

LITERATUR REVIEW: EFEK SPIRULINA PLANTENSIS PADA STRES OKSIDATIF DAN PERADANGAN PADA OBESITAS

Stefyne Sonya Y Kura¹, Adriyan Pramono^{*1}, Diana Nur Afifah¹, Rachmania A.Savitri¹, Endang Mahati¹, Ahmad Ni'matullah Al-Baarri¹

¹Departemen Ilmu Gizi, Fakultas Kedokteran, Universitas Diponegoro, Jawa Tengah, Indonesia

*Korespondensi : adriyanpramono@fk.undip.ac.id

ABSTRACT

Background: Obesity is a complex condition with multiple contributing variables, making it challenging to treat the obesity epidemic. The prevalence of obesity has increased in many sectors of society since the late 1970s, and this rising trend is concerning due to the negative health consequences and significant healthcare costs associated with excess body weight. Spirulina has gained interest due to its bioactive components and advantageous effects on health. This review focuses on the underlying molecular mechanisms that contribute to the occurrence of obesity. In addition, the role of antioxidants in the treatment of obesity is also discussed.

Objectives: To determine the Effects of Spirulina Platensis on Oxidative Stress and Inflammation Of Overweight/Obesity.

Methods: This research design used the literature review method. This technique is carried out with the aim of putting forward various theories that are relevant to the problem being faced or studied as a reference material in discussing the results of the study.

Results: The result of the research from the article review found that the causes of obesity based factors that cause the incidence of obesity consist of environmental factors, namely physical activity only as a trend and various food choices, health service factors, namely the influence of counseling, genetic factors namely age, parental fatness, gene mutation, and behavioral factors, namely diet and lack of health, physical activity

Conclusion: Obesity is caused by many factors including environmental factors, health services, genetics, and behavior

Keywords : Keywords; spirulina plantensis; obesity; Oxidative Stress

ABSTRAK

Latar belakang: Obesitas adalah kondisi yang kompleks dengan berbagai variabel yang berkontribusi, sehingga sulit untuk mengobati epidemi obesitas. Prevalensi obesitas telah meningkat di banyak sektor masyarakat sejak akhir 1970-an, dan tren yang meningkat ini mengkhawatirkan karena konsekuensi kesehatan yang negatif dan biaya perawatan kesehatan yang signifikan terkait dengan kelebihan berat badan. Spirulina telah menarik perhatian karena komponen bioaktifnya dan efek menguntungkan bagi kesehatan. Ulasan ini berfokus pada mekanisme molekuler yang mendasari yang berkontribusi terhadap terjadinya obesitas.

Tujuan : Untuk mengetahui efek spirulina plantensis pada stres oksidatif dan peradangan kelebihan berat badan/obesitas.

Metode: Desain penelitian yang digunakan dalam penelitian ini menggunakan metode tinjauan pustaka. Teknik ini dilakukan dengan tujuan untuk mengemukakan berbagai teori yang relevan dengan masalah yang sedang dihadapi atau yang sedang diteliti sebagai bahan acuan dalam pembahasan hasil penelitian

Hasil: Penelitian dari telaah artikel ditemukan bahwa penyebab obesitas berdasarkan faktor-faktor yang menyebabkan kejadian obesitas terdiri dari faktor lingkungan yaitu aktivitas fisik hanya sebagai tren dan pilihan makanan yang beragam, faktor pelayanan kesehatan yaitu pengaruh penyuluhan, faktor genetik yaitu usia, kegemukan orang tua, mutasi gen, dan faktor perilaku yaitu pola makan dan kurangnya aktivitas fisik.

Simpulan: Obesitas disebabkan oleh banyak faktor termasuk faktor lingkungan, pelayanan kesehatan, genetik, dan perilaku.

Kata kunci : spirulina plantensis; obesitas; stres oksidatif

INTRODUCTION

The obesity rate has experienced a substantial worldwide increase over the past five decades. Obesity is characterized by a body mass index (BMI) of 30 or above, which is calculated by

calculating a person's weight by the square of their height. Overweight, on the other hand, is described as having a BMI between 25.0 and 29.9 kg/m². Excessive weight or obesity is associated with a

higher number of mortalities compared to being underweight, and it is a more prevalent issue worldwide than being underweight. This is a worldwide issue that is happening in all regions except certain areas in sub-Saharan Asia and Africa, as well as countries with low rates of obesity, such as Sri Lanka, Indonesia, Sudan, Singapore, Djibouti, and others.^{1,2}

The prevalence of obesity has increased in many sectors of society since the late 1970s, and this rising trend is concerning due to the negative health consequences and significant healthcare costs associated with excess body weight.³ Obesity is a complex condition with multiple contributing variables, making it challenging to treat the obesity epidemic.⁴ Excessive adiposity at the individual level occurs when there is a persistent surplus of energy due to a combination of genetic, biochemical, behavioral, socioeconomic, and environmental variables.^{5, 6, 7,8,9}

Inflammation is a natural response that the body uses to restore balance when it is disrupted by many factors. However, if inflammation becomes chronic or if the body overreacts, it can have harmful implications.¹⁰

