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Review

The Role of Oxidative Stress in the Induction and Development of Psoriasis

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Abstract

Psoriasis cannot be completely cured and is often difficult to diagnose, which is why the search for new effective therapies and diagnostics is a highly relevant area of research. To identify new therapeutic compounds, the first step is to study the role of various factors underlying the development of psoriasis. One such factor is oxidative stress. In this review, we will consider the role of oxidative stress at different stages of psoriasis development, as well as biomarkers of oxidative stress that can potentially be used in the diagnosis of psoriasis and antioxidants, which are likely to be applied in the treatment of this disease.

Keywords: psoriasis; oxidative stress; skin

1. Introduction

Psoriasis is a chronic non-infectious skin disease with unclear etiology and lack of sufficiently effective therapy [1]. Psoriasis is a global health problem. There are more than 100 million people in the world affected by this disease [1]. Psoriasis is characterized by an unpredictable course of the disease, as well as a high likelihood of developing a number of serious comorbidities including arthritis, Crohn's disease, ulcerative colitis, cardiovascular disease, metabolic syndrome, and depression [1]. Psoriasis has an autoimmune nature, its key feature is the occurrence of stable inflammatory response as a result of increased infiltration of immune cells, which, in turn, leads to increased and uncontrolled proliferation of keratinocytes, which make up to 90% of epidermal cells, present from the basal to the stratum corneum, and are the primary protection of the skin from external factors [2]. The pathogenesis of psoriasis is very complex and is based on the intercellular interaction between keratinocytes, leukocytes, and other types of resident skin cells [2]. At the same time, keratinocytes play an important role both in the initial phase, accelerating inflammation, and during the maintenance phase, contributing to the development of a chronic inflammatory response [3]. The etiology of psoriasis is not completely clear, but includes both hereditary and non-hereditary factors. To date, numerous loci associated with predisposition to psoriasis have been identified, among which PSORS1 locus located on chromosome 6p21 plays the greatest role in predicting the development of this disease [4]. Non-hereditary factors include sunburn, trauma, various infectious diseases, alcohol and tobacco consumption, certain medications, and obesity [4]. Currently, there are no therapeutic agents that can completely cure psoriasis [5]. However, there are drugs that alleviate the condition of patients with psoriasis. The first line of defense for the treatment of mild to moderate psoriasis is the use of topical therapies, among which ointments and creams based on corticosteroids are most commonly used [5]. Phototherapy can also be used to treat moderate and severe psoriasis, which consists in exposing the skin to a certain dose of natural or artificial radiation [6]. For the treatment of moderate and severe psoriasis in the absence of a positive reaction to other drugs, injectable systemic drugs based on steroid hormones, retinoids, cytostatics, as well as biologics are used [6]. Each drug has side effects and should be used with caution, especially systemic drugs, for example, a known side effect of the cytostatic methotrexate is hepatotoxicity [7], for cyclosporine severe side effects include nephrotoxicity and myelosuppression [8] and for monoclonal antibodies immunosuppression may occur, which increases the risk of infection [6]. The existing imperfections of current therapeutic strategies make us think about new options for the treatment of psoriasis, which could level out the key targets of pathological foci of the disease and, thus, stop or even completely cure psoriasis. In this review, we propose to consider oxidative stress (OS), one of the significant pathological conditions of the cell, as a basis for the search for new therapeutic targets for psoriasis.

