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Mini Review Article

Obesity and oxidative stress intensify psoriasis through activating IL-17/IL-23 pathway

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ABSTRACT

Psoriasis is an autoimmune disease characterized by keratinocyte hyperproliferation and skin thickening. Psoriasis is caused by a complicated interaction between the innate and acquired immune systems. In the skin, this reaction produces abnormal T helper cell (Th1, Th17, and Th23) reactivation. Keratinocyte hyperproliferation is caused by increased cell signaling via cytokines interleukin-17A (IL-17A), IL-17, IL-23, tumor necrosis factor alpha (TNF-α), and interferon-gamma (INF-γ). Obesity, free fatty acids, microorganisms in the skin and digestive tract, free radicals in the body, and the cardiovascular system are also essential variables in psoriasis. Several variables influence the cytokine activation of the IL-17/IL-23 pathway. Obesity, which is marked by changes in lipid profile in psoriasis patients, is linked to increased oxidative stress and the generation of proinflammatory cytokines, both of which can potentially trigger psoriasis relapse. Antioxidant-rich diet and intake can be employed as one of the stages in preventing psoriasis recurrence.

Keywords:
Psoriasis
Autoimmune
Obese
Oxidative stress
IL-17/IL-23 pathway

Introduction

Psoriasis is a chronic autoimmune inflammation characterized by hyperproliferation and thickening of keratinocytes in the epidermis. The body areas that are commonly affected by psoriasis are the knees, elbows, and scalp (Hugh & Weinberg, 2018). The pathogenesis of psoriasis is complex, and the exact mechanism is not fully understood. It involves changes in the innate and acquired immune systems in the form of cellular or humoral responses. Psoriasis is caused by abnormal reactivation of T cells in the skin. The abnormal regulation of T cells is due to changes in the epidermis, innate defense mechanisms, and faulty inflammatory signaling processes (Orsmond et al., 2021). This study will focus in one of psoriasis's inflammation pathway that interleukin-23 (IL-23) activates T helper 17 (Th17) cells to release interleukin-17 (IL-17) (Liu et al., 2020).

The presence of these skin disorders causes the patient to experience emotional changes and social disturbances and reduces the patient's quality of life. The most critical

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risk factor for psoriasis is the presence of genetic background; besides, it can be due to intrinsic and extrinsic factors (Kamiya et al., 2019). Extrinsic factors that trigger psoriasis are mainly environmental, including drugs, mechanical stress, smoking, sun exposure, vaccination, trauma and infection of microorganisms (Kamiya et al., 2019; Lee et al., 2018). The intrinsic factors that trigger psoriasis are oxidative stress, metabolic syndrome disease, central obesity, hyper-triglycerides, hypertension, hyperglycemia, low serum high-density lipoprotein, and tonsilitis (Brandon et al., 2019; Kamiya et al., 2019).

The habit of consuming a diet high in fat, salt, and sugar, with excessive calorie intake, is one of the environmental factors that contribute to the increased prevalence of psoriasis (Kunz et al., 2019). Obesity and metabolic syndrome will result as a result of this. Obesity is a condition in which a person's body weight is abnormally high, and if a person's BMI is greater than 30, he is considered obese (Paroutoglou et al., 2020). Increased intestinal cell permeability and bacterial translocation are associated with obesity conditions brought on by high-fat diets, and this pathway—which also contributes to inflammation in psoriasis—allows IL-23 to trigger Th17 cells in the intestine (Martins et al., 2018). The onset and severity of psoriasis are linked to obesity-related characteristics such as body mass index, waist circumference, waist-to-hip ratio, and weight gain (Aune et al., 2018). Therefore, obesity and psoriasis have a pathophysiological relationship in the chronic inflammatory pathway by producing and exporting proinflammatory cytokines and drugs (Rodríguez-Cerdeira et al., 2019).

