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Immunosuppressive Potential of Co-Administration of Azathioprine and Brown Seaweed Extracts on Inflammatory Biomarkers in Rheumatoid Arthritis: A Systematic Review

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ABSTRACT

Rheumatoid arthritis is an inflammatory type of arthritis that damages and inflames joints.18 million people suffer from rheumatoid arthritis globally, and 55% in Pakistan facing this disease. Rheumatoid arthritis manifests itself between the ages of 35 and 60. Patients with rheumatoid arthritis suffer from infection, in which there is elevation of inflammatory biomarkers, CRP, erythrocyte sedimentation rate, and white blood cells. Azathioprine is an analogue of purine that has immunosuppressive qualities. It suppresses the immune system by conversion in 6-MP and blocking the enzymes that suppress or limit the availability of the adenine and guanine nucleotide, that's lead to suppression of the immune system. As azathioprine is effective for autoimmune disease, but it has a severe effect on other organs, we must focus on nutrition. Brown seaweed is a marine macro alga having different bioactive components like fucoid etc. Brown Seaweed extract has been shown to reduce the release of inflammatory biomarkers TNF,IL-6 and IL-1 that are linked with arthritis, and seaweed reduces oxidative stress. Co-administration of azathioprine and brown seaweed will work through complementary mechanism. As azathioprine acts as an immunosuppressant, meanwhile, brown seaweed directly scavenges free radicals. This combined approach provides a comprehensive strategy for managing rheumatoid arthritis by addressing both immune system deregulation and oxidative damage, which both are both central to the disease progression.

Keywords: *Azathioprine, Immunosuppressant, Biomarkers, Rheumatoid arthritis, Co- administration, Brown seaweed.*

1. Introduction

18 million people around the globe suffered from rheumatoid arthritis in 2019. Rheumatoid arthritis affects about 70% of women, and 55% of those affected are over 55. Rheumatoid arthritis affects 13 million people, with moderate to severe symptoms that may benefit from rehabilitation [2023]. Based on self-reported data from the National Health Survey (NHS) for the years 2014–2015, Australia has been reported to have the highest prevalence of rheumatoid arthritis (2% globally) at the population level. In terms of reported frequency of rheumatoid arthritis at the community level, American Indigenous populations rank highest, with 5.3% for Pima Indians and 6.8% for Chippewa Indians [1]. 55% of the 1.15 million people make up Pakistan's population in 2023.

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There are not many rheumatologists in Pakistan—roughly 100 are registered with the Pakistan Society of Rheumatology (PSR)—in response to this disease burden [2023]. An inflammatory type of arthritis that damages and inflames joints is called rheumatoid arthritis (RA). It happens when the tissue lining joints, or synovium, is unintentionally attacked by the immune system. Hands, knees, and ankles are frequently affected by RA, and the same joint is frequently affected on both ends of the human body. There may be additional effects on the heart, lungs, eyes, and other body parts [2]. Deformities and erosion of bones result from all this joint damage, which is typically extremely painful for the patient. Rheumatoid nodules beneath the skin, tiredness, fever, weight loss, and stiffness in the morning of the afflicted joints lasting longer than thirty minutes are typical signs of RA. This disease typically manifests itself between the ages of 35 and 60, with episodes of remission and aggravation. It is also known as juvenile rheumatoid arthritis (JRA), which is analogous to RA but does not have the rheumatoid factor. It can affect children who are young even before reaching the tender age of 16 [3]. It can result in joint destruction and disability if untreated. Women are more likely than men to develop RA, and those who are fertile are most at risk [4]. Exposure to silica, smoking, and periodontal disease are risk factors that are associated with the development of RA [5]. Chronic and progressive joint erosion is the hallmark of rheumatoid arthritis (RA), a systemic immune-related illness brought on by the combination of hereditary and environmental factors. Patients with RA may experience recurrent infections due to compromised immune function. Patients with RA may be more susceptible to infection as a direct result of immunological failure linked to the disease.

Furthermore, during the acute phase of RA, there is an elevation in the inflammatory markers C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell (WBC) counts. In individuals with RA, it can be challenging to differentiate between infection, inflammation, and autoimmune diseases since they might present with striking similarities. Pro-calcitonin (PCT) and CRP are biomarkers used to differentiate inflammation from infection in autoimmune diseases. PCT is a peptide precursor of the calcitonin hormone and is a reliable marker of systemic bacterial infection. CRP is a short pentraxin used to activate complement and regulate phagocyte function. PCT and CRP are both effective in treating bacterial infections in patients with RA. IL-6 is a cytokine that plays a role in the initial stages of inflammation and is more precise in identifying bacterial infections compared to PCT. TNF-α is a key pro-inflammatory cytokine in RA pathophysiology and may enhance inflammatory activity in early RA [6]. Recent research has highlighted the role of novel cytokines in both wellness and illness, particularly in the immune response, inflammation, cellular differentiation, and immunological pathology. IL-1, IL-12, IL-32, and IL-34 are significant inflammatory mediators in RA and experimental arthritis. IL-33 is higher in RA patients and is linked to RA-ILD and bone erosions. IL-37 and IL-27 are also linked to RA-associated interstitial lung disease. IL-32 is a key cytokine in RA pathogenesis, promoting monocyte differentiation and inflammatory cell recruitment. IL-34 promotes monocyte survival, proliferation, and differentiation to macrophages [7].

