yet the genetic code is uniform across the body. Nucleotide sequence alterations are unnecessary for inherited regulatory modifications in genomic expression, as demonstrated by epigenetic research [18]. One way to conceptualize epigenetic alterations is as differential DNA packaging that either promotes or inhibits the expression of particular genes in various tissues. The environment and intestinal microbes can influence the epigenetic programming of parental gametes and programming in later life stages [19].

Histone modifications, microRNA-mediated regulation, and DNA methylation are examples of known epigenetic processes, which can be handed down from generation to generation through meiosis or mitosis. Data indicate that the period of perinatal and embryonic–fetal development significantly influences the programming of human organs and tissues [18]. The most significant epigenetic method for controlling gene expression seems to be DNA methylation. Variations in DNA methylation have been linked to several illnesses, including cancer [20]. Leptin, also known as LEP, is crucial for controlling adipose tissue. The DNA methylation in the LEP profile at birth may be influenced by the metabolic remodeling associated with obesity due to the maternal metabolic state [21].

3. Disruption of Lipoprotein Metabolism in Obesity

Lipoproteins are complex particles that comprise free cholesterol, phospholipids, and apolipoproteins, which help lipoproteins form and function [22]. The central core of

lipoproteins contains cholesteryl esters and triglycerides [23]. Based on size and lipid structure, serum lipoproteins can be categorized into seven classes: apo-LP, VLDL, LDL, HDL, chylomicrons, and chylomicron remnants [24].

The exogenous lipoprotein pathway begins when dietary lipids are incorporated into intestinal chylomicrons. Triglycerides carried by chylomicrons are transformed into free fatty acids, then chylomicrons are transported into the adipose and muscular tissue to produce chylomicron remains. Then, the liver absorbs the chylomicrons remnants [24]. The endogenous lipoprotein pathway starts when VLDL is formed in the liver. After transforming to free fatty acids in muscle and fat tissue, the triglycerides in VLDL are converted to LDL, which is subsequently absorbed by the LDL receptor in various tissues, including the liver [24]. An imbalance in the plasma levels of lipids and lipoproteins is called dyslipidemia and is directly related to the pathogenesis of obesity.

The dyslipidemia that is observed in obese people is caused by a variety of anomalies [5]. These anomalies result from a confluence of factors, including insulin resistance, increased liver absorption of free fatty acids due to visceral and total adiposity, and an inflammatory state brought on by macrophages entering adipose tissue [25]. The primary abnormality is the overproduction of VLDL particles by the liver, which plays a significant role in the increase in blood triglyceride levels [26]. The number of fatty acids available for triglyceride synthesis in the liver determines the availability of triglycerides, which in turn affects the secretion rate of the VLDL particles. Triglycerides are abundant because they inhibit the liver's ability to break down apoB100, which increases its synthesis and release of VLDL.

Fatty acids in the hepatocytes come from three primary sources, all of which can change in obese individuals [5]. First, the number of fatty acids sent to the liver increases with a rise in the bulk of adipose tissue, particularly visceral tissue. Furthermore, insulin increases the number of triglycerides that are delivered to the liver by inhibiting the lipolysis of triglycerides into free fatty acids in adipose tissue [26]. Additionally, *de novo* fatty acid synthesis is the second source of fatty acids for the liver. The hyperinsulinemia observed in individuals with insulin resistance may act as a mediating factor for this rise [27]. Specifically, insulin enhances the expression of enzymes needed for fatty acid synthesis by activating the SREBP-1c transcription factor. The liver is susceptible to the effects of insulin, which promotes fat synthesis, even if it is resistant to the effects of insulin on the metabolism of carbohydrates [28]. The absorption of high triglyceride lipoproteins by the liver is the third way of obtaining fatty acids. Research has indicated that increased fatty acid production in the colon, along with elevated chylomicron secretion in obese individuals, results in enhanced fatty acid transport to the liver. Increased triglyceride synthesis and the preser-

vation of apoB100 from degradation result from a boost in fatty acids in the liver via these three routes, which increases VLDL production and secretion [29]. Moreover, consuming more calories may enhance the circulation of triglycerides via two different mechanisms: either dietary fat raises chylomicron triglyceride levels as well as facilitates the supply of fatty acids to the liver, or dietary carbohydrates stimulate *de novo* hepatic lipogenesis [30].

