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REVIEW

Omega-3 polyunsaturated fatty acids: a promising approach for the management of oral lichen planus

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Abstract

Background Oral lichen planus (OLP) is a T-cell-mediated inflammatory disease with a risk of malignant transformation. Although the etiology of OLP is still uncertain, growing evidence suggests that oral microbiota, antigen-specific, and non-specific mechanisms are involved in the pathogenesis of OLP. Antigen-specific mechanisms include antigen presentation, T-cell activation, nuclear factor-kappa B signaling pathway, and cytokine secretion, while non-specific mechanisms consist of matrix metalloproteinases (MMP)-9 upregulation, psychological pressure, oxidative damage, aberrant expression of microRNAs (miRNAs), and autophagy. Till now, there is no cure for OLP, and the main purpose of OLP therapy is symptomatic control.

Finding Seafood and its derivative omega-3 polyunsaturated fatty acids (*n*-3 PUFAs) can suppress antigen presentation, T-cell activation, and nuclear factor-kappa B signaling pathway, modulate the overexpressed inflammatory cytokines, inhibit the expression of MMP-9, as well as regulate the expression of miRNAs and autophagy. And they are possible agents for ameliorating psychological disorder and oxidative damage. Moreover, *n*-3 PUFAs supplementation has a beneficial effect on preventing tumorigenesis.

Conclusion *n*-3 PUFAs consumption may provide a non-toxic, inexpensive administration for OLP.

Keywords Omega-3 polyunsaturated fatty acids · Oral lichen planus · T cells · Treatment

Abbreviations

CTLs	Cytotoxic T lymphocytes
DCs	Dendritic cells
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
HPA	Hypothalamic–pituitary–adrenocortical
ICAM-1	Intercellular adhesion molecule 1
INF-γ	Interferon-γ
IL	Interleukin
LFA-1	Lymphocyte function-associated antigen 1
LCs	Langerhans cells
miRNAs	microRNAs
MHC II	Major histocompatibility class II
MMPs	Matrix metalloproteinases
NF-κB	Nuclear factor-kappa B
n-3 PUFAs	omega-3 Polyunsaturated fatty acids
OLP	Oral lichen planus
OPMD	Oral potentially malignant disorder
PPARα	Peroxisome proliferator-activated receptor alpha
ROS	Reactive oxygen species
Th	T helper
TIMPs	Tissue inhibitors of metalloproteinases
TNF-α	Tumor necrosis factor-α

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Introduction

OLP is a chronic immune and inflammatory disease mainly affecting the oral mucosa [1, 2]. The prevalence of OLP in general adult population is 0.5–2% with a female predisposition and children can also be involved [2, 3]. OLP carries a potential risk of malignancy, with an oral squamous cell

carcinoma transformation rate of 0.9–1.1% [4]. OLP classically affects the buccal mucosa, gingiva, and tongue, exhibiting a bilateral and symmetrical pattern [2, 5]. There are six clinical subtypes of OLP: reticular, plaque-like, atrophic, erosive, papular, and bullous [5, 6]. The dysbiosis of subgingival microbiota mainly result in periodontitis [7]. Similarly, the imbalance between protective and harmful bacteria in oral mucosa is associated with the pathogenesis of OLP [8]. On one hand, pathological features show dense subepithelial lymphocytes infiltration and intraepithelial $CD8^+$ cytotoxic T lymphocytes (CTLs) targeting the basal keratinocytes (Fig. 1) [1, 2, 9, 10]. Our group revealed that T helper (Th) 1-type immune response plays a prominent role in the pathogenesis of OLP. The expression of T-bet was related to different clinical features of OLP [11]. Th17 cells with the secretion of interleukin (IL)-17 highlighted its role in the development of different types of OLP [12]. On the other hand, MMP activation, psychological disorder, and oxidative damage are correlated with the exacerbation of OLP [2, 5, 10, 13, 14]. Currently, a permanent cure is not available and corticosteroids are well known as the first-line treatment for OLP. To some degree, long-term use of corticosteroids has side effects, ranging from acne to damage on most major organ systems such as musculoskeletal, gastrointestinal, and cardiovascular system [15]. Thus, it is crucial to find a novel and relatively safe substance for OLP.

