

REVIEW PAPER/PRACA POGLĄDOWA

Participation of reactive oxygen species in the pathogenesis of food allergies

Udział reaktywnych form tlenu w patogenezie alergii pokarmowych

Magdalena Skalska, Paulina Kleniewska, Rafał Pawliczak

Department of Immunopathology, Faculty of Medicine, Medical University of Lodz, Lodz, Poland

ABSTRACT

There has been a significant increase in the incidence of allergic diseases for several decades. There is even a talk of “an epidemic of the 21st century” in relation to, for example, food allergies (FAs). Modern lifestyle and environmental factors contribute to a further increase in disease incidence. The authors proved that the first three years of life are a very important period for the proper development of microflora and taking actions in the context of prevention/therapy; and antibiotic therapy and diet play a significant role in shaping a stable microbiota. An adverse immune reaction to food is referred to as a FA. Immune reactions to food allergens can generally be divided into: IgE-mediated, non-IgE-mediated and mixed. Reactive oxygen species (ROS) are involved in the pathogenesis of FAs. Oxidative stress induces inflammation in tissues; excessive amounts of ROS damage intestinal tissue, disrupt normal cell function, and in eosinophilic esophagitis (EoE) impair the Keap1/Nrf2 pathway.

KEY WORDS

food allergies, reactive oxygen species, oxidative stress, inflammation.

STRESZCZENIE

Od kilku dekad obserwuje się znaczny wzrost zachorowań na choroby o podłożu alergicznym. Mówi się nawet o „epidemii XXI wieku” w odniesieniu do na przykład alergii pokarmowej (AP). Współczesny styl życia oraz czynniki środowiskowe sprzyjają ich dalszemu wzrostowi. Autorzy udowodnili, że pierwsze 3 lata życia stanowią ważny okres dla prawidłowego rozwoju mikroflory oraz podejmowania działań w zakresie prewencji lub terapii, a antybiotykoterapia lub dieta odgrywają znaczącą rolę w kształtowaniu stabilnej mikrobioty. Niepożądana reakcja immunologiczna na pokarm nazywana jest AP. Reakcje immunologiczne na alergeny pokarmowe można ogólnie podzielić na: IgE-zależne, nie-IgE-zależne i mieszane. Reaktywne formy tlenu (RFT) biorą udział w patogenezie AP. Stres oksydacyjny indukuje stany zapalne w tkankach; nadmierne ilości RFT uszkadzają tkankę jelitową, zaburzają normalne funkcjonowanie komórek i w eozynofilowym zapaleniu przełyku (EoE) upośledzają szlak Keap1/Nrf2.

SŁOWA KLUCZOWE

alergie pokarmowe, reaktywne formy tlenu, stres oksydacyjny, stan zapalny.

ADDRESS FOR CORRESPONDENCE

Rafał Pawliczak MD, PhD, Department of Immunopathology, Faculty of Medicine, Medical University of Lodz, 7/9 Zeligowskiego, 90-752 Lodz, Poland (Bldg 2 Rm 177), e-mail: rafal.pawliczak@csk.umed.lodz.pl

ADVERSE REACTION TO FOOD – WHAT ARE FOOD ALLERGIES? CLASSIFICATION OF FOOD ALLERGIES

The term “food allergy” is used to describe an unfavorable health effect resulting from a specific immune response that recurrently occurs after exposure to a particular food. Together with eczema, allergic rhinitis and asthma, food allergies are among the symptoms of the so-called atopic march [1]. Depending on the pathological immune mechanism which underlies food allergies, they can be classified into three types (Table 1).

EPIDEMIOLOGY OF FOOD ALLERGIES

Practically any type of food can cause an allergic reaction, but some foods are considered to be those that cause the most allergic reactions [1]. It is considered that more than 90% of food allergies (FAs) are caused by the so-called “big eight”, with the prevalence of these allergies varying in the general population [2]. The group includes the following foods: eggs (1.3–1.6%), cow’s milk (1%), peanuts (0.6–1.5%), tree nuts (4.9%), wheat (0.2–1%), fish (5–7%), shellfish (0.5–2.5%) and soybean (0.3%) [2]. In clinical practice, IgE-mediated allergy is more common. It is estimated that 1 in 10 adults and 1 in 12 children in the UK suffer from this type of allergy [3].

