*British Journal of Nutrition*

**cambridge.org/bjn**

# The research progress and potential applications of *n*-3 fatty acids in orthopaedics: a narrative review

Hanze Mao[1,*], Guangqi Lu[1,*], Liming Zheng[1], Minghui Zhuang[1], Long Liang[1], Shuaiqi Zhou[1], Jing Li[1], Xinyue Sun[1], Yakun Liu[1], Mingming Ma[1], Jiaming Hu[1], Jie Yu[1,2] and Liguo Zhu[1,2]

[1]Wangjing Hospital, China Academy of Chinese Medical Sciences, Beijing, People's Republic of China and [2]Beijing Key Laboratory of Traditional Chinese Medicine Orthopaedic Techniques, Beijing, People's Republic of China

**Review**

**Cite this article:** Mao H, Lu G, Zheng L, Zhuang M, Liang L, Zhou S, Li J, Sun X, Liu Y, Ma M, Hu J, Yu J, and Zhu L (2025) The research progress and potential applications of *n*-3 fatty acids in orthopaedics: a narrative review. *British Journal of Nutrition* **134**: 57–69. doi: 10.1017/S0007114525103875

Received: 20 March 2025
Revised: 25 May 2025
Accepted: 25 June 2025
First published online: 10 July 2025

**Keywords:**
*n*-3 PUFA; Nutrition; Orthopaedics; Health benefits; Anti-inflammatory

**Abbreviations:**
AA, arachidonic acid; ALA, alpha-linolenic acid; mTOR, mammalian target of rapamycin; OA, osteoarthritis; OP, osteoporosis; $PGE_2$, prostaglandin $E_2$; RA, rheumatoid arthritis; SDD, spinal degenerative diseases

**Corresponding authors:** Hanze Mao; Email: winslow925@163.com, Jie Yu; Email: doctoryujie@aliyun.com, Liguo Zhu; Email: zhlg95@aliyun.com

*Hanze Mao and Guangqi Lu contributed equally to this work

## Abstract

*n*-3 PUFA, including ALA, EPA and DHA, are widely found in plant oils and marine organisms. These fatty acids demonstrate significant biological effects, and their adequate intake is essential for maintaining health. However, modern diets often lack sufficient *n*-3 PUFA, especially among populations that consume little fish or seafood, leading to a growing interest in *n*-3 PUFA supplementation in nutrition and health research. In recent decades, the role of *n*-3 PUFA in preventing and treating various diseases has gained increasing attention, particularly in cardiovascular, neurological, ophthalmic, allergic, hepatic and oncological fields. In orthopaedics, *n*-3 PUFA exert beneficial effects through several mechanisms, including modulation of inflammatory responses, enhancement of cartilage repair and regulation of bone metabolism. These effects demonstrate potential for the treatment of conditions such as osteoarthritis, rheumatoid arthritis, gout, osteoporosis, fractures, sarcopenia and spinal degenerative diseases. This review summarises the clinical applications of *n*-3 PUFA, with a focus on their research progress in the field of orthopaedics, and explores their potential in the treatment of orthopaedic diseases.

*n*-3 PUFA are widely found in foods such as plant oils and deep-sea fish and are named for the multiple double bonds in their chemical structure[1] (Fig. 1). They mainly include three types[2]: ALA, EPA and DHA. Among them, ALA[3] is the most common plant-based *n*-3 PUFA, typically found in certain plant oils (such as flaxseed oil, chia seed oil, hemp oil, etc.) and nuts (such as walnuts, hazelnuts, cashews, etc.). EPA and DHA[4] are primarily found in marine organisms, especially in deep-sea fish (such as salmon, mackerel and sardines) and certain algae.

EPA and DHA are considered the two types of *n*-3 PUFA with the strongest biological effects and play an important role in human health[2,4–6]. Since the human body cannot synthesise EPA and DHA on its own, and the conversion efficiency of ALA to EPA and DHA in the body is low[7–9], it is crucial to ensure an adequate intake of EPA and DHA to maintain overall health. The WHO recommends that adults should consume at least 250 mg of EPA and DHA daily, with the specific amount varying according to individual needs[10]. For example, pregnant and breastfeeding women have a higher demand for DHA, and it is recommended that they consume at least 200 mg more DHA per day than the general population[11]. In addition, the American Heart Association recommends that adults consume fatty fish rich in *n*-3 PUFA at least twice a week to ensure adequate intake of EPA and DHA, thereby promoting cardiovascular health[12].

However, in reality, most people consume far less *n*-3 PUFA than the recommended amount, especially those who do not frequently eat fish or seafood[13]. In addition, with the widespread consumption of processed foods and fast food, plant oils rich in *n*-6 PUFA, such as soybean oil, corn oil, sunflower oil, etc., are widely used in the production of foods like French fries, cookies, potato chips, mayonnaise, dressings and various snacks. Excessive consumption of these foods can lead to an imbalance in the *n*-3:*n*-6 PUFA intake ratio, which may negatively impact health[2,14,15]. Therefore, supplementing with *n*-3 PUFA through dietary supplements[16], such as fish oil, algae oil, etc., has become an important approach in modern nutrition and health management. This helps to address deficiencies in the daily diet, balance the intake of EPA and DHA and promote overall health.

Despite the generally insufficient intake of *n*-3 PUFA in modern diets, their potential health benefits have garnered widespread attention, especially regarding their role in the prevention and treatment of certain diseases. The purpose of this review is to outline the current clinical applications of *n*-3 PUFA, with a particular focus on research advancements and potential uses in the field of orthopaedics.

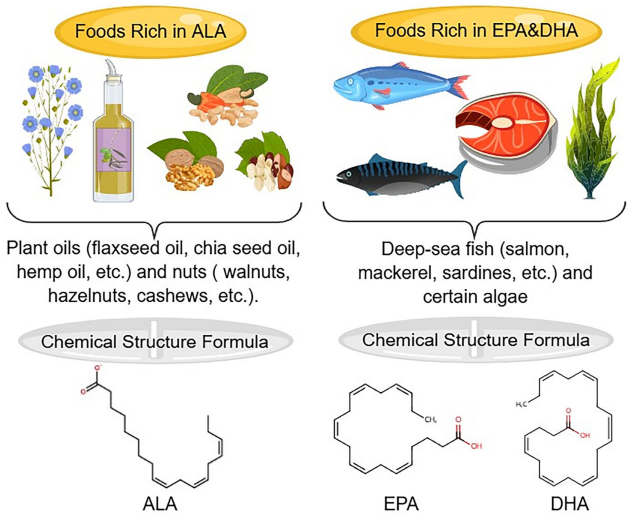


**Figure 1.** Sources of *n*-3 PUFA (ALA, EPA and DHA) in foods and their chemical structures.

## Clinical application progress

In recent years, *n*-3 PUFA have shown significant effects in the prevention and treatment of various diseases (Table 1), particularly in CVD and neurological disorders.[17–21]. In CVD, *n*-3 PUFA reduce the risk of heart attacks and strokes through multiple mechanisms, including lowering blood lipid levels, reducing triglycerides, inhibiting platelet aggregation and decreasing atherosclerosis and vascular inflammation[22–25]. In addition, *n*-3 PUFA can lower blood pressure in hypertensive patients by regulating ion channels in the blood vessels[26]. In neurological disorders, *n*-3 PUFA, especially DHA, are crucial for brain health[27]. Multiple studies have shown that *n*-3 PUFA can improve neural conduction, alleviate symptoms of depression, protect nerve cells, enhance memory and learning abilities and slow down cognitive decline in Alzheimer's disease[28–32].

The therapeutic potential of *n*-3 PUFA in ophthalmic diseases, allergic conditions and liver diseases is also gradually being recognised[33–35]. In ophthalmic diseases, *n*-3 PUFA alleviate dry eye symptoms by improving the ocular lipid layer and slowing down tear evaporation[36]; *n*-3 PUFA also slow the progression of age-related macular degeneration by promoting the survival and repair of retinal nerve cells, as well as protecting the retina from oxidative damage[37]; In addition, *n*-3 PUFA have shown some potential in controlling myopia[38]. In allergic diseases, *n*-3 PUFA can effectively alleviate symptoms of allergic rhinitis by inhibiting the production of pro-inflammatory cytokines. Additionally, *n*-3 PUFA have a relieving effect on airway inflammation, helping to improve lung function in asthma patients and thereby effectively alleviating their symptoms[39,40]. In liver diseases, *n*-3 PUFA can reduce hepatic fat accumulation, improve liver function, regulate inflammatory responses and slow down liver damage[33,41].

Additionally, although the potential of *n*-3 PUFA in cancer treatment has garnered widespread attention, their therapeutic efficacy remains somewhat controversial[42,43]. Some studies indicate that *n*-3 PUFA exert their effects through multi-target mechanisms[44,45], such as inhibiting cell proliferation, promoting apoptosis, suppressing angiogenesis, reducing inflammation, lowering metastasis and regulating epigenetic abnormalities. These actions may inhibit the growth of various types of tumours, including breast cancer[46], colon cancer[44] and prostate cancer[47].

In addition to the therapeutic effects in the aforementioned diseases, the application of *n*-3 PUFA in the field of orthopaedics is also gaining increasing attention[48–52] (Fig. 2). With the changes in modern lifestyle, the incidence of orthopaedic diseases, particularly osteoarthritis (OA)[53,54] and osteoporosis (OP)[55], has been rising year by year, significantly affecting patients' quality of life and posing a major challenge to the healthcare system. Therefore, exploring the application of *n*-3 PUFA in the field of orthopaedics holds important research value and practical significance.

## Research progress of *n*-3 PUFA in osteoarthritis

In recent years, research on the application of *n*-3 PUFA in OA has gradually increased[56,57].OA[54] is a chronic and degenerative disease, commonly linked with joint inflammation and cartilage degeneration. The clinical manifestations primarily include joint pain, stiffness, swelling and limited mobility, significantly affecting patients' quality of life. *n*-3 PUFA play a role in the prevention and treatment of OA through various mechanisms[58–62], primarily including altering the lipid composition of cell membranes, inhibiting pro-inflammatory signalling pathways, promoting the

**Table 1.** Clinical applications of *n*-3 PUFA in common diseases

| Disease area | Mechanism of action | Primary effects |
|---|---|---|
| CVD[22–26] | Lowering blood lipids, reducing triglycerides, inhibiting platelet aggregation, reducing atherosclerosis and inflammation, regulating ion channels in blood vessels | Reducing the risk of heart attacks and strokes, lowering blood pressure |
| Neurological disorders[28–32] | Improving neural conduction, protecting nerve cells, anti-depressive effects, improving memory and learning abilities | Alleviating depression symptoms, slowing cognitive decline in Alzheimer's disease |
| Ophthalmic diseases[36–38] | Improving ocular lipid layer, promoting retinal repair, antioxidant effects | Relieving dry eye symptoms, slowing the progression of age-related macular degeneration |
| Allergic diseases[39,40] | Inhibiting the production of pro-inflammatory cytokines, reducing airway inflammation | Alleviating symptoms of allergic rhinitis, improving lung function in asthma |
| Liver diseases[33,41] | Reducing hepatic fat accumulation, improving liver function, regulating inflammatory responses | Reducing liver fat accumulation, improving liver function, regulating inflammation |
| Cancer[44–47] | Inhibiting cell proliferation, promoting apoptosis, inhibiting angiogenesis, reducing inflammation, regulating epigenetic abnormalities | Inhibiting tumour growth in breast, colon and prostate cancers, potentially reducing metastasis and inflammation |

