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Review article

Obesity-Associated Health Risks and the role of Some Natural Phytochemicals: Diverse Physiological Mechanisms of Action

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HIGHLIGHTS

- Obesity is a global health risk linked to multi-organ dysfunction.
- Natural phytochemicals provide protective and therapeutic effects.
- Multi-targeted mechanisms support obesity prevention and management.
- Phytochemicals promote overall health benefits beyond weight control.
- Plant-based agents offer safer alternatives to synthetic drugs.

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ABSTRACT

Being the 5th highest risk of death globally, obesity has grown to be a significant public health concern. It is directly linked to several chronic illnesses, as well as diabetes, insulin resistance, hypertension, dyslipidemia, stroke, and arteriosclerosis. An astounding two billion adults are overweight, with 650 million being obese, according to the World Health Organization. More than one billion adults will be overweight by 2025, with an additional 2.7 billion expected to be overweight if current trends continue. People have been using medicinal plants to treat a variety of ailments since ancient times. In recent years, numerous dietary components and natural substances have been investigated for their potential as chemopreventive agents. Additionally, a greater inclination towards conventional treatments was brought on by low patient satisfaction with synthetic drug use, which was exacerbated by the high expense and adverse effects of these prescriptions. There's a rapidly growing trend of using herbs to treat a wide variety of illnesses. The protective benefits of antioxidants derived from natural substances against chemical agent poisoning have received particular focus in recent investigations. Natural antioxidants have been the subject of recent research due to their ability to protect against the toxicity of various contaminants and pathogenic causes. Several phytochemicals act through complementary mechanisms: fenugreek suppresses appetite and regulates lipid levels, green coffee reduces fat absorption and increases glucose balance, piperine enhances fat oxidation and increases curcumin bioavailability, while curcumin counteracts inflammation, oxidative stress, and adipogenesis. Collectively, they offer a multi-targeted strategy for obesity management.

1. Introduction

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When too much fat accumulates in the body, it can lead to health risks, a condition known as being overweight or obese. An imbalance between energy expenditure (the number of burned calories) and energy intake (the quantity of calories consumed) is the primary reason for obesity. This imbalance is well known to be a consequence of contributing factors, including genetic, metabolic, behavioral, and environmental factors. Obesity can be categorized into two main types: peripheral obesity, often described as a "pear shape," and abdominal or central obesity, which is commonly referred to as an "apple shape" [1].

One way to tell if someone is overweight or obese is to look at his/her body mass index (BMI). A person's height in square meters divided by their weight in kilograms (kg) is the formula for this measurement. The World Health Organization (WHO) defines overweight as a body mass index (BMI) of 25 kg/m2 or above, and obesity as a BMI of 30 kg/m2 or above [2].

Although body mass index (BMI) is a way to quantify obesity, it doesn't tell anything about fat content, which is crucial for determining concerns like cardiovascular risk. Two new clinical measures evaluating waist-to-hip proportion and abdominal circumference were developed to assist in differentiating between central and abdominal obesity. For a person to be considered centrally obese, their waist circumference must be greater than 102cm for men and 88cm for women. Heart disease is more likely to develop as a result. A waist-to-hip ratio more than 0.85 for women and 0.9 for males is considered central obesity [2].

2. Materials and Methods

A comprehensive and methodical literature search was conducted across several electronic databases, such as PubMed, Scopus, Web of Science, and Google Scholar, to find peer-reviewed publications that were pertinent to obesity, its related complications, and the preventive or therapeutic role of natural phytochemicals. The search strategy combined keywords such as “obesity,” “high-fat diet,” “phytochemicals,” “herbal medicine,” “curcumin,” “piperine,” “fenugreek,” and “green coffee bean extract.”

2.1. Inclusion and Exclusion Criteria

Included studies met the following criteria: (i) they had an English publication date, (ii) investigated the role of natural compounds, herbs, or plant-derived bioactive agents in obesity prevention or management, (iii) provided experimental (animal or clinical) or review data on metabolic, hematological, or organ-protective outcomes. Excluded were: (i) conference abstracts, commentaries, and non-peer-reviewed reports, (ii) studies lacking sufficient methodological detail, and (iii) articles not directly related to obesity or phytochemicals.

2.2. Data Collection and Screening

We first checked the titles and abstracts to make sure they were relevant, and then we read the whole texts to make sure they were eligible. We also manually scanned the reference lists of the publications that were included in order to find more relevant studies. Data were extracted regarding study design, animal or human model, type and dose of compound tested, duration of intervention, and observed outcomes (metabolic, hematological, biochemical, and histological parameters).

2.3. Verification

Data extraction was independently cross-checked by two reviewers to ensure accuracy and consistency. Any disagreements were resolved through consensus.

3. Review of literature and discussion

Our research shows that serious hematological and systemic problems are linked to obesity caused by a high-fat diet. The hematological parameters, which include hemoglobin, red blood cell count, and hematocrit value, showed a significant drop in obese rats, which is indicative of anemia. At the same time, there were increased levels of platelets, white blood cells, neutrophils, and lymphocytes, suggesting a state of chronic, low-grade inflammation and immune activation. These alterations were accompanied by hepatic and renal dysfunction, as evidenced by elevated liver enzymes and impaired kidney function markers. Collectively, these findings demonstrate that diet-induced

obesity not only promotes metabolic imbalance but also exerts hematotoxic, hepatotoxic, and nephrotoxic effects that contribute to the overall burden of obesity-related complications [3].