Omega-3 polyunsaturated fatty acids (*n*-3 PUFAs) are extracted from transgenic plants, fungi, and other microorganisms but mostly fatty fish [16, 17]. *n*-3 PUFAs and their derivatives, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), were reported to exert anti-inflammatory and immunomodulatory effects through multiple mechanisms [18]. Oral cavity is colonized with microbiomes and changes of these bacteria lead to oral diseases. Usage of DHA with low-dose aspirin influenced the periodontitis which is initiated by bacteria [7]. The T-cell activation can be suppressed by *n*-3 PUFAs through the modulation of plasma membrane microdomains [19, 20]. Consumption of *n*-3 PUFAs is a crucial determinant of inflammatory and immune processes. Omega-3 fatty acids could inhibit the polarization of splenic $CD4^+$ T cells into the inflammatory Th1 and Th17-cell subset [21–23]. Data suggested that *n*-3 PUFAs would be beneficial to inflammation and autoimmune diseases such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis, lupus erythematosus, and multiple sclerosis [24–28]. Of note, omega-3 fatty acids had a psychological-protective role due to their regulatory effects on hypothalamic–pituitary–adrenocortical (HPA) axis [29]. EPA and DHA were able to reduce salivary cortisol in healthy adults and defend against the increased oxidative stress [30, 31]. *n*-3 PUFAs are considered as safety seafood in many aspects [32].

Based on these facts, we speculate that *n*-3 PUFAs may have a therapeutic potency for OLP through antigen-specific and non-specific mechanisms involved in the pathogenesis of OLP.

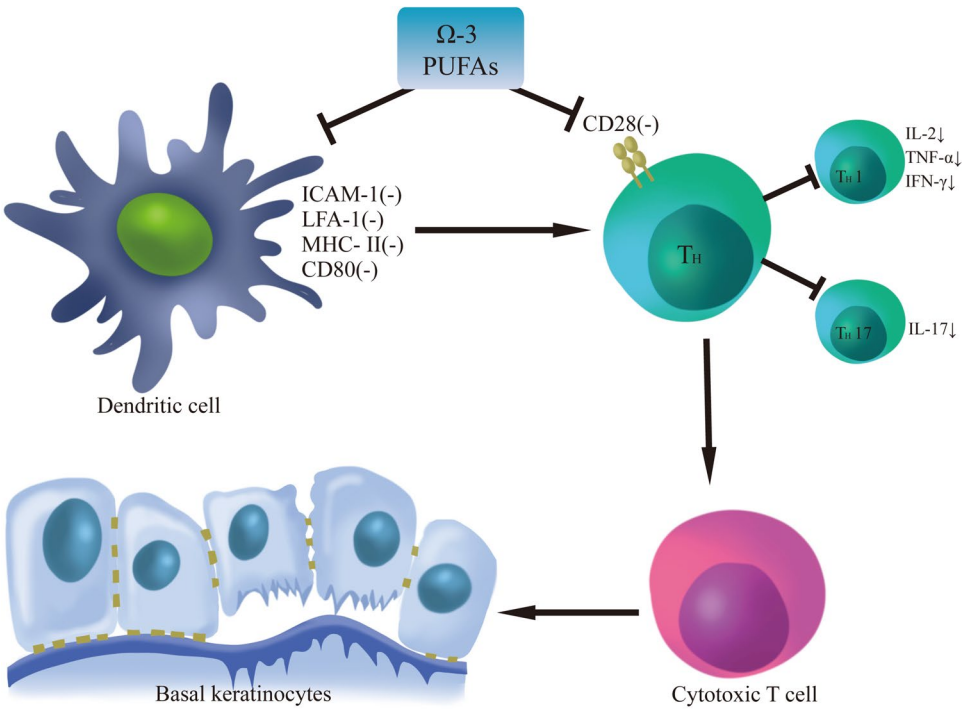

Fig. 1 *n*-3 PUFAs act on the immune cells of OLP. *n*-3 PUFAs could inhibit the expression of ICAM-1, LFA-1, MHC II, and CD80 on DCs, and suppress the expression of CD28 on Th cells, interfering the interaction between dendritic cells and Th cells and further restraining the activation of cytotoxic T cells which kill the basal keratinocytes. *n*-3 PUFAs also could inhibit the development of Th1 and Th17 through down-regulating the production of IL-2, TNF-α, IFN-γ, and IL-17