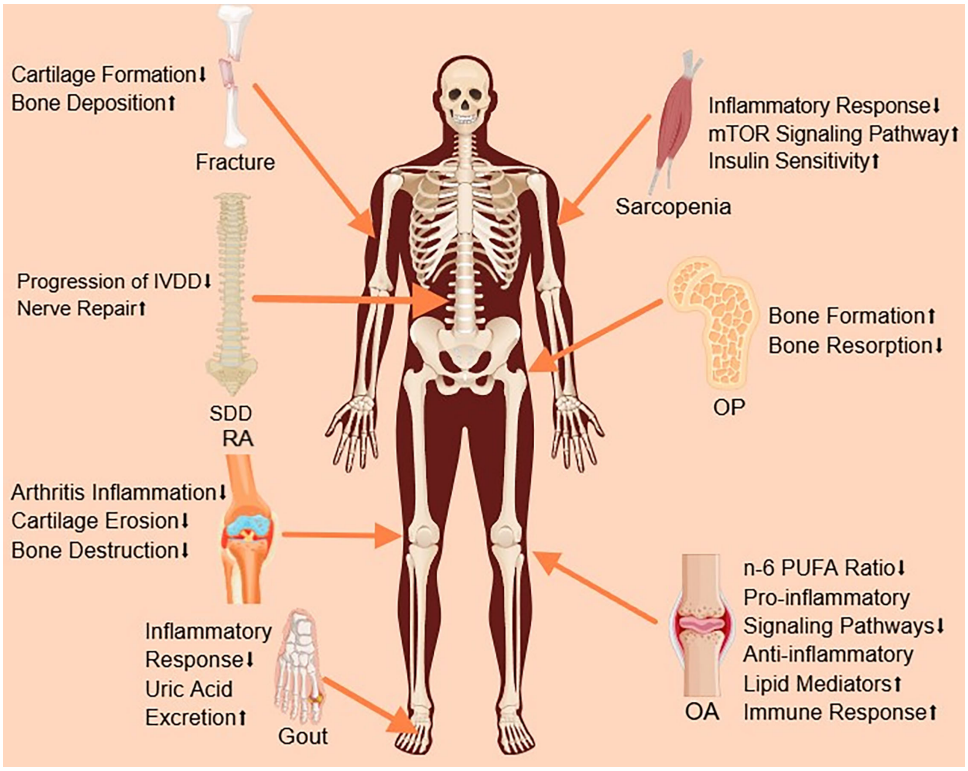


**Figure 2.** Application of *n*-3 PUFA in the field of orthopaedics.

production of anti-inflammatory mediators and regulating immune responses.

### *Alteration of the lipid composition of cell membranes*

*n*-6 PUFA, especially arachidonic acid (AA), occupy a crucial position in the phospholipid components of cell membranes[63]. AA is converted into prostaglandin $E_2$ ($PGE_2$) via the cyclo-oxygenase-2 pathway and into leukotriene $B_4$ via the 5-lip-oxygenase pathway. Both of these pro-inflammatory molecules regulate immune responses by chemotactically attracting immune cells to the site of injury, promoting the onset and maintenance of inflammation[64–66]. Therefore, the excessive accumulation of *n*-6 PUFA in the body is closely associated with many inflammation-related diseases.

In contrast, *n*-3 PUFA, particularly DHA and EPA, can competitively bind to cell membrane phospholipids with *n*-6 PUFA, thereby increasing the content of *n*-3 PUFA in the membrane and maintaining a healthy balance of lipid signalling in the body. This shift reduces the proportion of AA, thereby decreasing the production of pro-inflammatory substances such as $PGE_2$ and leukotriene $B_4$ derived from *n*-6 PUFA and mitigating the extent of the inflammatory response[67] (Fig. 3).

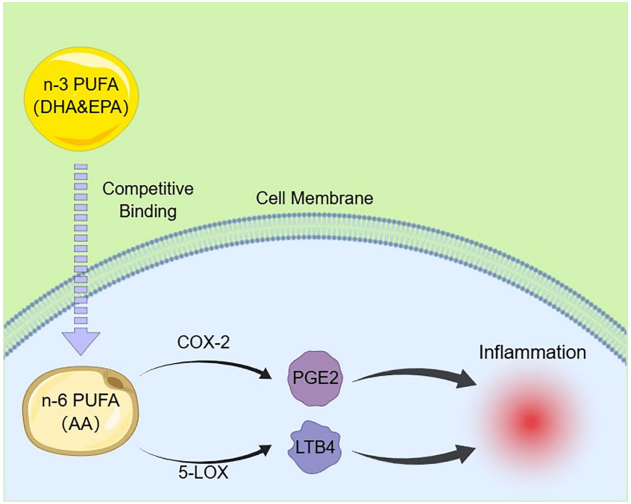


**Figure 3.** *n*-3 PUFA reduce inflammatory responses by competitively binding to cell membrane phospholipids with *n*-6 PUFA.

### *Inhibition of pro-inflammatory signalling pathways*

The NF-κB signalling pathway is a central pathway in many inflammatory responses (Fig. 4), playing a crucial role in inflammation-related diseases such as OA[68]. The NF-κB signalling pathway can activate the synthesis of pro-inflammatory cytokines, including TNF-$\alpha$ and IL-1$\beta$, promoting the initiation and persistence of inflammation[69]. DHA can inhibit the degradation of key proteins in the NF-κB pathway, thereby preventing the nuclear translocation of NF-κB, reducing its activity in the nucleus and decreasing the release of pro-inflammatory cytokines, ultimately alleviating the inflammatory response[59,70]. This mechanism is of significant importance in orthopaedic diseases such as OA. Jin *et al.*[71] found through animal models that a diet rich in *n*-3 PUFA inhibits the expression of the NF-κB signalling pathway, demonstrating anti-inflammatory and anti-OA effects. Zhang *et al.*[72] also found that edible oils with a low *n*-6/*n*-3 PUFA ratio can delay the progression of OA by inhibiting the NF-κB pathway.

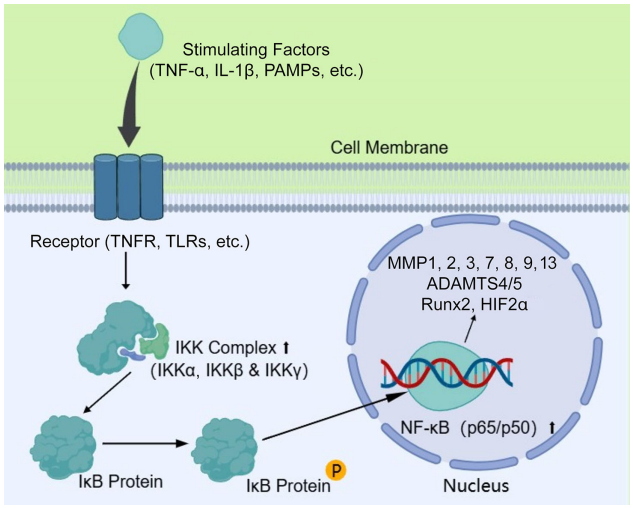


**Figure 4.** Classical NF-κB signalling pathway. This figure illustrates the main process of the classical NF-κB signalling pathway: pro-inflammatory cytokines and pathogen-associated molecular patterns bind to cell surface receptors, activating the IκB kinase complex. The IκB kinase complex phosphorylates IκB proteins, leading to their degradation and the release of NF-κB (p65/p50). Subsequently, NF-κB translocates to the nucleus, where it binds to specific DNA sequences and initiates the transcription of target genes. These target genes include matrix metalloproteinases, ADAMTS4/5, Runx2 and HIF2$\alpha$, which are involved in important biological processes such as inflammation, extracellular matrix degradation, osteogenesis and hypoxic response.

### *Promotion of anti-inflammatory lipid mediator production*

After metabolism, *n*-3 PUFA not only reduce the production of pro-inflammatory molecules but also promote the generation of active anti-inflammatory lipid mediators such as resolvins, protectins and maresins[73,74] (Table 2). These active anti-inflammatory lipids have shown potential in inhibiting cartilage degradation and promoting joint tissue repair, particularly playing an important role in inflammation resolution and tissue regeneration[75–77]. Park *et al.*[78] found through animal models that resolvins can reduce the release of inflammatory factors (such as TNF-$\alpha$, IL-1$\beta$, etc.) by binding to specific receptors on inflammatory cells in both neurogenic and inflammatory pain models, thereby alleviating the inflammatory response. Zhao *et al.*[79] demonstrated through a rat model that protectins possess pro-resolving properties, promoting autophagy to accelerate the clearance of damaged cells, thereby exerting anti-inflammatory effects. Lu *et al.*[80] similarly found through a rat model that maresins activate the PI3K/Akt pathway and inhibit the NF-κB pathway, reducing the secretion of matrix metalloproteinase-13, which increases type II collagen in cartilage, thereby exerting anti-inflammatory effects and protecting cartilage.

**Table 2.** Active anti-inflammatory lipid mediators derived from *n*-3 PUFA metabolism

| Active anti-inflammatory lipid mediator | Mechanism of action | Related literature |
|---|---|---|
| Resolvins | Inflammatory factors such as TNF-$\alpha$, IL-1$\beta$ ↓ | Park[78] |
| Protectins | Autophagy and clearance of damaged cells ↑ | Zhao[79] |
| Maresins | PI3K/AkT pathway ↑, NF-κB pathway ↓, MMP13 ↓, type II collagen in cartilage ↑ | Lu[80] |

MMP13, matrix metalloproteinase-13.

### *Regulation of immune responses*

*n*-3 PUFA can also modulate immune responses and alleviate chronic inflammation in OA[81,82] (Fig. 5). Dietary supplementation with *n*-3 PUFA effectively increases cell membrane fluidity, thereby modulating immune cell function, particularly the function of T cells and macrophages[62]. Studies have found that T cells play a crucial role in immune suppression and tissue repair. *n*-3 PUFA can alter the ratio of T cell subsets, promote the activity of anti-inflammatory T cells (such as Th2, Treg) and inhibit the activation of pro-inflammatory T cells (such as Th1, Th17), helping to reduce immune-mediated inflammatory responses in OA[83–85]. In addition, *n*-3 PUFA can modulate macrophage polarisation, promoting their transformation into anti-inflammatory M2 macrophages[86,87]. Numerous studies have shown that M2 macrophages play a key role in immune suppression and tissue repair. They alleviate inflammatory damage to joints and cartilage tissue and slow the progression of OA by secreting anti-inflammatory cytokines such as IL-10 and TGF-$\beta$[88–90].

## Research progress of *n*-3 PUFA in rheumatoid arthritis

Rheumatoid arthritis (RA)[91] is a chronic, systemic autoimmune disease characterised by chronic inflammation, swelling, pain and dysfunction of the joints. RA typically affects symmetrical joints, particularly those in the hands, feet, knees, wrists and elbows. As the disease progresses, RA can lead to joint structural damage, resulting in joint deformities and loss of function[92]. The current treatment strategies for RA mainly rely on immunosuppressants, anti-inflammatory drugs and biologics[93,94]. However, in recent years, an increasing number of studies have found that *n*-3 PUFA, as natural anti-inflammatory agents, demonstrate potential therapeutic value in the treatment of RA[95,96].