Although conventional treatments—such as lifestyle modification (diet and exercise), pharmacotherapy, and bariatric surgery—remain the cornerstone of obesity management, they are not without limitations. Lifestyle interventions often poor to long-term adherence and modest weight loss. Pharmacological agents typically achieve only 3%–9% excess body weight reduction over one year and may entail safety concerns and a limited impact on cardiovascular outcomes [4].

Bariatric surgery offers more substantial and sustained weight reduction (≈ approximately 25–30%), yet its high cost, invasiveness, and accessibility barriers limit its applicability [5].

In light of these obstacles, there has been a recent uptick in the amount of clinical and preclinical research demonstrating the promise of bioactive chemicals derived from plants in the fight against obesity. As a kind of alternative or supplemental therapy, herbal remedies are gaining popularity. Plant compounds like those of Nigella sativa, Hibiscus sabdariffa, and Coffea arabica, for instance, have been demonstrated to regulate lipid metabolism, enhance insulin sensitivity, decrease inflammation and oxidative stress, and suppress hunger through multiple pathways [6].

Nonetheless, the current evidence is limited by methodological constraints, small sample sizes, and inconsistent dosing protocols, further well-designed clinical trials are necessary to properly establish safety, optimal dosing, and long-term efficacy [7].

3.1. Pathophysiological Impacts of Obesity

As obesity progressed, adipose tissues suffered more, and these tissues started to produce elevated amounts of inflammatory cytokines like TNF-α and IL-6, which initiated a state of low-grade chronic inflammation. This inflammation, in turn, disrupted insulin action and metabolic pathways [8]. Furthermore, the increasing fat accumulation led to a surge in reactive oxygen species (ROS) production. This caused significant damage to proteins, lipids, and DNA, triggering apoptotic pathways and accelerating the decline of metabolic organs, particularly the skin, liver, and pancreas [9].

At the level of adipose tissue itself, hypertrophic adipocytes lose their ability to store fat safely, forcing the body to deposit excess lipids in ectopic sites, such as the liver and muscles, particularly in cases of visceral obesity. This further exacerbated insulin resistance and led to widespread metabolic disturbances [10]. From a hormonal perspective, elevated leptin levels are a hallmark of obesity, often accompanied by leptin receptor resistance, which disrupts appetite and energy regulation while exacerbating inflammation. Conversely, adiponectin levels decrease, despite its critical role in enhancing insulin sensitivity and protecting against oxidative stress. Moreover, leptin hormone itself has been shown to stimulate ROS production, adding another layer of oxidative stress-related damage [11].

Chronic inflammation, oxidative stress, dysfunctional adipose tissue, and hormonal imbalance are all interrelated processes that contribute to the overall picture of how obesity increases the risk of diabetes, cardiovascular disease, and harm to important organs such as the liver, kidney, pancreas, and heart [12,13].

3.1.1. Hematological Alterations Associated with Obesity

One of the adverse effects of obesity is hematotoxicity, which is mainly related to inducing physiological and immunological changes due to stress or direct contact with the blood cells. Obesity contributes to alterations in hematologic parameters. Chronic low-grade inflammation and adipose tissue dysfunction lead to changes in blood cell counts, such as those of white blood cells (WBC), red blood corpuscles (RBC), and platelets (PLT) [14].

Obesity may be associated with alterations in iron metabolism, which can potentially lead to iron deficiency anemia. Compared to control subjects, obese individuals are more likely to develop iron deficiency anemia. A decrease in the overall quantity of hemoglobin or red blood cells is known as anemia. Commonly referred to as iron deficiency anemia, this condition is caused by either chronic blood loss, insufficient iron intake, or a combination of the two [15]. In the bone marrow, cytokines including Interleukin-6 and Interleukin-1 (IL-6 and IL-1) may also

interact with erythropoietin, leading to reduced RBC synthesis. Additionally, cytokines decrease the number of red blood cells and increase the quantity of immature red blood cells, which leads to an increase in the Red Cell Distribution Width (RDW) [16].

Oxidative stress signaling pathways are eventually activated in obese individuals due to inflammation. Free radicals have the potential to activate Ca2+-permeable nonselective cation channels in the cell membrane and peroxidize lipids in the erythrocyte membrane. Phosphatidylserine translocation consequently increases causing eryptosis (suicidal killing of erythrocytes). Numerous studies have shown that obesity changes the distribution and population of pro-inflammatory leucocytes, the quantity of WBC, lymphocytes, neutrophils, and monocytes, as well as the lymphoid tissues [17].

Changes in white blood cell counts reveal the impact of obesity on immunological function and the systemic inflammatory response. When someone is overweight, his body goes into a chronic low-grade inflammatory state and releases cytokines that promote inflammation, like IL-6, IL-8, and Tumor Necrosis Factor (TNF-α). Pro-inflammatory cytokines induce leukocytosis, particularly neutrophilia, through mechanisms such as the demargination of intravascular neutrophils and the acceleration of neutrophil release from the bone marrow. Adipokines such as leptin hormone, are elevated in obesity, may also play a role in increasing white blood cell counts [18].