When a molecule has one or more unpaired electrons, it becomes a free radical, which is highly reactive and unstable. As a result, free radicals will capture electrons from surrounding molecules to remain stable, leading these molecules to lose electrons and transform into free radicals (Phaniendra et al., 2015). The electron capture chain reaction will harm the cells. The body generates the majority of reactive oxygen species (ROS) in mitochondrial peroxisomes, cytochrome P450, and other cellular elements. Furthermore, in a hypoxic environment, mitochondria can create nitric oxide (NO), which results in the formation of Radical Nitrogen Species (RNS). Excessive levels of free radicals, also known as ROS/RNS, can cause oxidative stress and trigger the creation of new reactive species which can alter and damage lipids, proteins, and DNA (Ahmadinejad et al., 2017)Alzheimers disease, Parkinsons disease, cancers, etc. Here, we discuss the significance of oxidative conditions in different disease, with the focus on neurodegenerative disease including Parkinsons disease, which is mainly caused by oxidative stress. Reactive oxygen and nitrogen species (ROS and RNS, respectively. Additionally, elevated ROS production affects the antioxidant system and inflammatory pathways in the pathology of psoriasis. ROS are often linked in obesity. Psoriasis pathogenesis is influenced by oxidative stress by Th1 and Th17 cytokines.

Figure 1 illustrates the association between extrinsic (environment) and intrinsic (genetic and obesity) factors on the recurrence of psoriasis. This article comprehensively discusses the connection between oxidative stress-induced obesity and the activation of psoriasis in the IL17/IL23 pathway. It will also discuss about a diet and intake rich in antioxidants to prevent psoriasis recurrence.

Materials and methods

In October 2021, a literature review was undertaken using the keywords psoriasis and pathophysiology, psoriasis and pathogenesis, psoriasis and risk factors, psoriasis and genetics, psoriasis and obesity, psoriasis and oxidative stress, psoriasis and antioxidant in the PubMed and Scopus Elsevier database. The tail tracing method was also used in the bibliography of chosen papers to perform a literature review on articles written after 2015.

Pathogenesis of Psoriasis

The pathogenesis of psoriasis associated with oxidative stress, immune system dysfunction, angiogenesis and neuropeptides. Immune system dysfunction is caused by increased cell signaling through chemokines and cytokines, ultimately resulting in the buildup of keratinocytes. Psoriasis can also be caused by excessive induction of fibronectin (cell adhesion molecules for adhesion to collagen or proteoglycans, which play a role in tissue repair, embryogenesis, blood clotting and migration and cell adhesion) (Chhabra et al., 2022; Vičić et al., 2021).

At first, when the environmental factors stress keratinocyte cells, it will also trigger the genotype to activate. Stressed keratinocyte cells will cause the secretion of antimicrobial peptides and proteins (AMPs) such

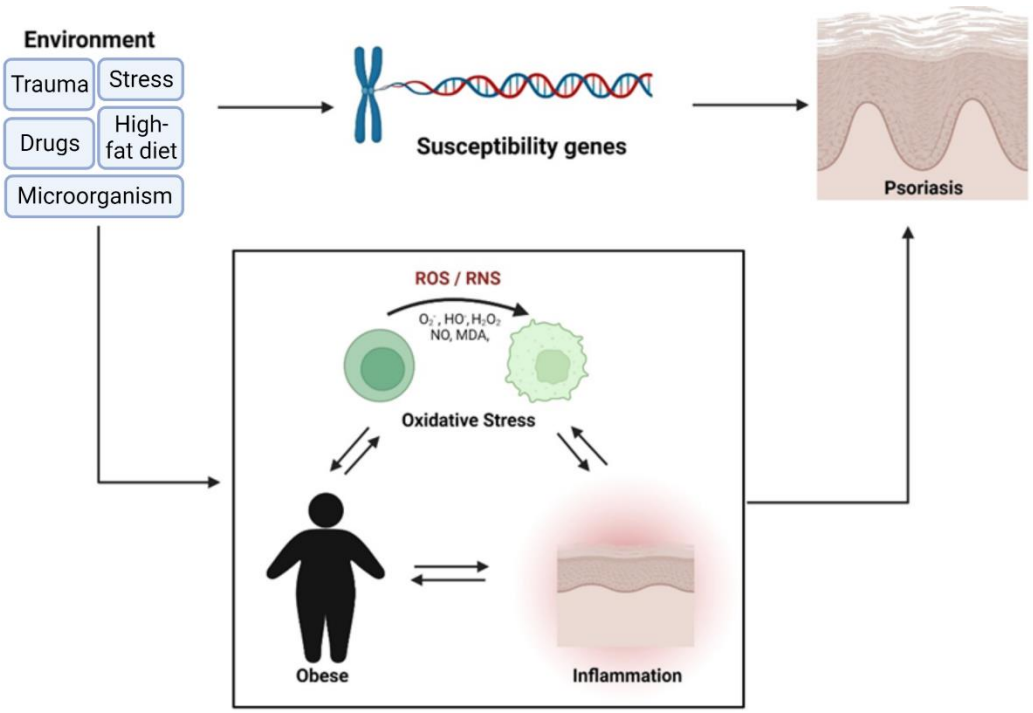

FIGURE 1. Potential contribution of obesity and oxidative stress mechanism in the pathogenesis of psoriasis. Created with BioRender.com.