2. Sources of Reactive Oxygen Species in the Cell

Reactive oxygen species (ROS) are important cell signaling molecules, which, however, at high concentrations can cause severe damage to biological macromolecules and lead to the development of a pathological condition known as OS [9]. OS plays an important role in the pathogenesis of various chronic diseases [10], including psoriasis, which will be discussed in more detail below. At acceptable concentrations, ROS perform an antimicrobial function and is involved in the activation of various important signaling pathways, including cell proliferation and differentiation, induction of apoptosis, and regulation of autophagy [9]. The main types of ROS include superoxide anion radical ($O_2^{\cdot -}$) and hydrogen peroxide (H_2O_2). As a result of the damaging effect of ROS on biological macromolecules, secondary radicals arise that also have oxidative activity, such as 4-hydroxynonenal and peroxynitrite, which lead to the formation of a chain reaction [11]. The main sources of ROS in the cell are mitochondria and NADPH oxidase, an enzyme located predominantly on the plasma membrane of macrophages and catalyzing the formation of $NADP^+$ from NADPH with the formation of extracellular $O_2^{\cdot -}$, which is involved in antimicrobial defense and can act as a signaling molecule, regulating some biological processes including apoptosis, and senescence [11]. In mitochondria, ROS is generated as a by-product in the course of electron transport chain (ETC) reactions occurring on the inner mitochondrial membrane, the final result of which is the formation of macroergic ATP molecules. In mitochondria, ROS are formed as $O_2^{\cdot -}$, which is then converted into H_2O_2 and other oxidative molecules [12]. In the Electron transport chain (ETC), the main sources of $O_2^{\cdot -}$ are complex I, from where ROS are transported to the mitochondrial matrix, and complex III, which produces $O_2^{\cdot -}$ in addition to the matrix into the intermembrane space [12]. Due to the constant generation of $O_2^{\cdot -}$ in mitochondria, there is an antioxidant defense system represented by enzymes that convert highly reactive radicals into neutral molecules. The best-known antioxidant enzymes are glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), and thioredoxin peroxidase [13]. Cellular sources of ROS also include peroxisomes, which perform a large number of metabolic functions:β-oxidation and α-oxidation of fatty acids, metabolism of purines, amino acids. During the reactions taking place in peroxisomes, various ROS and RNS (reactive nitrogen species) are synthesized: O_2, H_2O_2, hydroxyl radical (OH•), peroxynitrite ($ONOO^-$), and nitric oxide (NO) [14]. The main enzymes that catalyze the reactions leading to the formation of ROS in peroxisomes are xanthine oxidoreductase and urate oxidase [14]. Like mitochondria, peroxisomes also have an antioxidant defense system [15]. Thus, ROS are predominantly formed as a by-product during metabolic reactions, so there are also systems in the immediate vicinity that inactivate the oxidative action of ROS. When OS occurs, the antioxidative defense systems are exhausted or they themselves initially undergo dysfunction, as a result of which they cannot adequately resist the spread of OS.

3. Effect of Oxidative Stress on Keratinocytes

OS occurs as a result of an imbalance between the production of ROS and the functioning of the antioxidant system. A decrease in the antioxidant capacity of the cell may result from a decrease in the activity of enzymes of the antioxidant system, including (SOD), catalase (CAT), and(GSH-Px), as well as a decrease in the concentration of compounds that have an antioxidant effect, both endogenous (glutathione (GSH)) and exogenous (carotenoids, tocopherols) [16]. In a mouse model, it was shown that genetic knockout of extracellular SOD led to IL-23-mediated skin inflammation, which was determined by increased accumulation of immune cells: $CD4^+$ T-lymphocytes, $CD11b^+$ macrophages, and $CD11c^+$ dendritic cells, as well as high production of pro-inflammatory cytokines [17]. And in people with psoriasis, there is a decrease in the level of a-tocopherol [18]. Increased ROS production leading to OS in psoriasis can be caused by external factors, primarily ultraviolet radiation [16]. Also, an increase in ROS production may be associated with exposure to toxic substances and their metabolites [19]. It should be taken into account that the described OS inducers are possible factors that increase the risk of developing psoriasis, but they can also cause OS in healthy people who are not predisposed to this type of disease. In addition, it was found that OS affected the formation of a damaged stratum corneum, which was important in the pathogenesis of psoriasis [20]. The development of OS in keratinocytes affects the triggering of the inflammatory response through the impact on several signaling pathways, such as: NF-κB, MAPK and STAT3, which leads to the production of pro-inflammatory cytokines [21]. In a state of OS, keratinocytes release nucleotides and antimicrobial peptides, which contribute to the recruitment of dendritic cells [22]. The described events are initiating steps in the development of an autoimmune reaction in psoriasis. Special attention deserves the ability of ROS to influence lipid metabolism in psoriasis, which causes the formation of products of lipid peroxidation, including oxidized low-density lipoproteins (LDL) [23]. Increased accumulation of LDL leads to the activation of phospholipase A2, whose action is associated with the formation of metabolites of arachidonic acid. However, the most important point is the activation of cGMP during the process of lipid peroxidation with a simultaneous decrease in the level of cAMP, which leads to increased epidermal proliferation observed in patients with psoriasis [24].