Several studies have supported the link between obesity and hematological disturbances. It has been shown that platelet counts are positively correlated, platelet activation adds to the risk of cardiovascular disease in overweight children and adolescents, which increases the likelihood of metabolic syndrome [19]. Additional research found that white blood cell counts were significantly higher in male mice that were given a high-fat diet (HFD) for a duration of six months as neutrophils, lymphocytes, and platelets, confirming the role of obesity in leukocytosis and immune activation [20]. Likewise, feeding mice HFD for seven weeks was associated with a decrease in RBCs, hemoglobin, and hematocrit levels, along with an increase in WBCs, granulocytes, and lymphocytes' levels, reflecting a combined impact on erythropoiesis and immune cell proliferation [21]. Comparable findings were obtained in female Wistar rats, where prolonged HFD exposure induced anemia-like features such as reduced RBCs, Hb, HCT, MCV, and MCH, together with leukocytosis, particularly lymphocytosis [22]. In addition, long-term HFD consumption in male Wistar rats was found to lower erythrocytic indices (RBCs, Hb, MCV, HCT) while elevating platelet and WBC counts [23]. Therefore, these findings demonstrate that obesity, particularly when induced by chronic high-fat diet feeding, consistently alters hematological balance by inducing anemia-like changes alongside leukocytosis and thrombocytosis, which may represent a mechanistic link between obesity-related inflammation and hematological dysfunctions.

Also, it is believed that thrombocytosis indicates the existence of an inflammatory process, and PLT activation contributes significantly to the acceleration of atherothrombosis. Due to both hereditary and environmental variables, metabolic syndrome—a typical consequence of obesity—has emerged as a major public health concern on a worldwide scale. Insulin resistance, hyperglycemia, hyperinsulinemia, hyperlipidemia, and hypertension are some of the metabolic, hormonal, and blood pressure-related problems that accompany this condition. The combined risk of death from cardiovascular disease, stroke, and renal failure is much higher in those with both of these disorders [24].

3.1.2. Dyslipidemia and Obesity

One of the primary environmental variables contributing to obesity is diet. Studies on humans have demonstrated that consuming more fat, often at the expense of proteins and carbohydrates, is associated with weight gain, which can alter lipid metabolism and lead to other related metabolic disorders. Dyslipidemia affects 60-70% of obese people. Additionally, studies have revealed that animals given a high-fat diet for longer than 2 months gain weight, develop dyslipidemia, and hyperglycemia [25].

The disturbance of lipid metabolism known as dyslipidemia is typified by abnormalities in the blood lipid profile. Increased or decreased levels of certain lipid components are examples of these abnormalities. The majority of dyslipidemias are actually hyperlipidemias, in which HDL levels are low whereas triglyceride, cholesterol, and low-density lipoprotein levels are high [26].

Long-term excess calorie intake leads to excessive fat storage that exceeds the adipose tissue's limited capacity for storing fatty acids. When critical metabolic organs—including the liver, pancreas, and skeletal muscles store excess fatty acids, it results in elevated free fatty acid levels in the blood. This accumulation, both systemically and in these organs, contributes to a toxic state known as lipotoxicity, which then causes inflammation, oxidative stress, and metabolic problems [11].

3.1.3. Hormonal Dysregulation in Obese States

Several studies have demonstrated a clear association between obesity and an increase in adipose tissue mass, along with concurrent disruptions in metabolic and endocrine function. Disturbance in adipose tissue function has a significant impact on the secretion of hormones that influence energy homeostasis, glucose metabolism, lipid metabolism, and immune response [27].

The regulation of both lipid and glucose metabolism relies on the crucial role of insulin. In a healthy individual, pancreatic β-cells primarily produce insulin in direct response to increased plasma glucose levels following a meal. Other hormones, such as glucagon and catecholamines, are also controlled by changes in blood glucose and function antagonistically to insulin to preserve metabolic homeostasis [28].

Adipocytes are among the most insulin-responsive cell types, and insulin is a crucial regulator of almost every facet of adipocyte biology. Insulin has a physiological role in cellular growth and the metabolism of proteins, lipids, and carbohydrates. Its influence on lipid metabolism is similar to its function in glucose metabolism, as it promotes anabolism (building up) while preventing catabolism (breaking down). Specifically, insulin inhibits lipolysis and encourages both triglyceride synthesis (lipogenesis) and the transfer of glucose [29].

3.1.4. Liver enzymes

The liver plays an essential role in the breakdown, synthesis, storage, and detoxification of a wide range of chemicals; it is a principal metabolic organ. Its function in regulating energy and lipid levels is critical. Inflammation may be triggered by fat droplets, which is why fatty liver disease occurs when there is an excess of fat in the liver. Non-alcoholic fatty liver disease (NAFLD) is a chronic liver ailment that is often connected to high-calorie diets. NAFLD is also associated with metabolic syndrome and cardiovascular disease. Serious liver damage, such as cirrhosis, non-alcoholic steatohepatitis, advanced fibrosis, and simple steatosis, may develop from NAFLD. In addition, metabolic syndrome signs are often seen in rats fed a diet rich in carbohydrates and fat. Hepatic lipid dysregulation, oxidative stress, and pro-inflammatory cytokines are all involved in the complicated process of hepatic fat formation. A wide variety of carbohydrate and lipid combinations have been used in NAFLD experiments [30].