as cathelicidin (LL-37), β-defensin and S100 proteins (Rendon & Schäkel, 2019). LL-37 is expressed in keratinocyte cells in the skin. LL-37 is required during enzymatic processes by kallikreins in keratinocytes and protease 3 in neutrophils (Chinnappan & Harris-Tryon, 2021). Then the induced DNA and LL-37 will form a complex that causes the activation of dendritic cells to secrete type I IFN (IFN-α and IFN-β) (Chinnappan & Harris-Tryon, 2021; Takahashi & Yamasaki, 2020)neutrophils, dendritic cells, and keratinocytes. Antimicrobial peptides (AMPs. Activated dendritic cells move to the lymph nodes and induce differentiation of T cells. In the presence of IL-12, Th cells will differentiate into Th1 cells, and in the presence of IL-23, Th cells will differentiate into Th17 and Th22 (Armstrong & Read, 2020). Th1 and Th17 cells move to the skin tissue and act as autoantigens. Th1 cells secrete tumour necrosis factor α (TNF-α) and IFN-γ, while Th17 cells secrete IL-17A, IL-17F and TNF-α. The cytokines produced by these two cells will activate and increase keratinocyte proliferation (Armstrong & Read, 2020; Ogawa et al., 2018). In addition, Th17 and Th22 cells secrete IL-22 which will cause an inflammatory cascade in keratinocyte cells, which can also cause keratinocyte proliferation, erythema, and skin thickening (Armstrong & Read, 2020).

Genetics in Psoriasis

One of the leading causes of psoriasis is genetic inheritance, which is based on epidemiological and heritability studies. It is estimated that 60-90% of psoriasis conditions are due to these genetic factors (Mahil et al., 2015). With the research on genotyping technology that facilitates genome-wide association studies (GWAS), genetic markers associated with psoriasis can now be identified. Multiple areas on many chromosomes are involved in the genetics of psoriasis, and at least 16 distinct loci, spread across several chromosomes, play a role in the etiology of psoriasis (Gunter et al., 2019). The psoriasis susceptible region (PSORS), which includes PSORS1 to PSORS9, contains numerous loci vulnerable to psoriasis, while other loci are not positioned.

PSORS1 is found on chromosome 6p21.3, which also contains HLA-C sections for MHC class I protein-coding, stem cell transcription factor (OTF3), and embryonic phase cell growth regulator (TCF19), and coiled-coil α-helical rod protein 1 (CCHCR1). Corneodesmosin, a desmosome protein involved in epidermal cell cohesion and desquamation, is one of the psoriasis genes that target the HLA-C area. Corneodesmosin overexpression is