Status of Omega-3 polyunsaturated fatty acids in oral microbial community

As the entry part of the gastrointestinal tract, oral cavity and its microorganisms are essential to OLP. Streptococcus was decreased and gingivitis bacteria exhibited positive correlations with the levels of infiltrated $CD3^+$, $CD4^+$, and $CD8^+$ cells in OLP lesions [8]. Fusobacterium, Leptotrichia, and Lautropia were abundant in the buccal mucosa of OLP [33]. Fusobacterium nucleatum and Treponema denticola damaged the physical barrier of epithelial cells [34]. Saliva samples of OLP patients were different in the oral microbiota compared to control group, which were recommended as one of the diagnostic tools for OLP [35]. An 1-year clinical trial showed that oral microbial composition was individual, and the balance between health and disease was influenced by oral microorganism of bacteria and fungi, especially Malassezia [36]. 30% of OLP patients suffered oral candidiasis after corticosteroid therapy [37]. These studies emphasized the primary role of oral microbiota in the pathogenesis of OLP.

During a 3-month pilot trial, daily DHA consumption suppressed the Porphyromonas gingivalis growth and decreased the expression of local inflammatory markers [7, 38]. *n*-3 PUFAs as functional foods can be considered as prebiotics, because it shows capability of increasing anti-inflammatory molecules, like short-chain fatty acids [39]. On the other hand, *n*-3 PUFAs are beneficial to preventing chronic inflammatory disease such as inflammatory bowel disease and modulating the microbiota between intestinal wall integrity and host immune cells [16]. 4 g of mixed DHA/EPA supplement (as capsules and functional drink) for 8 week trail increased the amount of Bifidobacterium, Oscillospira, Roseburia, and Lachnospira species, while decreased that of Coprococcus and Faecalibacterium species in human intestinal microbiota [40]. Although the accurate mechanisms that *n*-3 PUFAs regulate the oral microbial community are unknown, *n*-3 PUFAs may affect oral microbial diversity.

Influence of *n*-3 PUFAs on antigen-specific mechanisms of OLP

Effects of *n*-3 PUFAs on antigen-presenting cells

Dendritic cells (DCs) are necessary and sufficient for the activation of naive T cells [41]. In OLP lesions, DCs primarily Langerhans cells (LCs) are significantly increased in the epithelial–stromal junction where epithelial damage predominantly occurs [42]. These cells have the principal function of capturing pathogens and presenting antigens to T cells, which leads to the primary immune response [10]. Lymphocyte function-associated antigen 1 (LFA-1) is involved in the process of mediated killing, and LFA-1/intercellular adhesion molecule 1 (ICAM-1) interactions have been shown to stimulate signaling pathways that influence T-cell differentiation [43]. When DCs recapture an antigen, the antigen is presented by major histocompatibility class II (MHC II) through an endosomal cellular pathway, triggering a secondary immune response which may explain the appearance of the clinical signs of OLP [10, 44]. DCs are involved in the pathogenesis of antigen-specific mechanisms of OLP.

Dietary intake of *n*-3 PUFAs inhibits the expression of MHC class II molecules and adhesion molecules ICAM-1 and LFA-1 on human peripheral blood monocytes [45–47]. A *n*-3 PUFAs-rich diet downregulates cell-mediated immune responses. It is possible that one of the mechanisms is the inhibitory function on antigen-presenting cells [45]. Treatment with omega-3 fatty acids gave rise to a significant reduction in DCs proportion when compared to control groups [48]. *n*-3 PUFAs diminished the antigen presentation activity of rat DCs via reducing the level of MHC II molecule [49]. The key aspects ($CD11c^+$, CD80) of DC surface expression are suppressed by *n*-3 PUFAs [50]. Therefore, *n*-3 PUFAs are beneficial to OLP in the antigen presentation aspect (Fig. 1).