Levels of the liver enzymes alanine transaminase (ALAT) and aspartate transaminase (ASAT) are key indicators of liver dysfunction. While gamma-glutamyl transferase (GGT) is present in many organs, its highest activity is in the pancreas, kidneys, and bile ducts. Similarly, alkaline phosphatase (ALP) is found in the liver, bones, intestines, and kidneys. Elevated levels of these four enzymes (ALAT, ASAT, ALP, and GGT) are linked to many different disorders, and they are commonly found at higher concentrations in obese individuals. The increase in these enzymes in the blood is primarily caused by them leaking from the liver's cells, which points to liver injury and a disruption of normal function. Furthermore, abnormally high levels of bilirubin, the final product of heme breakdown, can also signal hepatobiliary diseases. Another sensitive marker of liver function is albumin concentration, which reflects the liver's ability to synthesize proteins; obese people typically have lower albumin levels than healthy individuals [31].

3.1.5. Oxidative stress

When antioxidant and oxidant activities are out of order, it's called oxidative stress. Membrane lipids, protein structures, enzymes, and nucleic acids are only some of the macromolecules that can be directly oxidized when Reactive Oxygen Species (ROS) are produced, thereby impairing cell function and ultimately leading to cell death. Chronic oxidative stress, characterized by increased ROS production and a subsequent decline in antioxidant levels, including catalase and superoxide dismutase activity, as well as vitamins and minerals, is a common feature of obesity. Numerous metabolic anomalies, including hyperinsulinemia, alterations in the metabolism of fats and

carbohydrates, an increase in adipose tissue, and heightened systemic inflammation, are associated with this oxidative stress. Oxidative stress, linked to inflammation and organ dysfunction, can alter lipase activity. This includes adipose tissue and the liver [32].

3.1.6. Inflammation

When the immune system has an adverse reaction to substances in the environment, whether they are biological, chemical, or potentially harmful, inflammation ensues. According to many studies, obesity is linked to a chronic inflammatory disorder. The oxidative stress brought on by obesity was a key factor in regulating the chronic inflammatory state. Insulin resistance, high blood pressure, kidney disease, atherosclerosis, an inflammatory state, and an aberrant immune response are some of the chronic illnesses that are exacerbated by obesity. Many different kinds of cells, such as adipocytes and macrophages, make up adipose tissue. Inflammation and insulin resistance may be caused by the production of cytokines including IL-1, IL-6, and TNFα, as well as chemokines like Monocyte Chemoattractant Protein-1 (MCP-1). It is only in adipose tissue that you can find the anti-inflammatory molecule adiponectin, which protects against atherosclerosis, and the proinflammatory cytokines that cause metabolic problems. The family of hormones and proteins secreted by adipocytes known as adipokines has a profound effect on inflammation, immunological responses, and the control of endocrine systems. In overweight people, the dysfunctional fat cells release inflammatory chemicals like IL-6, TNF-α, C-Reactive Protein (CRP), plasminogen activator inhibitor-1 (PAI-1), and monocyte chemoattractant protein-1 (MCP-1). In comparison, the fat cells in normal people primarily release anti-inflammatory chemicals like transforming growth factor beta (TGF-β), IL-10, IL-4, and IL-13 [33].

3.1.7. Histological studies

Obesity causes structural and functional damage to various organs. Hepatocyte death, mitochondrial malfunction, and oxidative stress are the primary factors that harm the liver's cells. Hepatic lipid peroxidation is increased in obese individuals due to an increase in reactive oxygen species (ROS) generation. The inflammatory response and the formation of fibrosis are initiated and maintained by Kupffer cells, which are activated by lipotoxic mediators and intracellular signals. The kidney is an important organ that controls the quantity and make-up of all body fluids and keeps the acid-base balance in check. Because it is immediately exposed to the blood through open fenestra in the glomerular capillaries, it is more susceptible to poisoning. Furthermore, compared to other organs, the poison is concentrated many times greater. Numerous structural, hemodynamic, and metabolic changes in the kidney are brought on by obesity. Given the systemic rise in metabolic demand associated with obesity, the majority of these are probably compensatory reactions. However, compensatory failure can sometimes result in renal injury becoming clinically evident [34].

3.2. Treatment of obesity

As obesity has gained global concern for determining how far it causes health risks, there was a need to search for a suitable, effective therapeutic cure or at least a protective trial for the side effects of obesity, such as using medicines or by using natural compounds, such as specific herbs or spices, or even resorting to surgery in severe conditions.

Natural items, including plants, spices, and herbs, have been the subject of a great deal of research in the last several years, as protective and therapeutic agents, and safer alternatives to synthetic drugs for combating obesity. Those natural compounds address the enhancement of metabolic balance while decreasing body weight, but not all of them act through the same mechanisms. Some plants act as appetite suppressants, such as fenugreek (Trigonella foenum-graecum), which is rich in soluble fibers that promote satiety. Others work by enhancing metabolism and fat oxidation, exemplified by black pepper (Piper nigrum) due to the activity of its main compound, piperine. In addition, certain natural products function by reducing fat absorption, such as green coffee bean extract (Coffea arabica), which contains chlorogenic acid that lowers lipid uptake and improves glucose regulation. Curcumin, a bioactive polyphenol found in turmeric (Curcuma longa), has anti-inflammatory and anti-adipogenic effects, which is another significant mechanism, which prevents chronic inflammation and fat accumulation in adipose tissue. Moreover, the combination of Curcumin and piperine provides a remarkable effect as anti-obesity and anti-inflammatory agents.

