1 . Omega 3 EPA/DHA

Benefits:

- Reduction of joint pain and tenderness.
- Reduction of the need for nonsteroidal anti-inflammatory drugs (NSAIDs).
- Improvement of markers of disease activity and morning stiffness.
- Reduction of inflammatory mediators such as LTB4.
- Possible cardioprotective benefit in patients with RA.

Effective doses

Most studies used 2.7–5 g EPA+DHA daily for at least 12 weeks.

Mechanism of action

The mechanism of action of omega-3 fatty acids (mainly EPA and DHA) in rheumatoid arthritis is multifaceted and is based on the suppression of chronic inflammation and the modification of the immune response.The main mechanism is biochemical competition with arachidonic acid (AA), an omega-6 fatty acid. With increased intake of ω-3, EPA and DHA are incorporated into the phospholipids of the cell membranes of immune cells, displacing arachidonic acid. Thus, the enzymes cyclooxygenase (COX) and lipoxygenase (LOX) now use EPA instead of AA as a substrate. This leads to the synthesis of eicosanoids (prostaglandins series 3 and leukotrienes series 5) that have extremely weak or no pro-inflammatory activity, thus reducing pain and swelling in the joint. Synthesis of Specialized Pro-resolving Mediators (SPMs)In addition, omega-3 fatty acids are actively metabolized into a class of lipid molecules called Specialized Pro-resolving Mediators (SPMs) called resolvins and protectins, which are produced directly from EPA and DHA and do not simply passively stop inflammation, but actively act to terminate it (resolution), promoting the removal of cellular debris and the healing of joint tissues.Suppression of Pro-Inflammatory Cytokines Rheumatoid arthritis is characterized by the overproduction of cytokines that destroy cartilage. Omega-3s intervene in this process: They significantly reduce the levels of Tumor Necrosis Factor α (TNF-α), Interleukin-1β (IL-1β) and Interleukin-6 (IL-6).This is achieved through the inhibition of the transcription factor NF-κB, which signals the cell nucleus to start producing these inflammatory proteins.Immunomodulation and T-Cell RegulationAs an autoimmune disease, rheumatoid arthritis is driven by a faulty immune response.Omega-3s:Regulate the differentiation of T-lymphocytes, correcting the imbalance between Th1 and Th2 subsets.They reduce the expression of MHC class II molecules on antigen-presenting cells, thus reducing the intensity with which the immune system "attacks" the tissues of the joint itself.Reduction of Adhesion Molecules

ω-3 fatty acids reduce the expression of adhesion molecules (e.g. VCAM-1, ICAM-1) on the endothelial cells of the joints. In this way, the infiltration and migration of new leukocytes from the blood to the synovial membrane is prevented, limiting the ongoing swelling.

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Omega-3 polyunsaturated fatty acids for the treatment of rheumatoid arthritishttps://doi.org/10.1136/annrheumdis-2012-eular.613 Meta-Analysis

2 . Inulin

Benefits:

• Reduction of systemic inflammation markers.
• Improvement of the clinical picture of the joints.
• Regulation of the immune system through the gut-joint axis.
• As a prebiotic, inulin feeds the beneficial bacteria of the gut, leading to the production of metabolites with a strong anti-inflammatory effect.
• Reduction of Inflammation: Clinical studies show that the supplementary administration of inulin significantly reduces the levels of C-reactive protein (CRP), which is a key indicator of disease activity.
• Improvement of Clinical Symptoms: Contributes to the reduction of the number of tender and swollen joints.
•Reduction of Morning Stiffness: Helps reduce the duration and intensity of morning stiffness, improving daily mobility.
•Increase Muscle Strength: Studies have recorded a significant increase in hand grip strength, which translates into better functionality.
•Improvement of Quality of Life: Reduces the overall disability score and improves patients' ability to perform daily activities (based on the HAQ questionnaire).
Scientific Evidence & Clinical Data
The action of inulin has been confirmed both in preclinical models and in recent, high-quality clinical trials in humans:
• Triple-blind Randomized Controlled Trial (RCT, 2025): Published in Scientific Reports (Nature) and showed that daily intake of 10 grams of inulin for 8 weeks in adults with RA led to significant improvement in the disease activity index (DAS-28), CRP, grip strength and morning stiffness.
• Preclinical Studies: Studies in mice with collagen-induced arthritis (CIA) confirmed that a diet rich in inulin attenuates cartilage destruction through metabolic remodeling of CD4+ T cells.
• Synbiotic Action (Synbiotics): Co-administration of inulin with probiotics has been found to reduce the production of acute phase proteins, such as serum amyloid A (SAA) and fibrinogen.

Mechanisms of Action (Gut-Joints)

Production of Short Chain Fatty Acids (SCFAs): Fermentation of inulin by the microbiome increases butyrate in the gut.Regulation of T-Lymphocytes: Butyric acid restores the balance between Th17 cells (which cause inflammation) and Treg (regulatory cells) that suppress autoimmunity. Reduction of Pro-Inflammatory Cytokines: Suppresses the overproduction of TNF-α and IL-17, which are responsible for joint destruction.Gut Barrier Protection: Enhances intestinal mucosal integrity, preventing the leakage of bacterial toxins into the bloodstream, which triggers systemic flares.

