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BIOPHARMACEUTICALS: IMPORTANCE, APPLICATION, FUNCTION – A NARRATIVE REVIEW

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ABSTRACT – Biologically active medical products (biopharmaceuticals) are substances related to the natural molecules present in the organism that affect the process regulation. These drugs can exert effects imitating the functions of natural proteins, as well as by affecting cellular receptors or interacting with the natural, biologically active molecules in the organism, most frequently participating in signal transduction. Due to the structure and targeted activity mechanisms, they are characterized by high therapeutic specificity.

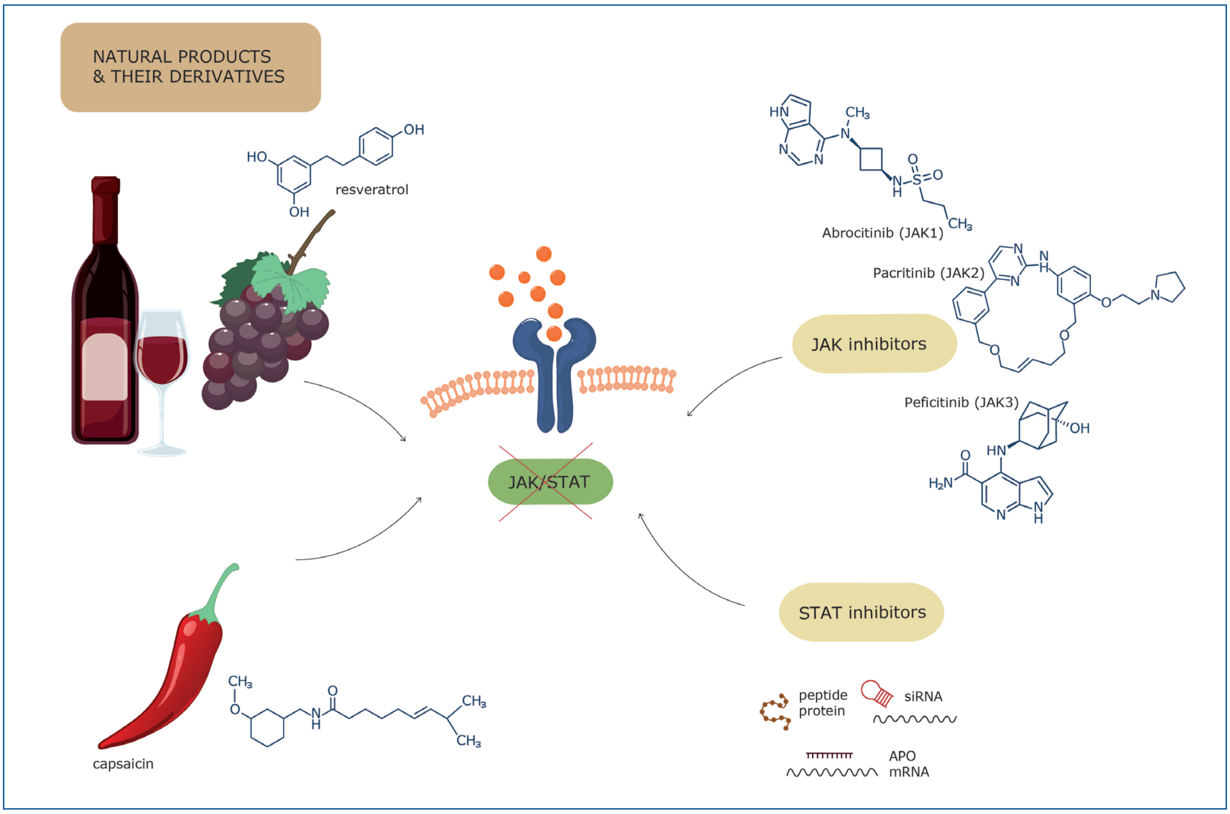
This article presents biopharmaceuticals that influence the modulation of the Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) and nuclear factor kappa B (NF-κB) transcriptional signaling pathways, which play a key role in the pathogenesis of autoimmune, neoplastic, hematological, skin, and rheumatic diseases. It is assumed that disturbed cellular signals within these pathways may also be significant for the development of oral cavity diseases, including periodontitis.

A thorough understanding of the ways of transmission and activation of the subsequent signaling pathways involved in protein synthesis will allow for a more accurate and in-depth knowledge of the mechanisms behind the onset and development of numerous diseases. It will facilitate the development and implementation of targeted therapies that directly inhibit the JAK-STAT and NF-κB signaling pathways, which initiate inflammatory reactions in the cell. In combination with the therapeutic methods used so far, modification of the host's response at the molecular level may offer promising therapeutic benefits.

KEYWORDS: Biopharmaceutics, Signaling pathways, Cytokines, JAK inhibitors, STAT inhibitors, Rheumatic diseases, Periodontitis.

INTRODUCTION

Biopharmaceuticals typically include products derived from microorganisms, animals or humans. Products called biopharmaceuticals may contain cells producing compounds that activate or suppress the immune response, recombinant proteins, allergens, blood components, genes and tissues. They are particularly dedicated to autoimmune diseases, rheumatoid arthritis, psoriasis, infertility, cancer, Crohn's disease, ulcerative colitis, heart attack, diabetic retinopathy, and many others. Biological drugs are directed at specific parts of the immune system. However, despite their partial effectiveness, there is also a risk of disorders of the immune system and the occurrence of many ailments.



Graphical Abstract. The influence of natural products (biopharmaceuticals) and their derivatives on the modulation of JAK/STAT signaling transcriptional pathways, which play a key role in the pathogenesis of autoimmune, neoplastic, hematological, skin, and rheumatic diseases, as well as in the development of diseases of the oral cavity, including periodontitis.

This article will concentrate on biological drugs directed at the Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) pathway. Advantages and disadvantages will be indicated; alternative biological methods and their possibilities will be discussed.

Together with the advancement of the knowledge and understanding of intracellular signaling pathways, as well as the increasing importance of the key signaling molecules in the cell[1,2], the biotechnological and pharmaceutical industries have become interested in the biological drugs dedicated to the immune system. Molecular signaling pathways produced by immune cells, receptors that link individual cells in the organism, intracellular reaction cascades evoked by the activity of metabolic enzymes, gene expression, or membrane permeability caused by cellular chemical reactions have all gained importance. On the cell surface or in the target cell cytoplasm, signaling molecules bind to receptors appropriate to their functions, causing a complex chain of reactions in the cell. The analysis of these pathways has provided information about the positive and negative feedback, changes in the release of inflammatory mediators, and, consequently, the possibility to regulate the intensity of inflammation, for example, by limiting the presence of the inflammatory mediators[3].

Inflammatory processes take place in the pathogenesis of many disorders. The primary aim of inflammation as a defense mechanism is to protect, alert and react to the threats. It is a non-specific immune response that occurs at the site of an injury, infection or pathogen invasion. In the case of many diseases, prolonged inflammation or disruption of the signaling pathways of this complicated and intricate process leads to deterioration of health and may even result in death in extreme cases[4]. High incidence of asthma, degenerative joint diseases or psoriasis indicates a relationship between destabilization of the immune system in the investigated diseased populations with co-existent chronic inflammation and the presence of such conditions is visible in Crohn's disease or ulcerative colitis.

The main and most frequently used therapies for the mentioned diseases are steroid and non-steroid anti-inflammatory drugs (NSAIDs). Unfortunately, long-term application thereof carries a risk of severe adverse effects. Chronic inflammatory conditions, such as rheumatoid arthritis or asthma, are treated with steroids. However, prolonged usage may lead to hypertension, cataract, glaucoma, elevated blood glucose levels or osteoporosis. NSAIDs, in turn, cause adverse effects in the form of stomach ulcers or gastrointestinal bleeding[5,6].

Cytokines play a crucial role in the pathogenesis of immunological and inflammatory diseases. Understanding the mechanisms through which they transmit signals and activate downstream cellular pathways affecting protein synthesis has enabled the development of targeted therapies for rheumatoid and other autoimmune diseases. Therapies directly inhibiting cytokines as initiators of inflammatory conditions have been developed. Particular attention has been paid to the importance of the JAK/STAT pathway, in which the JAK kinase proteins participate in the process of signal transduction, and the STAT proteins act as transcription factors and gene activators in the cell nucleus.

Periodontitis is a complex disease that is inherited due to numerous factors. In its early stage, a local response of the innate immune system takes place, resulting in the activation of signaling pathways and intensification of the cellular pro-inflammatory response. The mutually integrated transduction of the intracellular signaling pathways additionally increases the inflammatory response and exacerbates the pathological symptoms of the disease.

The therapeutic effectiveness of the methods used so far in the treatment of periodontitis is questionable; there is also a justified risk of potential adverse effects. Therefore, it seems essential to develop novel treatment methods, which would constitute a valuable complement to the existing therapies and effectively suppress the excessive immunological response disproportionate to the threat.

For this reason, and because of the adverse effects associated with steroidal and non-steroidal anti-inflammatory drugs used to date, biopharmaceuticals have generated considerable optimism among researchers and within the pharmaceutical industry.