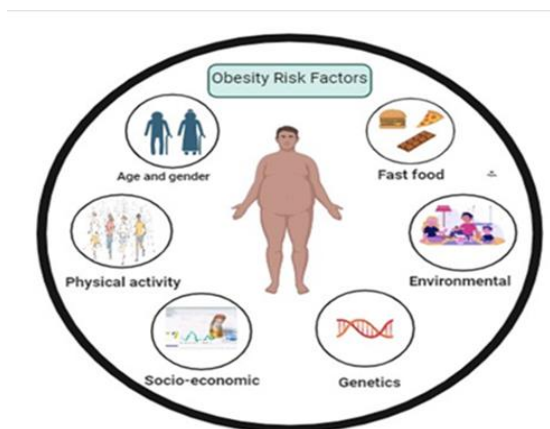
Overweight and obesity are characterized by a state of low-grade chronic inflammation. Recent research has revealed the intracellular pathways involved in inflammation associated with these conditions. Studies conducted on both mice and

humans have shown that the consumption of nutrients can immediately produce inflammatory responses

Obesity is associated with two main types of inflammation, metabolic inflammation and obesity-induced inflammation. Metabolic inflammation, a hallmark of obesity, is associated with cardiometabolic complications, including impaired fatty acid and cholesterol metabolism, leading to insulin resistance. Obesity-induced inflammation is characterized by chronic low-grade inflammation, which affects various metabolic organs, especially adipose tissue, where immune cells undergo significant changes in obesity, affecting metabolic regulation.¹¹

Morbid and non-morbid obesity exhibit inflammatory responses, the severity and extent of inflammation may vary between the two conditions, potentially influencing the development of metabolic disorders. Non-morbid inflammation, originates from an intense immune system response. It results in an increase in Basal Metabolic Rate (BMR) and usually diminishes over time. This type of inflammation is more acute and differs from the chronic nature of obesity-induced inflammation.¹²

Therefore, it is believed that the primary trigger for inflammation is excessive food intake, and the inflammatory pathway originates in metabolic tissues such as adipose tissue, liver, and muscle. These tissues respond to the stimulus by initiating the inflammatory response.^{10,13}



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Figure 1. Obesity is a multifactorial chronic disease caused by several factors, namely increased consumption of fast food, lack of physical activity, genetic, psychological, socio-economic status, age, and gender are factors that contribute to changes in energy balance that lead to the incidence of obesity.

In obese individuals, both men and women, there is a higher activation of kinases, such as c-jun N-terminal kinase and the inhibitor of k kinase, in the tissue and liver. These kinases have the ability to stimulate the production of inflammatory cytokines.^{14,15} These kinases control

subsequent transcriptional processes by activating specific transcription factors such as activator protein-1, nuclear factor κB, and interferon regulatory factor. This leads to an increase in the expression of genes that produce inflammatory mediators. The upregulation of cytokines

intensifies receptor activation by creating a feedback loop that promotes inflammation and suppresses the signaling of metabolic pathways.¹⁶

Visceral adipose tissue may generate inflammatory substances that stimulate the generation of acute-phase reactants in hepatocytes and endothelial cells. Adipocytes have been found to express and release TNF-alpha, suggesting that adipose body mass could play a significant role in explaining the connection between obesity and inflammation. Several studies have demonstrated a correlation between abdominal fat accumulation and increased levels of C-reactive protein (CRP), regardless of body mass index (BMI), which is a measure of abdominal obesity. The prevalence of persons with elevated hs-CRP was considerably greater in those with abdominal obesity compared to control patients, despite having a similar BMI.¹⁷

Nutraceuticals are naturally occurring chemicals with a molecular size typically below 3000 Da. They did not participate in essential metabolic processes and demonstrate a beneficial biological activity that supports healthy condition. Computational chemistry estimates over 400,000 bioactive molecules, which are categorized into several chemical families and are of significant pharmacological relevance.¹⁸ The natural products, particularly herbs, that include nutraceuticals have demonstrated efficacy in the prevention and treatment of non-genetic obesity, along with their presumed mode of action. Certain phytocomplexes stimulate the breakdown of fats but do not inhibit the growth of fat cells. While some substances may stimulate thermogenesis, they did not inhibit the enlargement of fat cells. Other substances are classified as prebiotics, which stimulate the proliferation of bacteria that consume fat. However, these substances did not inhibit the transformation of stem cells into adipocytes.¹⁹

Microalgae have gained interest for their potential use in the nutraceutical and pharmaceutical fields due to their bioactive components and advantageous effects on health. Several microalgae species, including *Euglena gracilis*, *Phaeodactylum tricornutum*, *Spirulina maxima*, *Spirulina platensis*, and *Nitzschia laevis*, have demonstrated anti-obesity properties.²⁰ The anti-obesity properties of microalgae can be assigned to various methods of action: 1) Suppression of pre-adipocyte differentiation: Microalgae have the ability to inhibit the process of pre-adipocyte differentiation, resulting in reduced the quantity of fully developed adipocytes; 2) Microalgae may restrict the accumulation of triglycerides (TG) by decreasing the process of de novo lipogenesis and TG assembly. 3)

Microalgae may stimulate lipolysis and enhance fatty acid oxidation, resulting in a decrease in lipid accumulation.²⁰

Research has demonstrated that consuming spirulina lipids in one's diet can reduce oxidative stress and inflammation caused by a diet high in fat and sugar (HFHSD) in mice. Spirulina contains antioxidants and has been linked to the reduction of chronic inflammation and oxidative stress, both of which are significant contributors to metabolic problems associated with obesity.²¹

Although calorie restriction and exercise are commonly used treatments for obesity, spirulina has demonstrated significant advantages in promoting weight loss. Spirulina contains phycocyanin, which has a light-harvesting chromophore called phycocyanobilin. This compound is capable to inhibit nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase, a major cause of oxidative stress in adipocytes. NADPH oxidase plays a crucial role in inducing insulin resistance and altering the production of adipokines and cytokines in enlarged adipocytes. Therefore, by reducing oxidative stress in adipocytes, spirulina can potentially have widespread anti-inflammatory and insulin-sensitizing effects throughout the body.²²