PATHOGENESIS OF FOOD ALLERGIES

An allergic reaction to a food allergen occurs mainly through the digestive tract, but it may also occur through contact with the skin or occasionally through the respiratory tract [4]. Allergic reactions to food are mainly caused by protein allergens, with the exception of the carbohydrate galactose- α -1,3-galactose (α -gal) [5]. Due to the involvement of immunoglobulin E (IgE), food allergies can be divided into: IgE-dependent, IgE-independent and partially IgE-dependent [6]. The group of IgE-related allergies is the most commonly recognized form of FA, characterized by the rapid onset of symptoms following the consumption of a specific food. This group is classified as type I allergic reaction, also known as immediate type reaction [5]. IgE is the primary antibody associated with FA, and its presence is a characteristic feature of progressive allergic sensitization. In the FA mechanism, Th2 lymphocytes are activated and cytokines are released, supporting the proliferation of B lymphocytes, switching antibody classes towards IgE and differentiating B lymphocytes into antibody-secreting plasma cells [4]. IgE has a strong affinity for Fc ϵ R1 receptors on the surface of mast cells and basophils [7]. These cells contain histamine and are capable of producing strong lipid mediators, including prostaglandins and leukotrienes. The release of these compounds from cells results in symptoms charac-

TABLE 1. Classification of food allergies and their characteristics [1]

Type of food allergies	Immunoglobulin (Ig) E-mediated	Non-IgE mediated (cell mediated)	Mixed (IgE- and cell-mediated)
Related diseases	Acute urticaria, anaphylaxis, pollen – food syndrome	Food protein – induced allergic proctocolitis of infancy, food protein – induced enterocolitis syndrome (FPIES), pulmonary hemosiderosis, celiac disease	Eosinophilic gastroenteritis, eosinophilic esophagitis (EoE), atopic dermatitis
Mechanisms	Type I hypersensitivity, prior exposure to the triggering agent (food allergens) is required – sensitization. Reactions following sensitization occur immediately, causing activation of mast cells and basophils. These cells release histamine, tryptase, prostaglandins and leukotrienes. These mediators recruit cells, like eosinophils, and lead to inflammation.	These reactions occur slower and are mainly driven by T lymphocytes, but also macrophages, eosinophils or neutrophils.	Combination of IgE-mediated and non-IgE-mediated reactions. For example, in EoE food allergens evoke type 2 T helper lymphocyte-mediated reactions. T helper produce interleukins: 5, 13 and eotaxin-3. These factors recruit eosinophils to the esophagus and cause local inflammation.

teristic of allergy, such as tissue swelling, drop in blood pressure and bronchial narrowing [8]. The production of leukotrienes, platelet-activating factor and interleukins: 4, 5 and 13 maintain inflammation in the body [6].

CHARACTERISTICS OF REACTIVE OXYGEN SPECIES

Oxygen (O_2), found in the atmosphere, is one of the most important components that sustain life in organisms. Reactive oxygen species (ROS) is the term used to describe partially reduced oxygen metabolites [9]. Depending on the number of unpaired electrons present on the outer shell, ROS can be classified into radical: superoxide anion ($O_2^{\cdot-}$), hydroxyl radical (OH^{\cdot}), hydroperoxide radical (HO_2^{\cdot}), peroxy radical (ROO^{\cdot}), alkoxy radical (RO^{\cdot}), and non-radical forms: hydrogen peroxide (H_2O_2), singlet oxygen (1O_2), ozone (O_3), hypochlorous acid (HOCl) (Tables 2 and 3) [10–14]. These molecules are most often formed as a result of metabolic changes taking place in the body, most notably the four-step reduction of O_2 to water molecule (Figure 1).

These compounds are highly reactive, under the influence of endogenous and exogenous stimuli, they cause

TABLE 2. Reactive oxygen species (ROS), examples of radicals and other non-radicals

Name	Symbol
Radicals:	
Hydroxyl radical	OH^{\cdot}
Superoxide anion	$O_2^{\cdot-}$
Hydroperoxide radical	HO_2^{\cdot}
Peroxy radical	ROO^{\cdot}
Alkoxy radical	RO^{\cdot}
Other non-radical ROS:	
Hydrogen peroxide	H_2O_2
Singlet oxygen	1O_2
Ozone	O_3
Hypochlorous acid	HOCl

the oxidation of intracellular macromolecules, making them the key element regulating cellular activity [9, 10]. ROS, initially considered potentially harmful byproducts of aerobic metabolism, are one of the elements of the intracellular signal transduction system and actively participate in the body's defense against infectious agents. A proper level of ROS is essential for cellular processes, like cell growth, signaling and apoptosis, however, an excessive amount of ROS contributes to exacerbating inflammation, ROS accumulation due to the inability to neutralize them, and ultimately to apoptosis and tissue damage [9].