This narrative review was based on a comprehensive literature search of electronic databases (PubMed, MEDLINE, Web of Science, Embase, and ClinicalTrials.gov). Relevant publications were identified up to May 2025, using the following key terms: "biologics," "biopharmaceuticals," "JAK inhibitors," "Janus kinase inhibitors," "STAT inhibitors," "interleukin inhibitors," "anti-TNF," "B-lymphocyte inhibitors," "plant-derived compounds," "natural products," and "natural derivatives.". All titles and abstracts were analyzed for relevance to the topics. No restrictions regarding publication date or study design were applied. Only articles in English and reporting data or discussion related to the investigated topics were included. In addition, the reference lists of all eligible studies were examined to ensure that no relevant publications were omitted from this review.

TYPES OF BIOPHARMACEUTICALS – APPLICATION

Biological agents targeted specifically at particular cytokines have been developed based on the recognition of the key role of these pro-inflammatory mediators in the pathogenesis of rheumatic diseases. The currently available cytokine blockers include inhibitors of the tumor necrosis factor α (TNF-α), interleukin 6 receptor, interleukin 1 and interleukin 17 inhibitors, as well as inhibitors of interleukin 12 and 23. The mechanism has been presented in Figure 1, while the adverse effects of drugs exhibiting an inhibitory effect on selected cytokines are presented in Figure 2.

Inhibitors of tumor necrosis factor alpha (anti-TNF-α, blockers of TNF-α)

Inhibitors of tumor necrosis factor alpha are the most frequently used medicines in autoimmune arthritis. They quickly reduce inflammation and prevent joint damage. These include adalimumab, certolizumab pegol, etanercept, golimumab and infliximab. Among the adverse effects of these drugs, the following can be listed: common cold, flu, sinusitis, headache, urinary tract infections, rash. Long-term use of TNF-a inhibitors increases the risk of lymphoma and skin cancer. In elderly people and individuals who previously experienced inflammation, a risk of infection has been noted within six months after the beginning of the treatment[7]. Long-term application of anti-TNF-α therapies is associated with an increased risk of infections and recurrence of latent tuberculosis[8,9]. TNF-α inhibitors are not recommended for patients diagnosed with cardiac failure. A higher incidence of skin cancers, lupus-like syndrome and demyelinating disease has also been observed.

TNF-α represents a pivotal mediator of the pro-inflammatory immune response. It is present in both a soluble form (soluble TNF-α, sTNF) and a membrane-bound form (transmembrane TNF, tmTNF). The biological effects of TNF-α are exerted through its interaction with two distinct receptors, TNFR1 and TNFR2 (tumor necrosis factor receptors). The pleiotropic activity of TNF-α encompasses the induction of pro-inflammatory cytokines such as IL-1 and IL-6, upregulation of adhesion molecules on endothelial cells, recruit-

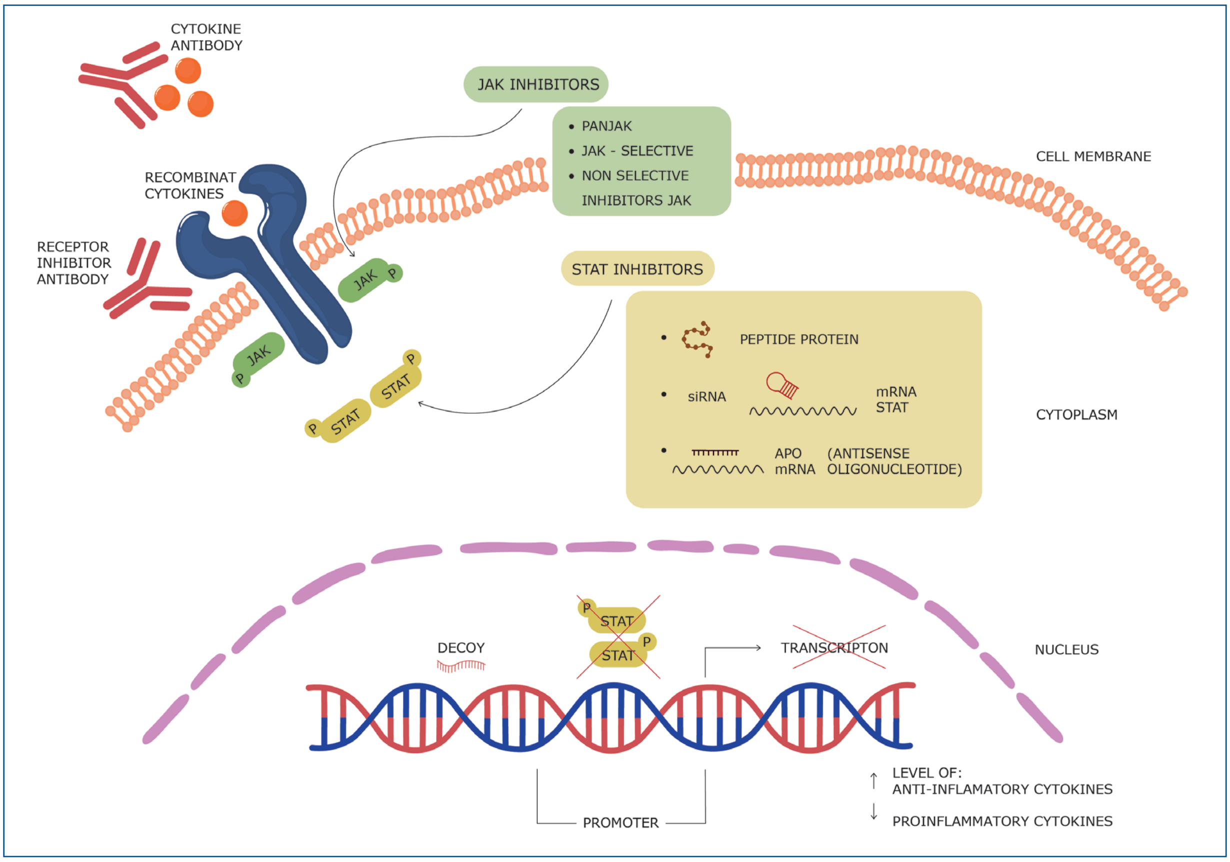


Figure 1. Therapeutic targets targeting the JAK-STAT pathway. JAK inhibitors – Janus kinase inhibitors; STAT inhibitors - target signal transducer and activator of transcription (STAT) proteins inhibitors; ASO - antisense oligonucleotides; peptide protein - (peptides peptidomimetics) inhibitors that act by disrupting STAT: STAT dimerization; DECOY – decoy oligonucleotides (ODNs) containing DNA binding consensus sequences of transcription factors (here STAT) selectively inhibit them by binding to the DNA-binding domain.

ment of neutrophils and monocytes, and activation of fibroblasts and osteoclasts. Dysregulated or excessive TNF-α activity contributes to the perpetuation of chronic inflammation, progressive tissue destruction, and the clinical manifestations of autoimmune and inflammatory diseases[10].

TNF-α inhibitors act by binding to circulating TNF-α and/or its transmembrane form, thereby preventing ligand engagement with TNFR1 and TNFR2 on the surface of target cells. This blockade attenuates downstream pro-inflammatory signaling cascades (including IL-1, IL-6, and chemokine pathways), reduces leukocyte recruitment to sites of inflammation through diminished adhesion molecule expression, and suppresses the activation of macrophages, fibroblasts, and osteoclasts. Clinically, the therapeutic consequences include attenuation of inflammatory symptoms and a deceleration in the progression of the underlying disease[11].

B-lymphocyte inhibitors

B-cell inhibitors include belimumab and rituximab, as well as rituximab biosimilars such as Riabni, Ruxience, and Truxima. Belimumab has been approved for the treatment of lupus nephritis in adults and children, as well as for the treatment of lupus. When methotrexate or a TNF blocker is not effective in the treatment of rheumatoid arthritis, rituximab is applied.

Belimumab is a fully human monoclonal antibody that exerts its therapeutic effect by inhibiting B-lymphocytes through binding to the soluble B-lymphocyte stimulator protein (BLyS, also known as BAFF – B cell activating factor). BLyS is a member of the tumor necrosis factor (TNF) superfamily and interacts with receptors expressed on B cells, promoting their maturation and differentiation. Furthermore, BLyS enhances the survival of B-lymphocytes and stimulates the production of autoantibodies[12].

Rituximab acts through a distinct mechanism compared with other biologic agents. It specifically targets the CD20 surface antigen present on B-lymphocytes, a subset of white blood cells. By binding to CD20, rituximab induces the depletion of both normal and malignant B cells expressing this antigen, thereby reducing pathogenic B cell activity and autoantibody production[13].