Analogous to its effects in OA, *n*-3 PUFA can also exert anti-inflammatory effects through multiple mechanisms, alleviating the inflammatory response in RA[81,82] (Table 3). Raad *et al.*[97] demonstrated through clinical samples that *n*-3 PUFA can significantly reduce the production of pro-inflammatory cytokines, such as TNF-$\alpha$ and IL-6, thereby helping to alleviate symptoms such as joint swelling, pain and

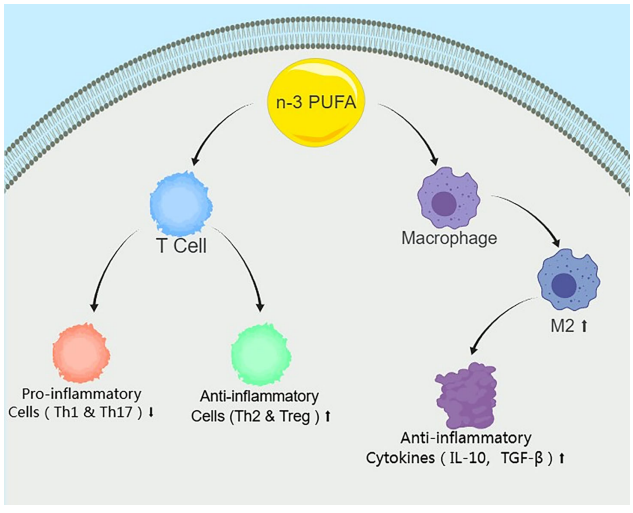


**Figure 5.** The regulatory role of *n*-3 PUFA in immune responses.

**Table 3.** Mechanisms of anti-inflammatory effects of *n*-3 PUFA in rheumatoid arthritis

| Study | Mechanism of action |
|---|---|
| Raad[97] | Pro-inflammatory cytokines ↓ |
| Navarini[98] | AA ↓, pro-inflammatory mediators ↓, anti-inflammatory cannabinoids and cytokines ↑, pro-inflammatory cytokines ↓ |
| Jin[99] | miR-20a ↑, NLRP3 inflammasome pathway ↓, Th17 cells and pro-inflammatory mediators ↓, Treg cells and anti-inflammatory cytokines ↑ |
| Su[101] | Osteoclast-related gene expression ↓, NF-κB pathway ↓, pro-inflammatory cytokines ↓, IL-10 ↑ |

AA, arachidonic acid.

morning stiffness caused by inflammation. Similarly, Navarini *et al.*[98] also demonstrated through animal experiments and clinical trials that *n*-3 PUFA reduce the levels of arachidonic acid (AA) in immune cells, inhibiting the production of pro-inflammatory mediators like $PGE_2$. Moreover, they promote the production of anti-inflammatory cannabinoids and cytokines, such as IL-10, while suppressing the levels of pro-inflammatory cytokines (e.g. TNF-$\alpha$, IL-1$\beta$ and IL-6), thus overall modulating immune responses and reducing the inflammatory symptoms of RA. Additionally, Jin *et al.*[99] first demonstrated in a collagen antibody-induced arthritis model that protectin DX (PDX), produced from *n*-3 PUFA metabolism, significantly inhibits the production of Th17 cells and pro-inflammatory mediators through the miR-20a-NLRP3 inflammasome pathway. This promotes Treg cells and anti-inflammatory cytokines, slows joint damage and improves the progression of RA. Furthermore, as persistent inflammation and joint destruction are major features of RA[100], Su *et al.*[101] found that lipid mediators produced from DHA exhibit significant anti-inflammatory effects. In the collagen antibody-induced arthritis mouse model, lipid mediators significantly alleviated arthritis, cartilage erosion and bone destruction by downregulating osteoclast-related gene expression, inhibiting the NF-κB pathway, reducing the production of pro-inflammatory cytokines and increasing IL-10 levels, thereby demonstrating potential for mitigating RA symptoms.

## Research progress of *n*-3 PUFA in gout

Gout[102] is a condition caused by abnormal purine metabolism, typically characterised by joint inflammation, pain and swelling. It is triggered by hyperuricaemia, which results in high levels of uric acid in the blood. Uric acid crystals accumulate in the joints and surrounding tissues, particularly in areas such as the toes, ankles and knees, leading to acute inflammatory responses[103,104] (Fig. 6).

It is generally believed that seafood may have an adverse impact on individuals with hyperuricaemia[105,106]. Because seafood is rich in purine compounds, which are metabolised into uric acid in the body. Excessive uric acid accumulation is a major trigger of gout. However, Zeng *et al.*[107], analysing data from 12 505 participants in the 2007–2016 NHANES database, found that seafood with low *n*-3 PUFA content is associated with a higher risk of gout, while seafood rich in *n*-3 PUFA does not carry this risk and may even counteract the negative effects of purines on gout through its anti-inflammatory properties. Similarly, Zhang *et al.*[108] confirmed this finding in a clinical study of 724 gout patients. Those who consumed at least two servings of *n*-3 PUFA-rich fish had a 26 % reduced risk of gout flare-ups compared with those who had not consumed such fish in the past 48 h.

Besides their excellent anti-inflammatory effects, *n*-3 PUFA have also been shown by Saito *et al.*[109] through cell models to inhibit renal urate transporter 1, which is responsible for the reabsorption of urate into the bloodstream. By inhibiting urate transporter 1, *n*-3 PUFA increase uric acid excretion and thereby reduce serum urate levels, alleviating gout symptoms.

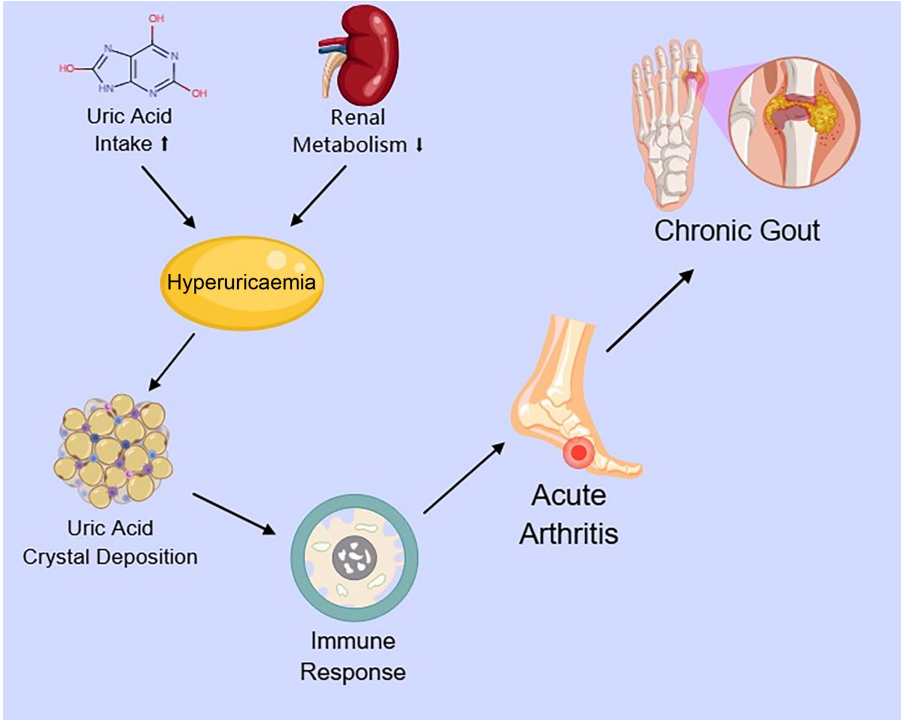


**Figure 6.** Pathogenesis and progression of gout. The pathogenesis and progression of gout begin with increased uric acid intake and decreased renal excretion capacity, leading to elevated blood uric acid levels and resulting in hyperuricaemia. As the uric acid concentration continues to rise, urate crystals accumulate in the joints and surrounding tissues, triggering an immune response and causing acute arthritis. Without treatment, this process can persist, ultimately leading to chronic gout, causing joint damage and long-term inflammation.

In conclusion, moderate consumption of seafood rich in *n*-3 PUFA or supplementation with *n*-3 PUFA through dietary supplements may provide an effective dietary intervention strategy for gout patients, helping to alleviate symptoms and significantly reduce the frequency of gouty arthritis flare-ups.

## Research progress of *n*-3 PUFA in osteoporosis

OP[110] is a chronic metabolic bone disease characterised by a significant decrease in bone density and destruction of bone microstructure, resulting in fragile bones and an increased risk of fractures. It is often referred to as a 'silent disease' because patients typically do not exhibit noticeable clinical symptoms until a fracture occurs[111]. The pathogenesis of OP is closely related to multiple factors, including an imbalance in bone remodelling, loss of minerals (particularly calcium) and abnormal regulation of the processes of bone formation and bone resorption[55,110]. *n*-3 PUFA, in addition to their anti-inflammatory effects, regulate bone metabolism through various mechanisms, promoting bone health[112,113] (Table 4).

### *Promotion of bone formation*

With the deepening of bone metabolism research, scholars have gradually revealed the regulatory mechanisms of *n*-3 PUFA on the osteogenic process. Chen *et al.*[114] found that in growing animals with rapid bone modelling, *n*-3 PUFA promote the differentiation of osteoblasts by enhancing the expression of osteoblast-related genes and proteins such as *β*-catenin, RUNX2 and osterix, thereby accelerating the process of bone formation. Hao *et al.*[115] also found through cell experiments that *n*-3 PUFA promote osteogenic differentiation and inhibit adipogenic differentiation of bone marrow stromal cells by upregulating the Wnt/*β*-catenin signalling pathway and promoting the expression of osteogenic transcription factors. Gao *et al.*[50] demonstrated through cell experiments that *n*-3 PUFA might promote osteogenic differentiation of bone marrow stromal cells through the miR-9–5p/extracellular signal-regulated kinase (ERK)/alkaline phosphatase (ALP) signalling pathway, providing support for bone repair and regeneration. Zhang *et al.*[116] demonstrated through cell experiments that *n*-3 PUFA enhance bone formation by promoting the transdifferentiation of chondrocytes into osteoblasts in the growth plate, which contributes to the improvement of OP.

In summary, numerous studies indicate that *n*-3 PUFA regulate osteoblast differentiation and function through various signalling pathways, promote osteogenic differentiation of bone marrow stromal cells, inhibit adipogenic differentiation and enhance bone formation by promoting the transdifferentiation of chondrocytes into osteoblasts, suggesting their potential therapeutic role in bone repair, regeneration and the improvement of OP.

**Table 4.** Application of *n*-3 PUFA in osteoporosis

| Effect | Mechanism | Related literature |
|---|---|---|
| Promoting bone formation | Expression of osteoblast genes and proteins, such as *β*-catenin, RUNX2 and osterix ↑ | Chen[114] |
| | Wnt/*β*-catenin signalling pathway ↑, BMSC osteogenic differentiation ↑, adipogenic differentiation ↓ | Hao[115] |
| | miR-9–5p/ERK/ALP signalling pathway ↑, BMSC osteogenic differentiation ↑ | Gao[50] |
| | Transdifferentiation of chondrocytes into osteoblasts ↑ | Zhang[116] |
| Inhibiting bone resorption | $PGE_2$ and EP4 ↓, OPG:RANKL ratio ↑, NF-κB signalling pathway ↓, osteoclast activity ↓ | Zhan[120], Wang[121] |

BMSC, bone marrow stromal cells; OPG:RANKL, osteoprotegerin: receptor activator of NF-κB ligand.