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3. β-Glucan

Benefits:

• Reduction of inflammation: Reduces swelling and tenderness in the joints.

• Cartilage protection: Helps reduce the degradation of joint tissues and protects cartilage cells.

• Synergistic action with drugs: Enhances the effectiveness of basic antirheumatic treatment, such as methotrexate (MTX), while reducing its side effects.

• Protection against infections: Protects the immune system of patients, who often take immunosuppressive drugs and are vulnerable to secondary infections.

Mechanism of Action

Beta-glucans act as a potent immunomodulator (biological response modifier) through the following cellular pathways:Binding with Specific Receptors: After oral ingestion, beta-glucans are bound by receptors (such as Dectin-1, CR3 and TLR-2/6) on the surface of innate immune cells (macrophages, dendritic cells and neutrophils) in the intestine.Suppression of Pro-Inflammatory Cytokines: They regulate the NF-κB transcriptional pathway, inhibiting the overproduction of cytokines that trigger RA, such as tumor necrosis factor alpha (TNF-α) and interleukins IL-1β and IL-6.Activation of Regulatory T-Cells (Tregs): Promotes the creation of Tregs cells, which are responsible for suppressing autoimmune reactions and restoring immune homeostasis.
Reduction of Oxidative Stress: Acts as antioxidants, reducing markers of oxidative damage (e.g. MDA , NO) in synovial fluid. The dosage is 3 g daily.

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4. Soluble Wheat Fiber

Benefits:

• Reduction of systemic inflammation: Reduces levels of circulating inflammatory cytokines and C-reactive protein (CRP).

• Clinical symptom improvement: Helps reduce pain, swelling and morning stiffness in joints.

• Enhancement of medication: Recent clinical trials show that the addition of fiber enhances the effectiveness of methotrexate (MTX).

• Bone protection: Helps to halt bone loss caused around affected joints.

Mechanism of Action

The mechanism of action is multi-layered and is based on the fermentation of fiber by the gut microbiota:Production of Short Chain Fatty Acids (SCFAs)Soluble fibers are not digested by the stomach, but reach the large intestine intact, where they serve as prebiotic food for beneficial bacteria. This fermentation produces SCFAs (acetic, propionic and butyric acid).
Restoration of Th17 / Tregs BalanceIn Rheumatoid Arthritis there is excessive activity of Th17 cells (which cause inflammation) and reduced activity of regulatory T-cells (Tregs - which suppress inflammation). SCFAs enter the bloodstream, stimulate the activation of Tregs cells and restore immune tolerance.Reduced Intestinal Permeability (“Leaky Gut”)

Dysbiosis (disruption of the microbiome) increases the protein zonulin, which damages the tight junctions of the intestine. This allows bacterial antigens to “leak” into the blood and migrate to the joints, triggering an autoimmune attack. Soluble wheat fiber reduces zonulin, shields the intestinal barrier and stops this antigen transfer.Reduced AutoantibodiesRegular fiber intake has been associated with reduced levels of anti-citrullinated antibodies (ACPA / anti-CCP) and rheumatoid factor (RF), which are the main markers of the disease. The recommended dosage for soluble wheat fiber in Rheumatoid Arthritis ranges between 5 and 15 grams per day.

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5.Pea Protein (PEA)

Benefits:

•Reduces Systemic Inflammation: Replaces animal proteins, which are rich in saturated fats and promote inflammation in the body.
•Protects against Rheumatic Cachexia: Chronic inflammation in RA causes intense catabolism and loss of muscle mass. Pea protein supplies the body with unparalleled amino acids to maintain muscle.
•Supports the Gut Barrier: It is rich in glutamine, which enhances gut health. The balance of the microbiome is directly linked to the reduction of RA flare-ups.
•Hypoallergenic Nature: It does not contain gluten, lactose or soy, ingredients that often trigger immune responses and worsen arthritic symptoms.

Mechanism of Action

The main biological mechanisms through which pea protein (especially its hydrolyzed form) acts include:Suppression of Pro-Inflammatory Cytokines: Pea bioactive peptides inhibit the secretion of Tumor Necrosis Factor-α (TNF-α) and Interleukin-6 (IL-6) from activated macrophage cells.
Reduction of Oxidative Stress: Reduces the production of nitric oxide (NO) and reactive oxygen species (ROS), protecting joint tissues from oxidative damage.
Anabolic Action via BCAAs: It is rich in branched-chain amino acids (Leucine, Isoleucine, Valine), which activate the mTOR pathway for the synthesis of new muscle mass, reversing RA myopathy.
The dosage is 1.1 to 1.5 grams of protein per kilogram of body weight per day

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The effect of pea protein (and more generally the shift to plant-based proteins) in reducing joint pain in Rheumatoid Arthritis is direct and multifaceted. It does not act as a simple painkiller, but acts “at the root” of the problem, reducing the stimuli that cause pain.