Influence of *n*-3 PUFAs on T cells

When $CD4^+$ T helper cells and $CD8^+$ CTLs binding to MHC II and MHC I molecules, respectively, T cells are activated in OLP lesions [10]. Most of $CD4^+$ T cells infiltrated in the lamina propria; on the contrary, the majority of intraepithelial lymphocytes in OLP are composed almost exclusively of $CD8^+$ CTLs [2, 10]. MHC class II antigen-presenting cells in OLP express high levels of CD40, CD80, and secrete IL-12 which are confirmed to promote a Th1 $CD4^+$ T-cell response with IL-2 and interferon (IFN)-γ secretion [10, 51–53]. CD28 is the receptor for CD80 and is one of the expressed molecules that provide signals required for T-cell activation and survival [54]. $CD8^+$ CTLs are involved in disease pathogenesis, and activated $CD8^+$ T cells trigger keratinocyte apoptosis in OLP [55]. The proportion of Th17 cells in patients with OLP was significantly higher than that in controls; furthermore, Th17 cells in atrophic-erosive OLP were elevated when compared with that in reticular OLP [12]. Our previous studies observed a higher T-bet mRNA level and T-bet/GATA-3 mRNA ratios, along with a significantly high expression of programmed cell death receptor-1 and programmed death ligand-1 in OLP patients [11, 56]. T-bet mRNA gives rise to IFN-γ which is the most critical mediators of Th1 [57]. It also manifested the dominance of

Th1 $CD4^+$ T lymphocytes in the inflammatory environment, which may stimulate the activities of $CD8^+$ CTLs in OLP [11, 56, 57]. This demonstrates that T-cell immunologic dysregulation plays a central role in the pathogenesis of OLP.

It is worth noting that T-cell proliferation was inhibited through a dietary with highly purified EPA and DHA in a mouse model [58]. *n*-3 PUFAs suppressed IL-2 secretion and IL-2 receptor α chain mRNA transcription [58, 59]. DHA reduced the production of IL-2 via modifying the important phospholipid-derived intracellular second messengers (e.g., phospholipase Cγ, diacylglycerol, and ceramide) of T cells [58]. *n*-3 PUFAs were reported to interfere with Ca^{2+} signaling and suppress mitochondrial translocation to the immunologic synapse, which is crucial in T-cell activation [19, 20]. CD28 and CD80 coreceptors are among the mechanisms by which *n*-3 PUFAs directly suppress T-cell activation [58–60]. Dietary *n*-3 PUFAs are incorporated into cellular membranes and phospholipids, consequently, affecting lipid metabolism [60–62]. *n*-3 PUFAs have regulatory effects on the suppression of Th1 and Th17 development (Fig. 1) [21, 63, 64].

Inhibition of *n*-3 PUFAs on the NF-κB signaling pathway

Our previous research revealed an elevation of NF-κB which can be regulated by p65 (a subunit of NF-κB) in the nuclei of infiltrated lymphocytes in OLP [65]. NF-κB signaling pathway is triggered by the Toll-like receptors via proinflammatory factors such as tumor necrosis factor (TNF)-α. The transcriptional downstream of NF-κB is promoted after the phosphorylation of IκBα protein. An overexpression of NF-κB leads to the chronic inflammatory process in OLP [66, 67]. Studies have shown that the expression of NF-κB is inhibited by *n*-3 PUFAs in the colonic mucosa, arterial endothelial cells, hepatocytes, and kidney [68–70]. In general, NF-κB is downregulated through the consumption of *n*-3 PUFAs in two different manners (Fig. 2): a decline in the activity of the NF-κB subunit p65/RelA by inhibiting phosphorylation, such as p65/RelA serine 536 phosphorylation (p-p65 (S536)) [71]; a high level of inhibition on NF-κB DNA-binding activity and NF-κB p65 subunit nuclear translocation which were observed in rats. Additionally, the mice with SLE were fed with *n*-3 PUFAs-DHA, which increased the most median life span to 658 days [72]. 4 weeks of feeding with a high ratio of omega-3 fatty acids mice resulted in the attenuation in p65 expression and nuclear localization, leading to the downregulation of NF-κB [73].