Apart from the liver and intestines producing excessive amounts of lipoproteins that are high in triglycerides, there are also disruptions in the following metabolism of these lipoproteins [5]. The concentration of apoC-III is elevated in obese individuals [27]. Insulin inhibits the expression of apoC-III; hence, the rise in apoC-III levels in obese individuals may be explained by insulin resistance [31]. Since apoC-III inhibits lipoprotein lipase activity, it may decrease the clearance and cellular absorption of lipoproteins high in triglycerides, which raises the levels of triglycerides in the blood of obese individuals [27].

Other lipoproteins are impacted by a rise in triglyceride-rich lipoprotein levels. Specifically, the equimolar exchange of chylomicrons and triglycerides from triglyceride-rich VLDL for cholesterol from LDL and HDL is mediated by cholesterol ester transfer protein (CETP) [5]. Triglycerides rise, CETP-mediated metabolism increases, and LDL and HDL cholesterol drop when triglyceride-rich lipoproteins increase in and of themselves. Furthermore, obesity raises the bulk and activity of CETP. The widely noted reciprocal link between low HDL cholesterol and high triglycerides and raised HDL cholesterol and lowered triglycerides is caused by this CETP-mediated exchange [32].

Subsequently, hepatic lipase and lipoprotein lipase hydrolyze the triglyceride of LDL and HDL, forming tiny, dense particles for the two lipoproteins [5]. Individuals with adiposity and increased visceral obesity have significantly higher levels of hepatic lipase activity, which helps to separate triglycerides from LDL and HDL and forms lipoprotein particles [33]. Reduced sensitivity of apo A-I for small HDL particles causes apo A-I to dissociate, which the kidneys remove and destroy [26]. In obese persons, these modifications lead to decreased levels of HDL cholesterol and apo A-I.

4. Relationship between Inflammation and Dyslipidemia in Obesity

Owing to the infiltration of macrophages into adipose tissue, obesity is considered an inflammatory condition. Lipid metabolism is also influenced by adipokines generated by fat cells and cytokines made by macrophages [34].

Lipid metabolism is regulated by adipokines, such as resistin and adiponectin. Obese people have lower amounts of adiponectin in their blood. Reduced HDL-cholesterol (HDL-C) levels and elevated blood triglycerides are linked to decreased adiponectin levels [34]. Mice stud-

ies have demonstrated that overexpressing adiponectin reduces triglycerides and raises HDL-C, while adiponectin-knockout animals, on the other hand, increase triglycerides and decrease HDL-C. These data suggest that the link between the two variables is causative. Increased degradation of triglyceride-rich lipoproteins due to elevated lipoprotein lipase activity and decreased levels of apoC-III, a molecule that inhibits lipoprotein lipase, mediates the adiponectin-induced reduction in triglyceride levels. Increases in hepatic apo A-I and ABCA1 facilitate the rise in HDL-C level caused by adiponectin, increasing HDL particle synthesis [35].

Human monocytes and macrophages produce the adipokine resistin. Obese people have higher resistin levels, and there is a clear correlation between resistin and plasma triglyceride levels. Furthermore, resistin has been demonstrated to increase the production of apoB, triglycerides, and cholesterol in the liver, stimulating the creation and secretion of VLDL [36]. Resistin is also linked to decreased levels of apo A-I and HDL cholesterol. It is also commonly recognized that resistin plays a part in inflammation. By promoting resistin gene expression, inflammatory cytokines cause macrophages to secrete more resistin, which encourages the synthesis of proinflammatory cytokines [37].

Tumor necrosis factor α (TNF- α) is a multipotent cytokine that is involved in all aspects of obesity-induced insulin resistance and the development of dyslipidemia. The main mechanism that links inflammation, especially TNF- α and interleukin (IL)-6, in insulin resistance is a decrease in the expression of glucose transporter type 4 (GLUT 4) in insulin-dependent tissues under their influence [38]. In addition, TNF- α activates serine kinases responsible for phosphorylation in immune reconstitution syndrome (IRS), particularly the Jun N-terminal kinase (JNK). The specific effect of TNF- α is associated with the acceleration of the inflammatory process due to the induction of the synthesis of other proinflammatory cytokines, such as IL-6 and IL-1, in adipose tissue macrophages [39]. It is also important to note that TNF- α , in cooperation with other inflammatory cytokines, induces the activation of the nuclear factor- κ B (NF- κ B) pathway and contributes to oxidative stress in adipose tissue. Activation of the transcription factor NF- κ B by TNF- α is one of the mechanisms that cause inflammation of β -cells and decrease insulin production [40].