Accordingly, this review examines the many plants and spices and their possible therapeutic and preventive benefits on obesity caused by the high-fat diet (HFD), with an emphasis on the ways in which these substances work. Natural products can help with the management of obesity and associated problems. The article gives an overview of these items by classifying them according to their mechanism of action.

3.2.1. Effect of Fenugreek (*Trigonella foenum-graecum*) on obesity management

Traditional uses for fenugreek include spice making and traditional medicine. The herbaceous plant is Trigonella foenum-graecum, and it is a member of the Fabaceae family. The seeds contain a wealth of bioactive chemicals, such as flavonoids, saponins, and soluble fibers, which provide them a variety of pharmacological effects. Fenugreek is a potential natural choice for the prevention and control of obesity since it regulates lipid metabolism by increasing satiety, decreasing food intake, and improving insulin sensitivity, as shown in multiple studies [35-38].

Using mice that had gained weight due to a high-fat diet (HFD), researchers looked at how fenugreek seed extract affected their condition and reduce plasma triglyceride levels.

The effect's mechanism was thought to be caused by the active ingredient 4-hydroxyisoleucine present in fenugreek seeds, which was identified as a key factor in reducing plasma triglyceride accumulation and thereby alleviating the metabolic disturbances associated with HFD-induced obesity. Fenugreek seed extract markedly decreased rates of weight gain due to appetite suppression that reduced food intake and consequently levels of plasma triglyceride [39].

3.2.2. Effect of Black Pepper [Piperine] on obesity management

Black pepper, scientifically known as Piper nigrum, is a popular spice known for its strong flavor and its principal active ingredient, piperine (PIP). According to recent research, piperine greatly decreases triglyceride, total cholesterol, LDL, and VLDL levels as well as body fat mass and weight, while increasing beneficial HDL levels. Interestingly, these effects occurred without any reduction in food intake, suggesting that piperine does not suppress appetite. Instead, it enhances metabolism and promotes fat oxidation processes. Piperine is also well known for improving the absorption and bioavailability of other substances, such as curcumin, increasing its effect by 2000% in humans and 154% in rat models. Moreover, it contributes to healthy weight loss by preventing or reducing hyperlipidemia caused by high-fat diets (HFDs) [40,41]. To further understand its role, researchers examined piperine's effect on obesity-induced dyslipidemia in male Sprague Dawley rats. After eight weeks of a high-fat diet, the rats were induced to develop obesity-related lipid abnormalities. The second step, in addition to maintaining HFD, was to give two groups separate medications for three weeks. One group was given 40 milligrams per kilogram of piperine, whereas the other group got 5 mg/kg of sibutramine, the reference drug. At 4,8, and 11 weeks before to and after treatment, participants in the normal, HFD-control, test, and standard groups had their weight, food intake, blood triglycerides, total cholesterol, LDL, VLDL, and HDL levels measured. Body fat percentages were measured at the end of week eleven. While the findings showed that taking piperine supplements and sticking to a high-fat diet had no effect on food consumption, they did show that body weight, triglycerides, total cholesterol, LDL, VLDL, and fat mass were significantly reduced, while HDL levels were significantly increased.

It also recorded strong effects of piperine on lipids and fats even at a modest dosage of 40 milligrams per kilogram, meanwhile no impact on appetite. The exact mechanism of action against obesity remains a mystery, however structural similarities to known agonists for the Melanocortin-4 (MC-4) receptor suggest it may be involved in pathways mediated by the MC-4 receptor [42].

3.2.3. Effect of Green Coffee Bean Extract (GCBE) on obesity management

The world's most consumed beverage, coffee, is also rich in phytochemicals. It is believed that coffee has health benefits for a variety of conditions, including type 2 diabetes [T2DM]- historically referred to as Non-Insulin Dependent Diabetes Mellitus (NIDDM). vascular function, metabolic syndrome (Mets), and others [43]. Unroasted coffee beans, or "green coffee" [44], may help stave off metabolic syndrome [45] and type 2 diabetes [46]. In addition, insulin resistance and obesity are important etiological factors for metabolic syndrome (Mets), and multiple studies have shown that green coffee can alleviate symptoms of Mets, including hypertension [47], diabetes [48,49], and lipid profile [48-50].

A study was carried out to assess the ability of GCBE to decrease fat absorption, improve insulin resistance, and regulate blood lipid levels in rats, as well as to assess its therapeutic role against metabolic abnormalities caused by a high-fat diet. This was done in order to delve more into these effects.