4. The Effect of Oxidative Stress on the Triggering of an Autoimmune Response in Psoriasis

The main symptom of autoimmune diseases, including psoriasis, is the destruction of the organism's own intact tissues by the immune system as a result of impaired antigen recognition, during which autoantigens are recognized as foreign. Both innate and adaptive immune cells are involved in the development of an autoimmune reaction in psoriasis [16]. Under conditions of increased OS, keratinocytes begin to secrete proteins into the extracellular space, which are recognized by immune cells as autoantigens. The characterized autoantigens in psoriasis are proteins: LL-37, ADAMTSL5, PLA2G4D, and keratin 17 [25]. Dendritic cells are a key population of immune cells responsible for the development of the autoimmune response in psoriasis. The autoantigens taken up by dendritic cells are fragmented and exposed to the surface of the cell membrane as part of the MHC, which leads to antigen presentation to T-cells. OS also contributes at this stage of psoriasis pathogenesis, since ROS are stimulators of antigen presentation by dendritic cells [26]. Skin dendritic cells are represented by epidermal dendritic cells (called Langerhans cells) and dermal dendritic cells (myeloid and plasmacytoid) [27]. The main pathological population of dendritic cells in psoriasis is myeloid $CD11c^{+}$ $BDCA\text{-}1^{-}$ dermal dendritic cells, the concentration of which is greatly reduced as a result of effective therapy in psoriasis [28]. The imbalance of redox condition in psoriasis is observed systemically, and not only in keratinocytes, which provides additional stimulation to the immune system, primarily by increasing the production of pro-inflammatory cytokines. Thus, through the production of TNF-α and IFNγ by dendritic cells, ROS initiate the proliferation and differentiation of T-helpers, the main populations of which in psoriasis are Th17, Th1 and Th22, which in turn produce such pro-inflammatory cytokines as: IL-17, IL -23, TNF-α, IL-22, IL-26 and IL-29 [16]. The key regulator among them is IL23, which acts on T-cells to increase IL-17 expression and also stimulates natural killer cells and neutrophil production of IL-17, which is the key player in the pathogenesis of psoriasis [16]. The pro-inflammatory cytokines contribute to increased proliferation of keratinocytes, which leads to the development of epidermal hyperplasia, which is one of the significant manifestations in patients with psoriasis [29]. Neutrophils also play a noticeable role in psoriasis, one of the characteristic features of which is the formation of neutrophil extracellular traps (NETs). And if, with infectious diseases, NETs play a positive role, being real savory traps against pathogens, whereas in the case of autoimmune diseases, NETs formation can aggravate the inflammatory state and tissue damage [30]. Some of inflammatory factors are the initiators of NETosis, during which a large amount of ROS is produced, additionally enhancing inflammation. At the same time, ROS play the role of agents which are feedback amplifiers relative to neutrophils: increased ROS levels released together with NETs activate the production of CXCL1/2 and CXCL8 by keratinocytes, which enhance the recruiting of neutrophils into the outbreak of autoimmune inflammation [31]. Schematically, the development of autoimmune response in psoriasis is presented in Fig. 1.

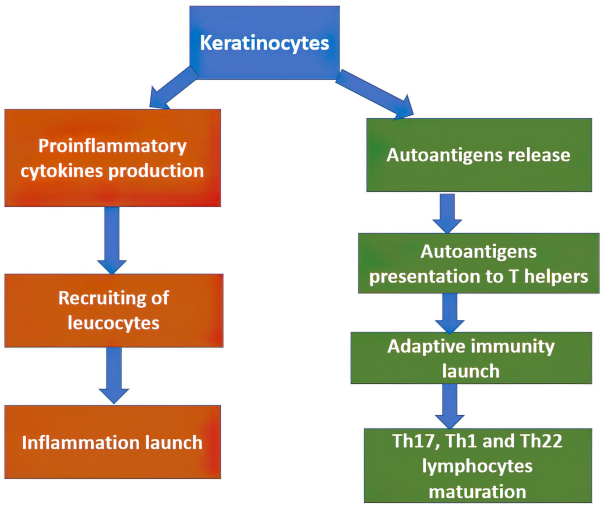

Fig. 1. Two ways of immune cells involvement in the development of psoriasis.

Keratinocytes are cells inducing an autoimmune reaction for psoriasis. In this case, the inducing effect of keratinocytes can be divided into 2 branches. The first is connected with the products of pro -inflammatory cytokines, which lead to the involvement of various leukocytes, such as: macrophages, neutrophils, dendritic cells, lymphocytes and further development with their participation of self -sustaining inflammation. The second branch is associated with the release of autoantigens, which are captured and processed by dendritic cells and are presented on their surface with T-lymphocytes, which cause an adaptive response, in which in psoriasis development Th1, Th17 and Th22 lymphocytes play the major role. At the same time, ROS directly affect the initiation and strengthening of autoimmune processes at each stage of the development of the disease.