•Reduction of nerve sensitivity (Pain Desensitization): Chronic inflammation in the joints “irritates” the nerve endings (peripheral sensitization), making them overly sensitive even to simple movement. The bioactive peptides of pea reduce neuroinflammatory factors, “silencing” pain signals to the brain.

•**Reduce Swelling and Pressure (Synovitis):** The pain of RA is largely due to the pressure exerted by the accumulated fluid inside the joint (synovitis). By suppressing cytokines, pea protein helps reduce swelling, immediately relieving the joint from internal pressure.
•**Protect Cartilage: The destruction of cartilage leaves the bones unprotected, causing intense friction pain. The antioxidant** action of pea amino acids blocks the enzymes that break down articular cartilage.
•**Avoid Pain Triggers**: Animal proteins contain high levels of arachidonic acid, which the body converts into prostaglandins (substances that cause acute pain). Peas, as a plant source, lack these pro-inflammatory fats.

Clinical studies on pain
Studies that evaluated the shift to strictly plant-based proteins (Plant-Based Diets) in patients with Rheumatoid Arthritis showed:
Significant drop in pain scale (VAS Score): Patients reported less intense pain during daily activities.
Reduction in morning stiffness: The time it took patients to "wake up" their joints in the morning was significantly reduced.
Less sensitive joints (Tender Joints): When palpated by doctors, the joints showed a less painful reaction.

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6. L – Carnitine

Patients with RA often have reduced plasma carnitine levels,
Benefits:
•Reduction of pain and stiffness: Significantly improves pain intensity (based on the VAS scale) and reduces the duration of morning stiffness.
•Reduction of disease activity: Contributes to the reduction of the DAS28 index (Disease Activity Score in 28 joints) and reduces the number of tender and swollen joints.
•Improvement of functionality: Enhances the physical capacity and daily functionality of patients (based on the MHAQ questionnaire).
•Reduction of systemic inflammation: Contributes to the reduction of key inflammatory markers in the blood.
Mechanism of Action
L-carnitine acts through multiple cellular and molecular pathways:
Inhibition of Inflammatory Cytokines: Inhibits the nuclear factor NF-κB pathway, reducing the production of pro-inflammatory cytokines, such as tumor necrosis factor (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β).Regulation of the JAK/STAT and TGF-β1 Pathways: Recent clinical studies show that L-carnitine attenuates the increase in the protein STAT3 (Janus kinase/signal transducer and activator of transcription), which triggers inflammation in RA.
Powerful Antioxidant Action: Activates the transcription factor PPAR-γ, increasing the levels of endogenous antioxidant enzymes, such as superoxide dismutase (SOD), while reducing malondialdehyde (MDA), an indicator of oxidative damage to lipids.
Mitochondrial Protection and Metabolism: Facilitates the transport of long-chain fatty acids into mitochondria for β-oxidation and ATP production, improving cellular energy homeostasis, protecting tissues from apoptosis. The dosage in recent randomized controlled clinical trials (RCTs) for Rheumatoid Arthritis was set at 1000 mg daily. Clinical benefits and reduction of inflammatory markers become apparent after continuous intake of 12 weeks (3 months).

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Carnitine and antioxidants levels in patients with rheumatoid arthritis (PubMed). Research linking low levels of carnitine in the plasma of RA patients with increased oxidative stress.

7. N-Acetyl-L-Cysteine (NAC)

Benefits:

•Reduction of clinical symptoms: Reduces the number of swollen joints and joint tenderness.
•Reduction of inflammatory markers: Helps reduce C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in the blood.
•Improvement of quality of life: According to clinical trials, it improves the general health status (Global Health score) and reduces the pain score of patients.
•Bone protection: Helps slow down bone erosion and cartilage destruction in the joints.

Mechanism of Action

NAC's action in RA is based on three main cellular mechanisms: Glutathione (GSH) Replenishment & ROS Neutralization NAC readily penetrates cell membranes and provides cysteine for the synthesis of glutathione (GSH). GSH neutralizes reactive oxygen species (ROS). In RA, ROS are oversecreted by immune cells, directly damaging joint tissue and exacerbating chronic pain.
Inhibition of the NF-κB & Cytokine PathwayOxidative stress activates the transcription factor NF-κB, which directs the production of inflammatory cytokines. NAC blocks this pathway, reducing the secretion of damaging factors such as TNF-α, IL-1β and IL-6.Th17 Cell Regulation & Osteoclastogenesis SuppressionTh17 Reduction: NAC limits the differentiation of CD4+ T-cells into Th17, which are the main autoimmune cells that drive the chronic inflammation of RA.
RANKL Blockade: Inhibits the production of RANKL by articular fibroblasts. This stops the differentiation of monocytes into osteoclasts (the cells that "eat" and destroy joint bone).