During inflammation, activated macrophages and neutrophils can produce large amounts of peroxides and

TABLE 3. ROS synthesis reactions

ROS	Reaction
Radicals:	
$O_2^{\cdot-}$	Enzymatic reaction (e.g. xanthine oxidase) [10] $O_2 \xrightarrow{\text{Xanthine oxidase}} O_2^{\cdot-}$
	Nonenzymatic reaction [10] $O_2 + e^- \rightarrow O_2^{\cdot-}$
	Autooxidation [10] $O_2 + Fe^{2+} \rightarrow O_2^{\cdot-} + Fe^{3+}$
OH^{\cdot}	Fenton reaction [11] $H_2O_2 + Fe^{2+} \rightarrow OH + OH^{\cdot} + Fe^{3+}$
	Haber-Weiss reaction [12] $H_2O_2 + O_2^{\cdot-} \rightarrow OH + OH^{\cdot} + O_2$
HO_2^{\cdot}	$O_2^{\cdot-} + H^+ \rightarrow HO_2^{\cdot}$
Other ROS:	
H_2O_2	Dismutation reaction of $O_2^{\cdot-}$ catalyzed by superoxide dismutase (SOD) [13, 14] $2O_2^{\cdot-} + 2H_2O \rightarrow H_2O_2 + O_2 + 2OH^-$
1O_2	$HOCl + H_2O_2 \rightarrow ^1O_2 + H_2O + Cl^- + H^+$ [11]
HOCl	Generated by neutrophils during inflammation in the reaction catalyzed by myeloperoxidase (MPO) [10]: $H_2O_2 + Cl^- \rightarrow H_2O + HOCl$

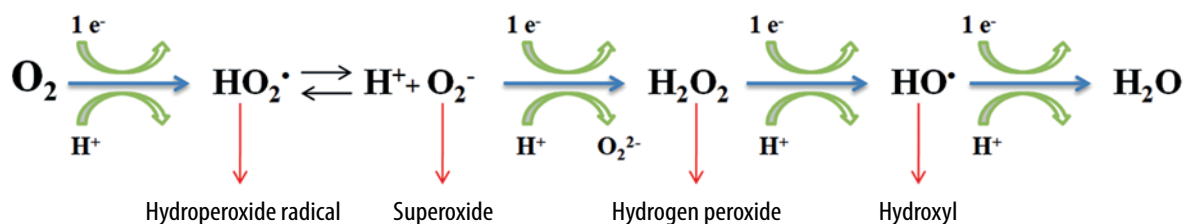


FIGURE 1. Four-step reduction of O_2 to H_2O

their derivatives, which maintains their high concentration in the vicinity of these cells. Massive overproduction of ROS is sometimes referred to as an “oxidative burst”, which is the first line of defense against pathogens. One of the most important enzymes involved in the body’s defense function is NADPH oxidase, which participates in the generation of ROS [15, 16]. Too high concentrations of ROS can damage cellular structures, DNA molecules, lipids and proteins. The highly reactive hydroxyl radical has the ability to react with all components of the DNA molecule, causing damage to the nitrogenous bases and the sugar ring itself. Any disruption of the DNA structure may lead to mutagenesis, carcinogenesis, or apoptosis of the entire cell. ROS react equally strongly with polyunsaturated fatty acid residues of phospholipids, which are extremely susceptible to oxidation. Peroxyl radicals (ROO[•]) produced by lipid peroxidation lead to the production of free malonaldehyde and 4-hydroxynonenal, which have a mutagenic effect. The side chains of all amino acid residues of proteins are particularly sensitive to oxidation [15, 16]. Reactive oxygen species are also involved in the pathogenesis of food allergies.

OXIDATIVE STRESS IN ALLERGIES. INVOLVEMENT OF ROS IN THE PATHOGENESIS OF FOOD ALLERGIES

It is well known that oxidative stress, a consequence of excessive ROS generation and failure of the body’s antioxidant system, is one of the main factors associated with occurrence of chronic inflammation. Many contemporary scientific reports further confirm that oxidative stress plays a significant role in the development and maintenance of the chronic inflammatory process in the course of atopic dermatitis, allergic rhinitis, asthma and also food allergies (Figure 2). During allergy attacks, large amounts of oxidative compounds are produced in local tissues, which can exceed capacity of antioxidants and thus induce disorder in local tissue cells [17].