Researchers observed that GCBE acts via an integrated regulatory mechanism to alleviate metabolic abnormalities linked to obesity caused by high-fat diets. By raising adiponectin hormone levels, the extract improved insulin sensitivity and set in motion mechanisms for fat breakdown. Additionally, it improved glucose absorption into cells and decreased blood glucose levels by upregulating the expression of the glucose transporter GLUT4 in adipose tissue. The insulin resistance index (HOMA-IR) was significantly lowered as a result of the extract's simultaneous reduction of Retinol Binding Protein-4 (RBP-4), a marker often associated with poor insulin signaling. These molecular and hormonal changes were reflected in the lipid profile, where treatment significantly decreased triglycerides harmful Low-density lipoproteins (LDL) and very Low-density lipoproteins, VLDL), while elevating protective HDL. Altogether, green coffee bean extract demonstrates anti-obesity efficacy by restoring metabolic balance and improving both lipid and glucose metabolism, underlining its promise as a non-invasive treatment for issues stemming from obesity. This suggests that green coffee bean extract may be useful as a natural remedy for metabolic diseases and obesity [51].

3.2.4. Effect of Curcumin on obesity management

The natural polyphenolic phytochemical curcumin, or diferuloylmethane, is derived from the rhizome of the Curcuma longa Linn plant, which belongs in the Zingiberaceae family. For thousands of years, people have utilized this spice, which is also known as "Indian Saffron," as a medicinal herb, food colorant, and dietary supplement. Its taste and coloring properties make it a versatile ingredient in many foods. About 60% to 70% of the turmeric extract contains curcumin, the compound responsible for the spice's signature yellow hue [52]. People who are overweight or at danger of becoming obese should take it to avoid or postpone the onset of organ dysfunction and its consequences because of its powerful antioxidant, anti-inflammatory, anti-toxic, and anti-obesity characteristics [53].

An earlier study aimed to investigate the possible anti-inflammatory and anti-obesity benefits of curcumin by analyzing the biochemical, histological, and molecular changes brought about by obesity in rats that was produced by a high-fat diet (HFD). This study looked at the effects of curcumin on metabolic dysfunction, oxidative stress, apoptosis, and inflammatory signaling in an assortment of important organs, including the heart, duodenum, and liver.

Every group of rats in that study had ten members: one received a standard diet, one consumed a high-fat diet, and one received a high-fat diet supplemented with curcumin. Biochemical analysis revealed that HFD-fed rats exhibited significant metabolic disturbances, characterized by elevated serum glucose, triglyceride, and insulin levels. These alterations were accompanied by marked histopathological injury in the liver, duodenum, and heart, along with enhanced oxidative stress, as reflected by higher Myeloperoxidase (MPO) levels, depletion of antioxidant defenses such as GSH and SOD, and increased hepatic apoptosis, as indicated by DNA fragmentation. Furthermore, qRT-PCR revealed a pronounced upregulation of inflammatory signaling genes, including TLR4, IL-6, and TNF-α, in adipose tissue. In contrast, curcumin supplementation significantly improved these parameters, resulting in reduced glucose, triglyceride, and insulin levels, restoration of antioxidant balance, attenuation of apoptosis, suppression of inflammatory mediators, and clear histological recovery in the examined organs. All things considered, these results point to curcumin's strong antioxidant, anti-inflammatory, and anti-obesity properties, thereby alleviating obesity-induced metabolic, oxidative, and histological impairments by modulating inflammatory and oxidative pathways. The study concludes that incorporating curcumin into nutritional strategies may help prevent or mitigate organ dysfunction and systemic inflammation associated with obesity [54].

3.2.5. Synergistic Effects of Curcumin and Piperine on Obesity Management

Traditional medicine has made extensive use of curcumin up until this day. The biological and pharmacological activities of curcumin are well-documented, and they include cardioprotective and neuroprotective properties in addition to antimicrobial, antifungal, antiviral, anti-diabetic, and anti-obesity effects. Because it can pass across the blood-brain barrier, curcumin shows neuroprotective characteristics in various parts of the brain, including the hippocampus, and holds great promise in the treatment of neurodegenerative diseases. Adipogenesis suppression is the mechanism by which curcumin exerts its anti-obesity actions, as proved in multiple experiments, regulation of lipid metabolism, stimulation of energy expenditure, and gut microbiome. Curcumin also improves metabolic

conditions linked to obesity, such as insulin resistance, inflammation, oxidative stress, dyslipidemia, NAFLD, CVD & some cancers. Administration of curcumin has been demonstrated in numerous studies to be safe for use in both humans and animals, even at dosages of up to 8g per day [55].

Additionally, gut flora, such as Blautia sp. and Escherichia coli metabolise curcumin. In a two-step decrease pathway from curcumin to the intermediate product, dihydrocurcumin, and the final product, tetrahydrocurcumin. These microorganisms are shown to be active through an NADPH-dependent reductase. Similarly, curcumin can be changed into tetrahydrocurcumin by microbial metabolism in the digestive tract, thanks to a combination of piperine. This metabolite can therefore enter the fat tissue. Curcumin's phenolic groups allow it to react with reactive species, this is probably one of the ways it prevents oxidative damage to cells. It is notable to find carbon-carbon double bonds, β-diketone groups, phenyl rings with hydroxyl and methoxy substituents, and other functional groups in curcumin's structure [56].

The action of curcumin is significantly influenced by the presence of phenolic OH in its structure. Inhibiting or eliminating tissue damage caused by the onset of oxidative stress at low doses may be made more effective by the synergistic impact of the components. By controlling key genes triggered by oxidative stress and preventing the production of cytokines responsible for inflammatory pathways. In order to prevent oxidative stress and inflammation, it is recommended to take a mixture of antioxidants. Curcumin can increase the production of antioxidant proteins such as catalase, superoxide dismutase, glutathione peroxidase, glutathione-S-transferase, and glutathione reductase (GR) [57].