Effects of *n*-3 PUFAs on cytokines

Abnormal secretion of cytokines, such as TNF-α, IFN-γ, IL-2, IL-6, and IL-17, is evident in the inflammatory-related cytokines involved in OLP [57]. In addition to TNF-α, increased IFN-γ, IL-6, and IL-17 are identified in the serum and lesions of OLP, respectively, indicating an imbalance in Th1 and Th17 cytokine profiles in OLP [56, 57]. *n*-3 PUFAs have a privilege effect on the inflammation led by Th1 and Th17. IL-17 is an important proinflammatory cytokine associated with the pathogenesis of OLP [12, 74]. *n*-3 PUFAs directly affect the development of Th17 cells by reducing expression of the Th17-cell signature cytokine IL-17A and transcription factor RORγt, implicating a *n*-3 PUFA-dependent, anti-inflammatory mechanism of action via the suppression of the development of this inflammatory T-cell subset [23]. A clinical trial showed the efficacy of 4 g omega-3 fatty acids on TNF-α, IL-6, and nitric oxide catabolites levels, which were decreased by involving competitive inhibition of arachidonic acid. *n*-3 PUFAs also inhibited the migratory activity of leucocytes via alteration of cytoskeletal components [75–77]. *n*-3 PUFAs may influence OLP by modulating TNF-α, IFN-γ, IL-6, and IL-17.

Effects of *n*-3 PUFAs on non-specific mechanisms in OLP

Influencing on MMPs via *n*-3 PUFAs in OLP

Matrix metalloproteinases (MMPs) containing more than 20 members are a family of zinc-containing endo-proteinases with the primary proteolytic function of connective tissue matrix proteins and basement membrane components [78, 79]. A balance can be achieved through the interaction between tissue inhibitors of metalloproteinases (TIMPs) and MMPs, because MMPs are reduced by tissue inhibitors of TIMPs through a stable, inactive enzyme-inhibitor complex with MMPs or pro-MMPs [2]. There is tissue destruction in the pathology of OLP due to an imbalance between MMPs and TIMPs which is found in the pathology of OLP. T cells release MMP-9 activators which assist in the activation of pro-MMP-9, resulting in basement membrane disruption in OLP [2, 10]. Increased MMP expression and an imbalance between MMPs and TIMPs play a pivotal role in the pathogenesis of OLP. Studies have shown an inhibitory effect of *n*-3 PUFAs on MMP-9 in multiple sclerosis and dystrophic cardiomyopathy [80, 81]. *n*-3 PUFAs significantly decrease immune cell-secreted MMP-9 levels in vivo [82, 83]. Shinto et al. [80] confirmed that EPA and DHA decreased MMP-9 protein levels and MMP-9 activity, and significantly suppressed human T-cell migration in vitro. *n*-3 PUFAs modulate the cardiac and skeletal muscle environment towards an anti-inflammatory influence by affecting proinflammatory mediators, including MMP-9 and TIMP-1 [81].