5. The Dev1elopment of Chronic Inflammation in Psoriasis as the Result of the ROS Action

Keratinocytes play a direct role in the intensification and subsequent development of the chronic phase of inflammation. As a result of exposure to pro-inflammatory cytokines, keratinocytes, in addition to high proliferative activity, acquire the ability to produce high levels of cytokines, such as: CXCL1/2/3, CXCL8, CCL2 and CCL20, which lead to increased recruitment of leukocytes involved in autoimmune inflammation, including: dendritic cells,

macrophages, neutrophils, and Th17 lymphocytes [3]. In addition, keratinocytes secrete antimicrobial peptides, such as S100A7/8/9/12, hBD2 and LL37, which contribute to additional stimulation of the innate immune system and increased inflammation [3]. Keratinocytes produce new portions of ROS, which act as strong chemoattractants for neutrophils, promoting their invasion and accumulation in skin psoriatic lesions [32]. Neutrophils, like other immune cells in the inflammatory focus, in turn release high levels of ROS, which lead to an even greater increase in OS and the development of the chain reaction of increased inflammation, which eventually develops into a state of chronic inflammation. The general scheme of the pathogenesis of psoriasis based on the effects of ROS is shown in Fig. 2.

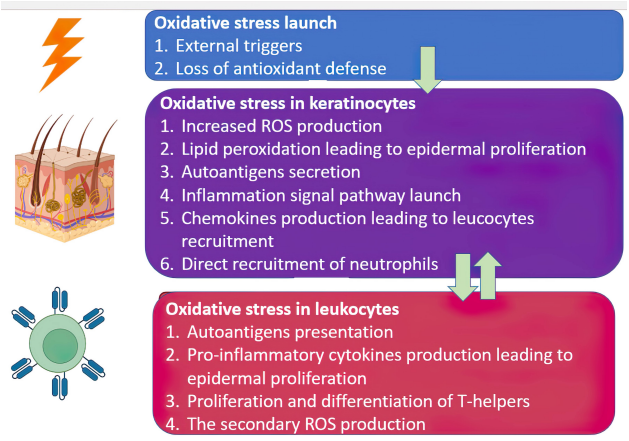

Fig. 2. General scheme of psoriasis pathogenesis based on ROS effects.

External factors (for example, UV) cause an increase in ROS production in keratinocytes and a weakening of antioxidant protection, which initiates OS, epidermal proliferation,the development of inflammation, which subsequently involves leukocytes and autoantigens released by keratinocytes resulting in an autoimmune reaction onset that becomes chronic, enhancing total inflammatory immune response.

6. Biomarkers of Oxidative Stress in Psoriasis

6.1. 8-Hydroxydeoxyguanosine

OS is a concomitant factor in many inflammatory diseases, but the level of OS biomarkers can vary for different diseases, so finding specific biomarkers can contribute to a more accurate diagnosis of psoriasis. Thus, in a study [33], it was shown that patients with atopic dermatitis had a high level of nitrates in the urine, and patients with psoriasis were characterized by a high level of both nitrates and 8-hydroxydeoxyguanosine (8-OHdG). Thereby the potential using of the 8-OHdG detection method as a convenient test for the diagnosis of psoriasis was demonstrated. 8-OHdG is a signal molecule that detects DNA damage [34]. A high level of 8-OHdG in psoriasis can be detected not only in urine, but also in serum, which was shown in a study [35].

6.2. Paraoxonase-1

Another promising biomarker of OS in psoriasis is the enzyme paraoxonase-1 (PON1), which has anti-inflammatory and antioxidant activity [23]. The function of PON1 is associated with the protection of high-density lipoproteins (HDL) from ROS peroxidation [36]. In a study [37], it was shown that the level of PON1 in tissues and serum was significantly lower in patients with psoriasis compared with the control group. It was also found that a low level of PON1 was inversely correlated with the main inflammatory markers: TNFα, IL-1, and CRP [36]. On the other hand, the results of studies on the restoration of the PON1 level in cases of psoriasis therapy were not so unambiguous: in some cases, the PON1 level increased, but in other experiments, therapy did not significantly affect the change in PON activity [37].

6.3. Sirtuin1

Another biomarker of OS in psoriasis is the sirtuin 1 protein (SIRT1) [23]. SIRT1 is an NAD-dependent deacetylase. It inhibits the inflammatory response through interference with MAP or NF-κB signaling pathways, as well as enhanced keratinocyte proliferation and angiogenesis [23]. SIRT1 activation plays an important role in restoring redox balance and mitochondrial function in skin fibroblasts [38]. Increased expression of SIRT1 leads to the activation of the antioxidant enzyme CAT, which reduces OS in the cell [39]. A study [38] found that SIRT1 levels were significantly reduced in patients with psoriasis compared to healthy study participants.