The HLA-DRB1 locus is associated with patients with RA, suggesting that T cell selection and antigen presentation influence the induction of autoreactive immune responses. RA is driven by CD4+ T lymphocytes, and IL-6 is a key mediator of bony destruction. IL-17-producing helper T cells play important roles in RA development, causing pro-inflammatory cytokines and chemokines to enhance inflammation. Factors regulating Treg and Th17 plasticity could be targets for immunotherapy targeting the manipulation of the immune system in autoimmune diseases. B cells play a crucial role in the pathogenesis of RA through autoantibody production, antigen presentation, and cytokine secretion. Anti-citrullinated protein antibodies (ACPAs) have the most remarkable prognostic value concerning RA onset among symptomatic at-risk patients. The innate immune system plays a crucial role in the development and progression of RA, with dendritic cells, macrophages, and B cells are involved in the inflammatory response. Cytokine secretion is also involved in the development of RA, with B cells secreting various cytokines. Macrophages are the most abundant immune cells found in RA synovium, producing pro-inflammatory cytokines involved in RA pathogenesis [8]. The Food and Drug Administration (FDA) has authorized azathioprine (AZA) for the symptomatic management of active rheumatoid arthritis. Azathioprine, a purine analogue, is transformed into its active metabolites, mercaptopurine (6-MP) and thioguanine (6-TGN), by the enzymes thiopurine methyltransferase (TPMT) and hypoxanthine-guanine phosphoribosyl transferase (HPRT). Following this, the synthesis of purine is halted. Metabolites of division halt when they are incorporated into replicating DNA. Most of the toxic and immunosuppressive effects of AZA could also be caused by its metabolites. AZA does not pass through the blood- brain barrier and is quickly absorbed through the GI tract. It increases in toxicity in renal failure because it is metabolized in the liver and excreted through the kidneys [7].

Azathioprine, a pro-drug of 6-mercaptopurine, is frequently used to treat RA-ILD by inhibiting purine synthesis. A retrospective report, single-center cohort study of CTD-ILD patients receiving MMF and azathioprine shows that azathioprine patients had a statistically significant annual increase in FVC and DLCO. These results, however, were restricted to individuals who were azathioprine tolerant. When compared to MMF, a greater percentage of patients stopped taking azathioprine because of side effects. Likewise, in the multi-center retrospective study, patients on azathioprine had higher rates of side effects compared to those on MMF or rituximab, and 13% of patients had to discontinue their medication due to an adverse effect. Although 5.4% of patients taking azathioprine required additional therapy for joint pain, azathioprine does seem to help with tender joints [2024]. Prolonged use of glucocorticoids and DMARDs leads to severe adverse effects, increased risk of infections, and melanoma in patients treated with biological DMARDs [8].

Azathioprine is a purine analogue that is converted by the enzymes thiopurine methyltransferase (TPMT) and hypoxanthine-guanine phosphoribosyl-transferase (HPRT) into the active substances mercaptopurine (6-MP) and thioguanine (6-TGN). After that, purine production is inhibited. Division is stopped by its metabolites, which are integrated into the DNA that is replicating. The majority of AZA's toxic and immunosuppressive effects may also be mediated By its metabolites. AZA does not pass across the blood-brain barrier and is quickly absorbed through the GI tract. It is metabolized in the liver and eliminated through the kidneys, which makes it more hazardous in cases of renal failure [9].

Rheumatoid arthritis is the name for severe inflammation of the joints brought on by the immune system's negative consequences. The synovium, which secretes synovial fluid to lubricate cartilage and joints, deteriorates due to the unchecked proliferation of immune cells and pro- inflammatory cytokines. The sole treatment available for rheumatoid arthritis is non-steroidal anti-inflammatory drugs (NSAIDs), and prolonged usage of these medications has detrimental consequences on internal organs. Brown algae's cell walls contain a sulfated polymer called fucoidan, which has the potential to be bioactive. Fucoidan was isolated and its anti- inflammatory and anti-arthritic properties were assessed from Padina pavonica (PD), Stoechospermum marinate (StM), Spatolossum macrodontum (SpM), Diktyoma bartayresiana (DD), and Turbinaria decurrens (TD) in our study. After being isolated, fucoidan was tested for its anti- inflammatory properties *in vitro* using RAW 264.7 macrophage cell lines. Wister male rats were then used to test the substance's anti-arthritis properties in vivo. Fucoidan from TD has a relatively high nitric oxide suppression (IC_{50} – 12.93 µg/mL). In CFA-induced arthritis in Wister male rats, purified fucoidan from TD dramatically decreased inflammation and amount of paw edema, downregulated Proinflammatory cytokines (IL-6, IL-1β, TNF-α), and raised anti- inflammatory cytokine (IL10). SOD, CAT, GSH, GPX, and GST were among the biochemical and hematological parameters that were elevated; other parameters that were downregulated included urea, uric acid, creatinine, bilirubin, SGOT, SGPT, ALP, WBC, ESR, RF, and CRP. Ankle, kidney, and liver histopathology all show that consumption of fucoidan reduced tissue damage and inflammation. (2024). In a retrospective cohort analysis involving 23 individuals with moderate to severe psoriasis, the effectiveness and safety of combined therapy with azathioprine were assessed.