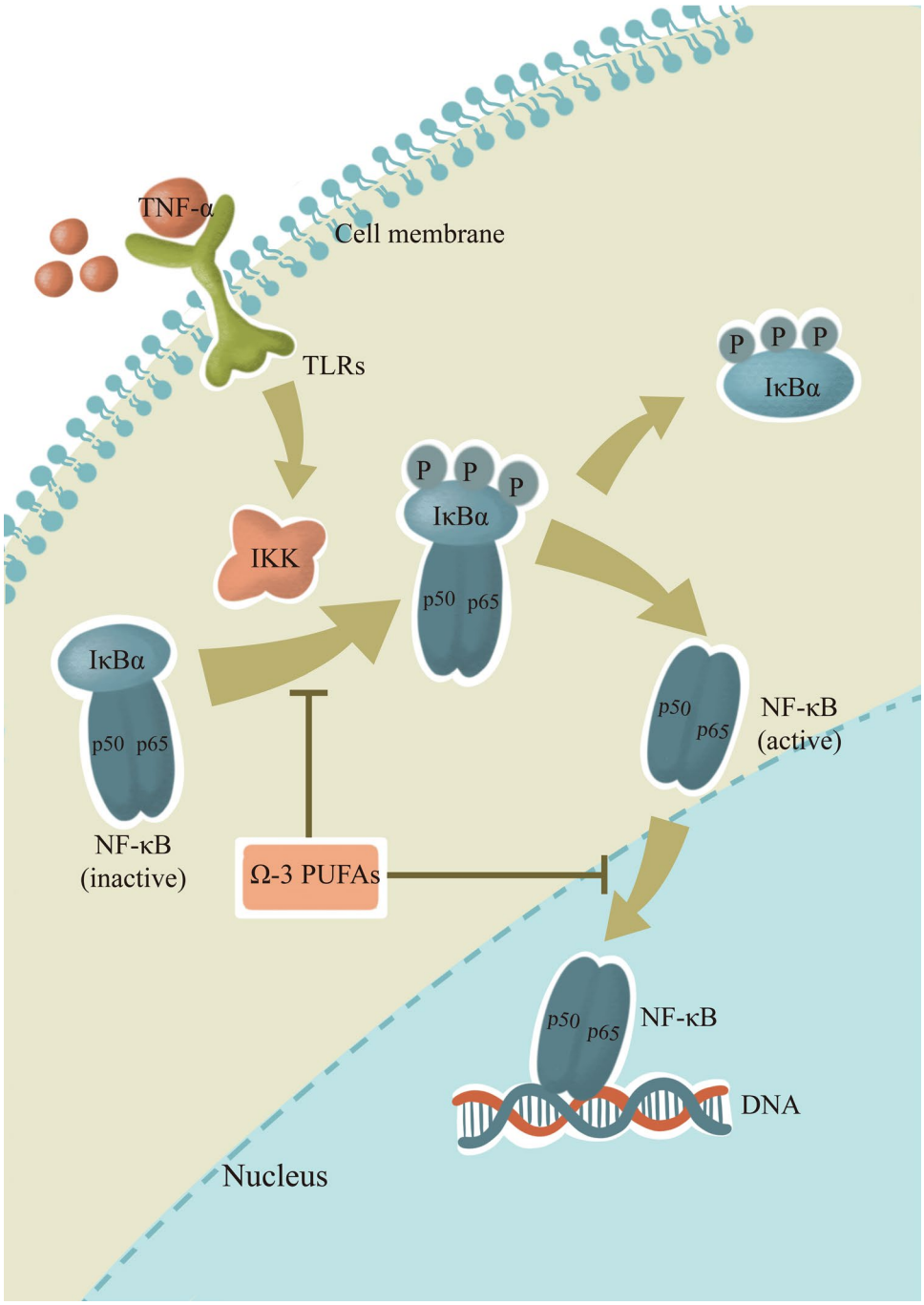

Fig. 2 Interactions between *n*-3 PUFAs and NF-κB signaling pathway. NF-κB signaling pathway triggered by TNF-α is promoted after the phosphorylation of IκBα protein. n-3 PUFAs are able to reduce the NF-κB pathway in two ways: inhibiting the phosphorylation of p65, or decreasing the binding activity of NF-κB with DNA and thus impeding the NF-κB p65 subunit nuclear translocation

n-3 PUFAs have anti-oxidative effects on OLP

Oxidative stress plays an essential role in the pathogenesis of several inflammatory and autoimmune diseases [84, 85]. In OLP serum, the level of malondialdehyde, a fundamental representative of oxidative stress, was significantly enhance, and the total antioxidant capacity was markedly declined [86], indicating the pathogenic role of oxidative stress in OLP. And reactive oxygen species (ROS), pro-oxidative free radicals, have been found participated in both the OLP pathogenesis and carcinogenesis [14, 85, 87]. It is evident that ROS damages cellular components via free amino acids, protein peroxidation of nucleic acids, and lipoproteins, disrupting cellular processes such as DNA repair and apoptosis [88]. Managing antioxidants in patients with OLP is useful to elaborate on a treatment strategy and to monitor OLP itself. Increased antioxidant genes might be an adaptive reaction against increased oxidative stress. Besides, a diet rich in *n*-3 PUFAs alters gene expression profiles to defend against excess peroxisome proliferator-activated receptor alpha

(PPARα) activation and ROS production [14, 30]. Cells isolated from rats' diet with *n*-3 PUFAs exhibited higher proportions of the *n*-3 PUFAs in their membrane phospholipids and were shown to be less sensitive to the effects of ROS. Anti-oxidative enzyme gene expression was enhanced after dietary supplemented with omega-3 fatty acids [30, 89].