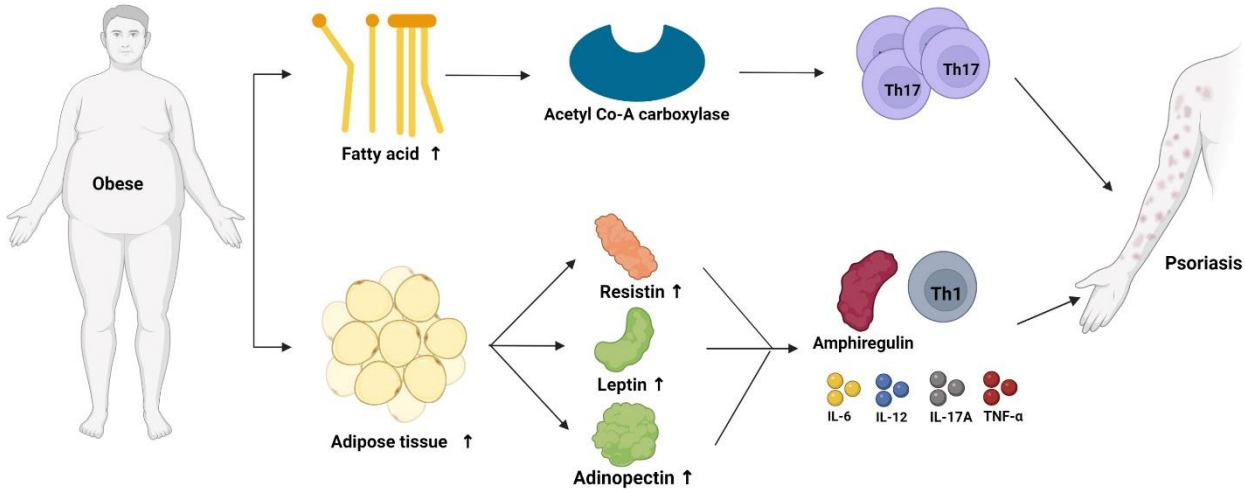

FIGURE 2. The correlation between obesity and psoriasis. Created with BioRender.com.

only detected in psoriasis and not in other inflammatory skin conditions like atopic dermatitis. HCR is a crucial protein in constructing tissues associated with the skin, causing trichohyalin, myosin, and laminin to be homologous (Capon, 2017; Nedoszytko et al., 2020).

PSORS2 is one of three psoriasis susceptibility genes found on chromosome 17q25. At this locus, the first gene for psoriasis susceptibility is an autosomal dominant gene with high penetration. However, its activation is influenced by environmental circumstances. The second gene, SLC9A3R1 and NAT9, is a scaffold protein that connects the plasma membrane and the cytoskeleton and plays a role in lymphocyte cell activation signal transduction. The third gene at this locus is a weak gene that is found in the third intron of regulatory associated protein of mTOR (RAPTOR), where mTOR (mammalian target of rapamycin) is a protein that regulates cell proliferation, apoptosis, and differentiation, as well as targeting the immunosuppressant rapamycin (Capon, 2017; Nedoszytko et al., 2020). Two loci, PSORS3 and PSORS9, are found on chromosome 4q, on the gene 4q28-4q34, which encodes the psoriasis-susceptible gene interferon regulatory factor (IRF2). The PSORS4 gene, which is found on chromosome 1q21 in the epidermal differentiation complex, is involved in regenerative epidermal maturation and keratinocyte terminal differentiation (Capon, 2017; Nedoszytko et al., 2020). PSORS5 is found on chromosome 3q21, together with SLC12A8, zinc finger protein 148 (ZFP 148), and the cysteine protease inhibitor cystatin A (CSTA) all of which are psoriasis-prone (Nedoszytko et al., 2020). The gene encoding the IL23R receptor is another genetic component that influences the occurrence of psoriasis. Mutations in the caspase recruitment domain 14 (CARD14) gene are also one of the genetic causes of psoriasis—the CARD14 gene functions to encode proteins for phosphorylation of BCL10, promoter of apoptosis and activating NF-ƙB.

The pathogenesis of psoriasis can be split into numerous cytokine signaling routes, including IL-17/IL23 signaling, NF-kB signaling, IFN signaling, antigen presentation, and additional pathways such as skin barrier function, IL-15 signaling pathway, and LRBA signaling (LPS). Toll-like receptors 2 and 3 (TLR 2 and TLR 3) and VEGF (responsive vesicle trafficking, beach and anchor-containing genes) (vascular endothelial growth factor) (Zhang et al., 2019). Several genes must act concurrently and constantly in each cytokine communication route.

Obese in Psoriasis

Increased levels of free fatty acids or their storage in adipose tissue are considered to be correlated with obesity and psoriasis. It impacts inflammation in various direct and indirect ways (Figure 2). Fatty acids will indirectly impact the expression of the enzyme acetyl Co-A carboxylase, which will cause Th17 to differentiate more slowly and interact with keratinocytes (Wong et al., 2019). Fatty acids, particularly saturated fatty acids, can trigger proinflammatory cytokines in human macrophages through de novo ceramide production pathways (Kunz et al., 2019). According to a study conducted on

85 people with psoriasis, the fatty acid patterns are abnormal. Decreased docosahexaenoic acid (DHA) and polyunsaturated fatty acid (PUFA) levels and an increase in the saturated to unsaturated fatty acid (SFA/UFA) ratio have an impact on the recurrence and severity of psoriasis (Myśliwiec et al., 2017).