TNF- α and IL-1 increase circulation-free fatty acids, which offer a substrate for hepatic triglyceride production, thereby stimulating lipolysis in adipocytes. Proinflammatory cytokines promote the *de novo* production of triglycerides (TG) and fatty acids (FA) in the liver [41]. The production and release of VLDL are increased due to these modifications. Angiopoietin-like protein 4 (ANGPLT4), a protein that inhibits lipoprotein lipase, is expressed more when proinflammatory cytokines are present in larger quantities than lipoprotein lipase [42,43]. These modifica-

tions slow the release of lipoproteins high in triglycerides by lowering lipoprotein lipase activity. Therefore, a rise in proinflammatory cytokines promotes the synthesis of triglyceride-rich lipoproteins and delays their clearance; these actions collectively lead to the elevation of blood triglyceride levels seen in obese individuals [44].

The effects of cytokines and adipokines on lipid metabolism and other manifestations of obesity pathogenesis are shown in Table 1 (Ref. [34–45]). The effects of pro-inflammatory cytokines are depicted on the Fig. 1.

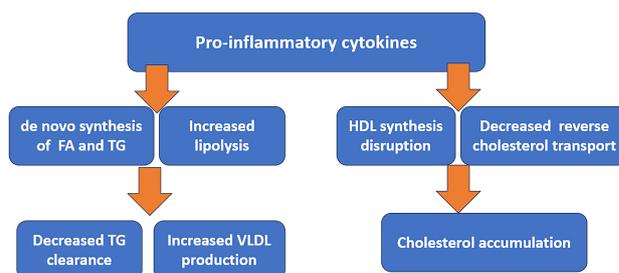


Fig. 1. The influence of proinflammatory cytokines on lipoproteins in obesity. TG, Triglyceride.

5. The Use of Alternative Medicines and Nanocarriers for Their Delivery in the Treatment of Obesity

The current approach to obesity therapy includes drugs such as orlistat, rimonabant, sibutramine, dexfenfluramine, fenfluramine, or phenylpropylamine [46]. However, these drugs have low efficacy and cause systemic drug toxicity and multiple side effects associated with mental disorders and cardiovascular diseases, which limits their use [47]. To overcome these limitations, innovative drug delivery vehicles, such as nanoparticles based on gold, phosphatidylcholine, and cholesterol; PLGA-b-PEG, PLGA, dextran, and dextran-PEG; liposomes based on peptides; nanoemulsions and lipase-sensitive nanocarriers have been developed to improve the therapeutic efficacy of targeted synthetic drugs [30].

A recent study described nanotechnology-based therapy as an alternative strategy using three different strategies: Inhibiting angiogenesis in white adipose tissues (WAT), converting WAT to brown adipose tissue (BAT), and photothermal lipolysis WAT. Generic nanocarriers (liposomes, polymeric, and gold nanoparticles) demonstrated high tolerability, reduced side effects, and increased efficacy in a reproducible manner, thus, supporting the concept of the hypothesis that targeted nanotherapy may act as a feasible tactic to combat obesity and prevent its comorbidities [48].

Many medicinal plants have been studied to treat obesity, dyslipidemia, and diabetes. Herbal medicines are considered an effective treatment strategy due to their establi-

Table 1. The effects of cytokines and adipokines on lipid metabolism and other manifestations of obesity pathogenesis.