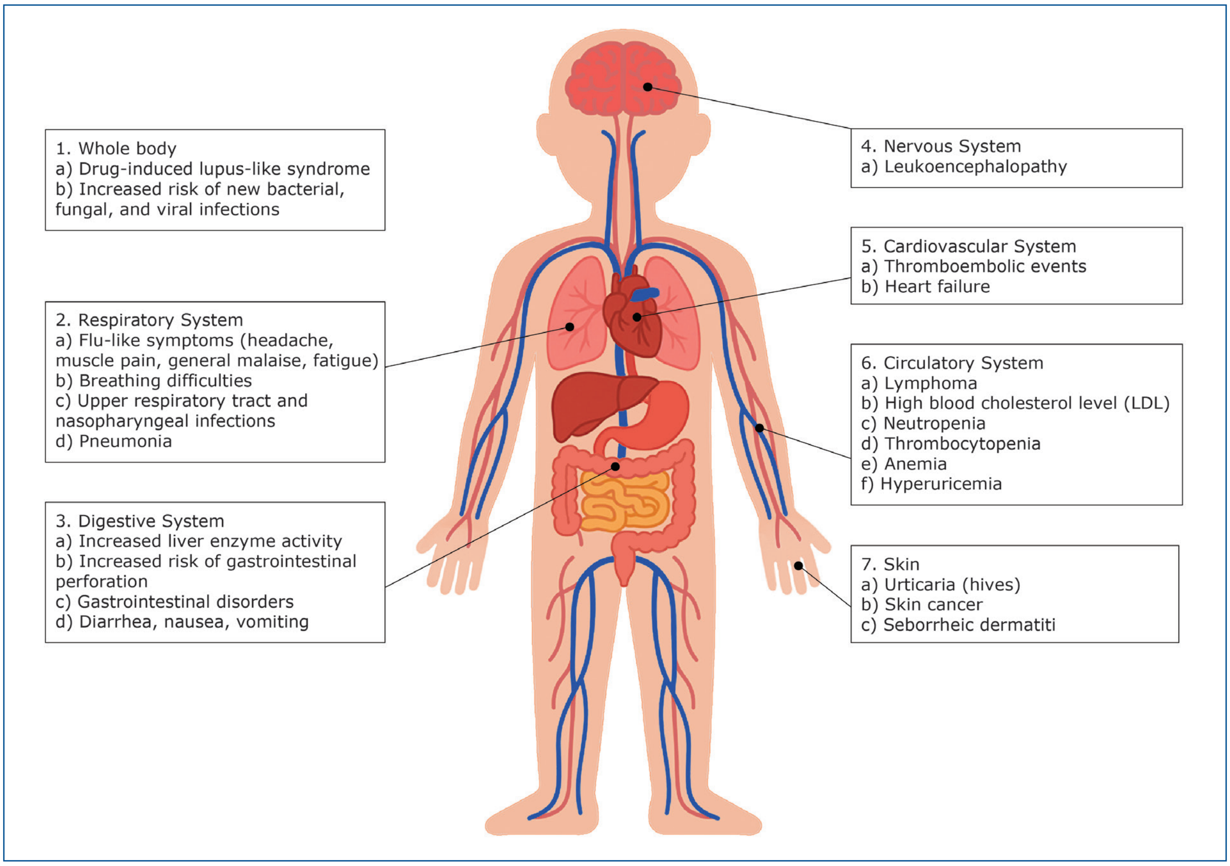


Figure 2. Adverse effects of biological agents targeting cytokines. The names of substances inhibiting enzymatic activity are listed, with specific diseases assigned to each inhibitor. TNF-α inhibitors (1a, 2a, 7b, 7c); B-lymphocyte inhibitors (2a, 2b, 2c, 4a); IL-6 inhibitors (3a, 3b, 6b, 6c); IL-1 inhibitors (2a); IL-17 inhibitors (1b); IL-12 and IL-23 inhibitors (1b); STAT inhibitors (3c); JAK I generation inhibitors (1b, 3b, 5a); JAK II generation inhibitors (1b, 2d, 3a, 3b, 3d, 5a, 5b, 6c, 6d, 6f, 7c).

The side effects of administering these inhibitors include chest pain, breathing difficulties, changes in blood pressure, flu-like symptoms and rash. Rituximab is associated with hepatitis B and progressive multifocal leukoencephalopathy. B-lymphocyte inhibitors are not recommended for pregnant women and for women at least six months before attempting conception. The use of belimumab carries a risk of severe and fatal infections. The most common adverse effects are reactions to infusions resulting in a low level of white blood cells, body aches, chills, infections, fatigue[14,15].

Interleukin inhibitors

These medications are targeted at different types of pro-inflammatory interleukins. They have been applied in psoriatic arthritis, psoriasis, rheumatoid arthritis, and ankylosing spondylitis. The most frequent adverse effects include liver problems, common cold, sinus infections, high blood pressure, skin pain or skin reactions at the injection site, nausea, cold symptoms, and headache. Serious risks associated with the use of interleukin inhibitors comprise an increased risk of severe infections, a higher risk of opportunistic infections (shingles, tuberculosis, toxoplasmosis), and even an elevated risk of cancer after long-term treatment with interleukin inhibitors[16].

Interleukin 6 inhibitors

Interleukin 6 plays an important role in maintaining homeostasis within the cell. It contributes to protection of the organism against infections and stress. However, when the balance is disrupted, excessive IL-6 synthesis leads to inflammatory reactions. Moreover, IL-6 fulfils a significant role in the regulation and differentiation of T helper cells providing the balance between regulatory T cells (Treg) and Th17 helper cells. Currently, two IL-6 receptor inhibitors are in use: sarilumab and tocilizumab. The side effects of tocilizumab include an increased risk of gastrointestinal perforation, skin infections, deterioration of the lipid profile and impaired liver function[17,18].

IL-6 inhibitors work by blocking IL-6 receptors (both membrane-bound and soluble), which prevents signaling of this cytokine and suppresses the development of inflammatory processes. As a result, cell proliferation, cell survival, acute-phase protein production, immune response, and other processes regulated by IL-6 are inhibited[19].

Interleukin 1 inhibitors

The importance of interleukin 1 has been confirmed in studies involving patients with cancer, in which IL-1 was administered to enhance the immune response. The reaction to the cytokine administration was fever, joint and muscle pain[20]. IL-1 inhibitors are effective in the treatment of gut, autoinflammatory disorders, and Still's disease. The discovery of a naturally occurring interleukin 1 receptor antagonist (IL-1RA), which binds to and competes with IL-1 receptor sites, helped scientists to develop a modified version of the receptor antagonist, known as the drug anakinra[21]. By competing for the receptor, IL-1RA prevents IL-1 from transmitting the signal from one cell to another. Anakinra is used in the treatment of rheumatoid arthritis. The currently used IL-1 inhibitors include anakinra, gevokizumab, rilonacept, and canakinumab[22].

Interleukin 17 inhibitors

Interleukin-17 (mainly IL-17A and IL-17F) is a pro-inflammatory cytokine produced primarily by Th17 lymphocytes. When overexpressed, it leads to increased recruitment of neutrophils and monocytes and overproduction of other inflammatory cytokines (IL-6, IL-8, TNF-α, IL-1β). Upregulation of chemokines and adhesion molecules in endothelial cells may result in chronic inflammation and/or tissue damage. IL-17 inhibitors work in a similar way. They target the IL-17 pathway by binding either the IL-17A/IL-17F ligands or the IL-17RA receptor. The main IL-17 inhibitors are secukinumab, ixekizumab, brodalumab, and bimekizumab[23,24]. They are primarily used to treat psoriatic dermatitis and psoriasis[23].

Interleukin 12 and interleukin 23 inhibitors

Interleukin 12 and interleukin 23 belong to the IL-12 family and share a common p40 subunit[25]. The activity of IL-12 affects the induction of the Th1 cell response, whereas that of IL-23 influences the Th17 cell response. IL-12 and IL-23 inhibitors are applied in the treatment of psoriasis and psoriatic arthritis. In the case of these diseases, ustekinumab is used – a monoclonal IgG1 antibody targeting the p40 subunit, neutralizing both IL-12 and IL-23[25].

Selective co-stimulatory modulators

The only representative of selective co-stimulatory modulators is abatacept. It is used when methotrexate or other non-biological disease-modifying drugs (DMARD) prove ineffective in moderation of severe rheumatoid arthritis, juvenile idiopathic arthritis and psoriatic arthritis in adults. Its mechanism of action involves the attenuation of overactive T cells. The most frequent adverse effects include headache, cold symptoms, sore throat and nausea, and they are similar to those of other biological drugs, in terms of cancer and infections[26].

JAK inhibitors

The effectiveness of JAK inhibitors lies in the inhibition of cytokine cellular pathway signaling. The JAK kinases affect IL-2, IL-6, IL-12, IL-23, and IFN cytokines, crucial for the immune system. The activity of these compounds reminds, to a certain extent, that of the proverbial "double-edged sword", as inhibiting the pathway of one kinase, they may simultaneously suppress other signaling pathways, which may lead to undesirable events.

Selectivity for the individual JAK kinase isoforms may depend on various factors, such as the dose, type of target cells, or drug metabolism[27].

JAK-STAT pathway, JAK-STAT inhibitors, activity and signaling pathways

The JAK/STAT pathway involves cytokine and growth factor receptors, which are located on the cell surface. The pathway subsequently includes kinases from the cytoplasmic part of JAK and proteins from the STAT transcription factor family[28]. To activate the JAK/STAT pathway, a cytokine specific to a given receptor must bind to that receptor, initiating the transmission of information from outside the cell. This event then triggers intracellular signal transduction, ultimately leading to transcription within the cell nucleus and conveying instructions for the synthesis of the compound appropriate to the received signal.

Four proteins belonging to the JAK family: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2) are primarily responsible for the process. Spatial interactions of the JAK kinase structure subsequently enable the phosphorylation of the STAT proteins, characteristic of the given activated receptor through a particular cytokine. The STAT proteins fulfill the function of transcription factors. Seven members of the STAT family have been identified: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. By translocating one of them into the cell nucleus in the form of a dimer, they transmit information by binding to the regulatory sites of the particular DNA sequence. There, they influence cell proliferation, differentiation or death, initiating or regulating particular transcription activity[29,30].