6.4. Thiols/Disulfides

Thiols are compounds containing a sulfidhydryl group; the most common compound of thiols in the cell is GSH [23]. Thiols are indicators of the redox balance inside the cell, which makes them effective markers of OS [23]. The mechanism underlying the indication of OS is based on the reversible reaction of the conversion of thiols into disulfides as a result of exposure to ROS [40]. The thiol/disulfide concentration ratio just makes it possible to determine the level of OS. It has been noted that thiol/disulfide balance is disturbed in psoriasis [41]. Based on this mechanism, a quantitative colorimetric test was developed to quickly determine the level of thiol/disulfide homeostasis in plasma [42]. When testing , serum samples were analyzed from healthy volunteers, patients with degenerative and proliferative diseases. The highest concentration of disulfides was found in patients with proliferative diseases, and the lowest in healthy volunteers.

Table 1. Biomarkers of OS in psoriasis

Biomarkers	Detectable medium	Determination algorithm
8-hydroxydeoxyguanosine	urine and serum	Increased level
Paraoxonase-1	tissues and serum	Decreased level
Sirtuin 1	skin fibroblasts	Decreased level
Thiols	serum	Transformation to disulfides
Biopyrrins	urine	Increased level

6.5. Biopyrrins

In a study [43], compounds of the biopyrrin group were identified as biomarkers of OS in psoriasis. This clinical study was conducted by measuring urinary levels of biopyrrins in patients with chronic plaque psoriasis and healthy controls. Bilirubin, which is a cellular antioxidant, is able to bind to ROS, which leads to the formation of a number of hydrophilic metabolites, which are biopyrrins and are excreted in the urine due to their hydrophilic properties. There was a significant difference between the level of biopyrrins in the control group and patients with psoriasis. Also, a certain level of biopyrrins correlated with the severity of the disease. It should be considered that the described markers of OS are not precisely markers of the development of psoriasis, however, as can be seen from the described studies, the definition of their levels can be used as one of the tools in the diagnosis of psoriasis. Data on biomarkers of OS in psoriasis are summarized in Table 1.

7. Development of Antioxidant Therapy for Psoriasis

7.1. Curcumin

Curcumin is a natural polyphenol found in the roots of the Curcuma longa plant. It is a strong antioxidant and is currently widely used in dietary supplements [44]. At the same time, there are a number of clinical studies that have shown the potential therapeutic efficacy of using curcumin as a therapeutic agent in the treatment of psoriasis. In studies with topical application of curcumin, an improvement in skin lesions was observed in patients with psoriasis [45,46]. Clinical efficacy has also been observed in studies with oral curcumin, including when curcumin is combined with conventional treatments for psoriasis. Thus, in a study [47], therapy of methylprednisolone in combination with oral curcumin was more effective than single therapy of methylprednisolone with the addition of placebo. In addition to a decrease in the Psoriasis Area and Severity Index (PASI), patients treated with curcumin, compared with the control group without curcumin, had a decrease in serum IL-22, however, when comparing IL-17, no differences were observed between groups. At the same time, the anti-inflammatory effect of curcumin, based, among other things, on a decrease in IL-17, was shown in a mouse model [48]. However, there is also evidence from a study in which curcumin had no significant effect in the treatment of patients with moderate to severe psoriasis [49]. The advantage of the potential use of curcumin in the treatment of psoriasis is the minimal side effects noted in several clinical studies [50,51]. It should be noted that the results of the use of curcumin monotherapy for the treatment of psoriasis are available only for phase I and II clinical trials, the results of phase III and IV clinical trials are available for combination therapy with curcumin and conventional treatments. Based on this, curcumin may find use in combination therapy as an adjuvant for the treatment of psoriasis in the coming years, but the introduction into clinical practice as a standalone drug will not happen soon in our opinion.

7.2. Coenzyme Q10 (CoQ10)

Coenzyme Q10 (CoQ10), also known as ubiquinone, is a component of the mitochondrial electron transport chain, as well as a strong antioxidant molecule, and is currently included in many dietary supplements [52]. As with curcumin, the most promising strategy to enter clinical practice is the combined use of CoQ10 in combination with drugs already proven effective in the treatment of psoriasis. For example, in a clinical study [53], it was shown that combined therapy with the biological drug adalimumab used in conjunction with CoQ10 led to an improvement in the correlation between PASI and Dermatology Life Quality Index (DLQI) indicators. At the same time, the combined use of several antioxidant agents may also have a high potential for further use. Thus, in a study [54], after the introduction of the nutritional supplements complex containing CoQ10, vitamin E and selenium to patients with psoriasis, the improvement in the clinical parameters of patients was observed, and the normalization of the value of OS markers was also shown.