MAIN CONTENTS

Definition

Energy balance refers to the balance between energy consumed through food and drink and energy expended through metabolic processes and physical activity. Thus indicating that obesity occurs when there is an excess of energy intake compared to energy expenditure.²³ When people consume more calorie than they expend, they are in a positive energy balance, which leads to the storage of excess energy in the form of body fat.²⁴

The differences between males and females of the same age establish the reference ranges for Body Mass Index (BMI, kg/m²). In general, a BMI more than 30 kg/m² is seen as characteristic of obesity. Adipocytes, specialized cells for lipid storage, accumulate fat which serves as an energy source. Excess energy derived from food is turned into fatty acids and stored in cells, which then multiply or increase in size to accommodate the additional energy. The regulation of the equilibrium between energy consumption and expenditure is regulated by various factors that might contribute to obesity, such as those that stimulate the development of immature fat cells (adipogenesis) or those that enhance the breakdown of lipids with the release of energy (lipolysis). Dysregulation of energy expenditure, lipolysis, and adipogenesis are the primary factors that contribute to the development of obesity.²⁶

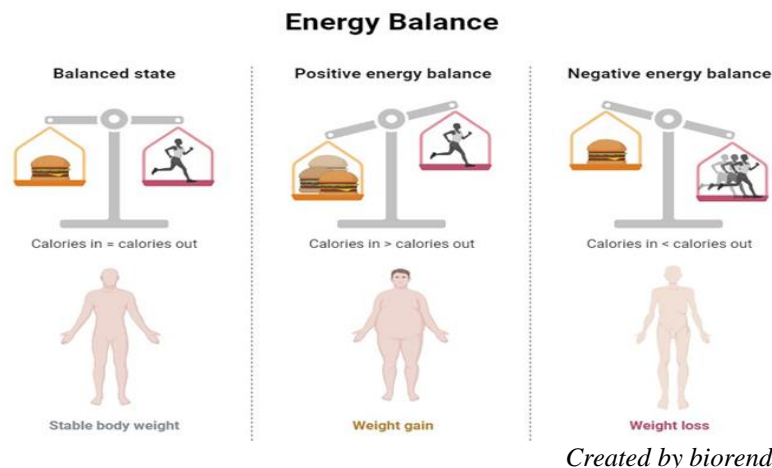


Figure 1. As physical activity has decreased, bodyweights have increased, which is accompanied by a corresponding increase in energy expenditure. In fact, it has been suggested that becoming obese is the body's way of increasing energy expenditure to achieve energy balance in an increasingly sedentary lifestyle.

Additionally, adipose tissue consists of diverse cell types such as adipocytes, fibroblasts, endothelial cells, and different immune cells, which communicate with each other through a paracrine and endocrine system. Preadipocytes have the ability to complete differentiation into three distinct forms: white adipocytes (WA), brown adipocytes (BrA), and beige adipocytes (BeA). Each of these types has unique biological activities. Furthermore, mature white cells have the ability to transform into cells that resemble brown or white cells, a process known as transdifferentiation (which refers to the conversion of white adipose tissue into brown adipose tissue).²⁷

The brown and beige adipocytes exhibit a greater abundance of mitochondria in comparison to white cells, indicating their dedication to fat oxidation. Fibroblast and endothelial cells, which surround the blood vessels, have the potential to induce inflammation, leading to obesity.²⁸ Likewise, the immune cells that infiltrate inflamed fat tissue, including the macrophages in fat tissue (ATMs), have a direct impact on the development of insulin resistance caused by obesity. Furthermore, it has been revealed that natural killer T cells (NKs) play a role in regulating inflammation in adipose tissue in cases of obesity. Multiple recruited cells contribute to the augmentation of fat mass, and research has demonstrated their association with insulin resistance and their connection to alterations in the extracellular matrix.²⁹

EFFECTS AND RISK FACTORS OF OBESITY

According to the World Obesity Federation's 2023 atlas, it is projected that a significant proportion of the world's population could be overweight or obese by 2035, unless significant actions are implemented to address this problem. The survey predicts that in the next 12 years, more than 4 billion people, making

up almost 51% of the world's population, would suffer from obesity or overweight. The incidence of obesity is seeing a fast escalation, with youngsters and lower-income countries being disproportionately affected. The societal economic impact of health problems linked to obesity is significant, with estimates indicating it will surpass \$4 trillion annually by 2035, amounting to around 3% of the global gross domestic product (GDP).³⁰

Within the United States, a significant section of 22 states has a prevalence of adult obesity that is equal to or exceeds 35%. The Centers for Disease Control and Prevention (CDC) stresses the significance of implementing interventions that target the entire population to ensure fair and equal access to healthy food, safe environments for physical activity, comprehensive obesity prevention and treatment programs, and healthcare services that are supported by evidence, such as medication and surgical interventions. On a global scale, there are about 1 billion individuals who are affected by obesity, including 650 million adults, 340 million adolescents, and 39 million children.³¹ Currently, over 33% of the global population suffers from obesity, which is a broad, preventable disease. According to ongoing long-term patterns, it is estimated that by 2030, approximately 38% of adults worldwide would display signs of being overweight, and an additional 20% will be categorized as obese.³²

Overweight and obesity rates are on the rise in low- and middle-income countries, especially in urban regions. A longitudinal research conducted in China analyzed a cohort of 12,543 people over a span of 22 years. The study results showed a notable rise in the incidence of obesity adjusted for age in both males and females. More precisely, the

incidence increased from 2.15% to 13.99% among the entire population. The incidence in females rose from 2.78% to 13.22%, and in males, it went from 1.46% to 14.99%.³¹