Cytokine (adipokine)	Level changes in obesity	Direct impact	Implications for the pathogenesis of obesity
Adiponectin	Decreased	(1) Increased <i>apoC-III</i> level and decreased lipase activity [35] (2) Decreased levels of <i>apo A-I</i> and <i>ABCA</i> [35]	(1) Increased triglyceride level [34] (2) Decreased HDL-C level [34]
Resistin	Increased	(1) Increased synthesis of <i>apoB</i> , triglycerides, and cholesterol [36] (2) Increased expression of proinflammatory cytokines [37]	(1) Increased VLDL level [36] (2) Increased inflammation [37]
TNF- α	Increased	(1) Decreased expression of <i>GLUT4</i> [38] (2) Increased oxidative stress [40] (3) NF- κ B activation [40]	(1) Insulin resistance [38] (2) Enhanced lipid peroxidation [40] (3) Increased inflammation [39]
TNF- α and IL-1	Increased	(1) Increased synthesis of fatty acids and triglycerides [41] (2) Decreased expression of lipase and <i>ANGPLT4</i> [42,43]	(1) Increased secretion of VLDL [41] (2) Decreased clearance of triglyceride-rich lipoproteins [44]
Other proinflammatory cytokines	Increased	(1) Decreased production of <i>apo A-I</i> [45] (2) Decreased expression of <i>ABCA1</i> and <i>ABCG1</i> [45] (3) Decreased production of <i>LCAT</i> [45] (4) Decreased <i>CEPT</i> level [45] (5) Decreased expression of <i>SR-B1</i> [45]	(1) Decreased HDL level [45] (2)–(5) Decreased reverse cholesterol transport [45]

*The numbers in the column: «Direct impact» correspond to the numbers in the column: «Implications for the pathogenesis of obesity». TNF- α , tumor necrosis factor α ; IL-1, interleukin-1; HDL-C, high-density lipoprotein-cholesterol; VLDL, very-low-density lipoprotein.