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8. Alpha-Lipoic Acid (ALA)

Benefits:

•Reduction of inflammation: Contributes to the reduction of markers such as CRP and the metalloproteinase MMP-3 that destroys cartilage.
•Bone protection: Prevents bone erosion by inhibiting osteoclast differentiation.
•Reduction of pain: Improves the clinical picture of joints, reducing swelling and tenderness.

•Improvement of the metabolic profile: Helps manage dyslipidemia and cardiovascular risk that often coexists with PA due to chronic inflammation.

Mechanism of Action

The mechanism of action of ALA is dual and is based on its amphiphilic nature (it is water-soluble and fat-soluble):Inhibition of the NF-κ B Pathway: The transcription factor NF-κ B activates genes that produce inflammatory cytokines. ALA blocks this pathway, reducing the production of TNF-α, IL-1β, IL-6 and IL-17A.Free Radical (ROS) Neutralization: ALA and its reduced form (DHLA) directly neutralize reactive oxygen radicals that cause cellular damage in the synovial membrane. Antioxidant Recycling: It has the ability to regenerate other depleted antioxidants in the body, such as glutathione (GSH), vitamin C and vitamin E. Immunomodulation: It reduces the number of circulating Th17 cells, which play a central role in the autoimmunity of PA.

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9. Corn Starch Resistant Starch

Benefits:

•Reduces the severity of arthritis: Reduces swelling, joint pain and protects against osteochondral erosion.

•Suppresses systemic inflammation: Reduces levels of circulating pro-inflammatory cytokines in the body.

•Protects the intestinal barrier: Strengthens the integrity of the intestine, preventing the leakage of endotoxins that activate the immune system.

Mechanism of Action

Resistant starch is not digested in the small intestine, but reaches the large intestine intact, where it functions as a powerful prebiotic. Its mechanism of action includes the following steps:
Step 1: Production of Short Chain Fatty Acids (SCFAs)Beneficial gut bacteria (such as Bacteroidetes) ferment resistant starch. This process produces large amounts of short chain fatty acids, mainly propionic and butyric acid.Step 2: Activation and Regulation of T-Regulatory Cells (Tregs) Propionic acid enters the circulation and stimulates the differentiation and proliferation of T-regulatory cells (Tregs) in the spleen and lymph nodes. Tregs are responsible for suppressing autoimmune reactions and restoring immune tolerance.Stage 3: Cytokine Balancing (IL-10 vs. Th17)Increase in IL-10: Tregs secrete interleukin-10 (IL-10), a potent anti-inflammatory cytokine that “extinguishes” joint inflammation.Suppression of Th17/NF-κB: At the same time, the NF-κB pathway is inhibited and the activity of Th17 cells is reduced, blocking the production of destructive pro-inflammatory factors, such as TNF-α, IL-1β, and IL-17.

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B-complex vitamins

B-complex vitamins act mainly as regulators of inflammation, oxidative stress and cellular metabolism, offering significant supportive action in the management of Rheumatoid Arthritis (RA). Their adequacy reduces systemic complications and chronic fatigue.

10. Vitamin B1 (Thiamine)

•**Benefit:**

•Reduction of chronic fatigue and protection of joint tissues from energy depletion.

Mechanism of Action: It functions as a coenzyme (thiamine diphosphate) in the Krebs cycle and the pentose phosphate pathway. It ensures the production of ATP in the mitochondria of synovial membrane cells, preventing metabolic dysfunction that exacerbates inflammation.

11. Vitamin B2 (Riboflavin)

•**Benefit:**

•Reduction of oxidative damage to cartilage and synovial membrane.

Mechanism of Action: It is a structural component of the coenzymes FMN and FAD. It participates directly in the glutathione reduction cycle (through glutathione reductase), neutralizing free radicals (ROS) produced by activated macrophages within the joint.

12. Vitamin B3 (Niacin)

•**Benefit:**

•Improvement of joint mobility and reduction of the need for non-steroidal anti-inflammatory drugs (NSAIDs).

Mechanism of Action: As a precursor of NAD/NADP, it regulates cell signaling. Niacinamide inhibits the excessive activation of the enzyme PARP-1 (poly-ADP-ribose polymerase), limiting the expression of inflammatory cytokines and protecting chondrocytes from apoptosis.

13. Vitamin B5 (Pantothenic Acid)

•**Benefit:**

•Supports endogenous cortisol production for the natural treatment of inflammation.

Mechanism of Action: It is the main component of coenzyme A (CoA). It is essential for the synthesis of steroid hormones in the adrenal glands. Its adequacy ensures optimal production of glucocorticoids, which suppress the activity of T-lymphocytes in RA.

14. Vitamin B6 (Pyridoxine)

•**Benefit:**

•Direct reduction of systemic inflammation markers.

Mechanism of Action: Its active form (PLP) acts as a coenzyme in immune metabolic pathways. Clinical studies show that B6 administration significantly suppresses the levels of pro-inflammatory cytokines IL-6 (interleukin-6) and TNF-α by inhibiting the NF-κB signaling pathway.