The toxicity of benzo(a)pyrene (BaP) in male mice was studied in connection to the antioxidant activities of curcumin and piperine. The animals were given curcumin (100 milligrams per kilogram of body weight) and piperine (20 milligrams per kilogram of body weight) orally for 7 days before they were exposed to BaP, either alone or in combination. An increase in glutathione (GSH), glutathione reductase (GR), superoxide dismutase (SOD), catalase (CAT), and glutathione (GST) levels, as well as a marked decrease in lipid peroxidation, all indicate to the more protection by combined treatment than curcumin alone [58].

Obese diabetic rats were studied for 4 weeks to determine the effects of varying concentrations of curcumin and black pepper (2.5% curcumin + 1.5% black pepper and 5% curcumin + 5% black pepper). Serum cholesterol, triglycerides, and LDL cholesterol were all reduced by the two combinations, alongside an increase in serum HDL. Furthermore, serum liver enzymes (GPT and GOT) were significantly decreased in treated rats. Histopathological examination revealed that the lower-dose combination produced minor alterations in kidney and liver tissues, whereas the higher-dose combination promoted noticeable hepatic parenchyma repair and improved regeneration of cardiac muscle fibers [59].

Treatment with curcumin in combination with piperine exerted a profound restorative action against the hematological and organ dysfunctions induced by high-fat diet–induced obesity. Animals in the obese control group had developed clear anemia-like features, demonstrated by significantly reduced hemoglobin concentration, red blood cell count, and hematocrit values. Following supplementation, these parameters were markedly improved and restored toward normal levels, indicating the ability of the combination to counteract obesity-induced hematotoxicity. In parallel, the treatment suppressed the exaggerated leukocytosis and thrombocytosis observed in obese animals, with white blood cell and platelet counts returning closer to control values, thereby alleviating the chronic inflammatory state and immune over activation triggered by obesity. The liver also showed remarkable recovery. Obese rats exhibited elevated serum GPT and GOT activities, accompanied by histological evidence of hepatocellular degeneration, necrosis, and sinusoidal dilatation. After treatment with curcumin and piperine, enzyme activities significantly decreased, and microscopic examination revealed regeneration of hepatocytes and repair of the hepatic parenchyma, especially in the higher-dose combination, where the tissue architecture approached normal. Equally striking improvements were detected in the kidneys. High-fat diet feeding had caused tubular epithelial swelling, desquamation, and even early hyaline cast formation, reflecting severe renal injury. With curcumin and piperine treatment, these pathological changes were almost completely reversed; renal tissue regained its integrity, swelling and desquamation were minimized, and the overall histological picture resembled that of normal controls.

Taken together, these findings demonstrate that curcumin and piperine act synergistically to reverse the adverse hematological alterations and to provide substantial hepatic and renal protection, effectively transforming the obese phenotype from one of multi-organ dysfunction into a state of near-normal physiological balance [3].

A comparative overview of the physiological effects of the discussed phytochemicals under high-fat diet conditions is summarized in (Table 1).

The relative improvement percentages in weight, lipid profile, insulin sensitivity, and oxidative stress observed in previous HFD-induced animal studies are presented in (Table 2).

Table 1: Comparative overview between the compounds mentioned.

Compound	Animal model / dose (approx.)	Improvements under HFD	Main mechanisms	Evidence strength	Refer-ences
Fenugreek	HFD-fed mice; seed extract; 4-hydroxyisoleucine	↓ Body weight gain, ↓ TG	Fiber & saponins promote satiety; 4-HIL lowers TG	Clear animal data + some human support	[39]
Piperine	40 mg/kg for 3 weeks after HFD induction	↓ Body weight & fat mass, ↓ TG/TC/LDL/VLDL, ↑ HDL, ↓ hepatic steatosis, ↑ insulin sensitivity	Boosts metabolism & fat oxidation; possible MC-4 receptor involvement	Multiple consistent HFD studies	[40]
Green Coffee	Extract supplementation with HFD	↓ Body/fat mass, ↓ TG/TC/LDL/VLDL, ↑ HDL, ↓ glucose & insulin resistance, ↑ adiponectin & GLUT4	Inhibits fat absorption, improves insulin signaling	Strong animal data + some human support	[48], [49], [51]
Curcumin	Dietary supplementation (≈2.5 g/kg diet)	↓ Glucose/insulin/TG, ↓ inflammation, ↓ oxidative stress / apoptosis, improved liver/heart/intestine histology	Potent anti-inflammatory & antioxidant; AMPK activation	Strong evidence, multi-organ effects; limited bioavailability	[54]
Curcumin + Piperine	Combination (CUR 2.5–5% + PIP 1.5–5% in diet, or CUR 100mg/kg + PIP 20mg/kg)	↓ Weight, ↓ TG/TC/LDL, ↑ HDL, ↓ liver enzymes, ↓ inflammation/oxidative stress, ↑ liver/heart/kidney regeneration	Synergy: Piperine enhances curcumin absorption + stronger antioxidant & lipid-lowering effects	Very strong (multiple animal studies with histological evidence)	[58], [59]

Table 2: Relative Improvement (%) – Based on HFD Animal Previous Studies.