Classical signaling pathway

In the classical signaling pathway, a cytokine binds to the receptor and causes its dimerization. As a result of this bond, the JAK kinase present in the vicinity of the receptor undergoes transphosphorylation and, once activated, triggers tyrosine phosphorylation of the associated receptor. This creates a docking site for STAT Afterward, STAT dissociates from the receptor and forms dimers (homodimers or heterodimers), which translocate to the cell nucleus, where they bind to gene promoters and regulate the transcription of the target genes[31,32]. A graphic representation of the signaling pathway mechanism has been schematically shown in Figure 3. The following mechanisms of transcription regulation by STAT have been observed. In the first one, STAT proteins bind directly to the target site on the DNA strand[33]. Another mechanism consists of STAT combining into a transcriptional complex with other transcriptional factors and participating in their activation[34]. In the next mechanism, the STAT protein binds to elements that do not belong to STAT and promotes STAT-dependent transcription[35]. In yet another mechanism, transcriptional factors not belonging to STAT may activate the transcription process by docking to a complementary sequence at independent sites on the DNA strand[36].

Most cytokines released by cells participate in the JAK/STAT signaling pathway. Understanding the signal transmission mechanism in this pathway has enabled the synthesis of medicines targeting its individual elements and structures[37].

Depending on the functions and range of activity, the inhibitors available for research and treatment are divided into the following classes of JAK inhibitors.

First-generation inhibitors

These inhibitors aim at suppressing the JAK kinase functions. They reduce the concentration of pro-inflammatory cytokines, whose levels are abnormally elevated in the signal transduction process in the JAK/STAT pathway, thus causing immunosuppression. They are small-molecule

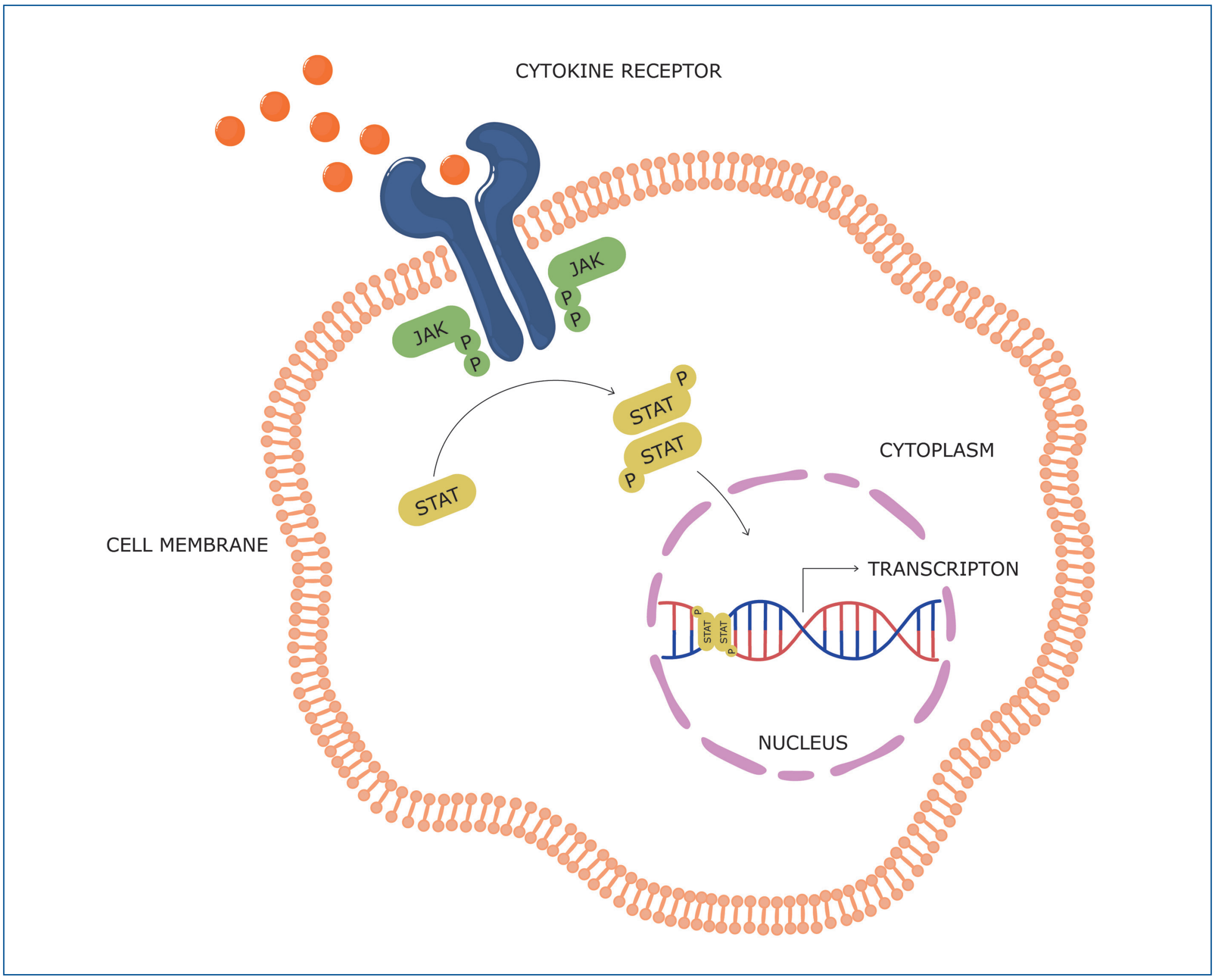


Figure 3. The mechanism of the JAK/STAT signaling pathway. Cytokines bind to their appropriate transmembrane receptors. This leads to the activation of JAK kinase. JAKs located on the receptor undergo phosphorylation and activate each other. As a result, the STAT protein can dock to the receptor. Then, STAT is phosphorylated by JAK, which makes it able to dimerize STAT: STAT. The dimers are translocated to the nucleus, where they bind to specific regulatory sequences, influencing gene expression. JAK – Janus kinase; STAT – signal transducer and activator of transcription.

compounds capable of freely penetrating the cell membrane, binding to kinases, and blocking the acceptor function.

The first-generation JAK inhibitors belong to compounds that may compete with the ATP (adenosine triphosphate) binding pocket. In its active conformation, the tyrosine kinase domain has a highly conserved structure of the ATP-binding site. This found its application in the design of a drug targeting the JAK1 kinase. The pocket structure is highly conserved and present in other JAK kinases, which may be affected by the competitive binding of inhibitors to other kinases. Consequently, the first-generation drugs act on more than one member of the JAK kinase family.

Representative examples of first-generation JAK inhibitors include baricitinib, ruxolitinib, and tofacitinib.

Baricitinib is a selective JAK1 and JAK2 inhibitor, with weaker activity towards JAK3 and TYK2. It is used in the treatment of rheumatoid arthritis, juvenile dermatomyositis, atopic dermatitis, lupus erythematosus, and auto-inflammatory diseases, where it shows activity in interferon-dependent disorders by reducing the inflammation and preventing the worsening of the symptoms. The most common dose-dependent adverse effect has been an increased risk of infections, including shingles, tuberculosis, and an increased level of lipoproteins. Caution has been advised in the case of patients with cardiovascular failure[38].

Ruxolitinib is a drug acting as an inhibitor of JAK1 and JAK2 kinases. It has been approved as a treatment for myelofibrosis (MF) in North America, and then in Europe to treat polycythemia vera. In the case of MF, the medicinal properties mainly consist of weakening the JAK/STAT cellular pathway activation and myelosuppression[39].

Tofacitinib mainly inhibits JAK1 and JAK3, and, to a lesser extent, JAK2 and TYK2. In consequence, the differentiation of Th1 and Th2 cells is disturbed, as is the formation of Th17 inflammatory cells. The compound has been used in atopic dermatitis, rheumatoid arthritis, psoriasis, ulcerative colitis, Crohn's disease, psoriatic arthritis, relapsing polychondritis, ankylosing spondylitis, and spot baldness. Among adverse effects, gastrointestinal perforations, shingles, and thrombosis have been observed. In patients with increased cardiovascular risk factors, thrombotic and embolismic events or venous thromboembolism have occurred[40].

Second-generation inhibitors

Medicines of a new generation, in which progress has been made in order to develop highly selective compounds towards the studied kinases, include the following categories.

JAK1 inhibitors

Filgotinib is an inhibitor of JAK1 kinase activity as well as JAK1-dependent cytokines: IL-2, IL-4, and IL-6, which play an important role in chronic inflammations and autoimmune diseases. In Europe, it is used in the treatment of rheumatoid arthritis when patients do not react to other therapeutic agents. It has been discovered that filgotinib can inhibit splicing and affect HIV splicing, in addition to inhibiting the JAK kinase. The adverse effects mainly include upper respiratory tract infections, nasopharyngitis, and headache[41].

Upadacitinib is an inhibitor of the JAK1 kinase that strongly inhibits IL-6, IL-2, and IFN-g cytokines, which are JAK1-dependent. The drug is used in the treatment of rheumatoid arthritis, in cases of a lack of response to or intolerance to methotrexate. New possibilities of application for this medicine are also being studied, such as in the treatment of ulcerative colitis, atopic dermatitis, Crohn's disease, psoriatic arthritis, and ankylosing spondylitis. The adverse effects are elevated parameters of liver aminotransferase, lipids, and creatine phosphokinase. Severe adverse effects include venous thromboembolism, stroke, or even death[42].

Abrocitinib is a JAK1 inhibitor, used in the treatment of atopic dermatitis. The most frequent adverse effects are nausea, diarrhea, headache, upper respiratory tract infections, nasopharyngitis, and hematological anomalies[43].