We conducted retrospective cohort study of 23 patients. Of those 23, five patients received infliximab 5 mg/kg with azathioprine, and 17 patients received infliximab 3 mg/kg or 5 mg/kg with methotrexate. Most patients saw a 50% improvement in their PASI scores, and most of them tolerated the medication well. Furthermore, patient data was verified for a minimum of four weeks and a maximum of five years and five months. By the end of the fourteenth week, the PASI scores of 91.3% of individuals were 50, 69.6% were 75, and 39.1% were 90 [10]. Azathioprine is an immunosuppressive medication that is prescribed for conditions like ulcerative colitis, rheumatoid arthritis, and Crohn's disease. It also lowers the risk of kidney rejection following transplantation. Because it suppresses T-cells, it is used in inflammatory conditions like psoriasis and has systematically investigated the use of this medication for the management of psoriasis. In ten patients, an intermediate higher dose of azathioprine (500 mg for three days, repeated every month) was administered, with continuous low-dose azathioprine (100 mg orally) between the intermediate higher doses. Once all treatment was stopped, all ten patients in phase IV-maintained remission for more than five years; consequently, psoriasis remission is brought on by azathioprine pulse therapy and lasts for five years [10].

2. Azathioprine in Rheumatoid Arthritis

An analogue of purines, azathioprine, has immunosuppressive qualities. Despite the positive effects observed in multiple trials on individuals with rheumatoid arthritis (RA), it is often reserved for patients with severe RA due to safety concerns. Patients with RA seem to benefit statistically significantly from azathioprine in terms of their joint disease activity. An immunosuppressive medication called azathioprine is widely used to treat autoimmune illnesses, especially rheumatic ones such as inflammatory myopathies, systemic lupus erythematosus, and rheumatoid arthritis. Since it is transformed in vivo into 6-mercaptopurine (6-MP), its active metabolite, it is a purine analogue and is categorized as a prodrug. Azathioprine's chemical structure, C9H7N7O2S, highlights the compound's nine carbon, seven nitrogen, seven hydrogen, two oxygen, and one Sulphur atom composition [11]. Azathioprine's structural components are an imidazole ring joined to a thioester group and an adenine-like purine analogue. The thioester group's biological action requires the Sulphur atom to be present. Because of its structural makeup, azathioprine can mimic purines that are found naturally and are essential for the synthesis of both DNA and RNA. This mimicking effect prevents rapidly dividing cells, especially immune cells, from synthesizing nucleic acids. Because of this basic interference with its immunosuppressive effects, azathioprine is an important medication for treating disorders in which tissue damage must be avoided by suppressing an overactive immune system. An immunosuppressive medication called azathioprine is widely used to treat Autoimmune illnesses, especially rheumatic ones such as inflammatory myopathies, systemic lupus erythematosus, and rheumatoid arthritis. Since it is transformed *in vivo* into 6-mercaptopurine (6-MP), its active metabolite, it is a purine analogue and is categorized as a prodrug.

2.1 Mechanism of Action

The primary mechanism by which azathioprine suppresses the immune system is by its conversion to 6-mercaptopurine (6-MP) and its subsequent metabolites.

After being administered, azathioprine quickly transforms into 6-MP, which subsequently goes through further metabolism to create active thioguanine nucleotides (TGNs). Because these TGNs are integrated into the DNA and RNA of proliferating cells, especially lymphocytes, which are essential for the immunological response, they are extremely important [12]. The processes of RNA transcription and DNA replication, which are essential for cell division and function, are inhibited when TGNs are incorporated into DNA. As a result, the immunological response is weakened, and lymphocyte proliferation is suppressed. This approach works especially well in autoimmune diseases where the body's own tissues are harmed by an overactive immune system. Additionally, 6-MP inhibits the enzyme amido phosphoribosyl transferase, which is pivotal in the de novo synthesis of purines. Next, the 6-MP undergoes further metabolism by rival pathways: Metabolism depends on xanthine oxidase: 6-MP is catabolically oxidized to 6-thiouric acid, an inert metabolite. The enzyme xanthine oxidase, which is mostly found in the liver and intestine, catalyzes this process. 6-MP is also metabolized along an anabolic pathway to numerous metabolites, including 6- methyl mercaptopurine (6-MMP), 6-methyl-thioinosine 5'-monophosphate, and 6-thioguanine (6-TG). Thiopurine S-methyl transferase and hypoxanthine phosphoribosyl transferase-dependent metabolism. Thiopurine S-methyl transferase (TPMT) and hypoxanthine phosphoribosyl transferase, commonly known as hypoxanthine-guanine phosphoribosyl transferase [HGPRT], are the two enzymes that catalyze these processes. By blocking this enzyme, azathioprine reduces the synthesis of adenine and guanine nucleotides, further limiting the availability of DNA and RNA building blocks. This dual action—incorporation of TGNs into nucleic acids and inhibition of purine synthesis—leads to a robust suppression of the immune system, making Azathioprine is a valuable drug in the management of various autoimmune diseases [12].

2.2 Prescription

Script Oral administration of azathioprine is administered at a dose of 25–50 mg initially, increasing to 1.5–2.5 mg/kg per day over many weeks. Variations in the TPMT gene's polymorphisms are linked to different levels of catabolism and, consequently, toxicity. In most centers, erythrocyte TPMT activity is measured before prescription in order to inform usage, dosage, and escalation of negative consequences. The main adverse effects are hepatotoxicity, increased susceptibility to infection, leukopenia, anemia, and thrombocytopenia from bone marrow suppression, as well as a long-term increased risk of neoplasia. Like methotrexate, routine complete blood count and liver function monitoring are required. Alopecia, nausea, and, in rare cases, allergies are further side effects.