15. Vitamin B7 (Biotin)

•Benefit:

•Regulation of the immune response and fatty acid metabolism.

Mechanism of Action: It acts as a coenzyme for carboxylases that regulate gluconeogenesis and lipogenesis. Proper lipid metabolism affects the synthesis of prostaglandins, shifting the balance towards the production of anti-inflammatory eicosanoids.

16. Vitamin B9 (Folic Acid)

•Benefit:

•Reduces methotrexate (MTX) toxicity and controls homocysteine.

Mechanism of Action: MTX (a key drug for RA) competes with folic acid, causing side effects. Supplementing with B9 restores DNA and cell synthesis in healthy systems without reducing the drug's effectiveness, while also converting toxic homocysteine to methionine.

17. Vitamin B12 (Cobalamin)

•Benefit:

•Treats neuropathic pain, anemia, and fatigue.

Mechanism of Action: Acts as an essential cofactor for methionine synthase. Together with B9, it reduces homocysteine levels (which activates NF-κB, causing inflammation). In addition, it stimulates the remyelination process of peripheral nerves, reducing nerve sensitivity and pain around affected joints.

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18. Vitamin A

•Benefit:

•Important immunomodulatory effect, suppression of autoimmunity and protection of articular cartilage in rheumatoid arthritis (RA), as its active metabolite (retinoic acid) restores balance to immune cells.

•Suppression of Autoimmune Attack: Helps the immune system recognize its own tissues, reducing aggression against joints.

•Reduction of Joint Destruction: Limits the action of enzymes that erode cartilage and bone.

•Anti-inflammatory Protection: Contributes to reducing the production of factors that maintain chronic inflammation and swelling.

•Mucosal Protection: Strengthens the intestinal barrier, which is often disrupted in RA, preventing the entry of antigens that trigger disease flares.

Mechanism of Action

Vitamin A (retinol) is converted intracellularly to all-trans retinoic acid (ATRA), which binds to specific nuclear receptors (RAR/RXR) and acts directly on DNA through the following biochemical pathways:Alteration of the Th17 / Treg Balance (Immunoregulation): In RA, pro-inflammatory Th17 cells are hyperactive, while regulatory Treg cells (which suppress inflammation) are hypofunctional. Retinoic acid inhibits the differentiation of naive T-cells into Th17 and promotes the generation of Foxp3+ Treg cells, stabilizing the immune system.Inhibition of Metalloproteinases

(MMPs): Synovial cells (synovial membrane cells) in RA secrete excessive amounts of destructive enzymes, such as MMP-1, MMP-3 and MMP-13. Vitamin A blocks the gene expression of these enzymes, protecting the cartilage collagen from erosion.Suppression of AP-1 and NF-κB Signaling: Retinoic acid directly antagonizes the transcription factors AP-1 (Activator Protein-1) and NF-κB. In this way, the production of the main pro-inflammatory cytokines of the disease, such as TNF-α and IL-1β, is reduced.Reduction of Angiogenesis (Pannus): In the affected joints, an inflammatory tissue (pannus) filled with new blood vessels forms that destroys the joint. Vitamin A downregulates vascular endothelial growth factor (VEGF), limiting this pathological angiogenesis.

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19. Vitamin C

•Benefit

•Protection and Regeneration of Cartilage (stimulation of collagen synthesis):
It is the ultimate catalyst for the creation of new collagen, which is the main “cushion” of the joints.
•Reduction of Disease Exacerbations (Strong antioxidant protection):It neutralizes the oxygen free radicals that are produced massively in the synovial fluid during inflammation.
•Vascular Protection (Cardioprotection):Patients with RA have an increased risk of cardiovascular disease due to systemic inflammation. Vitamin C protects the vascular endothelium.
•Better Iron Absorption:It helps in the treatment of anemia, which often appears as “anemia of chronic disease” in people with RA.

Mechanism of Action

Vit. C acts at both the structural and cellular levels through the following biochemical pathways: Coenzyme in Collagen Conjugation (Hydroxylation): Vit. C is an essential cofactor for the enzymes prolyl hydroxylase and lysyl hydroxylase. Without it, cells cannot stabilize the triple helix of collagen II, making articular cartilage vulnerable to erosion.Suppression of the Transcription Factor NF-κB: Acts as a regulator of intracellular redox signals. By reducing oxidative stress, it prevents the activation of NF-κB, thus inhibiting the secretion of destructive cytokines such as TNF-α andIL-1β. T-cell Regulation (Immunomodulation): Ascorbic acid influences the epigenetic regulation of immune cells. It promotes the stability of regulatory T-cells (Tregs) through DNA demethylation in the Foxp3 gene region, helping the body control the autoimmune response.
Vitamin E Recycling: Vitamin C regenerates the active (unmethylated) form of vitamin E (α-tocopherol) in joint cell membranes, doubling the tissue defense against lipid peroxidation.