7.3. Selenium

Selenium is a trace element widely used in food supplements. It is known that the level of selenium in patients with psoriasis is lower than in healthy people [55]. It was found that selenium is able to modulate the immune response by changing the expression of cytokines and their receptors, and also helps to increase the resistance of immune cells to OS [55]. In the clinical study [56], it was noted that the combined intake of selenium and vitamin E increased the activity of (GSH-Px), an enzyme with antioxidant activity, in serum and whole blood.It should be noted, that taking these supplements did not reduce the severity

of psoriasis. But the prospective study [57] showed that a decrease in serum selenium levels was associated with an increase in the severity of psoriasis. In another prospective study [58], it was found that daily intake of 400 mkg of selenium for 6 weeks led to an increase in the number of $CD4^+$ T-lymphocytes in the skin, but did not lead to a significant improvement in the condition of patients with psoriasis. A potentially important parameter on which drug efficacy may depend is the delivery system. In a study in a BALB/c mouse model, it was demonstrated that application of a selenium nanoparticle gel to skin lesions resulted in a reduction in the severity of psoriasis and also reduced keratinocyte hyperproliferation by inhibiting apoptosis and the inflammatory response by inhibiting the activity of key inflammatory mediators: STAT3, MAPK, Akt [59]. The studies conducted to date on the therapeutic effect of selenium in the treatment of psoriasis have been carried out on a small number of patients, and in some of them selenium has been used in combination with other therapeutic agents, which complicates the understanding of the selenium role in changing of the psoriasis pathogenesis. Thus, selenium can modulate some pathological processes in psoriasis, but its clinical efficacy has not yet been proven.

7.4. Omega-3 Polyunsaturated Fatty Acids

Omega-3 polyunsaturated fatty acids (PUFAs) are the main components of fish oil. The role of these compounds in reducing OS has been demonstrated in various tissues [60,61]. At the same time, the main omega-3 polyunsaturated fatty acids considered for the treatment of psoriasis are docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) [62]. Two ongoing prospective studies have shown that supplementation with omega-3 fatty acids improved PASI scores in patients with psoriasis [63,64]. In a study [65] in patients receiving daily capsules containing a mixture of EPA and DHA, it was shown to reduce itching, erythema and the area of the affected skin. In another clinical study, which also used a mixture of EPA and DHA, in addition to clinical improvement, the mechanisms underlying it were demonstrated: inhibition of the synthesis of leukotriene B4 in peripheral leukocytes *in vitro*, as well as a decrease in the production of malondialdehyde by platelets and a decrease in abnormalities in the structure of the lipid membrane in erythrocytes [60]. In a randomized trial [66] for patients treated with PUFAs as an additional treatment for psoriasis, it was possible to reduce the use of non-steroidal anti-inflammatory drugs (NSAIDs). Also, for these patients, compared with the control group, the levels of leukotriene B4 were reduced. In a clinical study [67], patients with psoriasis used a moisturizer containing linoleic acid and ceramide, which improved the therapeutic effect of topical glucocorticoids and delayed the occurrence of relapses. It has been shown that the use of this agent improves the PASI score. It is known that the imbalance between the formation and destruction of the extracellular matrix (ECM) is an important step in the pathogenesis of psoriasis, so a change in protein metabolism in the ECM can be a sign of both recovery and disease intensification. However, a clinical study on the level of protein biomarkers in the ECM in psoriasis did not reveal any differences between the control group and the group receiving PUFAs as therapy [68]. In addition, a number of studies have shown the effectiveness of combination therapy when taking omega-3 polyunsaturated fatty acids in conjunction with other treatments for psoriasis [62]. Although several studies have shown no clinical improvement in psoriasis patients with DHA and EPA, and some specific side effects such as fishy taste, nausea, and diarrhea, these compounds are promising treatment options for psoriasis [62]. However, phase III and IV clinical trials with a large number of participants and medical centers are required to fully demonstrate their clinical effectiveness.