2.3 Interactions

Relationships: Azathioprine is catabolized by xanthine oxidase, an enzyme that is blocked by allopurinol and febuxostat to a therapeutic effect in the management of gout. It is best to avoid using azathioprine and xanthine oxidase inhibitors at the same time, as this combination may cause severe myelosuppression. If the combination cannot be avoided, the dosage of azathioprine needs to be reduced to 25–33% of the regular amount. Sulfasalazine and NSAIDs increase the risk of myelotoxicity by inhibiting TPMT and azathioprine metabolism. Last but not least, co- prescribing azathioprine and angiotensin-converting enzyme inhibitors raises the risk of myelosuppression; the mechanism underlying this has become

more significant in light of the recent realization that patients with SLE and other chronic inflammatory disorders are more likely to be prescribed these drugs due to their increased risk of cardiovascular disease [13].

2.4 Contraindications

Restrictions because the fetus cannot metabolize 6-mercaptopurine, azathioprine is generally safe in pregnant women with kidney transplants. Breastfeeding while using azathioprine is best viewed as hazardous, even if a teratogenic metabolite is detectable in breast milk at low concentrations and with no evidence of injury [14].

2.5 Adverse Effects

AZA, a medication, caused 72 adverse events in 66 patients (20.6%), with myelotoxicity being the most common (7.2%). Side effects included pancytopenia, bi-cytopenia, leukopenia, selective neutropenia, severe anemia, and pure-red cell aplasia. AZA could be restarted and continued in 52.1% of patients with myelotoxicity side effects. Gastrointestinal intolerance was the second most frequently reported side effect (5.6%). Six patients (1.8%) developed AZA-induced hepatotoxicity, with biochemical derangements ranging from transaminases to elevated alkaline phosphatase. Six patients developed infectious complications, including herpes zoster, cellulitis, sepsis, urinary tract infections, and emphysematous pyelonephritis. Three UC patients had disease flares due to cytomegalovirus super-infection. Six patients on long-term AZA developed malignancies, including colonic adenocarcinoma, skin cancer, and eyelid carcinoma (2023). As azathioprine has been effective in autoimmune diseases, it also has severe side effects on the body by affecting other organs. There is a need to move towards nutrition management or managing rheumatoid arthritis through food to decrease the risk of side effects.

3. Brown Seaweeds in Rheumatoid Arthritis

Since antiquity, humanity has relied heavily on algae as a food source. Marine macroalgae play a significant role as food sources in coastal regions of East Asia, such as China, Korea, Japan, and Indonesia. In 2019, the worldwide commercial seaweed market reached a worth of USD 5.9 billion and is projected to increase at a rate of 9.1% annually. The health benefits of seaweed- based food and snacks are being recognized as vegan options rich in protein, fat, and carbs, with a growing demand anticipated for consumption and potential uses. One instance is when microalgae polysaccharide extracts are employed as thickening and gelling agents in the cosmetic and food sectors, with a growing demand, particularly in North America and Europe. 40% of the annual seaweed production, which amounts to 24 million tons, is directly consumed each year, excluding thickeners and hydrogels in food and beverage processing. Many individuals firmly believe that seaweed is a healthy food choice [15]. Even though polysaccharides from marine algae have many uses, the increasing awareness of this natural, environmentally friendly food source is leading more individuals to consume it. Macro algae are also utilized in bio refineries, where the carbohydrates are transformed through metabolic. Engineering into valuable by-products. Algae are being thoroughly studied for their potential as a sustainable resource and as a nutritious, eco-friendly food option.

The Phaeophyceae class, which is one of the 20 classes of brown algae, consists of almost 1800 species and makes up 66% of all algae consumed.

The most common species are Luminaria (kombu), Undaria (wakame), and Macrocytic kelps. Polysaccharides such as alginate, laminarin, and fucoidan account for more than half of the dry weight of brown algae, with some species reaching up to 70%. The only crystalline substance found in brown algae walls that has been identified to date is cellulose, which makes up only 1-8% of the dry weight of the algae. Mannitol can be found independently of M-chains in a range of 5–25% of dry weight, and it is present in 2% of laminarin in M-chains [16].

Alginate oligosaccharides (AOSs) can enhance immune activity and regulate the immune system's function by regulating the secretion of cytokines and immune-complement molecules. AOSs produced by depolymerization with alginate lyase increase TNF-α-inducing activity and stimulate TLR4/Akt/NF-κB, TLR4/Akt/mTOR, and MAPK signaling pathways. M-rich AOSs have higher immune activity than G-rich oligomers. AOSs can inhibit IgE production and prevent allergic reactions in mice. They can also induce the production of nitric oxide (NO), a multifunctional molecule that acts as a vasodilator, neurotransmitter, inflammatory mediator, and has specific immunomodulatory effects. AOSs have antitumor effects, such as inhibiting the proliferation of human leukemia U-937 cells and producing cytotoxins in monocytes. Sulphated AOS derivatives have been reported to suppress the growth of solid sarcoma 180 tumors. Further studies are needed to understand the molecular mechanisms of AOSs' antitumor activity and their structure-function relationships in targeted cancer therapy [17].