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20. Vitamin D

•Benefit:

Reduces Disease Exacerbations: Vitamin D sufficiency is associated with a lower Disease Activity Score (DAS28), fewer swollen joints, and reduced pain.
•Prevents Severe Osteoporosis: RA and cortisone use cause rapid bone loss. Vitamin D is essential for calcium absorption and the prevention of fractures.
•Improves Response to Treatment: Patients with normal vitamin D levels tend to respond better to biologics (e.g., anti-TNF) and disease-modifying drugs (DMARDs).
•Reduces Risk of Other Autoimmune Diseases: Protects the body from the development of additional autoimmune manifestations (e.g., thyroiditis) that often coexist with RA.

Mechanism of Action

The active form of vitamin D, 1,25-dihydroxyvitamin D3 [$1,25(OH)_2D_3$], enters immune cells and binds to the vitamin D nuclear receptor (VDR), which is highly expressed on T and B lymphocytes, macrophages, and dendritic cells:
Suppression of Th1 and Th17 cells: Th1 and Th17 cells are the main “soldiers” that attack the synovial membrane in RA. Vitamin D blocks their differentiation and proliferation, drastically reducing the production of the destructive interleukin-17 (IL-17) and interferon-γ (IFN-γ).
Strengthening Regulatory T-Cells (Tregs): Vitamin D stimulates the creation and function of Foxp3+ Treg cells, which are responsible for “quenching” the autoimmune attack and restoring immune tolerance.Inhibition of Proinflammatory Cytokine Production: Through the VDR receptor, vitamin D directly suppresses the transcription of genes that produce TNF-α, IL-6, IL-1 and IL-12 in synovial macrophages.Regulation of Dendritic Cell Maturation: It maintains dendritic cells (antigen-presenting cells) in a “tolerogenic” immature state. Thus, the incorrect presentation of joint proteins as “foreign” enemies is prevented.Suppression of the RANKL Pathway in Bone: Controls RANKL expression in osteoblast cells, preventing excessive activation of osteoclasts that break down bone around inflamed joints.

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21. Vitamin E

•Benefit:

•Reduces Pain and Stiffness: Clinical trials show that vit. E reduces joint pain, acting synergistically with classic anti-inflammatory drugs.
•Protection of Joint Fluid and Cartilage: Protects hyaluronic acid and synovial fluid lipids from degradation, maintaining proper joint lubrication.
•Delays Joint Wear (Joint Erosion): Limits the infiltration of free radicals that structurally destroy the collagen of the joints.
•Cardioprotective Action: As RA increases the risk of atherosclerosis due to chronic systemic inflammation, vitamin E prevents the oxidation of "bad" cholesterol (LDL), protecting the vessels.

Mechanism of Action

Vitamin E is incorporated into the lipid layers of the cell membranes of macrophages and synovial cells, acting through the following molecular pathways:Inhibition of Lipid Peroxidation (Chain-breaking Antioxidant): During inflammation in RA, reactive oxygen species (ROS) are produced in large quantities. These attack the lipids of the cell membranes of the joint. Vit. E neutralizes the peroxyl radicals, stopping the chain destruction of cells.Suppression of the NF-κB Transcription Factor: Oxidative stress activates the NF-κB pathway, which gives the order to produce inflammatory cytokines. Vit. E blocks this activation, reducing the levels of TNF-α and IL-1β. Regulation of the Arachidonic Acid Cascade: Vitamin E (particularly γ-tocopherol and its metabolites) inhibits the enzyme cyclooxygenase-2 (COX-2). This leads to a decrease in the production of prostaglandin E2 (PGE2), which is the main mediator of pain and swelling in the joint. Reduction of Metalloproteinases (MMPs): Suppresses the expression of enzymes such as MMP-1 and MMP-13, which are secreted by inflammatory cells and "eat" articular cartilage.

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22 . MAGNESIUM Mg

•Benefit:

•Reduces Systemic Inflammation: Magnesium intake is associated with a proven reduction in C-reactive protein (CRP) and other systemic inflammatory markers.
•Joint Protection: Helps slow the destruction of articular cartilage and subchondral bone.
•Reduces Pain and Stiffness: Has a calming effect on the nervous system and reduces muscle tension around affected joints.
•Improves Metabolic Health: Helps reduce insulin resistance, which often coexists in patients with chronic inflammatory arthritis.

Mechanism of Action

The mechanism by which magnesium suppresses the pathogenesis of Rheumatoid Arthritis is multifactorial and includes: Suppression of the NF-κB Pathway: Magnesium regulates and inhibits the activation of the nuclear factor NF-κB (Nuclear Factor kappa-B). This factor is mainly responsible for the expression of inflammatory genes. Reduction of Pro-Inflammatory Cytokines: Through the inhibition of NF-κB, the production and release of destructive cytokines from macrophages, such as TNF-α (Tumor Necrosis Factor), IL-6 (Interleukin-6) and IL-1β, is drastically reduced. Immunoregulation and Activation of Treg Cells: Recent studies have shown that magnesium increases the population of Foxp3+ T-regulatory cells (Tregs). These cells suppress the autoimmune attack and promote the production of the anti-inflammatory cytokine IL-10. Prevention of Cellular Aging (Senescence) & Oxidative Stress: Magnesium intervenes in the transcriptional control of synovial membrane tissues, reducing free radicals (ROS) and protecting cells from premature aging and iron overload (ferroptosis).Blockade of NMDA Receptors (Analgesia): It acts as a natural calcium antagonist and regulates NMDA receptors in the nervous system, reducing central sensitization and the perception of chronic pain.