In the year 2000, there was a notable increase of 24% in the occurrence of obesity among African children under the age of 5. Recent 2019 research reveals that a substantial percentage of Asian children under the age of 5 are affected by obesity or overweight issues, with more than half falling into this classification.³³ The data provided by the World Health Organization (WHO) about sub-Saharan Africa reveals a negative correlation between the prevalence of overweight and obesity among adults and the incidence of stunting, underweight, and wasting in children.³⁴

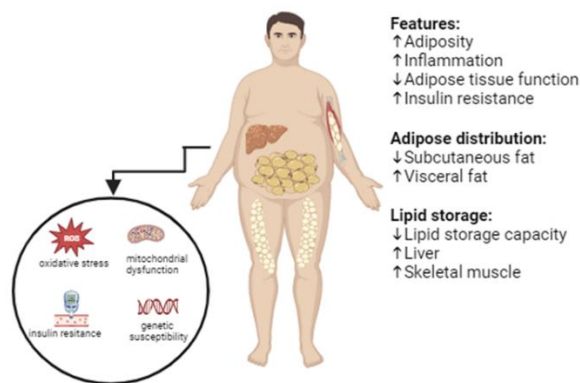
MECHANISMS OF OBESITY IN NON-COMMUNICABLE DISEASES

The primary variables that contribute to obesity remain a subject of continuing discussion and diverse perspectives within the academic community. The current health guidelines for addressing obesity are based on the fundamental physiological premise that the formation of fat is affected by an energy imbalance caused by an unequal ratio of energy intake to expenditure.³⁵ The growing prevalence of obesity is mainly caused by the increased consumption of energy-dense and highly palatable food, which has become more easily available. The dietary preferences made by

individuals, along with the interaction of social, economic, and environmental factors related to food accessibility, have a significant impact on a patient's ability to attain equilibrium.³⁶

The etiology of obesity includes various elements, including genetic, environmental, socioeconomic, and behavioral or psychological causes.³⁶ Obesity is associated with a variety of health issues, such as cardiovascular disease, dyslipidemia, and insulin resistance.

These problems are known to promote to the development of diseases including diabetes, stroke, gallstones, fatty liver, and other diseases. The development of obesity can be linked to the accumulation of fatty metabolites, the activation of inflammatory signaling pathways, or other mechanisms that cause harm to hypothalamic neurons. These factors may help to clarify the biological defense mechanism that explains the increase in body fat accumulation.³⁷ Insulin resistance is a major factor in the development of type 2 diabetes in individuals who are obese. Several elements have been suggested to explain the basic mechanisms of insulin resistance in the developing of obesity. The causes contributing to this condition include inflammation, mitochondrial dysfunction, hyperinsulinemia, lipotoxicity/hyperlipidemia, genetic susceptibility, endoplasmic reticulum (ER) stress, age, oxidative stress, fatty liver, hypoxia, lipodystrophy, and pregnancy.³⁸



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Figure 2. Overnutrition, sedentary lifestyle and genetic susceptibility are the leading factors associated with the development of obesity. In addition to dysfunctional angiogenesis, an obese state is characterized by an abnormal inflammatory response, low antioxidant capacity and reduced insulin sensitivity that may eventually lead to the generation of inflammation, oxidative stress and insulin resistance.

Mechanism of stress oxidative and inflammation in obesity

Obesity is characterized by inflammatory components that are directly and indirectly linked to

significant chronic diseases, including diabetes, atherosclerosis, hypertension, and many forms of cancer. Individuals who are overweight or obese experience changes in their circulating levels of

inflammatory cytokines, including IL-6, TNF α , C-reactive protein (CRP), IL-18, resistin, and visfatin.³⁹ Chronic inflammation affects the storage of fat in adipose tissue, leading to an excess of free fatty acids and triglycerides in the bloodstream. This, in turn, causes insulin resistance in muscle and liver. Adipocytes communicate with macrophages, which could infiltrate fat masses, resulting in obesity and causing the accumulation of fat in abnormal locations inside these tissues.⁴⁰

Enlarged adipose cells, together with the macrophages that inhabit them, collaborate to generate atypical chemicals that stimulate inflammation, including inducible nitric oxide, TNF- α , IL-6, and MCP-1. Tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) can promote insulin resistance by stimulating distinct crucial processes within the insulin signaling pathway. Multiple factors can initiate inflammation, particularly persistent low-grade inflammation that leads to obesity. The accumulation of fat mass can be affected by proinflammatory pathways, elevated levels of free radicals, and epigenetic alterations in certain genes, such as methylation of the IGF-1 gene. This path comprises many protein and metabolite complexes, including inflammasome activators, kinases, and associated coactivators.¹⁰

Pro-inflammatory cytokines are primary among the determinants of inflammation during obesity, although the precise molecular mechanisms underlying its occurrence remain unknown. Obesity is associated with elevated levels of inflammatory cytokines in the bloodstream compared to individuals who are overweight. It is hypothesized that these cytokines contribute to the development of insulin resistance. In obesity, the adipose tissue serves as the primary origin of pro-inflammatory cytokines. These cytokines are mostly produced by invading macrophages, although adipocytes also contribute to their production. Weight loss leads to a decrease in blood concentrations of these cytokines.^{10,13}