### *Inhibition of bone resorption*

The abnormal activity of osteoclasts is the main cause of excessive bone resorption[117,118]. Several studies have shown that the role of *n*-3 PUFA in bone metabolism is not only reflected in promoting bone formation but also in inhibiting bone resorption. It achieves this by inhibiting the key factor for osteoclastogenesis, receptor activator of NF-κB ligand, thereby reducing osteoclast activity and decreasing bone resorption, which helps maintain bone health[113,119]. Zhan *et al.*[120] discovered that *n*-3 PUFA can lower $PGE_2$ levels and the expression of EP4, thereby increasing the ratio of osteoprotegerin to receptor activator of NF-κB ligand, inhibiting the NF-κB signalling pathway and ultimately suppressing osteoclastogenesis. Similarly, Wang *et al.*[121] also reached a similar conclusion, further confirming the role of *n*-3 PUFA in inhibiting bone resorption in OP.

## Research progress of *n*-3 PUFA in fracture

Fracture[122] refers to the rupture or breakage of bone continuity, typically caused by direct or indirect external forces. It not only affects the structural integrity of the bone but may also be accompanied by soft tissue damage, haematoma and nerve injuries[122–124]. The treatment for fractures varies depending on the nature, location and severity of the fracture[125–131]. The preventive effect of *n*-3 PUFA on fractures primarily involves promoting bone formation and inhibiting bone resorption as part of anti-OP therapy. Several studies have verified this preventive effect[132,133]. In fracture treatment, the application of *n*-3 PUFA is generally used as an adjunctive therapy. Research by Kafadar *et al.*[134] indicated that the combined use of *n*-3 PUFA and vitamin $D_3$ had a positive effect on fracture healing.

In mechanistic studies, Chen *et al.*[135] found that in a mouse femur fracture repair model, *n*-3 PUFA promote fracture healing by enhancing the expression of insulin-like growth factors, reducing the formation of $PGE_2$, increasing calcium absorption and decreasing the release of inflammatory factors from osteoclasts. Huang *et al.*[52] demonstrated through animal experiments that treatment with *n*-3 PUFA-derived MaR1 significantly improved tibial fracture healing, which was manifested by reduced cartilage formation and increased bone deposition, thereby enhancing the stiffness of the bone structure. In the early stages of treatment, MaR1 reduced the number of pro-inflammatory macrophages in the callus and lowered the levels of inflammatory biomarkers. Subsequently, it promoted osteoblast differentiation and enhanced the osteogenic activity of bone marrow stromal cells.

In addition, *n*-3 PUFA also have certain effects on fracture-related complications. Zhang *et al.*[136] found through clinical studies that specialised pro-resolving mediators derived from DHA can promote the resolution of acute inflammation and effectively inhibit neuropathic pain caused by tibial fractures. Zheng *et al.*[137] also demonstrated through clinical research that

daily supplementation of *n*-3 PUFA can reduce the risk of pulmonary embolism and symptomatic deep vein thrombosis after fracture surgery, without increasing the risk of bleeding.

## Research progress of *n*-3 PUFA in sarcopenia

Sarcopenia[138] is a chronic condition characterised by the loss of muscle mass and strength, which is age-related and commonly observed in elderly populations. Patients with sarcopenia often experience mobility difficulties, which can significantly affect their daily lives. Early identification and active interventions, such as exercise, nutritional support and pharmacological treatments, can significantly improve the progression of sarcopenia and enhance the quality of life for the elderly[139–141]. In recent years, *n*-3 PUFA have garnered increasing attention in the treatment and prevention of sarcopenia. Their anti-inflammatory properties, ability to promote muscle synthesis and enhance muscle strength make them an effective adjunctive therapy[142–144]. The specific mechanisms of action are summarised in Table 5.

### *Anti-inflammatory effect*

The anti-inflammatory effects of *n*-3 PUFA have been widely recognised[58,71,72,88,90]. As individuals age, their immune system declines, leading to a phenomenon known as immunosenescence, which results in an increase in pro-inflammatory cytokines. Pro-inflammatory factors such as TNF-$\alpha$ and IL-6 can directly or indirectly affect muscle metabolism through multiple mechanisms, both promoting muscle breakdown and potentially inhibiting muscle synthesis[145–147]. However, it is noteworthy that some studies suggest IL-6 may play a regulatory role in skeletal muscle hypertrophy and satellite cell activity, indicating a bidirectional function[148,149].

The expert consensus report by Serhan *et al.*[150] highlights that *n*-3 PUFA have anti-inflammatory properties, which help maintain muscle mass and serve as precursors to specialised pro-resolving mediators. These mediators play a crucial role in immune modulation, tissue repair and the effective resolution of inflammation, while also preventing damage to host defense mechanisms. Additionally, Matthew *et al.*[151] demonstrated through an aged mouse model that EPA can improve muscle protein quality, particularly by reducing mitochondrial protein carbamylation induced by inflammation, which alleviates age-related mitochondrial dysfunction and improves mitochondrial protein quality. Lalia *et al.*[152] similarly demonstrated through samples from elderly individuals that *n*-3 PUFA reduce the production of mitochondrial oxidants, attenuate the inflammatory response, promote muscle protein synthesis and enhance the anabolic response to exercise in older adults, thereby improving overall muscle function.

**Table 5.** Mechanisms of *n*-3 PUFA in sarcopenia

| Effect | Mechanism | Related literature |
|---|---|---|
| Anti-inflammatory | Inflammation response ↓, mitochondrial protein acetylation ↓, mitochondrial function ↑, muscle protein quality ↑ | Matthew[151] |
| | Mitochondrial oxidative stress products ↓, inflammation response ↓, muscle protein quality ↑ | Lalia[152] |
| Activation of mTOR pathway | mTOR signalling pathway ↑, protein synthesis efficiency ↑, muscle protein ↑, muscle mass ↑ | Azzolino[155] |
| Improvement of insulin sensitivity | PPAR-$\gamma$ ↑, insulin sensitivity ↑, muscle protein catabolism ↓ | Moradi[161] |

mTOR, mammalian target of rapamycin.

### *Mammalian target of rapamycin activation*

The mammalian target of rapamycin (mTOR) signalling pathway is a key regulator of cell growth, proliferation and metabolism, playing an important role in the inhibition of skeletal muscle autophagy[153,154]. Research by Azzolino *et al.*[155] showed that *n*-3 PUFA not only exert independent effects but also synergize with amino acid intake. By activating the mTOR signalling pathway, *n*-3 PUFA increase the efficiency of protein synthesis, promoting muscle protein synthesis and enhancing muscle mass.

However, it is worth noting that in a randomised controlled trial, López *et al.*[156] found that while *n*-3 PUFA supplementation was beneficial for muscle protein synthesis rates, no effects on mTOR, protein kinase B or skeletal muscle gene expression were observed when measuring changes in skeletal muscle volume and mass. This suggests that the specific molecular mechanisms by which *n*-3 PUFA may enhance muscle mass and protein synthesis through the mTOR pathway still require further investigation and validation.

### *Improvement of insulin sensitivity*

Insulin is a key hormone that promotes muscle protein synthesis. Insulin resistance reduces insulin signalling, leading to an increase in protein catabolism and a decrease in protein synthesis in skeletal muscle. Chronic insulin resistance exacerbates this imbalance, resulting in muscle mass loss, which can eventually develop into sarcopenia[157–160]. PPAR-$\gamma$ is a key molecule involved in regulating skeletal muscle glucose homeostasis and insulin sensitivity. Its abnormal expression is closely related to skeletal muscle IR, particularly in obese or type 2 diabetic patients[155].

A 3-week double-blind randomised controlled trial by Moradi *et al.*[161] showed that supplementation with *n*-3 PUFA significantly enhanced PPAR-$\gamma$ activity, improving insulin sensitivity, thereby inhibiting muscle protein catabolism and promoting muscle health. Liu *et al.*[162], using a diet-induced diabetic rat model, demonstrated that supplementation with *n*-3 PUFA-rich fish oil controlled weight loss in diabetic rats and repaired impaired glucose tolerance. At the same time, *n*-3 PUFA improved insulin sensitivity, enhanced glucose metabolism and protected against muscle atrophy induced by diabetes. Therefore, *n*-3 PUFA have the potential to improve muscle mass and quality of life in diabetic patients.

## Research progress of *n*-3 PUFA in spinal degenerative diseases

Spinal degenerative diseases (SDD)[163]refer to a group of conditions involving the gradual degeneration of the spine and its components, including intervertebral discs, vertebrae and spinal joints. These diseases typically develop with age and may be influenced by genetic, environmental and lifestyle factors. The symptoms of SDD vary depending on the specific location and severity of degeneration but usually include pain, stiffness and limited range of motion. As the disease progresses, nerves may be

compressed, leading to radicular symptoms. In severe cases, compression of the spinal cord may occur, causing symptoms such as sensory loss, limb weakness, incontinence and even paralysis[164–167].

Currently, research on the application of *n*-3 PUFA in SDD is relatively limited. However, some preliminary studies suggest that *n*-3 PUFA may have a positive effect on the treatment of intervertebral disc degeneration. A study by NaPier *et al.*[168] found through a rat model that *n*-3 PUFA dietary supplements can reduce systemic inflammation by lowering the AA:EPA ratio in serum, potentially offering protective effects against the progression of intervertebral disc degeneration. Similarly, Shang *et al.*[169] verified this effect through cell experiments and found that the protective role of DHA on the intervertebral disc may be exerted by regulating the expression of long non-coding RNA nuclear-enriched abundant transcript 1, thereby exerting its anti-inflammatory effects and reducing extracellular matrix degradation in nucleus pulposus cells caused by oxidative stress, ultimately slowing the pathological progression of intervertebral disc degeneration.

The dorsal root ganglion is a key pathway for sensing external stimuli. In the case of lumbar disc prolapse, degenerated nucleus pulposus tissue compresses the nerve root, leading to increased and prolonged infiltration of macrophages in the dorsal root ganglion. This can alter the function of neurons, causing excessive neural activation, which ultimately results in persistent pain or sensory abnormalities[170,171]. A study by Manzhulo *et al.*[172] using an animal model concluded that DHA can effectively alleviate neurogenic pain in SDD by inhibiting the response of satellite glial cells in the dorsal root ganglion, reducing the expression of the pro-apoptotic protein p53 and promoting neuroprotective effects in the dorsal root ganglion. Additionally, a study by Wang *et al.*[173] using an lumbar disc prolapse rat model showed that mechanical and thermal hypersensitivity, increased inflammatory cytokines IL-1$\beta$ and IL-18 levels and nerve root pain induced by activation of the NLRP3 inflammasome caused by nucleus pulposus exposure could all be significantly reversed by MaR1 produced from *n*-3 PUFA metabolism. This indicates that *n*-3 PUFA not only alleviate the early damage caused by lumbar disc prolapse-induced changes but also promote long-term nerve repair and functional recovery.

In summary, the application of *n*-3 PUFA in SDD holds great promise, particularly in alleviating inflammation, oxidative stress and promoting nerve repair. These potential benefits highlight the therapeutic value of *n*-3 PUFA in the management of SDD and related conditions.