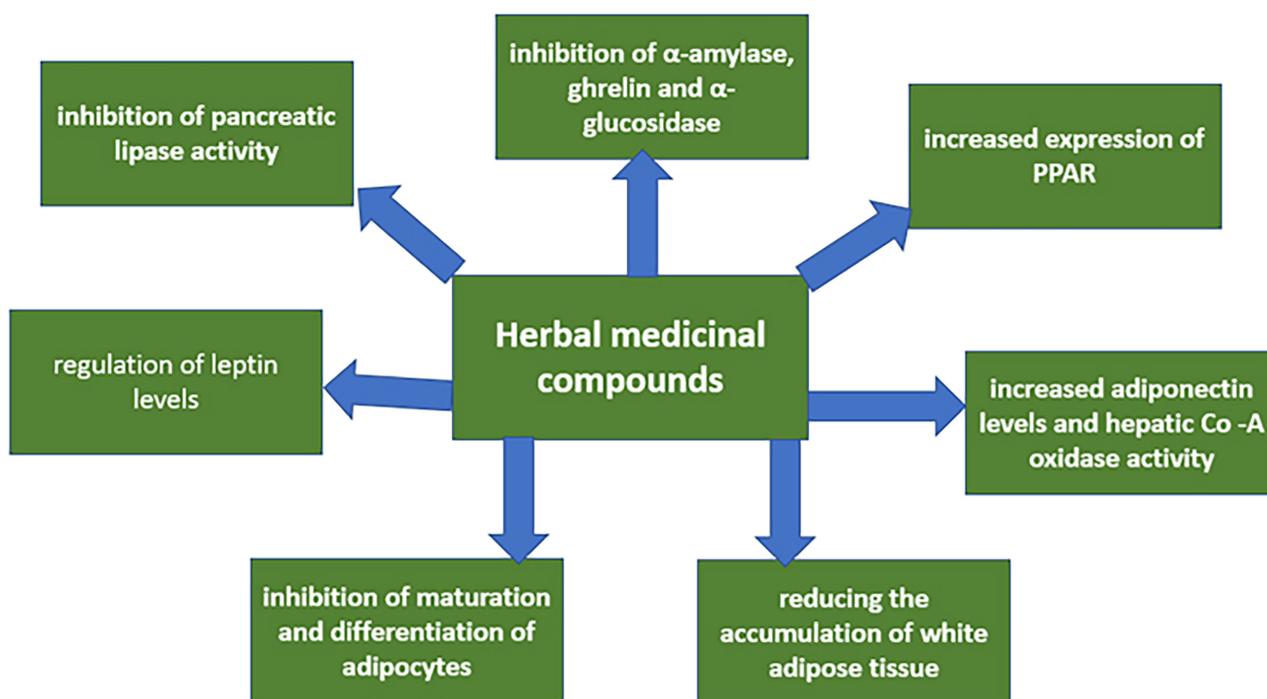


Fig. 2. Discovered mechanisms of action of herbal medicinal compounds. Legend: As can be seen from this diagram, specific molecular mechanisms of action of these compounds have been identified for a number of medicinal plant extracts. These mechanisms can be aimed at different processes but have a common result—decreased dyslipidemia. This allows us to consider plant compounds an effective and safe alternative to existing obesity therapy.

shed mechanisms of action, which are directed to lipid metabolism normalization [49]. A previous study showed [50] that synthetic drugs and natural compounds could modulate GLP1 expression. Such compounds, including curcumin, berberine, resveratrol, and cinnamon, can be effectively used as GLP1 agonists to reduce hyperglycemia. It was demonstrated in a clinical trial [51] that combination therapy with resveratrol and myo-inositol, compared with metformin and pioglitazone, resulted in significantly better results in weight loss and increased adiponectin concentrations in obese women with polycystic ovary syndrome. Curcumin positively reduced the inflammatory cytokine monocyte chemoattractant protein 1 (MCP-1) in obese patients, although there was no change in resistin and visfatin levels [52]. In a clinical study [53], patients in the experimental group received capsules containing *Momordica charantia* extract. They had significant reductions in triglycerides and very low-density lipoprotein (VLDL) levels compared to the placebo group, although the decrease in body weight was not statistically significant. Therefore, these compounds can be potentially used in treating diseases whose pathogenesis is connected with impaired lipid metabolism, including obesity. Discovered mechanisms of action of herbal medicinal compounds are shown in more detail in Fig. 2.

6. Discussion

Based on the features of the influence of lipoproteins on the pathogenesis of obesity described in this review, several important issues that were not addressed in this review require further, more detailed consideration in future research. First of all, it is of interest to study in detail the changes in the concentration, distribution, and metabolic transformation of some types of lipoproteins, such as chylomicrons, which are not fully described in this article. In terms of the development of new therapeutic agents, considering the multiple effects of TNF- α on the progression of obesity, in our opinion, in the treatment of obesity, using existing TNF- α inhibitors or developing fundamentally new drugs, including those based on nanoparticles, with increased accuracy of delivery of the active substance to adipose tissue, is promising in the treatment of obesity. In terms of nanoparticles, in addition to assessing their pharmacokinetic potential, it is important to conduct comprehensive preclinical and clinical studies of pharmacodynamic parameters and compare them with those of the same drugs for which other delivery forms and administration systems are used. Additionally, given the vast beneficial effects of discovered plant compounds on lipid metabolism, it is important to continue searching for potential drugs in this direction, as well as identifying new mechanisms for normalizing plasma lipoprotein levels, which will allow a better understanding of hitherto unaffected aspects

underlying the progression of obesity. Of course, lifestyle changes, which include increased mobility and reduced calorie intake, are fundamental factors in the fight against obesity; however, a pharmacological approach aimed at stopping certain “danger points” in the pathogenesis of obesity through the action of therapeutic compounds can speed up and make the recovery process more effective for obesity.

7. Conclusions

Dyslipidemia is a comorbid condition of various metabolic conditions, including obesity. Initially, it manifests as an increase in the content of VLDL particles, which is caused, conversely, by the overproduction of triglyceride-rich lipoproteins and, on the other hand, by an imbalance in the processes of their subsequent distribution, which is associated with inhibition of lipoprotein lipase activity. These disorders, in turn, affect the metabolism of other lipoproteins, including cholesterol ester transport proteins. Concurrently, dyslipidemia is also strongly influenced by inflammatory factors, including adipokines, such as resistin and adiponectin, and proinflammatory cytokines, primarily TNF- α . Adiponectin acts on lipid metabolism by lowering triglyceride levels and increasing cholesterol levels; resistin, such as TNF- α , has the opposite effect. Nanoparticles may be a potential solution to improve the pharmacokinetic characteristics of currently used drugs and promising natural drug compounds for treating dyslipidemia in obesity.