Compound	Weight reduction	Lipid profile (TG/TC/LDL)	Insulin sensitivity / Glucose	Appetite suppression	Anti-inflammatory / Oxidative stress

Fenugreek	↓ 20–25% [39]	↓ 15–20% TG [39]	↑10–15% [36],[38]	High ↑ satiety, ↓ intake [35], [36]	Mild [37]
Piperine	↓ 25–30% [40]	↓ 30–40%; ↑ HDL ~20% [40]	↑ 20–25% [40]	None	Moderate [40]
Green Coffee	↓ 20–25% [49]	↓ 25–30%; ↑ HDL ~15–20% [48],[49],[50]	↑ 30–35% ↑ adiponectin, ↑ GLUT4 [51]	None	Moderate [48],[49]
Curcumin	↓ 20–25% [54]	↓ 25–30% [54]	↑ 25–30% [54]	None	High ↓ cytokines, ↓ ROS, ↓ apoptosis [53], [54]
Curcumin + Piperine	↓ 30–35% [59]	↓ 35–45%; ↑ HDL ~25% [59]	↑ 30–35% [59]	None	Highest (stronger anti-inflammatory/ antioxidant + organ regeneration) [58],[59]

Data represents approximate ranges based on reported outcomes from several HFD animal studies; actual values may vary depending on the experimental model and conditions.

4. Conclusion

In conclusion, natural phytochemicals demonstrate distinct and complementary mechanisms in combating HFD-induced obesity and its complications. Among them, curcumin showed the most comprehensive protective effect by reducing inflammation and oxidative stress, improving glucose and lipid profiles, and repairing multi-organ damage. Piperine was particularly effective in lowering triglycerides, total cholesterol, and LDL levels, while also enhancing insulin sensitivity and protecting against hepatic steatosis. Green coffee bean extract has demonstrated strong efficacy in improving insulin resistance, elevating adiponectin levels, and reducing fat absorption. In contrast, fenugreek was most notable for its appetite-suppressing properties and its ability to reduce HFD-induced weight gain through 4-hydroxyisoleucine, which lowers postprandial triglycerides. Notably, the combination of curcumin and piperine exhibited a promising synergistic effect, as piperine significantly enhanced curcumin bioavailability and potentiated its lipid-lowering activity.

Credit authorship contribution statement

The study's organization, manuscript draught, and original idea came from N.M., H.R., and A.A.H. Animal experiments, data collection, and analysis were all done by E.O.M. The study's design, interpretation of data, and manuscript revision were all collaborative efforts between E.O.M. and A.A.H. The final text has been reviewed and approved by all authors.

Ethics statements

The Arish University Faculty of Science's Ethics Committee for Animal Research gave its permission to all of the study protocols (approval number: ARU010). We followed all applicable rules and regulations when we carried out

the procedures, and we published our findings in accordance with the ARRIVE standards (https://arriveguidelines.org).

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Data availability statement

You can obtain the datasets used in this work from the corresponding author if you're interested.

Declaration of competing interest

No relevant financial or non-financial competing interests have been declared by the authors.

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List of abbreviations

kg	kilogram
BMI	Body Mass Index
WHO	World Health Organization
WBCs	White Blood Cells
RBCs	Red Blood Corpuscles (Red Blood Cells)
PLTs	Platelets
RDW	Red Cell Distribution Width
TNF-α	Tumor Necrosis Factor-alpha
IL-6	Interleukin-6
IL-1	Interleukin-1
IL-8	Interleukin-8
ROS	Reactive Oxygen Species
DNA	Deoxyribonucleic Acid
Hb	Hemoglobin
HCT	Hematocrit
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Hemoglobin

HFD	High-Fat Diet
Mets	Metabolic Syndrome
T2DM	Type 2 Diabetes Mellitus
GCBE	Green Coffee Bean Extract
GLUT4	Glucose Transporter type 4
RBP-4	Retinol Binding Protein 4
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
PIP	Piperine
MC-4	Melanocortin-4
CD	Control Diet
HFDC	High-Fat Diet + Curcumin
MPO	Myeloperoxidase
GSH	Glutathione
SOD	Superoxide Dismutase
qRT-PCR	quantitative Real-Time Polymerase Chain Reaction
TLR4	Toll-Like Receptor 4
NAFLD	Non-Alcoholic Fatty Liver Disease
CVD	Cardiovascular Disease
ALAT	Alanine Transaminase
ASAT	Aspartate Transaminase
GGT	Gamma-Glutamyl Transferase
ALP	Alkaline Phosphatase
CRP	C-Reactive Protein
PAI-1	Plasminogen Activator Inhibitor-1
TGF-β	Transforming Growth Factor beta
CUR	Curcumin
BaP	Benzo(a)pyrene
GPx	Glutathione Peroxidase

GR	Glutathione Reductase
GST	Glutathione-S-Transferas
CAT	Catalase
GPT	Glutamate Pyruvate Transaminase
GOT	Glutamate Oxaloacetate Transaminase
TG	Triglycerides
TC	Total Cholesterol
NIDDM	Non-Insulin Dependent Diabetes Mellitus

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