7.5. Quercetin

Quercetin is a plant flavonoid used in many dietary supplements. Due to its antioxidant and anti-inflammatory properties, quercetin is often considered by researchers as a potential therapeutic agent for a number of inflammatory and autoimmune diseases, including psoriasis. In a study [69], a mouse model of imiquimod-induced psoriasis was created. It was found that administration of quercetin to mice reduced tissue damage and temperature, as well as reduced the inflammatory response, which was measured by reducing the concentration of TNF-α, IL-6 and IL-17 in serum. In addition, antioxidant activity increased due to an increase in the activity of antioxidant enzymes: GSH, CAT and SOD, and the accumulation of MDA (Malondialdehyde) in the skin decreased. The mechanism of action may be based on inhibition of NF-κB, IKKα and RelB expression with an alternative increase in TRAF3 expression. The effectiveness of the model treatment with quercetin was confirmed by an assessment of the reduction in PASI scores. The monocentric clinical study [70] evaluated the protective role of 1% quercetin-based cream in protecting the skin from exposure to various types of irritants. According to the results of the study, it was found that quercetin had a protective effect on the skin during damage associated with UV radiation and the application of irritating compounds, reducing itching, redness and inflammation of the skin, restoring its protective function. Thus, it has been demonstrated here that quercetin can also be used as a prophylactic agent to reduce the risk of developing psoriasis by minimizing effect to external factors on the skin which are the first steps in the induction of psoriasis, as indicated in Fig. 1. The protective function of quercetin against UV exposure to human skin was also demonstrated in a study [71]. This protective response was associated with inhibition of UV-induced expression of matrix metalloproteinase-1 (MMP-1) and cyclooxygenase-2 (COX-2) and blocked UV-mediated collagen degradation in human skin tissues.

Table 2. Antioxidants as the potential drugs for the treatment of psoriasis.

Antioxidant	Influence on the psoriasis pathogenesis	Clinical manifestation	Potential for introduction into clinical practice
Curcumin	IL22 and IL17 (in mouse model) decrease	Improvement in skin lesions, PASI decrease	Use in combination therapy
CoQ10	OS decrease	PASI and DLQI values normalization	Use in combination therapy
Selenium	Increase activity of GSH-Px, $CD4^+$ T-cells increase, Inhibition of apoptosis, Inhibition of MAPK, Akt, STAT3	Not detected	Unknown
PUFAs	Malondialdehyde and leukotriene B4 decrease	PASI decrease, Reducing of itching and erythema, Late relapses, Reducing of NSAIDs taking	Possible use in monotherapy
Quercetin	Increase activity of GSH, CAT and SOD, Inhibition of NF-κB, IKKα and RelB, Inhibition of MMP-1 and COX-2, MDA decrease	PASI decrease, Skin protection from UV and chemical compounds	Possible use as a prophylactic agent
Baicalein	Increase production of cytokines: IL-17A, IL-23, IL-22 b and TNF-α	Decrease in erythema and scaling	Unknown

PUFAs, Polyunsaturated fatty acids; GSH-Px, Glutathione Peroxidase; PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; NSAIDs, Non-steroidal anti-inflammatory drugs; UV, Ultraviolet light; CAT, Catalase; SOD, Superoxide dismutase; MMP-1, Metalloproteinase-1; COX-2, Cyclooxygenase-2; MDA, Malondialdehyde.

Several other molecular targets of quercetin have also been identified, such as protein kinase C delta (PKCδ), Janus kinase 2 (JAK2), and protein activator-1 (AP-1). Quercetin has the potential to be a therapeutic agent in the treatment of psoriasis, but this requires extensive clinical studies in patients with psoriasis, since the protective role of quercetin against skin lesions has been demonstrated either in animal models or in healthy volunteers. In addition, quercetin has poor solubility, which is an additional front for the selection of a suitable delivery system [72].

7.6. Baicalin

Baicalein, another plant flavonoid, is also being considered as a therapeutic agent for psoriasis. Baicalein was investigated in a study similar in design to that previously described for quercetin in an imiquimod-induced mouse psoriasis model [73]. In addition to improving the clinical picture, expressed in a decrease in erythema and scaling, baicalein significantly reduced the production of cytokines responsible for the development of psoriasis: IL-17A, IL-23, IL-22a and TNF-α. These results were confirmed in another study [74], where baicalein was also found to suppress Wnt signaling and inhibit the Th17/IL-17 axis via PPARγ activation. Baicalein is used as part of the "Inflammatory skin disease formula" (ISDF) cream, a Chinese traditional medicine that contains a number of other plant compounds in addition to baicalein [75]. However, at the moment there are no shown results of clinical trials of baicalein as a therapeutic agent for the treatment of psoriasis, which requires further work in this direction.

The effects of the described antioxidants on the course of psoriasis are summarized in Table 2.