Ameliorating psychological pressure by *n*-3 PUFAs in OLP

Psychological or mental disorders have a high correlation with OLP [90]. The HPA axis is involved in functional illnesses, such as anxiety disorder, insomnia, and major depressive disorder through regulating the expression of adrenocorticotropin [91]. Cortisol is one of the important substances and exhibits high serum and salivary levels in OLP patients [90, 92]. Sleep disturbances are considered a symptom of mood disorders which are associated with the initiation and relapse of OLP [90]. There is concrete evidence that *n*-3 PUFAs, notably DHA and EPA, have a stress-protective role, due to their inhibitory effects on stress-elicited adrenal activation through the central nervous system. *n*-3 PUFAs directly affect the adrenal glands [29, 93, 94]. A randomized trial showed that after treatment with *n*-3 PUFAs for 6 weeks, there was a decrease in salivary cortisol [31]. Consumption of oily fish rich in omega-3 consumption improved the sleep quality and showed an inverse association with the Pittsburgh sleep quality index [95].

n-3 PUFAs have positive effects on OLP via miRNAs and autophagy

MiRNAs are small non-coding RNA molecules containing about 18-25 nucleotides. MiRNAs function in RNA silencing and post-transcriptional regulation of gene expression [96]. Our previous studies showed that circulating miR-34a-5p and miR-130b-3p were upregulated, while miR-301b-3p and miR-125a were downregulated in OLP. Besides, miR-34a-5p was positively correlated with the severity of OLP [53, 97]. MiR-34a-5p was modulated in OLP progression through the PI3K/Akt signaling pathway. MiR-146a was higher in local lesion with OLP [98]. Several miRNAs, such as miR-let-7 family, are regulated by EPA, leading to the reductions in NF-κB, Toll-like receptor 4, and proinflammatory cytokines in the mouse liver [99]. *n*-3 PUFAs regulated immune homeostasis in an inflammation rat model through inflammatory pathways by targeting miR-19b-3p, -146b-5p, and -183-5p [100].

Autophagy is a catabolic process that mediates cellular degradation and recycling. Meanwhile, autophagy is an vital pathway for maintaining homeostasis and is connected with human oral diseases [101]. Dietary *n*-3 PUFAs reduce atherosclerosis inflammation by activating macrophage autophagy and attenuating intracellular ROS [102]. Above all, *n*-3 PUFAs might downregulate inflammation and help maintain homeostasis on OLP through miRNAs and autophagy.

Preventing malignancy in OLP

The World Health Organization (WHO) identified OLP as an oral potentially malignant disorder (OPMD), which rates approximately 1.1% [4, 103]. Researchers have been attempting to address the malignant transformation of OLP. Biomarkers that can predict malignant transformation have been validated in OLP lesions, such as the increased P53 and MMP-9, and the decreased caspase-3 [104]. Mignogna et al. reported the possible role of macrophages, mast cells, lymphocytes, and fibroblasts which contribute to the process of carcinogenesis in OLP via secreting cytokines, MMPs, and CCL5 molecules. Besides, overexpressed MMPs can cause DNA damage, bypassing p53 tumor suppression function [105]. We also reviewed OLP as one of the OPMD showed a higher expression of p53 and 8-nitroguanine [106].

It is illuminating that *n*-3 PUFAs have the ability to increase the expression of p53 and modulate Bcl-2 to induce apoptosis of cancer cells [107–111]. The high content of *n*-3 PUFAs with a decrease in *n*-6/*n*-3 PUFA ratio induces apoptosis by p53, Bcl-2, caspase-7, and caspase-3 in cancer cells [109–111]. During a 7,12-dimethylbenz(α)anthracene-induced mammary carcinogenesis rats' model, omega-3 fatty acids have the potential to limit mammary tumorigenesis in vivo by inducing apoptosis and suppressing the growth of the tumor cells [110]. Moreover, *n*-3 PUFA intake conferred additional benefits and lowered the risk of colorectal cancer-specific mortality to patients with colorectal cancer [112].