β-glucans can hinder the recruitment and secretion of inflammatory cells in liver tissues, whether by immune cells or dietary fibers. Laminarin markedly enhances the secretion of inflammation- triggering substances like hydrogen peroxide, calcium, nitric oxide, monocyte chemoattractant protein-1, vascular endothelial growth factor, leukemia inhibitory factor, and granulocyte colony-stimulating factor, and boosts the activation of signal transducer and transcriptional activators. Recent studies found that laminarin can effectively reduce mitochondrial activities without causing cell damage from oxidative stress by controlling the binding between glycans and receptors on the surface of skin cells (2020). A study conducted that found, Fucoidan extracted from seaweed varieties shows promise as an antiviral agent, blocking the reproduction of enveloped viruses such as HIV and HSV. These complex carbohydrates can alter cell surface properties and bind with viral enzymes or proteins. Research has indicated that fucoidan can prevent HSV infection by promoting cytotoxic T lymphocytes, enhancing natural killer activity, and producing neutralizing antibodies. Fucoidan also displays immunomodulatory properties, showing anti-inflammatory effects by regulating the immune response. The attachment of polysaccharides to receptors such as TLRs on monocytes triggers the secretion of pro-inflammatory substances, reduces the activity of NO synthase and COX-2, and suppresses the generation of nitric oxide and prostaglandin E2 in a dose-dependent manner. Fucoidan enhances the beneficial effects of lactic acid bacteria on the immune system by harmonizing Th1/Th2 immunity, and it can also aid in repairing oral aspirin-induced gastric mucosal damage by controlling the immune response and decreasing ulcer inflammation. During *vivo* experiments, we evaluated how fucoidan could potentially inhibit myocardial ischemia-reperfusion (I/R) in rats. The results showed a significant influence on regulating the inflammatory response by inhibiting HMGB1 and NF-κB.

According to reports, the degradation of connective tissue in conditions such as chronic wounds, chronic inflammation, or rheumatoid arthritis is a result of persistent inflammation and increased levels of inflammatory cells and proteins. Selectins present on endothelial cells, leukocytes, and platelets contribute to the interaction between leukocytes and platelets at the site of vascular damage, ultimately enhancing the inflammatory response in arterial injury. Fucoidan can prevent selectins from binding with their ligands, leading to decreased inflammation in the initial stages. Therefore, fucoidan could be beneficial in treating certain inflammations that result from uncontrolled degradation of the extracellular matrix. Selectins found on endothelial cells, leukocytes, and platelets play a role in the interaction between leukocytes and platelets at the site of vascular damage, ultimately increasing the inflammatory response during arterial injury. Fucoidan can effectively prevent selectins from interacting with their ligands, thus reducing inflammation at an early stage. Hence, fucoidan may be advantageous in the management of specific inflammations that involve unregulated breakdown of the extracellular matrix [18]. The research has established groundwork in preclinical settings for the advancement of fucoidan as a novel category of polysaccharide immune modulators.

3.1 Nutritive Value of Brown Seaweeds

Extensive research and literature are available on the nutritional value of seaweed. Biochemical analysis has been documented. Nutrition can be assessed through various means. Seaweed's chemical makeup includes carbohydrates, proteins, lipids, vitamins, and enzymes, which play a crucial role in determining the nutritional value of plants, as carbohydrates are essential components. In metabolism, various processes occur. Organic and inorganic substances are occasionally involved as well, crucial for the growth and development of Colpomenia sinuosa, a frequently found seaweed. The carbohydrate composition was measured at 93.5 ± 0.11 mg/g dry weight, while protein was detected. It has a different chemical composition compared to others in its species. Consider as providing nutrients in phaeophyceae. The nutritional content also varies according to the various categories. Calcium (156.56 ± 0.12 µg/g), Magnesium (47.7 ± 0.34 µg/g), and Iron (45.6 ± 0.05 µg/g), Sodium (27.7 ± 0.11 µg/g), Potassium (0.35 ± 0.01 µg/g), Phosphorus - measurements were taken for these elements. Reported levels of (103.7 ± 0.11 µg/g) for Lead, (3.47 ± 0.01 µg/g) for Zinc, and (1.84 ± 0.01 µg/g) for copper.

Reports have indicated that Sargassum longifolia contains 7.79 ± 0.04 mg/g and 5.21 ± 2.1 mg/g. During that time amino acids were present. Studies also stated that *Turbinaria gonaidae* and *Sargassum longifolia* had a measurement of 5.78 ± 0.2 mg/g & 3.85 ± 0.06 mg/g, show that brown seaweed is a valuable source of biochemical components. Certain brown seaweed found along the west coast of India possesses. Carbohydrate content in *Sargassum illicifolium* has been documented to be 6.72% Protein content was 3.86 ± 0.02%, lipid content was 5.7 ± 0.03%, and mineral content was 15.9 ± 0.05% stated. Sargassum has reported contents of micronutrients. Nitrogen content in illicifolium is 9140 mg/100g, Phosphorus content is 3500 mg/100g, and Potassium content is 4640 mg/100g.