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23. CALCIUM Ca

•Benefit:

•Prevention of Systemic Osteoporosis: It slows down the generalized loss of bone density caused by chronic autoimmune inflammation.

•Protection from Fragility Fractures: Patients with RA have up to a 40% increased risk of fractures (e.g. in the hip). Calcium protects the mechanical strength of bones.

•Compensation of Side Effects of Corticosteroids (Cortisone): These drugs reduce calcium absorption and accelerate bone destruction. Calcium replenishes these losses.

•Reduction of Periarticular Bone Erosion: It helps maintain the subchondral bone around the joints that are attacked by the disease.

•At the cellular level, its regulation is essential for controlling the hyperactivity of immune cells.

Mechanism of Action

The mechanism of action of Ca in RA focuses on bone homeostasis and intracellular signaling: Suppression of Secondary Parathyroid Hormone (PTH) Secretion: When calcium intake is low (common in RA due to malabsorption), the body secretes parathyroid hormone (PTH). PTH gives the order to “steal” calcium from the bones to cover the blood, worsening osteoporosis. Adequate calcium intake stops this destructive cycle.RANK/RANKL Pathway Antagonism (Osteoclast Suppression): In RA, proinflammatory cytokines (TNF-α, IL-6) overactivate the RANKL pathway, which converts immune cells into osteoclasts (bone-melting cells). Calcium, in conjunction with vitamin D, helps maintain the structural integrity of hydroxyapatite crystals, making bone more resistant to osteoclastic degradation. Regulation of Intracellular Signaling (Ca^{2+} Signaling): Calcium

ions act as secondary messengers in cells. Dysregulation of calcium flux in T-lymphocytes and synovial cells (synovial lining cells) is associated with the overproduction of inflammatory cytokines. Maintaining general metal homeostasis helps stabilize these cell membranes.

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24. Selenium Se

•Benefit:

•Neutralization of Oxidative Stress: RA patients often have low levels of selenium in the blood. Its replenishment neutralizes free radicals (ROS) that attack the joints.

•Protection of Articular Cartilage: Prevents the degradation of cartilage cells and subchondral bone from the chronic inflammatory process.

•Reduction of Symptoms (Morning Stiffness & Pain): Clinical studies show that selenium adequacy alleviates the intensity of pain and reduces the duration of morning stiffness.

• Thyroid Protection (Polyautoimmunity): As RA often coexists with autoimmune thyroiditis (Hashimoto), selenium simultaneously protects the thyroid gland, reducing autoantibodies (anti-TPO).

Mechanism of Action

Selenium does not act as a free metal, but is incorporated into DNA to create selenoproteins: Activation of Glutathione Peroxidase (GPx): Selenium is the active center of the GPx enzyme. This enzyme converts toxic hydrogen peroxide into water, stopping the oxidative damage of synovial membrane cells.Inhibition of the Transcription Factor NF-κB: Selenium blocks the NF-κB pathway. In this way, the cells are "instructed" to stop producing pro-inflammatory cytokines, such as TNF-α and IL-6.Regulation of Arachidonic Acid Metabolism: Selenoproteins interfere with the synthesis of prostaglandins and leukotrienes. This leads to a natural suppression of the acute and chronic inflammatory response.Quenching Macrophage Hyperactivity: Reduces the infiltration and activation of immune cells within the joint, limiting local edema.

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25. Zinc Zn

•Benefit:

•Reduction of Inflammation: Contributes to the decrease in the levels of pro-inflammatory cytokines.

•Chondrocyte Protection: Protects articular cartilage cells from oxidative degradation and apoptosis (cell death).

•Restoration of Immune Balance: Corrects the dysfunction of T-lymphocytes caused by chronic disease.

•Improvement of the Quality of the Skin and Mucous Membranes: Supports the regeneration of tissues, which often atrophy due to long-term use of cortisone or immunosuppressive drugs.

Mechanism of Action

Zinc functions as a structural and catalytic element in more than 300 enzymes, regulating inflammation through the following biochemical pathways:

Inhibition of the NF-κB Pathway (Through A20): Zinc activates the zinc finger protein A20. A20 acts as a natural "brake" on the activation of the transcription factor NF-κB. This results in blocking the production of TNF-α, IL-1β and IL-6.

Activation of the Enzyme Cu/Zn-SOD: It is a key component of Copper/Zinc Superoxide Dismutase. This enzyme neutralizes superoxide radicals in the synovial membrane, stopping the destruction of joint collagen.