Adipose tissue stores excess fat intake. White adipose tissue (WAT) and brown adipose tissue (BAT) are the two types of adipose tissue. WAT is usually deposited in intra-abdominal locations such as the intestines and peritoneal areas, whereas BAT is stored chiefly subcutaneously in the buttocks, thighs, and abdomen (Chait & den Hartigh, 2020)namely white, brown, and beige, that reside in various specific anatomical locations throughout the body. The cellular composition, secretome, and location of these adipose depots define their function in health and metabolic disease. In obesity, adipose tissue becomes dysfunctional, promoting a pro-inflammatory, hyperlipidemic and insulin resistant environment that contributes to type 2 diabetes mellitus (T2DM. The dermis of the skin also stores adipose tissue. Adipose tissue also contains mesenchymal stem cells, vascular endothelial cells, nerve cells, macrophages, T cells, B cells, and adipocytes (Wong et al., 2019). Adipocytes in adipose tissue secrete various cytokines to connect with neighboring cells and tissues. Increased cytokines TNF-α, IL-6, and C-reactive protein are linked to increased body weight alone. In addition to TNF-α, IL-1, and IL-6, WAT secretes adipokines and specialized cytokines. Adipokines function in fat and glucose metabolism, blood pressure management, vascular homeostasis, inflammation, and coagulation in the human body (Chait & den Hartigh, 2020)namely white, brown, and beige, that reside in various specific anatomical locations throughout the body. The cellular composition, secretome, and location of these adipose depots define their function in health and metabolic disease. In obesity, adipose tissue becomes dysfunctional, promoting a pro-inflammatory, hyperlipidemic and insulin resistant environment that contributes to type 2 diabetes mellitus (T2DM. By increasing the production of proinflammatory adipokines and lowering the production of anti-inflammatory adipokines, central and visceral obesity affects the activation of inflammation and immunological pathways (Ellulu et al., 2017).

Adipokines such as adiponectin, leptin, and resistin are intimately linked to psoriasis; however, leptin and resistin are proinflammatory adipokines, whereas adiponectin is an anti-inflammatory adipokine (Wong et al., 2019). Adiponectin is an anti-inflammatory cytokine that inhibits keratinocyte hyperplasia in response to IL-17 as well as TNF-α production. Adiponectin levels are low in psoriasis (Kyriakou et al., 2018). Compared to healthy people, the amount of adiponectin in psoriasis patients has declined (Bai et al., 2018). Leptin is an adipokine that regulates hunger, whereas psoriasis patients have greater leptin levels than normal (Dopytalska et al., 2020). Leptin is a proinflammatory cytokine that can increase the amount of Th1 and IL-17A cells in the body (Kyriakou et al., 2018). Leptin also causes fibroblasts to produce IL-6, CXCL-1, and IL-8, which could contribute to the hyperproliferative outbreak shown in psoriasis patients. Furthermore, leptin can cause the production of amphiregulin, an autocrine keratinocyte proliferation regulator (Wong et al., 2019). Resistin is a proinflammatory adipokine correlated with the severity of psoriasis (Kyriakou et al., 2018). Psoriasis patients, like leptin, are seeing an elevation in resistin compared to healthy people (Huang et al., 2015)including psoriasis. In this study we evaluated the significance of serum resistin levels in psoriasis patients using a meta-analysis approach.223 Methods: Relevant articles were retrieved by searching the following English and Chinese databases: Cochrane Library, PubMed, Springer Link, Chinese Biomedical Database (CBM. In addition to altering glucose metabolism, resistin also influences inflammation by promoting the production of IL-6, Il-12, and TNF-α cytokines through the nuclear factor-kB signal pathway in human macrophages and peripheral mononuclear cells (Wong et al., 2019). The cutaneous and systemic secretion of cytokines and adipokines can promote the differentiation and proliferation of keratinocytes and immune cells that induce psoriatic lesions (Kovács et al., 2020).

Obesity-induced oxidative stress

There is a reciprocal connection between obesity and oxidative stress (Colak & Pap, 2021). Oxidative stress conditions are characterized by an increase in reactive oxygen species (ROS) and a decrease in antioxidant defenses, both of resulting in an increase in adipose mass, hepatic steatosis, and insulin resistance. This increases the risk of obesity (Di Domenico et al., 2019). On the other side, fat accumulation (especially visceral adipose tissue) can cause oxidative stress. Obesity affects the

function of antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GSSG-R), and glutathione peroxidase (GSH-Px). Therefore, obesity stimulates the lipid peroxidation reactions of polyunsaturated fatty acids, unsaturated phospholipids, glycolipids, cholesterol, other lipids, and lipid-containing organic compounds in blood, tissues, and cellular membranes. It causes a significant increase in malondialdehyde (MDA) and conjugated dienes, resulting in an increase in oxidative stress and the potential for oxidative damage (Manna & Jain, 2015; Zhu et al., 2006).