JAK2 inhibitors

Fedratinib is a strong, selective JAK2 kinase inhibitor, competitive towards ATP. It has been approved in the USA for the treatment of primary and secondary myelofibrosis and authorized for marketing in Europe for the treatment of splenomegaly and primary myelofibrosis. It induces cancer cell apoptosis. Adverse events range from severe to fatal encephalopathies, including Wernicke's encephalopathy. The most common adverse effects of the drug have been nausea, diarrhea, anemia, vomiting, and thrombocytopenia[44].

Pacritinib is an oral JAK2 inhibitor, used in the treatment of MF and acute myeloid leukemia (AML). Application of pacritinib in the treatment of rectal cancer, colorectal cancer, and non-small cell lung cancer is also being studied. Adverse effects involve anemia, diarrhea, thrombocytopenia, cardiac failure, pneumonia, and fever[45].

Gandotinib is a JAK2 kinase inhibitor used in the treatment of chronic myeloproliferative neoplasms (MPNs), including polycythemia vera and thrombocythemia. In the study by Mesa et al[46], the drug reduced the number of Ba/F3 JAK2 cells in the spleens of immunodeficient mice. It has been proven to inhibit signaling dependent on the

JAK2 V617F mutation, simultaneously showing a minor impact on a number of wild-type JAK2-dependent cells[46]. The drug has been proven effective in the treatment of chronic myeloproliferative neoplasms (MPN) with the JAK2 V617F mutation, including in patients previously treated with ruxolitinib. A phase II study involved administration to patients with MPN, including myelofibrosis (MF), polycythemia vera, and essential thrombocytosis. The adverse effects are anemia, hyperuricemia, diarrhea, thrombocytopenia, and fatigue. In phase II of the studies involving patients with myelofibrosis previously treated with ruxolitinib, the treatment did not show hematological or neurological toxicity[47].

JAK3 inhibitors

Decernotinib strongly inhibits JAK3. It has reduced ankle edema in an animal model in a T-cell-dependent inflammatory skin response[48]. In phase II of clinical trials, the drug has alleviated the symptoms of rheumatoid arthritis. The adverse effects include lymphopenia, neutropenia, and increased concentration of liver aminotransferases[49].

Peficitinib is a JAK3 inhibitor, which suppresses T cell proliferation and STAT5 phosphorylation. It has been approved and developed in Japan to treat rheumatoid arthritis. An application of the drug to treat autoimmune diseases, e.g., ulcerative colitis and psoriasis, is also being sought. The adverse effects include nasopharyngitis, increased concentration of creatine kinase in blood plasma, pneumonia, bronchitis, shingles, and urocystitis. Severe effects include sepsis and gastrointestinal tract perforation[50].

Pan-JAK inhibitors

Momelotinib is a selective inhibitor, competitive towards the ATP site in the JAK1 and JAK2 kinases. In clinical trials of Verstovsek et al[51], it has proven effective in the treatment of MF. The most frequently occurring adverse effects are cough, nausea, diarrhea, anemia, thrombocytopenia, neutropenia, and distal neuropathy.

Gusacitinib is a multidirectional JAK inhibitor acting on JAK1, JAK2, JAK3, and TYK2, as well as SYK kinase. It affects the Th1 and Th2 inflammatory pathways in chronic hand eczema[52]. Gusacitinib may be applied in the studies of chronic hand eczema or basal cell carcinoma. Phase I studies are being conducted on the use thereof in the treatment of systemic lupus erythematosus[53].

Delgocitinib is an inhibitor of the entire JAK family. It has been approved in Japan as an ointment to treat atopic dermatitis. It is also effective in the treatment of atopic dermatitis, chronic hand eczema, and spot baldness. The adverse effects include contact dermatitis, nasopharyngitis, and acne. A severe adverse effect has been Kaposi's varicelliform eruption[54].

STAT inhibitors

The design of STAT inhibitors is focused on limiting their phosphorylation or dimerization. In the course of the design, direct inhibitors are targeted at SH2, DNA-binding, or N-terminal STAT3 domains. Peptides and peptidomimetic inhibitors are intended to disrupt STAT3 dimerization and effectively block its transcriptional activity, but they fail to fulfill this role due to low cell permeability and their instability. STAT3 decoy oligonucleotides and small RNA-interfering inhibitors seem to be a feasible way to selectively inhibit the STAT3 activity, though they are relatively unstable[55,56].

In research, non-peptide small molecules and inhibitors whose structure is based on oligonucleotides have been employed, which specifically bind to the DNA-binding STAT domain. Antisense oligonucleotides (ASO) may inhibit the function and expression of STAT3 by reducing STAT3 mRNA expression or drugs derived from plants. Compounds of plant origin, such as curcumin or resveratrol, bind to the STAT pathway.

The role of JAK/STAT in periodontitis

It is assumed that disruptions in cellular signal transduction within the JAK-STAT pathway may be significant for the development of periodontitis. A decreased concentration of IL-10 blocks the STAT3 and STAT5 function in mice, whereas an increased level of IL-12 and IL-1a accelerates differentiation of Th lymphocytes into Th1. Th1 lymphocytes, by positively affecting the cellular response, intensify the disease symptoms caused by infection with *Porphyromonas gingivalis*[57,58].

The immunological activity of proteins from the Suppressor of Cytokine Signaling (SOCS) family may contribute to inhibiting the progression of periodontitis by modulating the functions of immunocompetent cells and regulating the anti-inflammatory immune response. The SOCS proteins constitute a family of intracellular regulators (inhibitors) of immune mechanisms occurring in immunocompetent cells *via* JAK/STAT molecules and are associated with the activity of cytokines, interferons, and growth factors. The activity of the SOCS molecules (feedback principle) involves the influence on cytokine receptors and cytoplasmic JAK proteins, which mediate intracellular signal transduction, thus blocking the binding of the STAT molecules to protein complexes (adaptors)[59].

The study by Papathanasiou et al[60] using genetically modified knockout (KO) mice lacking the *SOCS-3* gene demonstrated that KO mice infected with Porphyromonas gingivalis exhibited greater bone loss compared to healthy controls. The lack of SOCS-3 also resulted in a higher number of osteoclasts and increased Receptor Activator for Nuclear kB Ligand (RANKL) expression. The inflammation induction *via* administration of the *Porphyromonas gingivalis* lipopolysaccharide stimulated the KO mice with the shortage of SOCS-3 to increase secretion of the pro-inflammatory cytokines IL-1b, IL-6, and IL-8. The study by Papathanasiou et al[60] demonstrated that SOCS-3 may affect the loss of bone tissue in the course of periodontitis.

Binding the SOCS proteins to the cytokine receptors alters the spatial positioning of the ligand bond, i.e., activators of transcription (STATs), thus influencing the activity of the intracellular JAK/STAT pathway.

The clinical trial by Ancuta et al[61] comparing the condition of the periodontium in individuals suffering from both periodontitis and rheumatoid arthritis simultaneously have shown that after oral administration of the JAK1 and JAK2 tyrosine kinase inhibitor (baricitinib), the symptoms of periodontitis have ceased. Likewise, studies by Kobayashi et al[62] confirmed high efficacy of treating periodontitis with tofacitinib, which inhibits the activity of the JAK kinase.

The *in vitro* studies by Iwasaki et al[63] and Leon et al[64] have demonstrated an increase in the activity of alkaline phosphatase (ALP) under the influence of IL-11 and IL-6. ALP positively influences the differentiation of osteogenic cells, bone mineralization and metabolism, and stimulates type I collagen synthesis.

A thorough understanding of the mechanisms behind the JAK-STAT signaling pathway will provide deeper insight into its regulatory action and pathogenesis of periodontitis. Further research is necessary to develop targeted therapies involving medicines that inhibit the JAK-STAT signaling pathway. When combined with the current methods used in the treatment of periodontitis, modifying the host's response at the molecular level may bring promising therapeutic benefits[65,66].

NATURAL PRODUCTS AND THEIR DERIVATIVES

Interest from both the pharmaceutical industry and researchers in plant-derived compounds has risen in the last few years. The properties of medicinal plants had been known to humanity for centuries, although their beneficial effects on health were recognized by conventional medicine much later. Many of the plant-derived compounds are currently undergoing preclinical studies, with particular attention given to those that exhibit inhibitory effects on the JAK/STAT pathway. The research is based on their primary structures or modifications by adding functional groups to the existing ones. Among the most well-known and valuable plant-derived compounds, due to their properties, the following should be listed due to their properties.

Arctiin

Arctiin belongs to the class of lignan glycosides – aromatic compounds of a polycyclic structure, in which the carbohydrate component forms a glycosidic bond with the lignan residue. It is isolated from the fruit of *Arctium lappa* L., a plant from the *Asteraceae* family. Arctiin shows medicinal activity in cases of ischemic and reperfusion injury, acute lung injury, and cardiac hypertrophy. It has antioxidant, anticancer, antidiabetic, anti-inflammatory, hepatoprotective, and antidepressant properties[67-69].

It inhibits JAK1, JAK2, and STAT3 activation in human multiple myeloma (MM) cells[70]. Lee et al[71] have shown anti-inflammatory activity by decreasing the expression of IL-6, IL-1β, and TNF-α through the inhibition of NF-κB. Arctiin induces cytotoxicity in the case of colorectal cancer, liver cancer, and prostate cancer[70,71].