The primary cytokines responsible for chronic inflammation include tumor necrosis factor- α (TNF α), interleukin-6 (IL-6), and the inflammasome-activated IL-1 β . TNF- α is a multifunctional molecule that has a key role in inflammation, the development of the immune system, programmed cell death, and the processing of fats, with various impacts on adipose tissue, including the regulation of fat metabolism and the transmission of insulin signals. The levels of circulating TNF- α are elevated in individuals with obesity and reduced during weight loss. TNF- α stimulates the release of IL-6, a potent pro-inflammatory cytokine, while inhibiting the

production of anti-inflammatory cytokines such as adiponectin. TNF- α triggers the programmed cell death of adipocytes and enhances the body's tolerance to insulin by blocking the signaling pathway of the insulin receptor substrate 1.⁴¹

IL-6 is a cytokine that has significant functions in acute phase reactions, inflammation, hematopoiesis, bone metabolism, and cancer progression. IL-6 regulates the balance of energy in the body and the response to inflammation. It has the ability to inhibit the activity of lipoprotein lipase, and it regulates appetite and energy consumption at the level of the hypothalamus. IL-6 plays a crucial role in the shift from acute inflammation to chronic inflammatory disease. Deregulation of this process contributes to chronic inflammation in various disorders including obesity, insulin resistance, inflammatory bowel disease, inflammatory arthritis, and sepsis.⁴²

IL-1 β is primarily synthesized by blood monocytes in reaction to infection, injury, or immunologic stimulus. It induces fever, low blood pressure, and the release of other pro-inflammatory cytokines, such as IL-6. The inflammasome converts the inactive precursor pro-IL-1 β into its active version, IL-1 β . IL-1 β has recently been recognized as a significant initiator of the inflammatory response in obesity.¹⁵ Peroxisome proliferator-activated receptors (PPARs) are transcription factors that belong to the ligand-inducible nuclear hormone receptor superfamily. They have the ability to regulate gene expression in both positive and negative ways, depending on the binding of various lipid-derived hormones and metabolites. The management of lipid metabolism involves three primary isoforms, namely PPAR α (or NR1C1), PPAR β/δ (or NR1C2), and PPAR γ (or NR1C3). These isoforms are not only involved in lipid metabolism but also serve as insulin sensors.⁴³

PPAR subunits are expressed in several tissues, such as adipose, liver, muscle, and endothelial tissues. The activation of PPAR γ primarily impacts lipid levels and influences fatty acid metabolism. Conversely, PPAR γ is primarily implicated in regulating adipogenesis, energy balance, and lipid biosynthesis; its activation influences insulin resistance.⁴⁴

PPAR β/δ is involved in the process of fatty acid oxidation, primarily in skeletal and cardiac muscles. Additionally, it plays a role in the regulation of blood glucose and cholesterol levels. PPARs can also create heterodimers with retinoid X receptor (RXR), which regulates the expression of genes related to lipid metabolism, adipogenesis, maintenance of metabolic balance, and inflammation.⁴⁵

PPAR γ is widely recognized as the primary regulator of adipogenesis, and blocking its activity is a popular approach for identifying anti-obesity compounds. PPAR γ inhibitors have demonstrated efficacy in the treatment of obesity by suppressing the expression of adipose tissue genes. However, these medications may have adverse effects on other tissues. PPAR γ agonists are employed as insulin sensitizers to enhance insulin resistance in individuals with diabetes. PPAR γ consists of seven gene isoforms, including PPAR γ 1 and PPAR γ 2, which are mostly expressed in adipocytes. In adipocytes, they play a role in lipid metabolism and cell differentiation. They are also found in macrophages, where they initiate the early inflammatory response. Several nutraceuticals have demonstrated the ability to influence the PPAR signaling pathway through various mechanisms. The oil derived from *Nigella sativa*, which contains Thymoquinone, a compound that activates PPAR γ , has been shown to reduce the levels of TNF- α and adipokines in individuals who are overweight or obese.^{46,47}

FUNCTIONAL FOOD

Obesity is a multifactorial problem that develops from a combination of genetic, environmental, behavioral, lifestyle, cultural, and metabolic variables. It could result in the development of further health conditions, such as cancer, hypertension, diabetes, dyslipidemia, atherosclerosis, and various others. Obesity results from a disparity between the amount of energy expended and the amount of energy consumed. The development of foods or components aimed at preventing obesity should focus on either one or both of these characteristics. Functional foods used for managing obesity should possess the capacity to promote satiety, decrease appetite, regulate lipid metabolism, influence the life cycle of adipocytes, and stimulate thermogenesis.⁴⁸

Food items contain bioactive substances in trace amounts, and their impact on human health is under constant investigation. Epidemiological statistics indicate that consuming significant amounts of natural functional foods, particularly certain fruits and vegetables that contain abundant bioactive components, is linked to a reduced likelihood of developing chronic conditions, including cardiovascular illnesses, cancer, metabolic syndrome, type II diabetes, and obesity.⁴⁹ Animal and clinical research have shown that some bioactive chemicals and functional food might have a positive impact on weight management and could help reduce the metabolic effects of increased body weight. Nevertheless, the evidence is open to

discussion and various effects have been seen in other research. According to the literature review study, scientific evidence indicates that combining certain functional foods into a balanced diet may be beneficial for weight control and reducing the metabolic effects of obesity.