## Discussion

This article introduces the main types of *n*-3 PUFA (ALA, EPA, DHA) and their important roles in human health, with particular emphasis on their application in orthopaedic diseases such as OA, RA, gout, OP, fractures, sarcopenia and SDD. It also describes in detail the effects of *n*-3 PUFA in anti-inflammatory responses, improving bone metabolism, enhancing muscle strength and protecting nerves. Particularly in terms of anti-inflammation, *n*-3 PUFA exert their effects by altering the lipid composition of cell membranes, inhibiting pro-inflammatory signalling pathways, promoting the production of anti-inflammatory lipid mediators and regulating immune responses. These mechanisms effectively alleviate inflammation related to orthopaedic diseases and promote the repair of bones and joints.

However, this review also has several limitations. First, as a narrative review, the literature selection did not follow the strict criteria of a systematic review, which may have resulted in the omission of relevant studies or selection bias. Second, the included studies exhibit considerable heterogeneity, covering different experimental models, dosage regimens and study populations, which complicates the comparison and synthesis of results.

Nonsteroidal anti-inflammatory drugs are currently the most widely used anti-inflammatory drugs in clinical practice, which primarily exert their anti-inflammatory, analgesic and antipyretic effects by inhibiting the activity of two cyclooxygenases, cyclooxygenase-1 and cyclooxygenase-2. Their effects are rapid, typically providing pain relief within a few hours after oral administration[174–176]. However, chronic or excessive use may lead to side effects such as gastrointestinal discomfort, renal damage, liver damage, elevated cardiovascular risks and allergic reactions[177–181]. In contrast, *n*-3 PUFA, as a therapeutic approach with both nutritional and medicinal properties, have fewer side effects and a higher clinical safety profile[182–186]. Therefore, its anti-inflammatory potential warrants further investigation and holds promise for widespread clinical application.

Despite extensive research demonstrating the anti-inflammatory effects and potential therapeutic value of *n*-3 fatty acids in orthopaedic diseases, several limitations remain in the current body of research. First, most studies are based on animal models or *in vitro* cell experiments, and their translation to clinical applications requires further validation through large-scale, high-quality human clinical trials. Second, there is considerable variability in the dosage, administration methods and intervention durations of *n*-3 fatty acids across studies, with a lack of standardised protocols, which limits the comparability and generalisability of results; the optimal dosage and administration regimen have yet to be established.

Moreover, the complexity and multifactorial nature of orthopaedic diseases make it difficult to fully assess the effects of a single nutritional intervention, necessitating comprehensive multidisciplinary and multifactorial studies to explore the underlying mechanisms and efficacy in depth. Regarding long-term clinical use, evidence on the efficacy and safety of *n*-3 PUFA remains insufficient, especially concerning efficacy differences among various populations and individualised treatment strategies.

Lastly, as a dietary supplement, research on the interactions between *n*-3 PUFA and conventional drugs (such as nonsteroidal anti-inflammatory drugs and immunomodulators) is limited. Long-term combined use may introduce uncertainties in drug responses, affecting safety and therapeutic outcomes. The precise mechanisms of action and clinical feasibility of *n*-3 PUFA in certain orthopaedic-related diseases remain unclear, particularly in terms of signalling pathways and molecular targets, which require further investigation.

To address these issues, future research should prioritise large-scale, high-quality randomised controlled trials to validate the efficacy and safety of *n*-3 PUFA, especially under conditions of long-term use and combination therapy. Additionally, integrating molecular biology and systems biology approaches to deeply explore molecular mechanisms and targets, supplemented by pharmacokinetic and pharmacodynamic studies, will clarify the specific impacts of various dosages and administration routes on humans. Such research will provide a more robust theoretical foundation and scientific guidance for the clinical application of *n*-3 PUFA.

In conclusion, the above studies not only deepen our understanding of the mechanisms of action of *n*-3 PUFA in orthopaedic diseases but also provide a solid scientific foundation for their clinical application. Looking ahead, *n*-3 PUFA is expected to become an important complement or alternative to traditional drugs and holds promise for synergistic use with other modern therapeutic approaches, such as gene therapy and stem cell therapy. Particularly in the complex treatment of orthopaedic diseases, *n*-3 PUFA may serve as a key adjunctive therapy, offering more scientific, precise and personalised therapeutic options, ultimately improving the clinical outcomes for patients.

**Acknowledgements.** Not applicable.

The authors' responsibilities were as follows: H. M. conceptualised the manuscript; H. M. and G. L. drafted the initial subsections of the manuscript, with further input from L. Z., M. Z., L. L., S. Z., J. L., X. S., Y. L., M. M., J. H., J. Y. and L. Z.; H. M. and G. L. edited the manuscript; and all authors read and approved the final manuscript.

Scientific and Technological Innovation Project of China Academy of Chinese Medical Sciences (CI2021B010).

The authors declare no conflicts of interest.

## References

1. Bhatt DL, Budoff MJ & Mason RP (2020) A revolution in *n*-3 fatty acid research. *J Am Coll Cardiol* **76**, 2098–2101.
2. Kousparou C, Fyrilla M, Stephanou A, *et al.* (2023) DHA/EPA (*n*-3) and LA/GLA (*n*-6) as bioactive molecules in neurodegenerative diseases. *Int J Mol Sci* **24**, 10717.
3. Yuan Q, Xie F, Huang W, *et al.* (2022) The review of alpha-linolenic acid: sources, metabolism, and pharmacology. *Phytother Res* **36**, 164–188.
4. Tomczyk M, Heileson JL, Babiarz M, *et al.* (2023) Athletes can benefit from increased intake of EPA and DHA—evaluating the evidence. *Nutrients* **15**, 4925.
5. Troesch B, Eggersdorfer M, Laviano A, *et al.* (2020) Expert opinion on benefits of long-chain *n*-3 fatty acids (DHA and EPA) in aging and clinical nutrition. *Nutrients* **12**, 2555.
6. Blaauw R, Calder PC, Martindale RG, *et al.* (2024) Combining proteins with *n*-3 PUFAs (EPA + DHA) and their inflammation pro-resolution mediators for preservation of skeletal muscle mass. *Crit Care* **28**, 38.
7. Doughman SD, Krupanidhi S & Sanjeevi CB (2007) *n*-3 fatty acids for nutrition and medicine: considering microalgae oil as a vegetarian source of EPA and DHA. *Curr Diabetes Rev* **3**, 198.
8. Takic M, Pokimica B, Petrovic-Oggiano G, *et al.* (2022) Effects of dietary $\alpha$-linolenic acid treatment and the efficiency of its conversion to eicosapentaenoic and docosahexaenoic acids in obesity and related diseases. *Molecules* **27**, 4471.
9. Richard C & Monk JM (2024) Docosahexaenoic acid. *Adv Nutr* **15**, 100161.
10. Salem N & Eggersdorfer M (2015) Is the world supply of *n*-3 fatty acids adequate for optimal human nutrition? *Curr Opin Clin Nutr* **18**, 147–154.
11. von Schacky C (2020) *n*-3 fatty acids in pregnancy—the case for a target *n*-3 index. *Nutrients* **12**, 898.
12. Kris-Etherton PM, Harris WS & Appel LJ (2003) *n*-3 fatty acids and cardiovascular disease. *Arterioscler Thromb Vasc Biol* **23**, 151–152.
13. Koutentakis M, Surma S, Rogula S, *et al.* (2023) The effect of a vegan diet on the cardiovascular system. *J Cardiovasc Dev Dis* **10**, 94.
14. Yamashima T, Ota T, Mizukoshi E, *et al.* (2020) Intake of ω-6 polyunsaturated fatty acid-rich vegetable oils and risk of lifestyle diseases. *Adv Nutr* **11**, 1489–1509.
15. Mostafa H, Gutierrez-Tordera L, Mateu-Fabregat J, *et al.* (2024) Dietary fat, telomere length and cognitive function: unravelling the complex relations. *Curr Opin Lipidol* **35**, 33–40.
16. Sherratt SCR, Lero M & Mason RP (2020) Are dietary fish oil supplements appropriate for dyslipidemia management? A review of the evidence. *Curr Opin Lipidol* **31**, 94–100.
17. Rodriguez D, Lavie CJ, Elagizi A, *et al.* (2022) Update on *n*-3 polyunsaturated fatty acids on cardiovascular health. *Nutrients* **14**, 5146.
18. Innes JK & Calder PC (2020) Marine *n*-3 (*n*-3) fatty acids for cardiovascular health: an update for 2020. *Int J Mol Sci* **21**, 1362.
19. Elagizi A, Lavie CJ, O' Keefe E, *et al.* (2021) An update on *n*-3 polyunsaturated fatty acids and cardiovascular health. *Nutrients* **13**, 204.
20. Wysoczański T, Sokoła-Wysoczańska E, Pękala J, *et al.* (2016) *n*-3 fatty acids and their role in central nervous system – a review. *Curr Med Chem* **23**, 816.
21. von Schacky C (2021) Importance of EPA and DHA blood levels in brain structure and function. *Nutrients* **13**, 1074.
22. Sherratt SCR, Libby P, Budoff MJ, *et al.* (2023) Role of *n*-3 fatty acids in cardiovascular disease: the debate continues. *Curr Atheroscler Rep* **25**, 1–17.
23. Backes J, Anzalone D, Hilleman D, *et al.* (2016) The clinical relevance of *n*-3 fatty acids in the management of hypertriglyceridemia. *Lipids Health Dis* **15**, 118.
24. Spector AA & Kim H (2019) Emergence of *n*-3 fatty acids in biomedical research. *Prostaglandins, Leukotrienes Essent Fatty Acids* **140**, 47–50.
25. Sala-Vila A, Fleming J, Kris-Etherton P, *et al.* (2022) Impact of $\alpha$-linolenic acid, the vegetable ω-3 fatty acid, on cardiovascular disease and cognition. *Adv Nutr* **13**, 1584–1602.
26. Musazadeh V, Kavyani Z, Naghshbandi B, *et al.* (2022) The beneficial effects of *n*-3 polyunsaturated fatty acids on controlling blood pressure: an umbrella meta-analysis. *Front Nutr* **9**, 985451.
27. DiNicolantonio JJ & O'Keefe JH (2020) The importance of marine *n*-3s for brain development and the prevention and treatment of behavior, mood, and other brain disorders. *Nutrients* **12**, 2333.
28. Zuo J, Wu Y, Xiang R, *et al.* (2021) ω-3 polyunsaturated fatty acids facilitate the repair of peripheral nerve defects with chemically extracted acellular allograft in rats. *Biomed Res Int* **2021**, 1–6.
29. Gao X, Su X, Han X, *et al.* (2022) Unsaturated fatty acids in mental disorders: an umbrella review of meta-analyses. *Adv Nutr* **13**, 2217–2236.
30. Wei B, Li L, Dong C, *et al.* (2023) The relationship of *n*-3 fatty acids with dementia and cognitive decline: evidence from prospective cohort studies of supplementation, dietary intake, and blood markers. *Am J Clin Nutr* **117**, 1096–1109.
31. Lin PY, Cheng C, Satyanarayanan SK, *et al.* (2022) *n*-3 fatty acids and blood-based biomarkers in Alzheimer's disease and mild cognitive impairment: a randomized placebo-controlled trial. *Brain Behav Immun* **99**, 289–298.
32. Lu Y, Qiao D & Mi G (2024) Clinical impacts of *n*-3 fatty acids supplementation on depression symptoms: an umbrella review of meta-analyses. *Br J Nutr* **131**, 841–850.
33. Jump DB, Lytle KA, Depner CM, *et al.* (2018) *n*-3 polyunsaturated fatty acids as a treatment strategy for nonalcoholic fatty liver disease. *Pharmacol Therapeut* **181**, 108–125.
34. Pellegrini M, Senni C, Bernabei F, *et al.* (2020) The role of nutrition and nutritional supplements in ocular surface diseases. *Nutrients* **12**, 952.
35. Li Y, Li Q, Cao Z, *et al.* (2022) The causal association of polyunsaturated fatty acids with allergic disease: a two-sample Mendelian randomization study. *Front Nutr* **9**, 962787.
36. Downie LE, Ng SM, Lindsley KB, *et al.* (2019) *n*-3 and *n*-6 polyunsaturated fatty acids for dry eye disease. *Cochrane Database Syst Rev 2019*, issue 12, CD011016.
37. Jiang H, Shi X, Fan Y, *et al.* (2021) Dietary *n*-3 polyunsaturated fatty acids and fish intake and risk of age-related macular degeneration. *Clin Nutr* **40**, 5662–5673.
38. Pan M, Zhao F, Xie B, *et al.* (2021) *Dietary ω-3 polyunsaturated fatty acids are protective for myopia. Proc Natl Acad Sci* **118**, e2104689118.
39. Heras A, Gomi R, Young M, *et al.* (2022) Dietary long-chain *n* 3 fatty acids modify sphingolipid metabolism to facilitate airway hyperreactivity. *Sci Rep-Uk* **12**, 19735.
40. Wake M & Kobayashi D (2021) Associations between plasma levels of *n*-3 fatty acids and subsequent allergic diseases. *Clin Nutr ESPEN* **42**, 318–324.
41. Shama S & Liu W (2020) *n*-3 fatty acids and gut microbiota: a reciprocal interaction in nonalcoholic fatty liver disease. *Dig Dis Sci* **65**, 906–910.