Artemisinin

Artemisinin is extracted from sweet wormwood (*Artemisia annua*) and is used in Chinese medicine to treat fever. Artesunate is a soluble, semi-synthetic derivative of artemisinin, used in the treatment of malaria. Research by Ilamathi et al[72] has examined the application of artemisinin to treat cancer. It exhibits anti-cancer activity by binding cancer cells through the SH2 domain, thus disrupting STAT3 dimerization and expression. Cell-based assays have shown that artesunate inhibits dimerization and modulates the expression of the STAT3 target genes. Moreover, studies on acute leukemia cell lines have demonstrated that artesunate induces apoptosis by reducing STAT3 expression[73].

Bergamottin

Bergamottin is a naturally occurring furanocoumarin found in grapefruit, bergamot oil, and citrus essential oils. The compound inhibits the activity of cytochrome P-450, involved in the metabolism of many substances.

In the study by Sekiguchi et al[74] on multiple myeloma (MM) cells, bergamottin has been shown to inhibit the constitutive activation of JAK1 and JAK2, as well as the constitutive activation of STAT3 induced by IL-6. It also displays cytotoxicity against liver and stomach cancers.

Betulinic acid

Betulinic acid is a pentacyclic triterpene obtained from the bark of *Zizyphus mauritiana*, birch, sycamore, and eucalyptus, as well as many fruits and vegetables. It has anti-inflammatory, anti-cancer, antibacterial, anthelmintic, antidepressant, hepatoprotective, antiviral and antimalarial properties. Betulinic acid inhibits the constitutive activation of STAT3, Src kinase, JAK1, and JAK2. It reduces the expression of STAT3-regulated gene products, such as Bcl-xL, Bcl-2, cyclin D1, and survivin[75].

Butein

Butein is a glycoside, a yellow pigment in the flowers of numerous plants, including species of threadleaf coreopsis (*Coreopsis verticillata L.*) and plains coreopsis (*Coreopsis tinctoria Nuttall*). It is also obtained from the stem bark of *Semecarpus anacardium*, *Rhus verniciflua Stokes,* and the sapwood of *Dalbergia odorifera*[76]. This glycoside is used in Asian countries in traditional medicine for the treatment of pain, gastritis, stomach cancer, thrombotic diseases, and parasitic infections. Moreover, the compound inhibits liver fibrosis, reduces glomerulonephritis, and suppresses the formation of skin tumors. Butein may inhibit the proliferation of colorectal and breast cancer, acute myeloid leukemia, multiple myeloma, and melanoma[77]. It has been demonstrated that butein inhibits the constitutive activation of STAT3. Butein induces the production of ROS, which, in turn, blocks STAT3 signaling. The compound also inhibits JAK2 phosphorylation in HepG2 cells[78].

Catechins

Catechins are polyphenols present in green tea[79]. Research results suggest that the metabolites can activate many signaling pathways, which, in turn, influence cell survival, alter the expression of pro-apoptotic and anti-apoptotic proteins, or enhance antioxidant defence[80]. Catechins have been used for diabetes, hypertension, obesity, and hyperlipidemia. Research is also being conducted into their potential use in acute oesophagitis, hepatitis, or multiple sclerosis. Catechins exhibit local analgesic activity.

They affect the JAK/STAT pathways and partially inhibit STAT1 and STAT3. They reveal anti-inflammatory, anticancer, and antioxidant properties[81].

Caffeic acid

Caffeic acid is a secondary metabolite synthesized by plants, found mainly in edible ones. It belongs to the group of hydroxycinnamic acids. The best-known group of derivatives includes caffeic acid phenethyl ester (CAPE) and esters formed with quinic, tartaric, and α-hydroxydihydrocaffeic acids. Together with its natural derivatives, caffeic acid is a very strong antioxidant, protecting cells from oxidative stress, scavenging reactive oxygen species, and chelating metal ions[82]. Both caffeic acid and CAPE inhibit NF-κB activation, contribute to the inhibition of angiogenesis, metastases, and tumor invasion, and have anti-inflammatory properties[83]. CAPE shows the strongest antioxidant activity.

Caffeic acid and its synthetic derivative participate in the inhibition of STAT3 activity. Caffeic acid and CADPE have inhibited STAT3 phosphorylation, thereby blocking its nuclear translocation and recruitment, and consequently preventing the formation of the STAT3–p300–HIF-1α transcriptional complex for the VEGF promoter, which plays a key role in angiogenesis and tumor progression[84,85].

Capsaicin

Capsaicin is an alkaloid found in the fruits of plants from the *Capsicum sp.* genus, and a component of chili peppers. In traditional medicine, powdered *Capsicum* fruits were rubbed into painful gums. These analgesic properties have been used in modern pharmacology, where transdermal preparations are applied in postherpetic pain, rheumatoid arthritis, fibromyalgia, and neuropathic pain. Capsaicin also exhibits antioxidant properties due to the presence of a phenolic group in its molecular structure. The *Capsicum* alkaloid also has antibacterial properties.

This alkaloid triggers a reduction in STAT3-regulated expression of survivin, Bcl-xL, and Bcl-2, thereby inducing apoptosis of multiple myeloma cells[86]. Capsaicin also inhibits IL-6-induced activation of STAT3 and JAK1. Additionally, it has chemopreventive properties[86,87].

Casticin

Casticin is a methoxylated flavonol obtained from *Artemisia annua*. It has analgesic, anti-inflammatory, anti-angiogenic, anti-asthmatic properties. The antiproliferative potential of casticin is being investigated in cases of liver, breast, lung, pancreas, colon cancer, glioma, leukemia, or stomach cancer. Inhibition of the JAK2/STAT3 signaling pathway has been demonstrated as a result of casticin activity[88].

Celastrol

Celastrol is a pentacyclic quinone methide triterpenoid compound derived from the Chinese medicinal plant *Tripterygium wilfordii*, commonly known as thunder god vine. Due to its anti-inflammatory, antioxidant, and antifungal properties, it is used in Chinese medicine as an agent against rheumatoid arthritis, fever, and psoriasis[89]. It also possesses anticancer, neuroprotective, anti-obesity and anti-atherosclerotic properties. It exhibits its strong anticancer activity, inhibits proliferation and induces apoptosis[90].

Celastrol inhibits the constitutive activation of STAT3 in cells. The compound suppresses the ability of STAT3 to bind DNA. It is assumed that it can inhibit the function of transcriptional factors by inhibiting STAT3 translocation to the nucleus[91]. Moreover, it may inhibit IL-6-induced phosphorylation of STAT3. In age-related macular degeneration, celastrol causes alleviation of the symptoms by inhibiting the induction of pro-inflammatory cytokines together with the inhibition of apoptotic death of the epithelial cells in the human retina[92].

Cucurbitacins

They are used in traditional Chinese medicine. Chemically, cucurbitacins exhibit a high degree of structural diversity, comprising various forms designated from A to T. In the species of *Cucurbitaceae*, cucurbitacin B is one of the most common forms[93]. It shows anti-inflammatory activity. Its properties have been used in the treatment of hepatitis[94]. Cucurbitacin B may inhibit the growth of human cancer cell lines and tumor xenografts. It inhibits STAT3 activation, which may be promising for the treatment of non-small cell lung cancer[95]. In the human liver cancer lines, cucurbitacin B has reduced the level of phosphorylated STAT3[96].

Curcumin

Curcumin is a dietary spice and an active compound in turmeric, obtained from the rhizome of *Curcuma longa*[97]. The compound modulates the expression of inflammatory cytokines, transcriptional factors, enzymes, and gene products associated with vital cellular functions, proliferation, invasion, and angiogenesis. Turmeric has been shown to exhibit pro-apoptotic and anti-proliferative activity on many cancer cell lines *in vitro*[98]. Panknin et al[99] reported on clinical findings related to curcumin. The studies presented in this paper most often considered the compound's effect on the development of oral diseases, periodontitis, oral submucous fibrosis, cancer, cardiovascular diseases, autoimmune and neurological disorders, COVID-19, diabetes, nonalcoholic fatty liver disease, migraine, and polycystic ovary syndrome. Research on T-cell lymphoma lines has shown that the expression levels of both STAT3 and phosphorylated STAT3 were decreased in these cells compared to the untreated controls. Weissenberger et al[100] have proven that curcumin inhibited the tyrosine phosphorylation of JAK1, JAK2, and STAT3 in the glioma cell lines in mice. Curcumin reduced the transcription of the STAT3 target genes. It has also been shown to inhibit IL-6-induced phosphorylation and nuclear translocation of STAT3[101]. Research findings[102,103] have demonstrated that curcumin inhibits STAT3 by inducing ROS gene activity. Thus, by suppressing STAT3, curcumin disrupts the JAK/STAT signaling pathway[102]. Drugs such as FLLL11, FLLL12, FLLL32, and FLLL62 are produced from curcumin[103].

Diosgenin

Diosgenin is a steroid sapogenin present in the following families: *Leguminosae*, *Scrophulariaceae*, *Solanaceae*, *Dioscoreae*, *Rhamnaceae*, *Liliaceae*, *Amaryllidaceae*, and *Agavaceae*. It is also abundantly found in *Trigonella foenum graecum, Dioscorea rhizome, Smilax china Rhizoma polgonati, Dioscorea villosa,* among other plants with medicinal properties. In the pharmaceutical industry, diosgenin has been a precursor in the synthesis of steroid drugs. Li et al[104] have shown that diosgenin inhibits proliferation and induces apoptosis in a wide range of cancer cells. Diosgenin has inhibited STAT3 activation in C3A cells of human hepatocellular carcinoma. The compound has suppressed constitutive phosphorylation of JAK1 and JAK2.