ANTIGEN TOLERANCE AND ANTIOXIDANT RESPONSE IN THE INTESTINES

The gastrointestinal tract is the largest immune organ in the human body, which is exposed to a huge number of

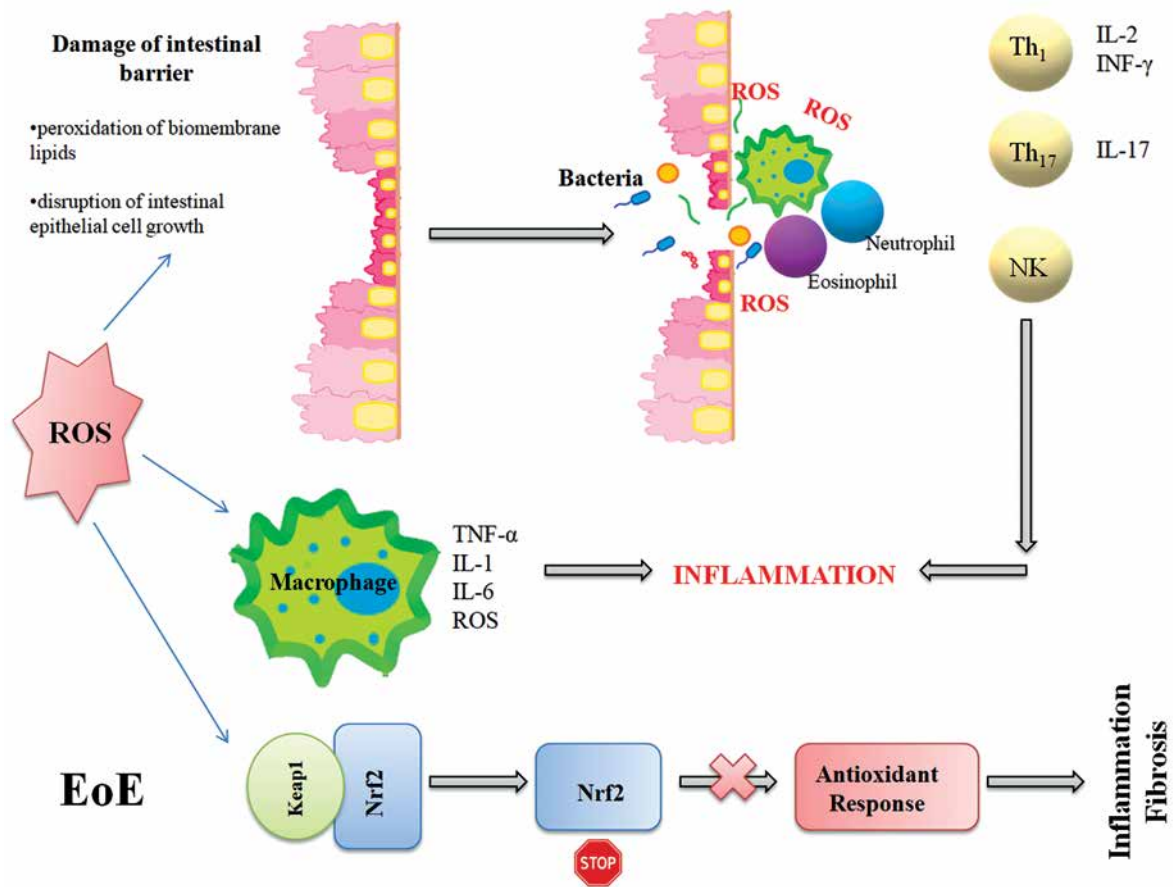


FIGURE 2. Participation of ROS in the pathogenesis of food allergies

foreign antigens every day. As such, food allergy is considered a failure to generate oral tolerance, or a failure of oral tolerance mechanisms. In overall terms, tolerance can occur in any tissue, but antigens in the gut are under specialized pathways that lead to oral tolerance, which includes suppression of both cellular and humoral immune responses [18]. Tolerance to food antigens can be induced through the presence of various immune cells and tissues in the intestinal mucosal system. Intestinal epithelial cells (IECs) are tightly connected, forming the intestinal mucosal barrier. In addition, various secretory cells are found among IECs, such as goblet cells – they secrete mucin, which protects IECs and effectively prevents food antigens from penetrating the intestinal mucosa. Dendritic cells (DCs) and macrophages play an important role in antigen presentation – they interact with antigens to help activate regulatory T cells, which can promote immune tolerance and suppress food allergy [19]. The integrity of this barrier is important and depends on both physical and immunological components, for example, mucus, epithelial connections and secretory IgA. Small amounts of antigen cross the intestinal barrier intact, and tolerance mechanisms allow it to do so harmlessly. However, excessive permeability can increase the antigen load and be harmful [18]. The human body is equipped with a number of antioxidant mechanisms to balance ROS. Antioxidant defenses include enzymatic and non-enzymatic antioxidants. Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px) and glutathione reductase (GR) are enzymatic antioxidants that are not specific to the intestines alone, but to the entire body. Non-enzymatic antioxidants, on the other hand, include the following compounds: glutathione, melatonin and irisin [20].

OXIDATIVE STRESS IN THE INTESTINES, ROS AND FOOD ALLERGIES

Oxidative stress damage mainly manifests itself as damage to proteins, lipids and DNA. As fundamental components of tissues and organs with important physiological functions in organisms, proteins are important target molecules for ROS attack. ROS can modify amino acid residues, cross-link proteins, and damage peptide chains [20]. Due to the strong affinity between ROS and unsaturated fatty acids in the phospholipid bilayer, peroxidation of biomembrane lipids plays a significant role in oxidative stress-induced damage, as it can lead to changes in biofilm structure, permeability and fluidity, finally destroying normal cellular functions. During oxidative stress, the redox status of glutathione and glutathione disulfide impacts the growth cycle of intestinal epithelial cells. The consequence of abnormal proliferation, growth