HUMAN STUDY EFFECT OF SPIRULINA PLANTENSIS

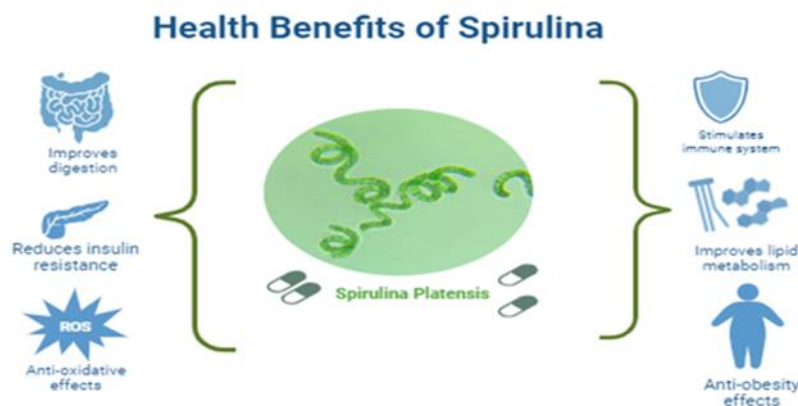
In 2008, Lee et al conducted research on 37 Korean individuals with type 2 diabetes mellitus (T2DM) and BMI > 23 testing the effects of consuming 8g/day of spirulina for 12. The study found that this intervention led to a significant decrease in triglyceride levels, specifically from 125.8 to 98.5 mg/dL, with a statistical significance of $p < 0.05$. Individuals with elevated plasma triglyceride (TG) levels experienced more significant decreases in their TG levels. In the same way, individuals who had elevated levels of TC and LDL-C exhibited more substantial reductions in TC and LDL-C, as well as improvements in blood pressure. The study also found a significant decrease in plasma malondialdehyde levels ($p < 0.05$) and a slight increase in plasma adiponectin levels ($p < 0.1$) with spirulina intake. These changes suggest a reduction in oxidative stress.⁵⁰

Bermejo-Bescós et al. investigated the capacity of *Spirulina platensis* to suppress lipid peroxidation and its impact on the functions of SOD, CAT, glutathione peroxidase (GPx), and glutathione reductase (GR) following the exposure of SH-SY5Y neuroblastoma cells to oxidative stress caused by iron. *Spirulina platensis* preserved the functionality of cellular antioxidant enzymes, including total GPx, GPx-Se, and GR, while also enhancing the amounts of reduced glutathione in these cells. Interestingly, the antioxidant capability of *Spirulina platensis* can be heightened when subjected to increased environmental stress.⁵¹

Abd El-Baky et al. investigated the potential for enhancing the levels of some bioactive chemicals in *Spirulina platensis* by growing cells in a medium containing different concentrations of hydrogen peroxide (H₂O₂). A beneficial links was discovered between rising H₂O₂ concentrations and higher levels of cellular lipophilic antioxidants (total carotenoids and α -tocopherol) as well as hydrophilic antioxidants (glutathione and ascorbic acid). Furthermore, elevating the levels of H₂O₂ resulted in a significant and consistent increase in the activity of antioxidant enzymes in *Spirulina platensis*. These enzymes include catalase (CAT), peroxidase (PX), superoxide dismutase (SOD), and ascorbate peroxidase (APx). Therefore, *Spirulina platensis* has the potential to be beneficial in the treatment of

diseases that are exacerbated by reactive oxygen species (ROS), as well as in the development of

innovative therapies for neurological disorders like Alzheimer's or Parkinson's disease.⁵²



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Figure 3. Spirulina has many health benefits, including antioxidant, immunomodulatory, anti-inflammatory, anticancer, anti-viral, and anti-bacterial activities, as well as positive effects on hyperlipidemia, malnutrition, obesity, and diabetes.

Konicůková et al. (2014) revealed similar findings, wherein they investigated the anticancer properties of *Spirulina platensis* using in vitro cell-based models. The findings demonstrated that *Spirulina* had both anti-proliferative properties and the ability to suppress the generation of mitochondrial ROS, hence influencing the redox status of glutathione.⁵³ The capacity of spirulina to activate cellular antioxidant enzymes including GPx, GPx-Se, and GR accounts for its significant antioxidant capacity in vitro. Additionally, there is a high correlation between its antioxidant activity and the activity of scavenging enzymes including SOD, CAT, PX, and APx, as well as other antioxidants like GSH and β -carotene. Remarkably, increased environmental stress increases antioxidant activity.

CONCLUSIONS

Spirulina plantensis supplements can be used as an antioxidant supplement, as an alternative in obesity treatment, and to control weight under calorie restriction conditions. *Spirulina* antioxidant content has the effect of reducing and preventing inflammation in obesity. *Spirulina* functional compounds, such as phenolics and ficocyanins, have anti-inflammatory effects that help modulate the inflammatory response. In addition, *Spirulina*'s antioxidant properties, including its ability to scavenge free radicals, have been linked to its anti-inflammatory effects, making it effective in controlling and improving the inflammatory process in obesity.

Overall, *Spirulina*'s antioxidant and anti-inflammatory properties play an important role in reducing inflammation associated with obesity, making it a promising natural intervention for managing obesity-related inflammatory conditions. The causes of obesity are multifactorial, so in obesity management not only make changes in terms of intake, either by consuming spirulina supplements, but to be more optimal it needs to be balanced with increasing physical activity.