Author Contributions

AB, VS and AO designed the review plan. KR, AG, EP and KI performed the data collection and analysis. AG, EP and AB wrote the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity. All authors contributed to editorial changes in the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

References

- [1] Jukaku SA, Williams SRP. The cause of obesity is multifactorial but GPs can do more. *BMJ (Clinical Research Ed.)*. 2021; 373: n956.
- [2] Bosity-Westphal A, Müller MJ. Diagnosis of obesity based on body composition-associated health risks-Time for a change in paradigm. *Obesity Reviews: an Official Journal of the International Association for the Study of Obesity*. 2021; 22: e13190.
- [3] Bray GA, Kim KK, Wilding JPH, World Obesity Federation. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. *Obesity Reviews: an Official Journal of the International Association for the Study of Obesity*. 2017; 18: 715–723.
- [4] Engin A. The Pathogenesis of Obesity-Associated Adipose Tissue Inflammation. *Advances in Experimental Medicine and Biology*. 2017; 960: 221–245.
- [5] Bays HE, Toth PP, Kris-Etherton PM, Abate N, Aronne LJ, Brown WV, *et al.* Obesity, adiposity, and dyslipidemia: a consensus statement from the National Lipid Association. *Journal of Clinical Lipidology*. 2013; 7: 304–383.
- [6] Jakubiak GK, Cieślak G, Stanek A. Nitrotyrosine, Nitrated Lipoproteins, and Cardiovascular Dysfunction in Patients with Type 2 Diabetes: What Do We Know and What Remains to Be Explained? *Antioxidants (Basel, Switzerland)*. 2022; 11: 856.
- [7] Chen Z, Zhong C. Oxidative stress in Alzheimer’s disease. *Neuroscience Bulletin*. 2014; 30: 271–281.
- [8] Senoner T, Dichtl W. Oxidative Stress in Cardiovascular Diseases: Still a Therapeutic Target? *Nutrients*. 2019; 11: 2090.
- [9] Jakubiak GK, Osadnik K, Lejawa M, Osadnik T, Goławski M, Lewandowski P, *et al.* “Obesity and Insulin Resistance” Is the Component of the Metabolic Syndrome Most Strongly Associated with Oxidative Stress. *Antioxidants (Basel, Switzerland)*. 2021; 11: 79.
- [10] Yoo S. Dynamic Energy Balance and Obesity Prevention. *Journal of Obesity & Metabolic Syndrome*. 2018; 27: 203–212.
- [11] Obri A, Claret M. The role of epigenetics in hypothalamic energy balance control: implications for obesity. *Cell Stress*. 2019; 3: 208–220.
- [12] Honce R, Karlsson EA, Wohlgemuth N, Estrada LD, Meliopoulos VA, Yao J, *et al.* Obesity-Related Microenvironment Promotes Emergence of Virulent Influenza Virus Strains. *mBio*. 2020; 11: e03341–19.
- [13] Sender R, Fuchs S, Milo R. Revised Estimates for the Number of Human and Bacteria Cells in the Body. *PLoS Biology*. 2016; 14: e1002533.
- [14] Jandhyala SM, Talukdar R, Subramanyam C, Vuyyuru H, Sasikala M, Nageshwar Reddy D. Role of the normal gut microbiota. *World Journal of Gastroenterology*. 2015; 21: 8787–8803.
- [15] Thaker VV. Genetic and epigenetic causes of obesity. *Adolescent Medicine: State of the Art Reviews*. 2017; 28: 379–405.
- [16] Huvenne H, Dubern B, Clément K, Poitou C. Rare Genetic Forms of Obesity: Clinical Approach and Current Treatments in 2016. *Obesity Facts*. 2016; 9: 158–173.
- [17] Czajkowski P, Adamska-Patrano E, Bauer W, Fiedorczuk J, Krasowska U, Moroz M, *et al.* The Impact of *FTO* Genetic Variants on Obesity and Its Metabolic Consequences is Dependent on Daily Macronutrient Intake. *Nutrients*. 2020; 12: 3255.
- [18] Koochakpour G, Esfandiari Z, Hosseini-Esfahani F, Mirmiran P, Daneshpour MS, Sedaghati-Khayat B, *et al.* Evaluating the interaction of common *FTO* genetic variants, added sugar, and trans-fatty acid intakes in altering obesity phenotypes. *Nutrition, Metabolism, and Cardiovascular Diseases: NMCD*. 2019; 29: 474–480.
- [19] Rosen ED, Kaestner KH, Natarajan R, Patti ME, Sallari R, Sander M, *et al.* Epigenetics and Epigenomics: Implications for