stagnation, differentiation and apoptosis is intestinal cell damage and damage to the intestinal barrier [20]. ROS are one of the causes of the inflammatory response. Macrophages and neutrophils infiltrating the gut can produce reactive oxygen species, leading to more severe oxidative stress and inflammation. This is the cause of positive macrophage feedback and a key reason for the difficulty in mitigating intestinal inflammation [20]. ROS can also mediate the maturation and function of dendritic cells. These cells stimulated with excess ROS can stimulate T-cell proliferation more than normal dendritic cells [19].

Macrophages are cells that aim to eliminate various types of pathogens. Incoming activated macrophages secrete very large amounts of ROS and pro-inflammatory cytokines such as tumor necrosis factor α (TNF α), interleukin (IL)-1, and IL-6, which increase inflammation [21]. The gastrointestinal tract as a barrier, also protects against the entry of bacteria into the intestinal lumen, affected by oxidative stress “leaky gut” facilitates translocation of bacteria into the intestinal lumen. To induce antimicrobial defense, there is an activation of phagocytes and macrophages, which generate even more ROS, effector cells (Th1, Th17, NK) secrete pro-inflammatory cytokines, which perpetuates inflammation [22].

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease of allergic origin that includes transmural inflammation of the esophagus and fibrosis, which eventually leads to esophageal stricture. The clinical manifestation of EoE includes dysphagia [23]. One of the most important transcription factors regulating oxidative stress is nuclear factor E2-related factor 2 (Nrf2). When the redox balance is maintained, Nrf2 can bind to Kelch-like ECH-associated protein 1 (Keap1), which leads to ubiquitination and degradation of Nrf2 thus maintaining low levels of this factor in the cell. During oxidative stress, Nrf2 degradation is impaired, the factor accumulates in the cell nucleus, and antioxidant mechanisms are activated. This pathway (Keap1/Nrf2) is mainly responsible for regulating antioxidant enzymes such as SOD, GSH-Px or CAT [20]. In EoE, Nrf2 is suppressed, which weakens antioxidant defense. The cytokines generated by immune cells, IL-5, IL-13, TNF- α and transforming growth factor β (TGF- β), induce large amounts of ROS. Accumulation of excess ROS and an inefficient antioxidant response contribute to increased inflammation and fibrosis [23].