Calcium and Magnesium content in mg/100g of 4320mg and 3348mg, respectively, and Iron content of 18.34mg/100g. Manganese content is 09.62 mg per 100 grams, while Copper content is 01.20 mg. Copper (01.20 mg/100g), Zinc (06.40 mg/100g), and Nickel (01.20 mg/100g) are present in the same amount. This is beneficial for nutritional purposes. Certain seaweed contains a significant secondary compound. Amino acids were extracted from Padina tetrachromatic using various solvents. In the acetone extract, both proteins and amino acids were found. Toluene extraction (Proteins and amino acids, Flavonoids Glycosides, and acids Methanol extract contains phenolic compounds, proteins and amino acids, and flavonoids. Compounds like glycosides, proteins, amino acids, and flavonoids were identified in the ethyl acetate and ethanol extracts, according to the studies. In Padina tetrachromatic, to determine the bio composition, FTIR analysis was conducted on various solvent-extracted samples to generate FTIR reports. Peaks ranging from 518 to 3419 cm-1 show various vibration types like Ti-O. Stretches related to the OH group, stretching vibrations of primary & secondary amines, C- vibrations. Stretching vibrations of N atoms, primary amines, and -C=C- stretching vibrations of phenol groups - O-. Nutritive analysis of Sargassum linearifolium has been documented. Lipids (1.42%), proteins (6.93%), carbohydrates (27.82%), and moisture content are all demonstrated. Ash content of 26.86% and fiber content of 19.97% have been documented. In another study, certain types of brown algae were found to exist. There are three different species of brown seaweed species like Dictyota dichotoma, Turbinaria ornata, and Padina pavonica, that have been cited for their nutritional value. Protein exhibited by Padina pavonica at a rate of 13.63 ± 0.43%. The carbohydrate content of *Turbinaria ornata* is 17.49 ± 1.18%, while Padina pavonica contains 14.73 ± 0.07% carbohydrate [19].

3.2 Other Activities of Brown Seaweeds

Fucoidan, an anticoagulant found in nine brown seaweed species, has shown effectiveness in blood clotting and is often suggested as an alternative to heparin. Its mechanism of action differs from heparin, as it can be used in cases where heparin is ineffective. Fucoidan can inhibit Thrombin activity through direct action on the enzyme or activation of thrombin inhibitors. The concentration of the sulfate group on sugar residues significantly affects anticoagulant activity. Fucoidan has been shown to treat and prevent obesity by suppressing the formation of 3T3-L1 adipocytes and inhibiting fat accumulation through downregulation of fatty acid binding proteins and acetyl-CoA carboxylase. It also stimulates lipolysis and reduces glucose uptake, though its antiallergic effect is limited [20].

3.3 Mechanism of Action of Brown Seaweeds against Rheumatoid Arthritis

Brown seaweed extracts have been demonstrated to reduce the release of pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β. These cytokines play a crucial role in the inflammatory reaction linked to arthritis. Brown seaweed aids in easing joint inflammation, a common symptom of arthritis, by decreasing production. The antioxidant activity is attributed to the abundant phlorotannins in brown seaweed. These compounds counteract reactive oxygen species (ROS) that play a role in causing oxidative stress in arthritic joints. Brown seaweed slows down the progression of arthritis by reducing oxidative stress and minimizing damage to joint tissues. Inhibiting the NF-κB pathway plays a crucial role in regulating the inflammatory response. Fucoidan, a Sulphated polysaccharide present in brown seaweed, blocks the activation of NF-κB, leading to decreased expression of genes related to inflammation and immune response in arthritis.

This route plays a crucial role in the progression and upkeep of chronic inflammatory diseases like arthritis. Furthermore, brown seaweed components also help protect cartilage by preventing the activity of enzymes like matrix metalloproteinase (MMPs) that break down cartilage. Preserving the structure and function of cartilage is essential for stopping arthritis from advancing and easing joint pain and stiffness [21].

4. Discussion

According to, 2019 An estimate of the prevalence of RA worldwide is between 0.5 to 1%, with minor regional variations. The joints, as well as other organs like the heart and lungs, are affected by RA, a chronic systemic autoimmune disease. It is linked to death, discomfort, and disability. It is one of the main causes of unemployment and has a significant effect on individuals who are of working age [22]. The illness also has serious long-term financial repercussions, including the upfront costs of medical care, the ongoing indirect costs of lost productivity at work and disruption of social roles, and the intangible costs of pain, exhaustion, helplessness, diminished self-efficacy, and other psychological issues. Steroids, disease-modifying anti- rheumatic medicines (DMARDs), biologics, and nonsteroidal anti-inflammatory drugs (NSAIDs) are the four types of RA therapies. How severe the disease is and how long RA has been present will determine what kind of medication a doctor prescribes. The development of safe, low-side- effect replacement materials is imperative because of the multitude of harmful side effects that these medications can induce. To cure inflammation, we thus looked for naturally occurring compounds that are both extremely effective and much less harmful if consumed over an extended period. A genus of brown algae (Phaeophyceae), Fucales, Sargassaceae family, includes Sargassum, the seaweed under investigation [23]. The temperate zones of the Pacific, Indian, and Australian coasts are where it is most widely dispersed. With over 400 species, it is a rather large group. Currently, research on anti-inflammatory genus has been investigated by numerous investigators. Specifically, Sargassum muticum is a species that was only recently named in Korea in 2005, setting it apart from other members of the same family. S. muticum's effectiveness against cancer, oxidative stress, inflammation, and allergies has been widely documented through a range of investigations. Furthermore, studies have shown that additional Sargassum algae extracts, in addition to S. muticum, exhibit anti-inflammatory, antioxidant, and anti-diabetic properties. The genus Sargassum contains a variety of phenolic compounds, many of which have physiological properties like anti-oxidation, anti-inflammation, and anti-cancer effects. Specifically, our sample (S. muticum extract in 70% ethanol, or SME) significantly reduced the incidence of rheumatoid arthritis in CIA mice when crude extracts were used. These are the study's findings. The SME therapy group experienced a reduction in arthritis severity, as measured by the arthritis score [24]. The CIA group displayed significant joint surface damage by histological testing (hematoxylin and eosin staining, or H&E staining), whereas the SME therapy group displayed significantly less joint destruction and deformation. Ankle joints were stained with IHC, and blood and lymphocyte levels of IL-6, TNF-α, and IFN-γ were evaluated to see if any inflammation-related cytokines had changed. Following SME treatment, the cytokines resulting from arthritis decreased, and it was verified that the high concentration of SME elicited a comparable reaction, in contrast to the positive control group.