Guggulsterone

Guggulsterone is a plant steroid, a bioactive component of the gum resin from *Commiphora wightii*. The resin is used in traditional medicine to treat various ailments, including malignant wounds and ulcers, edema, sudden paralytic attacks, liver diseases, urinary tract disorders, internal tumors, obesity, intestinal worms, leukoderma, and sinus disorders[105]. By regulating transcription factors such as NF-κB and STAT3, guggulsterone modulates the expression of genes involved in inflammation, cell survival, and proliferation. In addition, the compound exhibits antitumor properties by inhibiting the proliferation of various human cancer cell types. Consistent with these effects, guggulsterone induces apoptosis in human prostate cancer cells through activation of the c-Jun N-terminal kinase (JNK) signaling pathway[106].

Honokiol

Honokiol is a small biphenyl ligand, an active compound classified as an adaptogen, obtained from a few species of the genus *Magnolia* (*officinalis, obovate,* and *grandiflora*). It is applied in traditional Chinese medicine to alleviate inflammation, bacterial infections, and gastrointestinal disorders. The compound can modulate the constitutive activation of STAT3 in human hepatocellular carcinoma (HCC) cells[107]. Honokiol has inhibited the DNA-binding activity of STAT3 and suppressed the JAK2 phosphorylation in HepG2 cells. Honokiol has also been studied by Dutch researchers who concluded that honokiol inhibited the replication of SARS-CoV-2 in cells, as well as that of other pathogenic coronaviruses, e.g., SARS-CoV or MERS-CoV[108].

Nimbolide

Nimbolide is the main tetranortriterpenoid isolated from the leaves of *Azadirachta indica* (*neem*). It has antibacterial, antimalarial, insecticidal, antiparasitic, and anticancer properties. Furthermore, nimbolide has been used in traditional Indian Ayurvedic medicine as a component of an herbal mixture for the treatment of acne, wounds, gastric ulcers, and infections[109]. In prostate cancer cells, nimbolide has decreased cancer cell viability and inhibited the activity of STAT3, JAK1, and JAK2. It exhibited anti-proliferative activity in preclinical cancer models[110].

Oleanolic acid

Oleanolic acid is a pentacyclic triterpene found in numerous plant species, particularly in the *Oleaceae* family. It is abundant in the fruits, stem bark, and leaves of various medicinal plants, including the European olive tree. Ayeleso et al[111] have shown its anti-inflammatory, antioxidant, neuroprotective, anti-aging, and even hepatoprotective activity. Its properties have been used in the treatment of diabetes, hyperlipidemia, and obesity. Oleanolic acid disturbs the formation of STAT3 dimers, and STAT1/STAT3 and TYK2 signalling[112]. Derivatives with structurally modified rings are most frequently studied. One of the most investigated derivatives is bardoxolone[113].

Resveratrol

Resveratrol is a naturally occurring polyphenol found in grapes, blueberries, and even peanuts[114]. In nature, resveratrol exists in *cis* and *trans* forms. The latter is dominant and exhibits greater biological activity. Resveratrol is produced by plants in response to fungal infections, mechanical damage or intense exposure to ultraviolet radiation. This important compound exhibits anti-inflammatory, anticancer, antioxidant, hepatoprotective, anti-diabetic, cardioprotective, neuroprotective, and many other types of activities. Resveratrol exerts therapeutic effects and interacts with numerous signaling pathways by inhibiting the phosphorylation of STAT1, STAT3, and NF-κB[115]. However, due to poor bioavailability of resveratrol, its derivatives with a modified structure demonstrate better bioavailability. For instance, the compound LYR71 has proven to be more effective in inhibiting STAT3[116]. Apart from resveratrol, its derivatives are being studied and considered as a potential treatment; thanks to ligand modifications, they achieve better spatial structure, facilitating appropriate binding to specific therapeutic protein targets. Clinical studies of Berman et al[117] on the use of resveratrol involved cardiovascular and neurodegenerative diseases, diabetes, obesity, cancers, and muscular issues dystrophies. Observations of improved physical condition have shown that resveratrol promotes the regeneration of muscle mass and bone[118]. Moreover, the application of resveratrol combined with regular physical exercise has significantly improved mitochondrial function and physical efficiency in elderly individuals. Resveratrol modulates the STAT3 pathway and inhibits the growth of head and neck squamous cell carcinoma (HNSCC). Resveratrol stimulates autophagy, inhibits STAT3 signaling, and induces apoptosis of ovarian cancer cells[119].

In order to overcome the broad spectrum of activity of natural medicines, their poor water solubility or short half-life, progress is being made in targeted delivery of the substances through the application of exosomes, phospholiposomes, liposomes, and nanoparticles, or through the synthesis of the natural product derivatives.

NF-κB

NF-κB is a nuclear transcription factor that affects the expression of gene-coding proteins associated with inflammation, cell proliferation, and apoptosis. Increased and uncontrolled activation of NF-κB caused by ongoing inflammation encourages the development of many diseases, including those within the oral cavity.

Inhibition of the NF-κB signaling pathway weakens the inflammatory response of the organism. Drugs that act antagonistically towards the NF-κB receptors may be helpful in fighting pathological symptoms[120]. Yet, the effect of the activation of the signaling pathway triggering transcription of the gene-coding proteins associated with inflammation in periodontitis still remains unclear. There are no drugs or materials that would control the disease progression in a satisfactory way through regulation of the NF-κB pathway. Therefore, there is a continuous need to widen the theoretical and clinical knowledge in this area[121].

Activation mechanisms

The name of the proteins belonging to the NF-κB families originates from the nuclear factor (NF), first described by Sen and Baltimore[122] in 1986, which binds to the promoter of the gene encoding the kappa chain of immunoglobulins in type B-lymphocytes (κB, kappa-light-chain-enhancer of activated B cells). They are among the key elements controlling the course of the organism's inflammatory reaction and the bone remodeling process. The NF-κB expression level and its activity are tightly regulated by feedback loops[123].

Under the influence of a range of environmental factors, cells activate signaling pathways, which are cascades of interdependent and biochemically connected intracellular processes. In the case of the NF-κB factor, several distinct pathways function differently depending on the type of stimulating factor, cell type, and its current needs. The activation of the NF-κB factor occurs in two ways: *via* the classical pathway or an alternative one[124]. The mechanisms of their activities have been graphically presented in Figure 4.

The mechanism of the classical NF-κB activation pathway is related to the response to pro-inflammatory stimulation (e.g., by TNF and IL-1 cytokines or bacterial lipopolysaccharides). The basis of the mechanisms is IκB phosphorylation, catalyzed by IKK kinases (IκB Kinase), followed by degradation of the phosphorylated (and ubiquitinated) inhibitory protein. The IKK complex consists of two catalytic subunits, IKKa and IKKb, as well as a regulatory unit called NEMO (NF-κB Essential Modulator), referred to as IKKg. In the case of the classical activation of NF-κB, the phosphorylation process of the IκB inhibitors mainly depends on the activity of the IKK kinase, which, together with the regulatory unit NEMO, catalyzes the transfer of the phosphate group to two serine residues present in the amino acid chain of these proteins. As a result, a conformational change occurs, enabling the binding of the ubiquitin ligase complex and the degradation by the 26S proteasome. The active NF-κB dimer, released in this way, can translocate from the cytoplasm to the cell nucleus.

The alternative activation pathway of the NF-κB factor requires the participation of the IKKα and NIK (NF-κB-inducing kinase) kinases. The first stage of the signaling cascade is the activation of the IKKa homodimer by the NIK kinase. The active IKKa kinase phosphorylates the p100 precursor unit of the NF-κB2/RelB heterodimer. This protein is next subjected to proteolytic treatment with the use of ubiquitin, after which the mature p52/RelB heterodimer is transported to the cell nucleus[125].

The role of NF-κB in periodontitis

NF-κB is a nuclear transcription factor regulating the expression of the genes coding proteins