Regulation of Th17 / Treg Cell Balance: Zinc deficiency leads to an overproduction of Th17 cells (which cause autoimmunity) and a decrease in regulatory T-cells (Tregs). Its sufficiency restores this balance, limiting the aggressiveness of the immune system against the joint.

Quenching the NLRP3 Inflammasome: Zinc prevents the activation of the NLRP3 complex within macrophage cells, drastically reducing the release of the highly inflammatory interleukin IL-1α/β.

Regulation of Metalloproteinases (MMPs): Although MMPs are enzymes that depend on zinc for their structure, levels of free intracellular zinc control the expression of their endogenous inhibitors (TIMPs), preventing uncontrolled cartilage erosion.

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26. Cranberry

•Benefit:

•Reduction in Disease Activity (DAS28): Clinical trials have shown that daily consumption of cranberries significantly reduces the DAS28 index, reducing the number of painful and swollen joints.

•Decrease in Autoantibodies (Anti-CCP): Its systematic intake helps reduce the levels of anti-citrullinated antibodies (anti-CCP), which are a key indicator of the autoimmune attack in RA.
•Synthetic Action with Omega-3: When cranberry is combined with Omega-3, a drastic reduction in systemic inflammation markers (CRP and IL-6) and in the Erythrocyte Sedimentation Rate (ESR) is achieved.
•Reduction of Oxidative Stress: Protects synovial membrane proteins and lipids from oxidation caused by free radicals, preventing premature destruction of chondrocytes.
•Regulation of the Gut Microbiota: Strengthens the intestinal barrier. As gut dysbiosis is closely linked to the triggering of RA, protecting the gut helps reduce systemic flare-ups.

Mechanism of Action
Cranberry is extremely rich in type A proanthocyanidins (PACs), quercetin (resveratrol) and anthocyanins. These substances act at the cellular level through the following pathways: Inhibition of the NF-κB Pathway: Cranberry polyphenols (particularly quercetin and proanthocyanidins) block the activation of the transcription factor NF-κB in macrophage cells. As NF-κB is the "master switch" of inflammation, its suppression stops the production of destructive cytokines such as TNF-α and IL-6.Epigenetic Regulation (Suppression of Histone Acetylation): Recent research has shown that cranberry extract suppresses histone acetylation, an epigenetic modification required for the expression of the inflammatory p65 genes of immune cells. Inhibition of COX-2 and LOX Enzymes: Cranberry flavonoids act in a similar way to nonsteroidal anti-inflammatory drugs (NSAIDs), inhibiting the enzymes cyclooxygenase (COX-2) and lipoxygenase (LOX). This prevents the synthesis of prostaglandin E2, which causes local swelling and pain in the joint.Direct Neutralization of Superoxide Radicals (ROS Scavenging): Cranberry antioxidants donate electrons to free oxygen radicals that are produced en masse in inflamed synovial fluid, stopping the chain reaction of collagen degradation in the joints.

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•**Critical Reviews in Food Science and Nutrition:** Cranberry antioxidant power on oxidative stress, inflammation and cardiovascular health.

27. CURCUMINE

•Benefit:
•Dramatically Reduces Pain and Swelling: Suppresses inflammation directly in the joint tissue, reducing swelling and morning stiffness.
•Improves Joint Mobility: Facilitates movement of affected joints, significantly improving the quality of life of patients.
•Protects Articular Cartilage: Prevents bone erosion and collagen destruction caused by the chronic inflammatory tissue of RA.
•Reduces Inflammatory Markers: Contributes to the proven drop in C-reactive protein (CRP) and Erythrocyte Sedimentation Rate (ESR) in the blood.

•Gastric Protection: Unlike chemical anti-inflammatories, it does not damage the stomach lining, making it safe for long-term supportive intake.

Mechanism of Action

Curcumin is an extremely versatile molecular regulator that intervenes at multiple levels of the inflammatory process: Potent Inhibition of the NF-κB Pathway: Blocks cell signaling that activates the nuclear factor NF-κB. In this way, it prevents white blood cells from "reading" the genes of inflammation, stopping the massive production of the main RA cytokines, such as TNF-α, IL-1β and IL-6. Natural Inhibition of COX-2 and 5-LOX Enzymes: It acts as a dual inhibitor of the enzyme's cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX). This results in stopping the production of prostaglandins (PGE2) and leukotrienes, which are the main biochemical culprits for the feeling of pain and the creation of edema. Suppression of Metalloproteinases (MMPs): It drastically reduces the expression and activity of the enzymes MMP-1, MMP-3 and MMP-13 in synovial cells. These enzymes are the ones that literally "eat" cartilage, so their inactivation protects the structure of the joint. Inhibition of the JAK/STAT Pathway and MAPKs: Downregulates MAP kinases and the JAK/STAT pathway, preventing the pathological proliferation of synovial membrane cells. Activation of the Nrf2 Antioxidant Pathway: Stimulates the transcription factor Nrf2, leading the cell to produce its own endogenous antioxidant enzymes (such as glutathione), neutralizing local oxidative stress.

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