Safety of *n*-3 PUFAs

There is a good image of *n*-3 PUFAs in public. Fish oil is considered as nutritious supplement for inflammatory bowel disease, cardiovascular, and many other inflammatory diseases. Public health advice is different across countries. European Food Safety Authority suggests that a consumption of 250 mg per day of EPA and DHA appears to be sufficient for healthy subjects, while the American Heart Association (AHA) is more positive [113]. AHA recommends 720 mg per day of EPA and DHA supplements for adults from dietary supplements than from foods (410 mg per day) [114]. Excessive usage of *n*-3 PUFAs leads to potential risks. Overdose of EPA and DHA may affect platelet activation and significantly reduce platelet aggregation which leads to side effect for wound healing [115]. Public concerns about the low doses of chemical pollutant mixtures

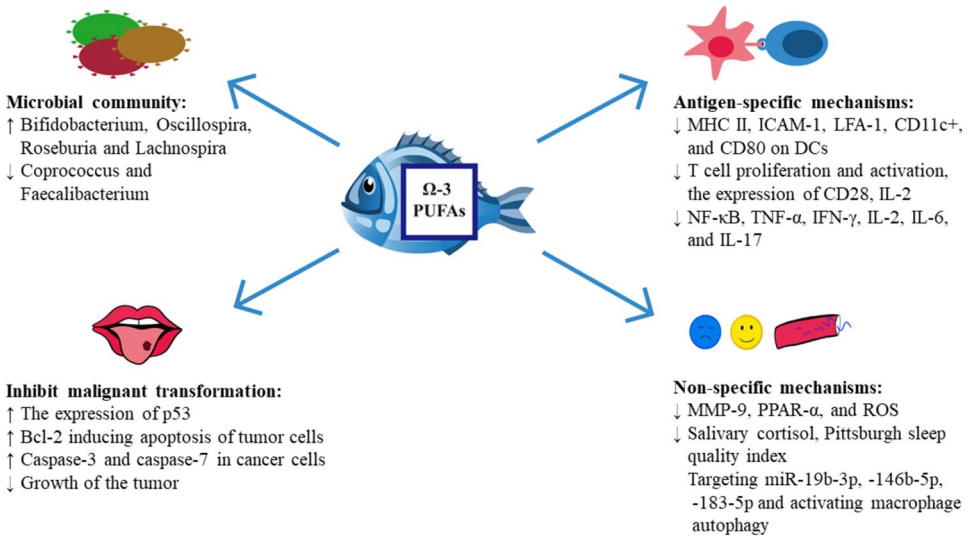

Fig. 3 *n*-3 PUFAs is a promising approach for the management of OLP. *n*-3 PUFAs may play therapeutic roles in OLP by affecting oral microbial community, antigen-specific mechanisms, non-specific mechanisms, and inhibiting malignant transformation

(organochlorine pesticides, methylmercury, dioxins, and dibenzofurans) contained in seafood [32]. To minimize the risk of pollutant, it would be necessary to control the quality of seafood products. More importantly, clinicians should balance the potential benefits of *n*-3 PUFAs supplementation against the potential risks when recommending *n*-3 PUFAs.

Conclusion

n-3 PUFAs have the properties of inhibiting antigen presentation, T-cell activity, and NF-κB signaling pathway, reducing the production of MMP-9, alleviating psychological disorders oxidative, maintaining miRNAs and autophagy, and preventing malignancy (Fig. 3). In addition, *n*-3 PUFAs modulate the number of different bacteria in oral cavity and are potential adjunctive management for OLP. Nevertheless, studies about *n*-3 PUFAs in OLP are still void. To translate theoretical assumption to clinical application, basic experimental studies are needed to figure out what the potential effects of *n*-3 PUFAs on OLP are in vitro and in vivo. Meanwhile, multi-center randomized blinded controlled trials are necessary to provide evidence-based data of the optimized usage and dosage of *n*-3 PUFAs for the management of OLP. Given all these possessions of *n*-3 PUFAs, it is possible to take *n*-3 PUFAs as a candidate for OLP management. In conclusion, *n*-3 PUFAs might be a safe, inexpensive, and non-conventional adjunctive therapy for OLP.

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Compliance with ethical standards

Conflict of interest No potential conflicts of interest were disclosed.

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