42. Manson JE, Cook NR, Lee I, *et al.* (2019) Marine *n*-3 fatty acids and prevention of cardiovascular disease and cancer. *New Engl J Med* **380**, 23–32.
43. Lee KH, Seong HJ, Kim G, *et al.* (2020) Consumption of fish and ω-3 fatty acids and cancer risk: an umbrella review of meta-analyses of observational studies. *Adv Nutr* **11**, 1134–1149.
44. D'Angelo S, Motti ML & Meccariello R (2020) ω-3 and ω-6 polyunsaturated fatty acids, obesity and cancer. *Nutrients* **12**, 2751.
45. Liput KP, Lepczyński A, Ogłuszka M, *et al.* (2021) Effects of dietary *n*-3 and *n*-6 polyunsaturated fatty acids in inflammation and cancerogenesis. *Int J Mol Sci* **22**, 6965.
46. Fabian CJ, Kimler BF & Hursting SD (2015) *n*-3 fatty acids for breast cancer prevention and survivorship. *Breast Cancer Res* **17**, 62.
47. Liang P, Henning SM, Grogan T, *et al.* (2024) Effect of *n*-3 fatty acid diet on prostate cancer progression and cholesterol efflux in tumor-associated macrophages-dependence on GPR120. *Prostate Cancer Prostatic Dis* **27**, 700–708.
48. Li X, Lu Z, Qi Y, *et al.* (2023) The role of polyunsaturated fatty acids in osteoarthritis: insights from a Mendelian randomization study. *Nutrients* **15**, 4787.
49. Huang T, Liu C, Cui C, *et al.* (2023) Potential of fatty acids in treating sarcopenia: a systematic review. *Nutrients* **15**, 3613.
50. Gao X, Hong G, Zhan W, *et al.* (2022) DPA promotes hBMSCs osteogenic differentiation by miR-9–5p/ERK/ALP signaling pathway. *Int J Med Sci* **19**, 1879–1887.
51. Wu L, Ying M, Ye Y, *et al.* (2024) Correlation of meniscus tear type with synovial inflammation and the therapeutic potential of docosapentaenoic acid. *BMC Musculoskel Dis* **25**, 375.
52. Huang R, Vi L, Zong X, *et al.* (2020) Maresin 1 resolves aged-associated macrophage inflammation to improve bone regeneration. *FASEB J* **34**, 13521–13532.
53. Allen KD, Thoma LM & Golightly YM (2022) Epidemiology of osteoarthritis. *Osteoarthr Cartilage* **30**, 184–195.
54. Bijlsma JW, Berenbaum F & Lafeber FP (2011) Osteoarthritis: an update with relevance for clinical practice. *Lancet* **377**, 2115–2126.
55. Ayers C, Kansagara D, Lazur B, *et al.* (2023) Effectiveness and safety of treatments to prevent fractures in people with low bone mass or primary osteoporosis: a living systematic review and network meta-analysis for the American College of Physicians. *Ann Intern Med* **176**, 182–195.
56. Cordingley DM & Cornish SM (2022) *n*-3 fatty acids for the management of osteoarthritis: a narrative review. *Nutrients* **14**, 3362.
57. Shawl M, Geetha T, Burnett D, *et al.* (2024) *n*-3 supplementation and its effects on osteoarthritis. *Nutrients* **16**, 1650.
58. Calder PC (2017) *n*-3 fatty acids and inflammatory processes: from molecules to man. *Biochem Soc T* **45**, 1105–1115.
59. Liu B, Zhang Y, Yang Z, *et al.* (2021) ω-3 DPA protected neurons from neuroinflammation by balancing microglia M1/M2 polarizations through inhibiting NF-κB/MAPK p38 signaling and activating neuron-BDNF-PI3K/AKT pathways. *Mar Drugs* **19**, 587.
60. Chen X, Chen C, Fan S, *et al.* (2018) *n*-3 polyunsaturated fatty acid attenuates the inflammatory response by modulating microglia polarization through SIRT1-mediated deacetylation of the HMGB1/NF-κB pathway following experimental traumatic brain injury. *J Neuroinflamm* **15**, 116.
61. Cucchi D, Camacho-Muñoz D, Certo M, *et al.* (2019) *n*-3 polyunsaturated fatty acids impinge on CD4+ T cell motility and adipose tissue distribution via direct and lipid mediator-dependent effects. *Cardiovasc Res* **116**, 1006–1020.
62. Gutiérrez S, Svahn SL & Johansson ME (2019) Effects of *n*-3 fatty acids on immune cells. *Int J Mol Sci* **20**, 5028.
63. Das UN (2021) 'Cell Membrane Theory of Senescence' and the role of bioactive lipids in aging, and aging associated diseases and their therapeutic implications. *Biomolecules* **11**, 241.
64. Pang Y, Liu X, Zhao C, *et al.* (2022) LC–MS/MS-based arachidonic acid metabolomics in acute spinal cord injury reveals the upregulation of 5-LOX and COX-2 products. *Free Radical Bio Med* **193**, 363–372.
65. Wang B, Wu L, Chen J, *et al.* (2021) Metabolism pathways of arachidonic acids: mechanisms and potential therapeutic targets. *Signal Transduct Target Therapy* **6**, 30–94.
66. Hoxha M (2020) What about COVID-19 and arachidonic acid pathway? *Eur J Clin Pharmacol* **76**, 1501–1504.
67. Peña-de-la-Sancha P, Muñoz-García A, Espínola-Zavaleta N, *et al.* (2023) Eicosapentaenoic and docosahexaenoic acid supplementation increases HDL content in *n*-3 fatty acids and improves endothelial function in hypertriglyceridemic patients. *Int J Mol Sci* **24**, 5390.
68. Yao Q, Wu X, Tao C, *et al.* (2023) Osteoarthritis: pathogenic signaling pathways and therapeutic targets. *Signal Transduction Targeted Ther* **8**, 56.
69. Zhong Y, Liang B, Zhang X, *et al.* (2024) NF-κB affected the serum levels of TNF-$\alpha$ and IL-1$\beta$ via activation of the MAPK/NF-κB signaling pathway in rat model of acute pulmonary microthromboembolism. *Pulm Circ* **14**, e12357.
70. Jiang Z, Zeng Z, He H, *et al.* (2023) Lycium barbarum glycopeptide alleviates neuroinflammation in spinal cord injury via modulating docosahexaenoic acid to inhibiting MAPKs/NF-kB and pyroptosis pathways. *J Transl Med* **21**, 770.
71. Jin X, Dong X, Sun Y, *et al.* (2022) Dietary fatty acid regulation of the NLRP3 inflammasome via the TLR4/NF-κB signaling pathway affects chondrocyte pyroptosis. *Oxid Med Cell Longev* **2022**, 1–25.
72. Zhang T, Dai Y, Zhang L, *et al.* (2020) Effects of edible oils with different *n*-6/*n*-3 PUFA ratios on articular cartilage degeneration via regulating the NF-κB signaling pathway. *J Agr Food Chem* **68**, 12641–12650.
73. Dyall SC, Balas L, Bazan NG, *et al.* (2022) Polyunsaturated fatty acids and fatty acid-derived lipid mediators: recent advances in the understanding of their biosynthesis, structures, and functions. *Prog Lipid Res* **86**, 101165.
74. Chiang N & Serhan CN (2020) Specialized pro-resolving mediator network: an update on production and actions. *Essays Biochem* **64**, 443–462.
75. Oppedisano F, Bulotta RM, Maiuolo J, *et al.* (2021) The role of nutraceuticals in osteoarthritis prevention and treatment: focus on *n*-3 PUFAs. *Oxid Med Cell Longev* **2021**, 4878562.
76. Caron JP, Gandy JC, Brown JL, *et al.* (2019) *n*-3 fatty acids and docosahexaenoic acid oxymetabolites modulate the inflammatory response of equine recombinant interleukin1$\beta$-stimulated equine synoviocytes. *Prostag Oth Lipid M* **142**, 1–8.
77. Shih YV, Tao H, Gilpin A, *et al.* (2024) Specialized pro-resolving mediator Maresin 1 attenuates pain in a mouse model of osteoarthritis. *Osteoarthr Cartilage* **S1063–4584**, 1477–1478.
78. Park J, Roh J, Pan J, *et al.* (2023) Role of resolvins in inflammatory and neuropathic pain. *Pharmaceuticals* **16**, 1366.
79. Zhao Q, Wang Y, Wang S, *et al.* (2022) Protectin DX attenuates lumbar radicular pain of non-compressive disc herniation by autophagy flux stimulation via adenosine monophosphate-activated protein kinase signaling. *Front Physiol* **12**, 784653.
80. Lu J, Feng X, Zhang H, *et al.* (2020) Maresin-1 suppresses IL-1 $\beta$ -induced MMP-13 secretion by activating the PI3K/AKT pathway and inhibiting the NF- κ B pathway in synovioblasts of an osteoarthritis rat model with treadmill exercise. *Connect Tissue Res* **62**, 508–518.
81. Poggioli R, Hirani K, Jogani VG, *et al.* (2023) Modulation of inflammation and immunity by *n*-3 fatty acids: a possible role for prevention and to halt disease progression in autoimmune, viral, and age-related disorders. *Eur Rev Med Pharmaco* **27**, 7380–7400.
82. Coniglio S, Shumskaya M & Vassiliou E (2023) Unsaturated fatty acids and their immunomodulatory properties. *Biology* **12**, 279.
83. Hou TY, McMurray DN & Chapkin RS (2016) *n*-3 fatty acids, lipid rafts, and T cell signaling. *Eur J Pharmacol* **785**, 2–9.
84. Oner F, Alvarez C, Yaghmoor W, *et al.* (2021) Resolvin E1 regulates Th17 function and T cell activation. *Front Immunol* **12**, 637983.
85. Perez-Hernandez J, Chiurchiù V, Perruche S, *et al.* (2021) Regulation of T-cell immune responses by pro-resolving lipid mediators. *Front Immunol* **12**, 768133.
86. Schwager J, Bompard A, Raederstorff D, *et al.* (2022) Resveratrol and ω-3 PUFAs promote human macrophage differentiation and function. *Biomedicines* **10**, 1524.