- Diabetes and Obesity. *Diabetes*. 2018; 67: 1923–1931.
- [20] Holmes D. Epigenetics: On-off switch for obesity. *Nature Reviews. Endocrinology*. 2016; 12: 125.
- [21] Lopomo A, Burgio E, Migliore L. Epigenetics of Obesity. *Progress in Molecular Biology and Translational Science*. 2016; 140: 151–184.
- [22] Burgio E, Lopomo A, Migliore L. Obesity and diabetes: from genetics to epigenetics. *Molecular Biology Reports*. 2015; 42: 799–818.
- [23] Sherwood WB, Bion V, Lockett GA, Ziyab AH, Soto-Ramírez N, Mukherjee N, *et al.* Duration of breastfeeding is associated with leptin (LEP) DNA methylation profiles and BMI in 10-year-old children. *Clinical Epigenetics*. 2019; 11: 128.
- [24] Feingold KR. Introduction to Lipids and Lipoproteins. 2021. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK305896/> (Accessed: 5 January 2023).
- [25] Xiao C, Dash S, Morgantini C, Hegele RA, Lewis GF. Pharmacological Targeting of the Atherogenic Dyslipidemia Complex: The Next Frontier in CVD Prevention Beyond Lowering LDL Cholesterol. *Diabetes*. 2016; 65: 1767–1778.
- [26] Klop B, Elte JWF, Cabezas MC. Dyslipidemia in obesity: mechanisms and potential targets. *Nutrients*. 2013; 5: 1218–1240.
- [27] Björnson E, Adiels M, Taskinen MR, Borén J. Kinetics of plasma triglycerides in abdominal obesity. *Current Opinion in Lipidology*. 2017; 28: 11–18.
- [28] Jacome-Sosa MM, Parks EJ. Fatty acid sources and their fluxes as they contribute to plasma triglyceride concentrations and fatty liver in humans. *Current Opinion in Lipidology*. 2014; 25: 213–220.
- [29] Dash S, Xiao C, Morgantini C, Lewis GF. New Insights into the Regulation of Chylomicron Production. *Annual Review of Nutrition*. 2015; 35: 265–294.
- [30] Trandafir LM, Dodi G, Frasinariu O, Luca AC, Butnariu LI, Tarca E, *et al.* Tackling Dyslipidemia in Obesity from a Nanotechnology Perspective. *Nutrients*. 2022; 14: 3774.
- [31] Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG, Tybjaerg-Hansen A. Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. *The New England Journal of Medicine*. 2014; 371: 32–41.
- [32] Vekic J, Zeljkovic A, Stefanovic A, Jelic-Ivanovic Z, Spasojevic-Kalimanovska V. Obesity and dyslipidemia. *Metabolism: Clinical and Experimental*. 2019; 92: 71–81.
- [33] Masuda D, Yamashita S. Postprandial Hyperlipidemia and Remnant Lipoproteins. *Journal of Atherosclerosis and Thrombosis*. 2017; 24: 95–109.
- [34] Feingold KR, Grunfeld C. The Effect of Inflammation and Infection on Lipids and Lipoproteins. *Endotext*. 2022.
- [35] Christou GA, Kiortsis DN. Adiponectin and lipoprotein metabolism. *Obesity Reviews: an Official Journal of the International Association for the Study of Obesity*. 2013; 14: 939–949.
- [36] Rashid S, Kastelein JJP. PCSK9 and resistin at the crossroads of the atherogenic dyslipidemia. *Expert Review of Cardiovascular Therapy*. 2013; 11: 1567–1577.
- [37] Kwon H, Pessin JE. Adipokines mediate inflammation and insulin resistance. *Frontiers in Endocrinology*. 2013; 4: 71.
- [38] Leguisamo NM, Lehnen AM, Machado UF, Okamoto MM, Markoski MM, Pinto GH, *et al.* GLUT4 content decreases along with insulin resistance and high levels of inflammatory markers in rats with metabolic syndrome. *Cardiovascular Diabetology*. 2012; 11: 100.