8. Discussion

OS is an important factor in the pathogenesis of psoriasis, on the basis of which tools for the diagnosis and therapy of this disease can be developed, as shown in the previous sections. Nevertheless, several important questions remain, the answers to which will help shed light on the further fight against psoriasis, as well as other chronic autoimmune diseases. First of all, an important step is the search for new biomarkers of OS, which can be effectively used as useful tools for differential diagnosis of psoriasis, OS as was shown in the example of 8-OHdG. It is also important to differentiate the quantitative values of the biomarkers content depending on the severity of psoriasis. The creation of these test systems will contribute to more accurate prognosis of the disease, as well as a more informed prescription of therapy, which will help to avoid "unnecessary" side drug effects. It should be noted that the biomarkers presented in this review were selected based on the criterion of a high probability of introduction into clinical practice based on the available studies in our opinion, however, this choice is subjective and does not mean that other compounds are less promising (see review [76]). It is also worth pointing out that despite the fact that the considered biomarkers of OS can be used to diagnose psoriasis, none of them is the specific marker of psoriasis, so they cannot be used as the only tool for diagnosing psoriasis. With regard to antioxidant therapy, it makes sense to understand which combinations of antioxidants and traditionally used drugs provide the best therapeutic effect in the treatment of psoriasis. The use of antioxidant monotherapy currently does not seem appropriate, as stated in the previous section. An important direction is the search for compounds capable of restoring the natural antioxidant function of cells. In this regard, the

question arises: what factors are predominant in the occurrence of OS in psoriasis (external, including exposure to ultraviolet radiation, or internal, associated with a decrease in the activity of antioxidant enzymes)? In the context of the described studies, a promising strategy may be to search for compounds with theragnostic properties, which will allow combining efforts to develop new drugs and diagnostic tests. Also an important direction in the treatment of psoriasis is the search for new therapeutic targets that play a significant effect in the pathogenesis of this disease. An example of these targets is the transcription factor NRF2, the exact mechanism of which in the context of psoriasis requires a thorough study. On the one hand, the NRF2 activates the genes of an antioxidant response (ARE) [77], on the other hand, it triggers the proliferation of keratinocytes in psoriasis [78]. Another issue requiring attention is the degree of development of OS in different types of immune cells, which may allow the identification of new subtypes of leukocytes that play a key role in the pathogenesis of psoriasis. It is also worth paying attention to additional factors that initiate excessive proliferation of keratinocytes, for example, a shift in the prevailing metabolic pathways. In this regard, it is important to consider the relationship between OS and the work of mitochondria under these conditions, as well as to identify the possibility of developing mitochondrial dysfunction and its effect on metabolic changes. This strategy could potentially lead to the discovery of new therapeutic targets in the treatment of psoriasis. So, in the study [79], a change in the content of some metabolites was revealed, as well as the modulation of the main metabolic pathways in response to OS in the skin. So, an increase in the pentose phosphate pathway and β-oxidation of fatty acids and the weakening of the Krebs cycle was noted. The important step in this direction is the development of diagnostic tests to assess oxidative stress directly in damaged tissues of the body. The measurement of oxidative stress markers in biological fluids can often inaccurately correlate with the actual levels of damage and inflammation, since the concentrations of biomarkers in these cases primarily characterize the rate of their formation and excretion. Determination of biomarkers of oxidative damage can give accurate results not only in *in vivo* tests, which can be difficult to implement, but also in biopsy specimens, since, unlike ROS themselves, they have a longer half-life.

9. Conclusions

OS is a detectable phenomenon in cells for various chronic diseases; its development is based on an increase in the concentration of ROS, which shifts the redox balance in cells and leads to a stress state. In psoriasis, ROS are important participants in all stages of pathogenesis, from the initial triggering of OS in keratinocytes to the development of a chronic inflammatory response. Various compounds can be used as markers of OS in psoriasis, while the detection signal indicating the onset of pathology can manifest itself in various ways: an increase in concentration, a decrease in concentration, and also the transformation of the marker into another compound. Several antioxidants are potentially being considered as potential therapies for psoriasis in combination with drugs that have proven efficacy. The use of antioxidants as monotherapeutic agents is unlikely to provide the desired therapeutic effect.

Abbreviations

ROS, reactive oxygen species; OS, oxidative stress; ETC, electron transport chain; SOD, superoxide dismutase; RNS, reactive nitrogen species; CAT, catalase; GSH, glutathione; LDL, low-density lipoproteins; HDL, high-density lipoproteins; MHC, major histocompatibility complex; NETs, Neutrophil extracellular traps; PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; PUFAs, Omega-3 polyunsaturated fatty acids; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MDA, malondialdehyde; MMP-1, metalloproteinase-1; COX-2, cyclooxygenase-2; JAK-2, Janus kinase 2; AP-1, protein activator-1.

Author Contributions

AB and AO designed the review plan. SG and DZ provided help and advice as experts in this phield. IE analyzed the data. VS interpreted data for the clinical and preclinical studies cited in the manuscript. AB, IE, VS and AO wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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