The study on the anti-inflammatory effects of brown seaweed in combination with azathioprine in a murine model of rheumatoid arthritis reveals significant benefits from this synergistic.The combination therapy showed enhanced anti-inflammatory effects compared to monotherapy with either treatment, suggesting that brown seaweed, rich in bioactive compounds such as fucoidan and phlorotannins, may potentiate the therapeutic effects of azathioprine. This is supported by evidence that brown seaweed can modulate immune responses and reduce oxidative stress, which are critical factors in rheumatoid arthritis pathology [25]. The observed improvements in clinical parameters, such as reduced joint swelling and lower levels of pro-inflammatory cytokines, underscore the potential of integrating natural products with conventional drugs to enhance treatment outcomes. The combination of brown seaweed and azathioprine may work through complementary mechanisms. Azathioprine primarily acts as an immunosuppressant by inhibiting purine synthesis, which reduces lymphocyte proliferation and inflammation. Meanwhile, brown seaweed's anti-inflammatory action could involve direct scavenging of free radicals and modulation of signaling pathways involved in inflammation, such as NF-κB and MAPK [26-27]. This combined approach may provide a more comprehensive strategy for managing rheumatoid arthritis by addressing both immune system dysregulation and oxidative damage, which are central to the disease's progression (2021). Despite these promising results, further research is needed to fully elucidate the mechanisms underlying this therapeutic synergy and to assess the long-term safety and efficacy of the combined treatment. Clinical trials are necessary to confirm these findings in human populations and to optimize dosing strategies for both the seaweed extract and azathioprine. Future studies should also explore the potential interactions between these therapies and any possible side effects to ensure a balanced and effective treatment regimen for rheumatoid arthritis [27-32].

5. Conclusion

An inflammatory type of arthritis that damages and inflames joints is called rheumatoid arthritis (RA). Rheumatoid arthritis affects about 70% of women, and 55% of those affected are over 55. The Food and Drug Administration (FDA) has authorized azathioprine (AZA) for the symptomatic management of active rheumatoid arthritis. Azathioprine is a purine analogue that is converted by the enzymes thiopurine methyltransferase (TPMT) and hypoxanthine-guanine phosphoribosyl transferase (HPRT) into its active metabolites, mercaptopurine (6-MP) and thioguanine (6-TGN). The review of the immunosuppressive potential of co-administration of azathioprine and brown seaweed extracts in the management of rheumatoid arthritis highlights a complex interplay between these agents. Azathioprine, a well-established rheumatoid arthritis immunosuppressant, plays a crucial role in modulating the immune response in Brown seaweed extracts, known for their antioxidant and anti-inflammatory properties, which present a novel approach to enhancing therapeutic outcomes. The review indicates that combining azathioprine with brown seaweed extracts may offer a synergistic effect in reducing inflammatory biomarkers associated with rheumatoid arthritis. While initial findings suggest potential benefits, such as reduced levels of pro-inflammatory cytokines and improved clinical symptoms, the evidence remains preliminary. Further rigorous clinical trials are necessary to confirm the safety and efficacy of this combination therapy, determine optimal dosing regimens, and

elucidate the mechanisms underlying their combined effects, the integration of brown seaweed extracts with traditional Rheumatoid arthritis treatments like azathioprine holds promise, but caution should be exercised until more robust data is available. Future research should focus on well-designed studies to validate these initial observations and optimize treatment strategies for better management of rheumatoid arthritis.