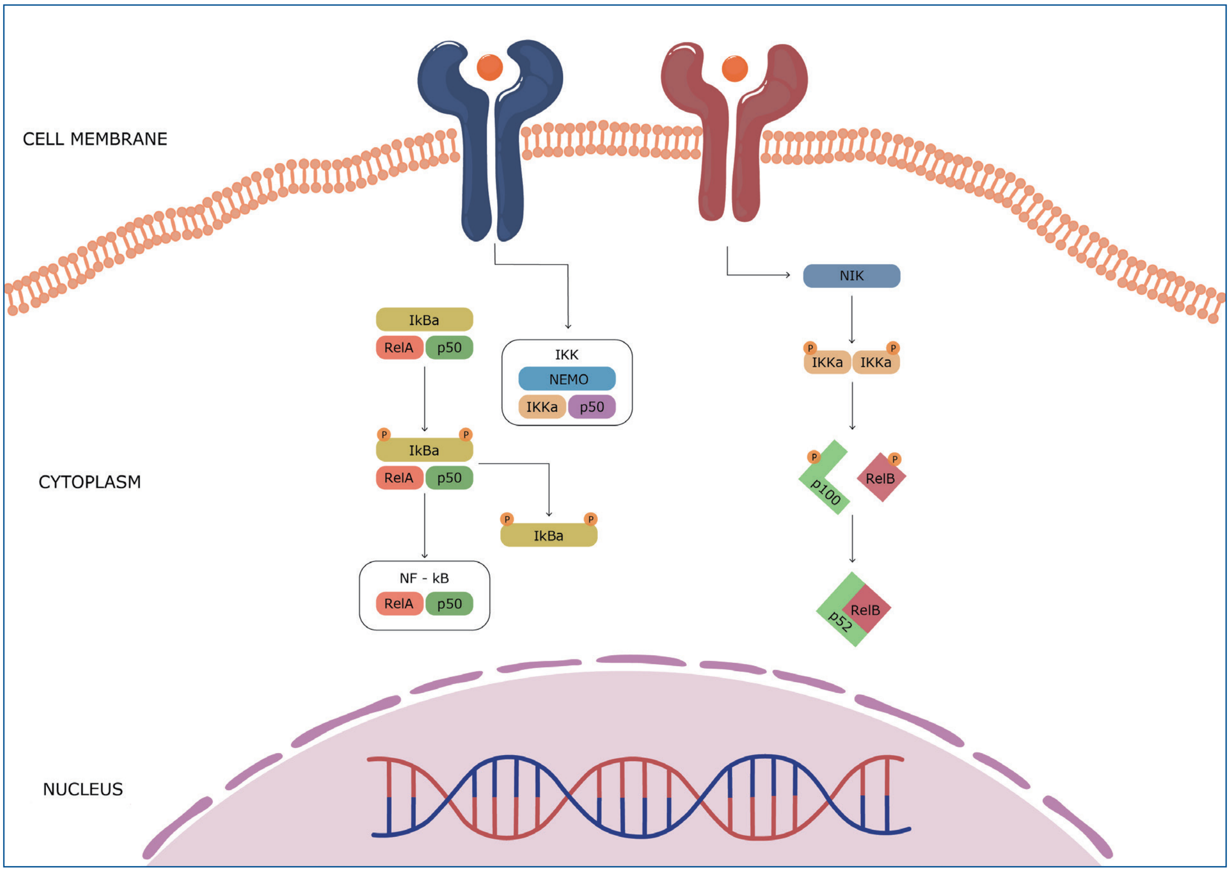


Figure 4. Classical and alternative activation pathway of NF-κB. Classical pathway involves phosphorylation reaction of IκB, catalyzed by IKK kinase, followed by degradation of phosphorylated and ubiquitinated inhibitory protein. Active NF-κB dimer released in this way may relocate from cytoplasm to nucleus. Alternative activation pathway of NF-κB factor requires participation of IKKa and NIK kinases. Active IKKa kinase phosphorylates NF-κB2/RelB heterodimer, and after proteolytic treatment, mature p52/RelB heterodimer is transported to nucleus.

associated with the response to oxidative stress, cell adhesion, proliferation, apoptosis, viral and bacterial stimuli, antigens, UV radiation, and cytokines, such as IL-2 (interleukin-2) and TNF-α. Uncontrolled activation of the NF-κB signaling pathway is connected with the pathogenesis of such diseases as atherosclerosis, asthma, AIDS, diabetes, inflammatory bowel disease, stroke, muscle atrophy, septic shock, rheumatoid arthritis, and other autoimmune diseases. Abnormal transcription of NF-κB has also been determined in intestinal mucosa biopsy samples taken from patients with ongoing Crohn's disease and ulcerative colitis (IBD). Disturbed expression of the NF-κB subunits has been reported in T cells of patients with systemic lupus erythematosus (SLE). The existing evidence indicates a connection between inflammation and cancer progression, which makes NF-κB a therapeutic target in the development of new chemopreventive and/or chemotherapeutic drugs. Constitutive expression and activation of NF-κB have been observed in the cancer cells of the mammary gland, colon, pancreas, liver, ovary, lymphoma, and melanoma. It has been proven that it participates in increasing cell proliferation, blocking apoptosis, promoting angiogenesis, and conditioning invasiveness and predisposition to metastases; therefore, one of the therapeutic strategies may be inhibition of the molecular activation mechanisms of this pathway[126].

NF-κB also regulates the progression of inflammation in periodontal tissues; the relationship of the signaling pathway with periodontitis is undisputable[120]. Increased expression of the NF-κB (p50/p65) transcription factors and a lowered level of IκB have been noticed in patients with periodontitis, compared to healthy individuals[127]. The NF-κB activation rates have been significantly higher (75-90%) in the tissues affected by periodontitis, in comparison to the tissues unaffected by the disease process (5-30%). Conversely, the IκB expression (5%) in the tissues of patients suffering from periodontal diseases has been considerably lower than in the healthy ones (50%), which indicates an important role of NF-κB in the pathogenesis of periodontitis[128]. Inhibition of the signaling pathway of NF-κB reduces the production of pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α[129]. Inhibition of the signaling pathway of NF-κB (p-IκBa, N-p65) significantly decreased the expression of IL-6 and IL-8 in human periodontal ligament stem cells (hPDLSC)[130]. The NF-κB pathway activation consists of the phosphorylation of p65 in hPDLSCs and excessive overexpression of visfatin, which consequently leads to an increase in the production of pro-inflammatory cytokines (TNF-a, IL-1β, and IL-6)[131].

The function of controlling the NF-κB pathway signaling in periodontitis may be performed by long non-coding RNA (lncRNA), including the small nucleolar RNA host gene 5 (SNHG5). The overexpression of lncRNA-SNHG5 leads to its binding to the NF-κB p65 subunit and inhibits the translocation thereof. The level of inflammasomes (i.e., large, intracellular pro-inflammatory protein complexes, whose function is, among others, to activate NF-κB) decreases[132].

The NF-κB signaling in the pathogenesis of periodontitis is also regulated by short non-coding RNA molecules (miRNA) that bind to the complementary mRNA sequences, which may lead to its degradation or protein translation inhibition[133]. In periodontitis, microRNA-21 (miR-21) inhibits the expression of the phosphorylated NF-κB; a lack of miR-21 leads to a decreased amount of IκB[134].

NF-κB regulates bone metabolism; a lack of the NF-κB1 and NF-κB2 coding genes in mice results in osteopetrosis[135]. Phosphorylation of NF-κB p50 and p-65, as well as the level of TNF,a has been significantly higher in the mice in which bone atrophy was observed[136]. Magnoflorine considerably reduces the expression of TNF-a and the level of the phosphorylated proteins p50 and p65, inhibiting the bone loss. Inhibition of IKK/p65/NF-κB facilitates the differentiation of osteoblasts; the quantity of bone trabeculae and bone density increase[137].

The expression level of Receptor Activator for Nuclear Factor κB Ligand (RANKL) is significantly higher in patients suffering from periodontitis. The cells that accompany the loss of bone mass in the course of periodontitis are osteoclasts. Activation thereof is regulated by complex physiological processes, in which the key role is played by a set of proteins that includes osteoprotegerin (OPG), receptor activator for nuclear factor NF-κB (RANK), and RANK ligand (RANKL)[138]. The activity of the bone-resorbing cells – osteoclasts – is inhibited when RANKL is previously bound by OPG, which competes with RANK[139]. Pirfenidone suppresses NF-κB and the expression of *Porphyromonas Gingivalis* lipopolysaccharide-induced (LPS) pro-inflammatory cytokines IL-1β, IL-6, and TNF-a, thus inhibiting the progression of periodontitis[140].

The alternative NF-κB factor activation pathway plays a crucial role in regulating the course of periodontitis. To activate it, NF-κB Inducing Kinase (NIK) is required, as it phosphorylates the p100 protein, which is part of the transcriptionally inactive p100/RelB dimer. The application of the NIK inhibitor (Cpd33) blocks the formation of osteoclasts, which may suggest its therapeutic importance[141]. The activity of NF-κB (p-p65, p-IκBa) is inhibited by the expression of lncRNA Dancr in

MC3Tc-E1 cells, facilitating osteogenesis, whereas NF-κB (p-p65) activation by the transcription factor Tcf7l2 accelerates the formation of cementum and helps to regenerate the periodontal tissues[142]. Inhibiting the phosphorylation of IkBa and p65 with the use of proanthocyanidins (PACs) may stimulate gingival fibroblasts (hPDLF) to mineralize and deposit new bone tissue. Human cathelicidin (LL37), a protein with antibacterial properties, increases the level of NF-κB p65 phosphorylation in hPDLC. The cascade of enzymatic reactions accelerates the production of the vascular endothelial growth factor A (VEGF-A)[143,144].

CONCLUSIONS

Biologically active medical products (biopharmaceuticals) are modern drugs used in the treatment of many chronic autoimmune and inflammatory diseases. They enable effective treatment by inhibiting individual components of the immune system, which are overactive in the course of these diseases. They act selectively on the immune system; hence, they cause fewer side effects compared to conventional treatment. There is a continuing need to develop new standards based on molecular targeted therapy so that biopharmaceuticals can be cheaper and widely available.

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Conflict of Interest
The authors declare no conflict of interest.

Informed Consent
This study only used data already published and does not contain data from patients from the author's institutions. Therefore, informed consent was not necessary.

Ethics Approval
This study only used data already published and does not contain data from patients from the author's institutions. Therefore, Ethics Committee approval was not necessary.

Authors' Contributions
Brozek R. and Lorenz A. contributed to the conceptualization, methodology, and supervision of the study and writing – original draft. Kurpisz M. and Dorocka-Bobkowska B. contributed to the investigation, data curation and writing – review and editing. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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