87. Videla LA, Valenzuela R, Del Campo A, *et al.* (2023) *n*-3 lipid mediators: modulation of the M1/M2 macrophage phenotype and its protective role in chronic liver diseases. *Int J Mol Sci* **24**, 15528.
88. Lu J, Zhang H, Pan J, *et al.* (2021) Fargesin ameliorates osteoarthritis via macrophage reprogramming by downregulating MAPK and NF-κB pathways. *Arthritis Res Ther* **23**, 142.
89. Sun AR, Wu X, Liu B, *et al.* (2019) Pro-resolving lipid mediator ameliorates obesity induced osteoarthritis by regulating synovial macrophage polarisation. *Sci Rep-Uk* **9**, 426.
90. Zhou K, Yang C, Shi K, *et al.* (2023) Activated macrophage membrane-coated nanoparticles relieve osteoarthritis-induced synovitis and joint damage. *Biomaterials* **295**, 122036.
91. Gravallese EM & Firestein GS (2023) Rheumatoid arthritis – common origins, divergent mechanisms. *N Engl J Med* **388**, 529–542.
92. Brown P, Pratt AG & Hyrich KL (2024) Therapeutic advances in rheumatoid arthritis. *BMJ* **384**, e70856.
93. Hwang JJ, Rim YA, Nam Y, *et al.* (2021) Recent developments in clinical applications of mesenchymal stem cells in the treatment of rheumatoid arthritis and osteoarthritis. *Front Immunol* **12**, 631291.
94. Smolen JS (2020) Insights into the treatment of rheumatoid arthritis: a paradigm in medicine. *J Autoimmun* **110**, 102425.
95. Nikiphorou E & Philippou E (2023) Nutrition and its role in prevention and management of rheumatoid arthritis. *Autoimmun Rev* **22**, 103333.
96. Vadell AKE, Bärebring L, Hulander E, *et al.* (2023) Anti-inflammatory Diet In Rheumatoid Arthritis (ADIRA) — a randomized, controlled crossover trial indicating effects on disease activity. *Am J Clin Nutr* **111**, 1203–1213.
97. Raad T, Griffin A, George ES, *et al.* (2021) Dietary Interventions with or without *n*-3 supplementation for the management of rheumatoid arthritis: a systematic review. *Nutrients* **13**, 3506.
98. Navarini L, Afeltra A, Gallo Afflitto G, *et al.* (2017) Polyunsaturated fatty acids: any role in rheumatoid arthritis? *Lipids Health Dis* **16**, 197.
99. Jin S, Sun S, Ling H, *et al.* (2021) Protectin DX restores Treg/Th17 cell balance in rheumatoid arthritis by inhibiting NLRP3 inflammasome via miR-20a. *Cell Death Dis* **12**, 280.
100. Deng C, Zhang Q, He P, *et al.* (2021) Targeted apoptosis of macrophages and osteoclasts in arthritic joints is effective against advanced inflammatory arthritis. *Nat Commun* **12**, 2174.
101. Su Y, Han Y, Choi HS, *et al.* (2024) Lipid mediators obtained from docosahexaenoic acid by soybean lipoxygenase attenuate RANKL-induced osteoclast differentiation and rheumatoid arthritis. *Biomed Pharmacother* **171**, 116153.
102. Dalbeth N, Gosling AL, Gaffo A, *et al.* (2021) Gout. *Lancet* **397**, 1843–1855.
103. Danve A, Sehra ST & Neogi T (2021) Role of diet in hyperuricemia and gout. *Best Pract Res Clin Rheumatol* **35**, 101723.
104. Zhang Y, Chen S, Yuan M, *et al.* (2022) Gout and diet: a comprehensive review of mechanisms and management. *Nutrients* **14**, 3525.
105. Clebak KT, Morrison A & Croad JR (2020) Gout: rapid evidence review. *Am Fam Physician* **102**, 533–538.
106. Li R, Yu K & Li C (2018) Dietary factors and risk of gout and hyperuricemia: a meta-analysis and systematic review. *Asia Pac J Clin Nutr* **27**, 1344–1356.
107. Zeng G, You D, Ye L, *et al.* (2023) *n*-3 PUFA poor seafood consumption is associated with higher risk of gout, whereas *n*-3 PUFA rich seafood is not: NHANES 2007–2016. *Front Nutr* **27**, 1344–1356.
108. Zhang M, Zhang Y, Terkeltaub R, *et al.* (2019) Effect of dietary and supplemental *n*-3 polyunsaturated fatty acids on risk of recurrent gout flares. *Arthritis Rheumatol* **71**, 1580–1586.
109. Saito H, Toyoda Y, Takada T, *et al.* (2020) *n*-3 polyunsaturated fatty acids inhibit the function of human URAT1, a renal urate re-absorber. *Nutrients* **12**, 1601.
110. Wen C, Xu X, Zhang Y, *et al.* (2024) Bone targeting nanoparticles for the treatment of osteoporosis. *Int J Nanomed* **19**, 1363–1383.
111. Zhou S, Huang G & Chen G (2020) Synthesis and biological activities of drugs for the treatment of osteoporosis. *Eur J Med Chem* **197**, 112313.
112. Sharma T & Mandal CC (2020) *n*-3 fatty acids in pathological calcification and bone health. *J Food Biochem* **44**, e13333.
113. Abshirini M, Ilesanmi-Oyelere BL & Kruger MC (2021) Potential modulatory mechanisms of action by long-chain polyunsaturated fatty acids on bone cell and chondrocyte metabolism. *Prog Lipid Res* **83**, 101113.
114. Chen F, Wang Y, Wang H, *et al.* (2019) Flaxseed oil ameliorated high-fat-diet-induced bone loss in rats by promoting osteoblastic function in rat primary osteoblasts. *Nutr Metab* **16**, 71.
115. Yue H, Bo Y, Tian Y, *et al.* (2022) Docosahexaenoic acid-enriched phosphatidylcholine exerted superior effects to triglyceride in ameliorating obesity-induced osteoporosis through up-regulating the Wnt/*β*-Catenin pathway. *J Agr Food Chem* **70**, 13904–13912.
116. Zhang T, Tian Y, Wang Q, *et al.* (2021) Comparative study of DHA with different molecular forms for ameliorating osteoporosis by promoting chondrocyte-to-osteoblast transdifferentiation in the growth plate of ovariectomized mice. *J Agr Food Chem* **69**, 10562–10571.
117. Xue C, Luo H, Wang L, *et al.* (2023) Aconine attenuates osteoclast-mediated bone resorption and ferroptosis to improve osteoporosis via inhibiting NF-κB signaling. *Front Endocrinol* **14**, 1234563.
118. McDonald MM, Khoo WH, Ng PY, *et al.* (2021) Osteoclasts recycle via osteomorphs during RANKL-stimulated bone resorption. *Cell* **184**, 1330–1347.
119. Song J, Jing Z, Hu W, *et al.* (2017) *α*-linolenic acid inhibits receptor activator of NF-κB ligand induced (RANKL-Induced) osteoclastogenesis and prevents inflammatory bone loss via downregulation of nuclear factor-KappaB-inducible nitric oxide synthases (NF-κB-iNOS) signaling pathways. *Med Sci Monit* **23**, 5056–5069.
120. Zhan Q, Tian Y, Han L, *et al.* (2020) The opposite effects of Antarctic krill oil and arachidonic acid-rich oil on bone resorption in ovariectomized mice. *Food Funct* **11**, 7048–7060.
121. Wang Z, Wu J, Li L, *et al.* (2023) Eicosapentaenoic acid supplementation modulates the osteoblast/osteoclast balance in inflammatory environments and protects against estrogen deficiency-induced bone loss in mice. *Clin Nutr* **42**, 1715–1727.
122. Tai T & Chen C (2023) Isolated ulnar shaft fractures. *New Engl J Med* **388**, e59.
123. Nayagam S, Jacob N, Amin A, *et al.* (2015) Management of high-energy tibial pilon fractures. *Strateg Trauma Limb Reconstr* **10**, 137–147.
124. Casas CC & Gonzalez MM (2024) Hemotympanum with a basilar skull fracture. *New Engl J Med* **390**, e38.
125. Steinmetz S, Brgger A, Chauveau J, *et al.* (2020) Practical guidelines for the treatment of patellar fractures in adults. *Swiss Med Wkly* **150**, w20165.
126. Kußmaul AC, Kuehlein T, Langer MF, *et al.* (2024) The conservative and operative treatment of carpal fractures. *Dtsch Arztebl Int* **121**, 594–600.
127. Handoll HHG & Elliott J (2015) Rehabilitation for distal radial fractures in adults. *Cochrane Database Syst Rev 2015*, issue 9, CD003324.
128. Kim D, Kim D, Kim B, *et al.* (2020) Current concepts for classification and treatment of distal clavicle fractures. *Clin Orthopedic Surg* **12**, 135.
129. Midtgaard KS, Ruzbarsky JJ, Hackett TR, *et al.* (2020) Elbow fractures. *Clin Sport Med* **39**, 623–636.
130. Cimerman M, Kristan A, Jug M, *et al.* (2021) Fractures of the acetabulum: from yesterday to tomorrow. *Int Orthop* **45**, 1057–1064.
131. Herterich V, Baumbach SF, Kaiser A, *et al.* (2021) Fifth metatarsal fracture–a systematic review of the treatment of fractures of the base of the fifth metatarsal bone. *Dtsch Arztebl Int* **118**, 587–594.
132. Sadeghi O, Djafarian K, Ghorabi S, *et al.* (2017) Dietary intake of fish, *n*-3 polyunsaturated fatty acids and risk of hip fracture: a systematic review and meta-analysis on observational studies. *Crit Rev Food Sci* **59**, 1320–1333.
133. Martyniak K, Wei F, Ballesteros A, *et al.* (2020) Do polyunsaturated fatty acids protect against bone loss in our aging and osteoporotic population. *Bone* **143**, 115736.
134. Halil Kafadar İ, Yalçın Y & Çakar B (2024) Vitamin D3 and *n*-3 polyunsaturated fatty acids have beneficial effects on fracture union in an experimental rat model. *Joint Dis Relat Surg* **35**, 121–129.