REFERENCES

1. Mbogori, T., Kimmel, K., Zhang, M., Kandiah, J. & Wang, Y. Nutrition transition and double burden of malnutrition in Africa: A case study of four selected countries with different social economic development. *AIMS Public Heal.* **7** (3), 425–439 (2020).
2. Muhammed, G. & Kibria, A. Prevalence and factors affecting underweight, overweight and obesity using Asian and World Health Organization cutoffs among adults in Nepal: Analysis of the Demographic and Health Survey 2016. *Obes. Res. Clin. Pract.* 1–8 (2019) doi:10.1016/j.orcp.2019.01.006.
3. Id, Z. J. W., Id, S. N. B., Long, M. W. & Gortmaker, S. L. Association of body mass index with health care expenditures in the United States by age and sex. **097**, 1–10 (2021).
4. Rodgers, A., Woodward, A., Swinburn, B. & Dietz, W. H. Comment Prevalence trends tell us what did not precipitate the US obesity epidemic. *Lancet Public Heal.* **3**, e162–e163

- (2000).
5. Cockerham, W. C. Theoretical Approaches to Research on the Social Determinants of Obesity. *Am. J. Prev. Med.* **63**, S8–S17 (2022).
 6. Romieu, I. *et al.* Energy balance and obesity : what are the main drivers? *Cancer Causes Control* **28**, 247–258 (2017).
 7. Malik, V. S. & Hu, F. B. The role of sugar-sweetened beverages in the global epidemics of obesity and chronic diseases. **18**, (2022).
 8. Aparecida, E. *et al.* Clinical Nutrition ESPEN Sedentary behavior , physical inactivity , abdominal obesity and obesity in adults and older adults : A systematic review and meta-analysis. *Clin. Nutr. ESPEN* **50**, 63–73 (2022).
 9. Loos, R. J. F. & Yeo, G. S. H. The genetics of obesity : from discovery to biology. **23**, (2022).
 10. Emanuela, F. *et al.* Inflammation as a Link between Obesity and Metabolic Syndrome. *J. Nutr. Metab.* **2012**, 7 (2012).
 11. Sean Curley, Julie Gall, PhD. Rachel Byrne, MSc. Laurent Yvan-Charvet, PhD. Fiona C. McGillicuddy, P. Metabolic Inflammation in Obesity—At the Crossroads between Fatty Acid and Cholesterol Metabolism. *Mol. Nutr. Food Res.* **65**, 1–24 (2020).
 12. Elham Alipoor, M. J. H.-A. Obesity Induced Inflammation – A Complex Condition. *Obes. Res.* **2**, 12–14 (2015).
 13. Gregor, M. F. & Hotamisligil, S. Inflammatory Mechanisms in Obesity. (2011) doi:10.1146/annurev-immunol-031210-101322.
 14. Solinas, G. & Karin, M. JNK1 and IKK α : molecular links between obesity and metabolic dysfunction. doi:10.1096/fj.09-151340.
 15. Stienstra, R., Tack, C. J., Kanneganti, T., Joosten, L. A. B. & Netea, M. G. Review The Inflammasome Puts Obesity in the Danger Zone. *Cell Metab.* **15**, 10–18 (2011).
 16. Boura-halfon, S. & Zick, Y. Phosphorylation of IRS proteins , insulin action , and insulin resistance. (2009) doi:10.1152/ajpendo.90437.2008.
 17. Emanuela Lapice, MD Simona Maione, BS Lidia Patti, PHD Paola Cipriano, B. & Angela A. Rivellese, MD Gabriele Riccardi, MD Olga Vaccaro, M. *Abdominal Adiposity Is Associated With Elevated C-Reactive Protein Independent of BMI in Healthy Nonobese People. Cardiovascular and Metabolic Risk* vol. 32 (2009).
 18. Sorokina, M. & Steinbeck, C. Review on natural products databases : where to find data in 2020. *J. Cheminform.* 1–51 (2020) doi:10.1186/s13321-020-00424-9.
 19. Tomas Cerdo, Jose antonio Garcia-Santos, Mercedes G. Bermudez, C. C. The Role of Probiotics and Prebiotics in the Prevention and Treatment of Obesity. *Nutrients* **11**, 1–31 (2019).
 20. Saioa Gómez-Zorita, Jenifer Trepiana, Maitane González-Arceo, Leixuri Aguirre, Iñaki Milton-Laskibar, Marcela González, I. E. & Alfredo Fernández-Quintela, M. P. P. Anti-Obesity Effects of Microalgae. *Mol. Sci.* **21**, 1–17 (2019).
 21. Yang, Y., Du, L., Hosokawa, M. & Miyashita, K. Spirulina lipids alleviate oxidative stress and inflammation in mice fed a high-fat and high-sucrose diet. *Mar. Drugs* **18**, (2020).
 22. Dinicolantonio, J. J., Bhat, A. G. & Okeefe, J. Effects of spirulina on weight loss and blood lipids: A review. *Open Heart* vol. 7 at <https://doi.org/10.1136/openhrt-2018-001003> (2020).
 23. Bernard, S. & Spalding, K. L. Implication of lipid turnover for the control of energy balance. *R. Soc. Publ.* **378**, 1–10 (2023).
 24. Blair, S. N., Hand, G. A. & Hill, J. O. Energy balance : a crucial issue for exercise and sports medicine. *J. Sport Med.* **49**, 970–971 (2024).
 25. Khalil, S. F., Mohktar, M. S. & Ibrahim, F. The Theory and Fundamentals of Bioimpedance Analysis in Clinical Status Monitoring and Diagnosis of Diseases. 10895–10928 (2014) doi:10.3390/s140610895.
 26. Sekar, M. & Thirumurugan, K. Autophagy : a molecular switch to regulate adipogenesis and lipolysis. *Mol. Cell. Biochem.* (2022) doi:10.1007/s11010-021-04324-w.
 27. Machado, S. A. *et al.* Browning of the white adipose tissue regulation : new insights into nutritional and metabolic relevance in health and diseases. *Nutr. Metab. (Lond)*. 1–27 (2022) doi:10.1186/s12986-022-00694-0.
 28. Spencer, M. *et al.* Adipose Tissue Extracellular Matrix and Vascular Abnormalities in Obesity and Insulin Resistance. *J Clin Endocrinol Metab* **96**, 1990–1998 (2011).
 29. Lee, B. *et al.* Adipose Natural Killer Cells Regulate Adipose Tissue Macrophages to Promote Insulin Resistance in Obesity. *HHS Public Acces* **23**, 685–698 (2017).
 30. George Boon Bee Goh, MBBS, MRCP, Kwang Wei Tham, M. Bc. B. *Combating obesity : a change in perspectives. Singapore Medical Journal* (2020) doi:10.1136/bmjopen.
 31. Chen, Y. *et al.* The prevalence and increasing trends of overweight , general obesity , and abdominal obesity among Chinese adults : a repeated cross-sectional study. (2019).