SUMMARY

Nowadays, the prevalence of food allergies and food intolerances is increasing. Food allergy does not manifest only in the gut, it also affects the skin, respiratory tract and cardiovascular system. It is clear that ROS also have a role in the pathogenesis of food allergies. Among other

things, oxidative stress leads to damage and impairment of the intestinal barrier, lowered immunity and increased inflammation. However, there is still a need for a more detailed understanding of the relationship between ROS, oxidative stress and food allergy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Cosme-Blanco W, Arroyo-Flores E, Ale H. Food allergies. *Pediatr Rev* 2020; 41: 403-15.
2. Zhao X, Hogenkamp A, Li X, et al. Role of selenium in IgE mediated soybean allergy development. *Crit Rev Food Sci Nutr* 2022; 63: 7016-24.
3. Warren CM, Jiang J, Gupta RS. Epidemiology and burden of food allergy. *Curr Allergy Asthma Rep* 2020; 20: 6.
4. Xu R, Lu R, Zhang T, et al. Temporal association between human upper respiratory and gut bacterial microbiomes during the course of Covid-19 in adults. *Commun Biol* 2021; 4: 240.
5. Sampson HA, O'Mahony L, Burks AW, et al. Mechanisms of food allergy. *J Allergy Clin Immunol* 2018; 141: 11-9.
6. Wasserman S, Begin P, Watson W. IgE-mediated food allergy. *Allergy Asthma Clin Immunol* 2018; 14: (Suppl 2): 55.
7. Yu W, Hussey Freeland DM, Nadeau KC. Food allergy: immune mechanisms diagnosis and immunotherapy. *Nat Rev Immunol* 2016; 16: 751-65.
8. Stone KD, Prussin C, Metcalfe DD. IgE mast cells, basophils, and eosinophils. *J Allergy Clin Immunol* 2010; 125 (2 Suppl 2): S73-80.
9. Wang L, Cao Z, Wang Z, et al. Reactive oxygen species associated immunoregulation post influenza virus infection. *Front Immunol* 2022; 13: 927593.
10. Phaniendra A, Jestadi DB, Periyasamy L. Free radicals: properties, sources, targets, and their implication in various diseases. *Ind J Clin Biochem* 2015; 30: 11-26.
11. Kubo D, Kawase Y. Hydroxyl radical generation in electro-Fenton process with in situ electro-chemical production of Fenton reagents by gas-diffusion-electrode cathode and sacrificial iron mode. *J Cleaner Product* 2018; 203: 685-95.
12. Kehrler JP. The Haber-Weiss reaction and mechanism of toxicity. *Toxicology* 2000; 149: 43-50.
13. Dołęgowska B, Błogowski W, Domański L. Association between the perioperative antioxidative ability of platelets and early post-transplant function of kidney allografts: a pilot study. *PLoS One* 2012; 7: e29779.
14. Bielski BHJ, Cabelli BH, Arudi RL, Ross AB. Reactivity of HO₂/O₂ Radicals in aqueous solution. *J Phys Chem Ref Data* 1985; 14: 1041-100.
15. Sies H, Berndt C, Jones DP. Oxidative stress. *Annu Rev Biochem* 2017; 86: 715-48.
16. Taylor JP, Tse HM. The role of NADPH oxidases in infectious and inflammatory diseases. *Redox Biol* 2021; 48: 102159.
17. Twardoch AM, Lodwich M, Mazur B. Allergy and oxidative stress. *Ann Acad Med Siles* 2016; 70: 15-23.
18. Bowman CC. Food allergies. In: *Immunotoxicity, Immune Dysfunction and Chronic Disease*. Dietert RR, Luebke RW (eds.). Springer 2012; 127-49.
19. Gu S, Yang D, Liu C, Xue W. The role of probiotics in prevention and treatment of food allergy. *Food Sci Human Wellness* 2023; 12: 681-90.
20. Wang Y, Chen Y, Zhang X, et al. New insights in intestinal oxidative stress damage and the health intervention effect of nutrients: a review. *J Functional Foods* 2020; 75: 104248.
21. Mittal M, Siddiqui MR, Tran K, et al. Reactive oxygen species in inflammation and tissue injury. *Antioxid Redox Signal* 2014; 20: 1126-67.
22. Aviello G, Knaus UG. ROS in gastrointestinal inflammation: rescue or sabotage? *Br J Pharmacol* 2017; 174: 1704-18.
23. Muir AB, Wang JX, Nakagawa H. Epithelial-stromal crosstalk and fibrosis in eosinophilic esophagitis. *J Gastroenterol* 2019; 54: 10-8.