- [39] Branchetti E, Bavaria JE, Grau JB, Shaw RE, Poggio P, Lai EK, *et al.* Circulating soluble receptor for advanced glycation end product identifies patients with bicuspid aortic valve and associated aortopathies. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2014; 34: 2349–2357.
- [40] Rehman K, Akash MSH. Mechanisms of inflammatory responses and development of insulin resistance: how are they interlinked? *Journal of Biomedical Science*. 2016; 23: 87.
- [41] Ramasamy I. Recent advances in physiological lipoprotein metabolism. *Clinical Chemistry and Laboratory Medicine*. 2014; 52: 1695–1727.
- [42] Poggio P, Branchetti E, Grau JB, Lai EK, Gorman RC, Gorman JH, 3rd, *et al.* Osteopontin-CD44v6 interaction mediates calcium deposition via phospho-Akt in valve interstitial cells from patients with noncalcified aortic valve sclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2014; 34: 2086–2094.
- [43] Zanobini M, Saccocci M, Tamborini G, Veglia F, Di Minno A, Poggio P, *et al.* Postoperative Echocardiographic Reduction of Right Ventricular Function: Is Pericardial Opening Modality the Main Culprit? *BioMed Research International*. 2017; 2017: 4808757.
- [44] Errico TL, Chen X, Martin Campos JM, Julve J, Escolà-Gil JC, Blanco-Vaca F. Basic mechanisms: structure, function and metabolism of plasma lipoproteins. *Clinica E Investigacion en Arteriosclerosis: Publicacion Oficial De La Sociedad Espanola De Arteriosclerosis*. 2013; 25: 98–103. (In Spanish)
- [45] Feingold KR, Grunfeld C. Effect of inflammation on HDL structure and function. *Current Opinion in Lipidology*. 2016; 27: 521–530.
- [46] Su X, Zhang G, Cheng Y, Wang B. New insights into the emerging effects of inflammatory response on HDL particles structure and function. *Molecular Biology Reports*. 2021; 48: 5723–5733.
- [47] Wyatt HR. Update on treatment strategies for obesity. *The Journal of Clinical Endocrinology and Metabolism*. 2013; 98: 1299–1306.
- [48] Sibuyi NRS, Moabelo KL, Meyer M, Onani MO, Dube A, Madiehe AM. Nanotechnology advances towards development of targeted-treatment for obesity. *Journal of Nanobiotechnology*. 2019; 17: 122.
- [49] Karri S, Sharma S, Hatware K, Patil K. Natural anti-obesity agents and their therapeutic role in management of obesity: A future trend perspective. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie*. 2019; 110: 224–238.
- [50] Yaribeygi H, Jamialahmadi T, Moallem SA, Sahebkar A. Boosting GLP-1 by Natural Products. *Advances in Experimental Medicine and Biology*. 2021; 1328: 513–522.
- [51] Hassan S, Shah M, Malik MO, Ehtesham E, Habib SH, Rauf B. Treatment with combined resveratrol and myoinositol ameliorates endocrine, metabolic alterations and perceived stress response in women with PCOS: a double-blind randomized clinical trial. *Endocrine*. 2023; 79: 208–220.
- [52] Sedighyan M, Abdolahi M, Jafari E, Vahabi Z, Sohrabi Athar S, Hadavi S, *et al.* The effects of nano-curcumin supplementation on adipokines levels in obese and overweight patients with migraine: a double blind clinical trial study. *BMC Research Notes*. 2022; 15: 189.
- [53] Cortez-Navarrete M, Méndez-Del Villar M, Martínez-Abundis E, López-Murillo LD, Escobedo-Gutiérrez MDJ, Rosales-Rivera LY, *et al.* Effect of *Momordica charantia* Administration on Anthropometric Measures and Metabolic Profile in Patients with Obesity: A Pilot Clinical Trial. *Journal of Medicinal Food*. 2022; 25: 645–651.