32. Rodrigo, C. P. Current Mapping of Obesity. *Nutr. Hosp.* **28**, 21–31 (2013).
33. Wariri, O. Trends in obesity by socioeconomic status among non-pregnant women aged 15 – 49 y: a cross-sectional , multi-dimensional equity analysis of demographic and health surveys in 11 sub-Saharan Africa. 436–445 (2021) doi:10.1093/inthealth/ihaa093.
34. Tydeman-edwards, R., Cornel, F., Rooyen, V. & May, C. Obesity , undernutrition and the double burden of malnutrition in the urban and rural southern Free State , South Africa. *Heliyon* e00983 (2018) doi:10.1016/j.heliyon.2018.e00983.
35. Yoo, S. Dynamic Energy Balance and Obesity Prevention. 203–212 (2018).
36. Lin, X. & Li, H. Obesity: Epidemiology, Pathophysiology, and Therapeutics. *Front. Endocrinol. (Lausanne)*. **12**, 1–9 (2021).
37. Obri, A. & Claret, M. The role of epigenetics in hypothalamic energy balance control : implications for obesity. **3**, 208–220 (2019).
38. Ye, J. Mechanisms of Insulin Resistance in Obesity. *NIH Public* **7**, 14–24 (2014).
39. Jukaku, S. A. & Williams, S. R. P. The cause of obesity is multifactorial but GPs can do more. *BMJ (Clinical research ed.)* vol. 373 n956 at <https://doi.org/10.1136/bmj.n956> (2021).
40. Russo, L. & Lumeng, C. N. Properties and functions of adipose tissue macrophages in obesity. doi:10.1111/imm.13002.
41. Wang, B. & Trayhurn, P. Acute and prolonged effects of TNF- α on the expression and secretion of inflammation-related adipokines by human adipocytes differentiated in culture. 418–427 (2006) doi:10.1007/s00424-006-0055-8.
42. Naugler, W. E. & Karin, M. The wolf in sheep ' s clothing: the role of interleukin-6 in immunity , inflammation and cancer. 109–119 (2008) doi:10.1016/j.molmed.2007.12.007.
43. Fanale, D., Amodeo, V. & Caruso, S. The Interplay between Metabolism , PPAR Signaling Pathway , and Cancer. **2017**, (2017).
44. Rebecca Wafer, Panna Tandon, J. E. N. M. The Role of Peroxisome Proliferator-Activated Receptor Gamma (PPAR γ) in Adipogenesis : Applying Knowledge from the Fish Aquaculture Industry to Biomedical. *Front. Endocrinol. (Lausanne)*. **8**, 1–10 (2017).
45. Grygiel-górniak, B. Peroxisome proliferator-activated receptors and their ligands : nutritional and clinical implications – a review. 1–10 (2014) doi:10.1186/1475-2891-13-17.
46. Mahdavi, R., Namazi, N., Alizadeh, M. & Farajnia, S. Nigella sativa oil with a calorie-restricted diet can improve biomarkers of systemic inflammation in obese women: a randomized double-blind, placebo-controlled clinical trial. *J. Clin. Lipidol.* (2016) doi:10.1016/j.jacl.2015.11.019.
47. Razmpoosh, E. *et al.* Effects of oral Nigella sativa oil on the expression levels and serum concentrations of adiponectin , PPAR- γ , and TNF- α in overweight and obese women : a study protocol for a crossover-designed , double- blind , placebo-controlled randomized clinical trial. 1–8 (2019).
48. Ostrowska, L., Fiedorczuk, J. & Adamska, E. Effect of diet and other factors on serum adiponectin concentrations in patients with type 2 diabetes. **64**, 61–66 (2013).
49. Marli, M., Karasawa, G. & Mohan, C. Fruits as Prospective Reserves of bioactive Compounds : A Review. *Nat. Products Bioprospect.* **8**, 335–346 (2018).
50. Lee, E. H., Park, J.-E., Choi, Y.-J., Huh, K.-B. & Kim, W.-Y. A randomized study to establish the effects of spirulina in type 2 diabetes mellitus patients. *Nutr. Res. Pract.* **2**, 295 (2008).
51. Bermejo-bescós, P., Piñero-estrada, E. & Ángel, M. Toxicology in Vitro Neuroprotection by Spirulina platensis protean extract and phycocyanin against iron-induced toxicity in SH-SY5Y neuroblastoma cells. **22**, 1496–1502 (2008).
52. Abd, H. H., Baky, E. & El-baz, F. K. Enhancement of antioxidant production in Spirulina platensis under oxidative stress Enhancement of Antioxidant Production in Spirulina Plantensis Under Oxidative Stress. (2009) doi:10.1007/s11738-009-0273-8.
53. Koníčková, R. *et al.* natural source of bilirubin-like tetrapyrrolic compounds. **13**, 273–283 (2019).