135. Chen Y, Cao H, Sun D, *et al.* (2017) Endogenous production of *n*-3 polyunsaturated fatty acids promotes fracture healing in mice. *J Healthc Eng* **2017**, 1–6.
136. Zhang L, Terrando N, Xu Z, *et al.* (2018) Distinct analgesic actions of DHA and DHA-derived specialized pro-resolving mediators on post-operative pain after bone fracture in mice. *Front Pharmacol* **9**, 412.
137. Zheng X, Jia R, Li Y, *et al.* (2020) *n*-3 fatty acids reduce post-operative risk of deep vein thrombosis and pulmonary embolism after surgery for elderly patients with proximal femoral fractures: a randomized placebo-controlled, double-blind clinical trial. *Int Orthop* **44**, 2089–2093.
138. Cruz-Jentoft AJ & Sayer AA (2019) Sarcopenia. *Lancet* **393**, 2636–2646.
139. Sayer AA & Cruz-Jentoft A (2022) Sarcopenia definition, diagnosis and treatment: consensus is growing. *Age Ageing* **51**, c220.
140. Chen L, Woo J, Assantachai P, *et al.* (2020) Asian Working Group for Sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. *J Am Med Dir Assoc* **21**, 300–307.
141. Sayer AA, Cooper R, Arai H, *et al.* (2024) Sarcopenia. *Nat Rev Dis Primers* **10**, 68.
142. Jimenez-Gutierrez GE, Martínez-Gómez LE, Martínez-Armenta C, *et al.* (2022) Molecular mechanisms of inflammation in Sarcopenia: diagnosis and therapeutic update. *Cells-Basel* **11**, 2359.
143. Dupont J, Dedeyne L, Dalle S, *et al.* (2019) The role of *n*-3 in the prevention and treatment of Sarcopenia. *Aging Clin Exp Res* **31**, 825–836.
144. Bird JK, Troesch B, Warnke I, *et al.* (2021) The effect of long chain *n*-3 polyunsaturated fatty acids on muscle mass and function in sarcopenia: a scoping systematic review and meta-analysis. *Clin Nutr ESPEN* **46**, 73–86.
145. Suzuki K (2019) Chronic inflammation as an immunological abnormality and effectiveness of exercise. *Biomolecules* **9**, 223.
146. Liang Z, Zhang T, Liu H, *et al.* (2022) Inflammaging: the ground for sarcopenia? *Exp Gerontol* **168**, 111931.
147. Vinel C, Lukjanenko L, Batut A, *et al.* (2018) The exerkine apelin reverses age-associated sarcopenia. *Nat Med* **24**, 1360–1371.
148. Serrano AL, Baeza-Raja B, Perdiguero E, *et al.* (2008) Interleukin-6 is an essential regulator of satellite cell-mediated skeletal muscle hypertrophy. *Cell Metab* **7**, 33–44.
149. McKay BR, De Lisio M, Johnston APW, *et al.* (2009) Association of interleukin-6 signalling with the muscle stem cell response following muscle-lengthening contractions in humans. *Plos One* **4**, e6027.
150. Serhan CN, Bäck M, Chiurchiù V, *et al.* (2024) Expert consensus report on lipid mediators: role in resolution of inflammation and muscle preservation. *FASEB J* **38**, e23699.
151. Johnson ML, Lalia AZ, Dasari S, *et al.* (2015) Eicosapentaenoic acid but not docosahexaenoic acid restores skeletal muscle mitochondrial oxidative capacity in old mice. *Aging Cell* **14**, 734–743.
152. Lalia AZ, Dasari S, Robinson MM, *et al.* (2017) Influence of *n*-3 fatty acids on skeletal muscle protein metabolism and mitochondrial bioenergetics in older adults. *Aging (Albany, NY.)* **9**, 1096–1129.
153. Zeng Z, Liang J, Wu L, *et al.* (2020) Exercise-induced autophagy suppresses sarcopenia through Akt/mTOR and Akt/FoxO3a signal pathways and AMPK-mediated mitochondrial quality control. *Front Physiol* **11**, 583478.
154. Hsu WH, Wang SY, Chao YM, *et al.* (2024) Novel metabolic and lipidomic biomarkers of sarcopenia. *J Cachexia, Sarcopenia Muscle* **15**, 2175–2186.
155. Azzolino D, Bertoni C, De Cosmi V, *et al.* (2024) *n*-3 polyunsatured fatty acids and physical performance across the lifespan: a narrative review. *Front Nutr* **11**, 1414132.
156. López-Seoane J, Jiménez SL, Del Coso J, *et al.* (2023) Muscle hypertrophy induced by *n*-3 PUFA supplementation in absence of exercise: a systematic review of randomized controlled trials. *Crit Rev Food Sci* **63**, 6536–6546.
157. Liu Z & Zhu C (2023) Causal relationship between insulin resistance and sarcopenia. *Diabetol Metab Syndr* **15**, 46.
158. Ye C, Kong L, Wang Y, *et al.* (2023) Causal associations of sarcopenia-related traits with cardiometabolic disease and Alzheimer's disease and the mediating role of insulin resistance: a Mendelian randomization study. *Aging Cell* **22**, e13923.
159. Li CW, Yu K, Shyh Chang N, *et al.* (2022) Pathogenesis of sarcopenia and the relationship with fat mass: descriptive review. *J Cachexia, Sarcopenia Muscle* **13**, 781–794.
160. Marcotte-Chénard A, Oliveira B, Little JP, *et al.* (2023) Sarcopenia and type 2 diabetes: pathophysiology and potential therapeutic lifestyle interventions. *Diabetes Metab Syndrome: Clin Res Rev* **17**, 102835.
161. Moradi S, Alivand M, KhajeBishak Y, *et al.* (2021) The effect of *n*-3 fatty acid supplementation on PPAR*γ* and UCP2 expressions, resting energy expenditure, and appetite in athletes. *BMC Sports Sci Med Rehabil* **13**, 48.
162. Liu S, Lin W, Tzeng H, *et al.* (2023) Attenuation of diabetes-mediated muscle atrophy in rats by fish oil enriched *n*-3 polyunsaturated fatty acids supplementation. *J Food Drug Anal* **31**, 458–472.
163. Zhao X, Ma H, Han H, *et al.* (2022) Precision medicine strategies for spinal degenerative diseases: injectable biomaterials with *in* situ repair and regeneration. *Mater Today Bio* **16**, 100336.
164. Bumann H, Nüesch C, Loske S, *et al.* (2020) Severity of degenerative lumbar spinal stenosis affects pelvic rigidity during walking. *Spine J* **20**, 112–120.
165. Koyama K, Wada K, Kumagai G, *et al.* (2021) Association between mild cognitive impairment and lumbar degenerative disease in a Japanese community: a cross-sectional study. *Plos One* **16**, e258852.
166. Stephens ME, O'Neal CM, Westrup AM, *et al.* (2022) Utility of machine learning algorithms in degenerative cervical and lumbar spine disease: a systematic review. *Neurosurg Rev* **45**, 965–978.
167. Witiw CD & Fehlings MG (2017) Degenerative cervical myelopathy. *Can Med Assoc J* **189**, E116.
168. NaPier Z, Kanim LEA, Arabi Y, *et al.* (2019) *n*-3 fatty acid supplementation reduces intervertebral disc degeneration. *Med Sci Monit* **25**, 9531–9537.
169. Shang L, Ma H, Zhang X, *et al.* (2023) Docosahexaenoic acid alleviates the excessive degradation of extracellular matrix in the nucleus pulposus by reducing the content of lncRNA NEAT1 to prevent the progression of intervertebral disc degeneration. *Clin Exp Pharmacol P* **50**, 403–414.
170. Naratadam GT, Mecklenburg J, Shein SA, *et al.* (2024) Degenerative and regenerative peripheral processes are associated with persistent painful chemotherapy-induced neuropathies in males and females. *Sci Rep-Uk* **14**, 17543.
171. Lu X, Chen L, Jiang C, *et al.* (2023) Microglia and macrophages contribute to the development and maintenance of sciatica in lumbar disc herniation. *Pain* **164**, 362–374.
172. Manzhulo IV, Ogurtsova OS, Lamash NE, *et al.* (2015) Analgetic effect of docosahexaenoic acid is mediated by modulating the microglia activity in the dorsal root ganglia in a rat model of neuropathic pain. *Acta Histochem* **117**, 659–666.
173. Wang Y, Li Y, Wang J, *et al.* (2020) A novel mechanism of specialized proresolving lipid mediators mitigating radicular pain: the negative interaction with NLRP3 inflammasome. *Neurochem Res* **45**, 1860–1869.
174. Leow MQH, Zheng Q, Shi L, *et al.* (2021) Non-steroidal anti-inflammatory drugs (NSAIDs) for trigger finger. *Cochrane Database Syst Rev 2021*, issue 4, CD012789.
175. Sisignano M & Geisslinger G (2023) Rethinking the use of NSAIDs in early acute pain. *Trends Pharmacol Sci* **44**, 193–195.
176. Eisenstein A, Hilliard BK, Pope SD, *et al.* (2022) Activation of the transcription factor NRF2 mediates the anti-inflammatory properties of a subset of over-the-counter and prescription NSAIDs. *Immun* **55**, 1082–1095.
177. Bindu S, Mazumder S & Bandyopadhyay U (2020) Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: a current perspective. *Biochem Pharmacol* **180**, 114147.
178. Schjerning A, McGettigan P & Gislason G (2020) Cardiovascular effects and safety of (non-aspirin) NSAIDs. *Nat Rev Cardiol* **17**, 574–584.
179. Ribeiro H, Rodrigues I, Napoleão L, *et al.* (2022) Non-steroidal anti-inflammatory drugs (NSAIDs), pain and aging: adjusting prescription to patient features. *Biomed Pharmacother* **150**, 112958.

180. Panchal NK & Prince Sabina E (2023) Non-steroidal anti-inflammatory drugs (NSAIDs): a current insight into its molecular mechanism eliciting organ toxicities. *Food Chem Toxicol* **172**, 113598.
181. Minaldi E & Cahill K (2023) Recent updates in understanding NSAID hypersensitivity. *Curr Allergy Asthm R* **23**, 181–188.
182. Stonehouse W, Benassi-Evans B, Bednarz J, *et al.* (2022) Krill oil improved osteoarthritic knee pain in adults with mild to moderate knee osteoarthritis: a 6-month multicenter, randomized, double-blind, placebo-controlled trial. *Am J Clin Nutr* **116**, 1454.
183. Shields A, Ly S, Wafae B, *et al.* (2023) Safety and effectiveness of oral nutraceuticals for treating acne. *JAMA Dermatol* **159**, 1373.
184. Salmon J, Wallace DJ, Rus V, *et al.* (2024) Correction of *n*-3 fatty acid deficiency and improvement in disease activity in patients with systemic lupus erythematosus treated with krill oil concentrate: a multicentre, randomised, double-blind, placebo-controlled trial. *Lupus Sci Med* **11**, e1201.
185. Mori T, Murasaki K, Hayashi K, *et al.* (2022) Efficacy and safety of self-emulsifying formulation of highly purified eicosapentaenoic acid ethyl ester (MND-2119) *v.* highly purified eicosapentaenoic acid ethyl ester in patients with hypertriglyceridemia: results from a 12-week randomized, double-blind, active-controlled, phase 3 study. *J Clin Lipidol* **16**, 704–714.
186. Mori T, Murasaki K & Yokoyama Y (2022) Long-term safety and efficacy of MND-2119 (self-emulsifying formulation of highly purified eicosapentaenoic acid ethyl ester) in patients with hypertriglyceridemia: results from a multicenter, 52-week, open-label study. *J Clin Lipidol* **16**, 737–746.