Besides, hormonal abnormalities in obesity can also trigger oxidative stress. The hormones in concern include adepsin, adinopectin, angiotensinogen, leptin, and resistin. A decrease in adiponectin in obesity will impact the availability of NO and the production of O2-. Hyperleptinemia can increase ROS levels and monocyte chemotactic protein 1 (MCP1) expression, indicating chronic oxidative stress (Antara & Maliawan, 2022; Zhou et al., 2021).

Oxidative stress in Psoriasis

The existence of free radicals, ROS/RNS, the generation of superoxide anions, and disruptions in the antioxidant balance and oxidative stress markers cause the chronic inflammatory process in the skin of psoriasis. The generation of ROS by keratinocytes, fibroblasts, and endothelial cells can induce chemotaxis in neutrophils (Cannavò et al., 2019; Pleńkowska et al., 2020). Isoprostane serves as a sensitive and specific oxidative stress marker in psoriasis patients. Other markers include oxLDL, MDA, thiobarbituric acid reactive substance (TBARS), peroxide, diene, and total oxidant capacity (TOC), also known as total oxidant status (TOS), and total plasma antioxidant capacity (TAC), also known as total antioxidant status (TAS), total antioxidant response (TAR), antioxidant potential (AOP), or nonenzymatic antioxidant capacity (NEAC) (Peluso et al., 2016).

In patients with psoriasis, the severity of the disease worsens with an increase in serum malondialdehyde and nitric oxide end products and a decrease in erythrocyte-superoxide dismutase activity, catalase activity, and total antioxidant status, indicating a worsening of the disease. Thiol and disulphide levels, reported as biomarkers of total oxidant status, have been shown to rise in inflammatory disorders. Despite the increase in blood disulphide levels in psoriasis vulgaris, indicating a thiol/disulphide imbalance, this does not correlate with the severity of psoriasis (Üstüner et al., 2018).

Oxidative stress in psoriasis alters lipid profiles in patients, leading to increased serum total cholesterol, triglycerides, low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL), and a reduction in serum high-density lipoprotein (HDL) (Jha et al., 2021). Furthermore, oxidative stress in psoriasis decreases folic acid, increases homocysteine, and causes alterations in apolipoproteins by creating MDA and oxidized LDL (Winiarska-Mieczan et al., 2020).

Psoriasis Recurrence Prevention Due to Obesity and Antioxidant Deficiency

Psoriasis recurrence can be affected by obesity and antioxidant deficiency, making dietary interventions a valuable non-pharmacological treatment option. The signs and symptoms of psoriasis can be strongly impacted by diet. It is believed that psoriasis patients' condition improves when they maintain a healthy weight and consume sufficient nutrients. Obesity can be avoided by having a healthy diet (Junior & Silva, 2018).

Psoriasis patients will benefit from consuming antioxidant-rich foods such as fresh fruits and vegetables, tea, coffee, herbs, and spices (Katsimbri et al., 2021). Some vitamins (A, E, and C), carotenoids, and minerals (iron, copper, manganese, zinc, and selenium) are supposed to have antioxidant properties that reduce oxidative stress and ROS generation, especially in systemic inflammation like psoriasis (Kurutas, 2016). Dietary control affects psoriasis redox balance through enzymatic and nonenzymatic mechanisms. Dietary variables also influence DNA methylation levels and reduce proinflammatory cytokines (Winiarska-Mieczan et al., 2020).

Conclusion

Obesity and oxidative stress can trigger psoriasis recurrence. Both affect the induction of Th1 and Th17 cells, which influences the secretion of IL-6, IL-17, TNF-α, and INF-γ, all of which are involved in the pathophysiology of psoriasis. In particular, dietary modification can be considered a non-pharmacological therapy to avoid psoriasis recurrence. The study's limitations include the small population size and the insufficient number of clinical trials on the application of antioxidants to psoriasis patients. Therefore, larger population studies

will be required in the future in order to get uniform and homogeneous data.

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Conflict of interest

Authors declare no conflict of interest.

Ethics approval

There are no ethics approval for this mini review.

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