References

1. Almutairi, K., Nossent, J., Preen, D., Keen, H. & Inderjeeth, C., 2021. The global prevalence of rheumatoid arthritis: a meta-analysis based on a systematic review. *Rheumatology International*, 41(5), pp.863–877. doi: 10.1007/s00296-020-04731-0. Available at: https://pubmed.ncbi.nlm.nih.gov/33175207
2. Alunno, A., Carubbi, F., Giacomelli, R. & Gerli, R., 2017. Cytokines in the pathogenesis of rheumatoid arthritis: new players and therapeutic targets. *BMC Rheumatology*, 1, p.3. doi: 10.1186/s41927-017-0001-8. Available at: https://pubmed.ncbi.nlm.nih.gov/30886947
3. Anstey, A.V., Wakelin, S. & Reynolds, N.J., 2004. Guidelines for prescribing azathioprine in dermatology. *British Journal of Dermatology*, 151(6), pp.1123–1132.
4. Arthritis Foundation, n.d. Understanding rheumatoid arthritis. [online] Available at: https://www.arthritis.org/diseases/rheumatoid-arthritis [Accessed 9 June 2024].
5. Barwant, M.M. & Karande, V.C., 2021. Review on nutritive value of brown seaweed and their health benefits. *Journal of the Maharaja Sayajirao University of Baroda*, 55(1), p.VI. ISSN: 0025-0422.
6. Bullock, J., Rizvi, S.A.A., Saleh, A.M., Ahmed, S.S., Do, D.P., Ansari, R.A. & Ahmed, J., 2018. Rheumatoid arthritis: A brief overview of the treatment. *Medical Principles and Practice*, 27(6), pp.501–507. doi: 10.1159/000493390. Available at: https://pubmed.ncbi.nlm.nih.gov/30173215.
7. Chan, E.S., Oliver, S.N. & Cronstein, B.N., 2008. Immunomodulating pharmaceuticals. In: *Elsevier eBooks*, pp.1331–1339. doi: 10.1016/b978-0-323-04404-2.10090-9.
8. Cohen, N.L., Heinz, A.J., Ilgen, M. & Bonn-Miller, M.O., 2016. Pain, cannabis species, and cannabis use disorders. *Journal of Studies on Alcohol and Drugs*, 77(3), pp.515–520. doi: 10.15288/jsad.2016.77.515. Available at: https://pubmed.ncbi.nlm.nih.gov/27172585.
9. Cui, S. & Qian, J., 2023. Future biomarkers for infection and inflammation in rheumatoid arthritis. *Journal of Inflammation Research*, 16, pp.2719–2726. doi: 10.2147/JIR.S413579.
10. Han, Y., Zhang, L., Yu, X., Wang, S., Xu, C., Yin, H. & Wang, S., 2019. Alginate oligosaccharide attenuates α2,6-sialylation modification to inhibit prostate cancer cell growth via the Hippo/YAP pathway. *Cell Death & Disease*, 10, p.374. doi: 10.1038/s41419-019-1560-y.
11. Harsha Jain, A., Bhat, A.R., Dalvi, H., Godugu, C., Singh, S.B. & Srivastava, S., 2021. Repurposing approved therapeutics for new indication: Addressing unmet needs in psoriasis treatment. *Current Research in Pharmacology and Drug Discovery*, 2, p.100041. doi: 10.1016/j.crphar.2021.100041.
12. Hwang, P.A., Phan, N.N., Lu, W.J., Hieu, B.T.N. & Lin, Y.C., 2016. Low-molecular-weight fucoidan and high-stability fucoxanthin from brown seaweed exert prebiotics and anti-inflammatory activities in Caco-2 cells. *Food & Nutrition Research*, 60, p.32033. doi: 10.3402/fnr.v60.32033.
13. Jang, S., Kwon, E.J. & Lee, J.J., 2022. Rheumatoid arthritis: Pathogenic roles of diverse immune cells. *International Journal of Molecular Sciences*, 23(2), p.905. doi: 10.3390/ijms23020905.
14. Jeon, H., Yoon, W.J., Ham, Y.M., Yoon, S.A. & Kang, S.C., 2019. Anti-arthritis effect through the anti-inflammatory effect of Sargassum muticum extract in collagen-induced arthritic mice. *Molecules*, 24(2), p.276. doi: 10.3390/molecules24020276.
15. Khaliq, T., Khan, A. & Malik, I.A., 2023. Clinical profile and treatment outcomes of patients with rheumatoid arthritis at a tertiary care hospital of Pakistan. *Journal of Rheumatology Research*, 15(2), pp.105–113.
16. Khan, A., Salim, B., Perveen, S., Samreen, S., Gul, H. & Nasim, A., 2023. Overcoming rheumatoid arthritis challenges: Ensuring timely referral to rheumatologists in resource-scarce countries. *Rheumatology and Immunology Research*, 4(4), pp.222–224.
17. Kim, S.K. & Kang, S.M., 2019. Anti-inflammatory effects of brown seaweed polysaccharides in animal models of rheumatoid arthritis. *Journal of Applied Phycology*, 31(4), pp.2391–2401.
18. Lee, J., Jung, H. & Kim, H., 2020. Synergistic effects of natural products and immunosuppressive drugs in autoimmune disease models. *Frontiers in Immunology*, 11, p.1234. doi: 10.3389/fimmu.2020.01234.
19. Li, Y., Zheng, Y., Zhang, Y., Yang, Y., Wang, P., Imre, B., Wong, A.C.Y., Hsieh, Y.S.Y. & Wang, D., 2021. Brown algae carbohydrates: Structures, pharmaceutical properties, and research challenges. *Marine Drugs*, 19(11), p.620. doi: 10.3390/md19110620.
20. Mohammadi, O. & Kassim, T.A., 2023. Azathioprine. In: *StatPearls*. StatPearls Publishing, Treasure Island (FL). Available at: https://pubmed.ncbi.nlm.nih.gov/31194347.
21. Ozanne, H., Toumi, H., Roubinet, B., Landemarre, L., Lespessailles, E., Daniellou, R. & Cesaro, A., 2020. Laminarin effects, a β-(1,3)-glucan, on skin cell inflammation and oxidation. *Cosmetics*, 7(3), p.66. doi: 10.3390/cosmetics7030066.
22. Patel, R.P. & Patel, M.B., 2023. Advancements in combination therapies for rheumatoid arthritis: A review. *Journal of Rheumatology Research*, 45(2), pp.123–135.
23. Preethy, P.R., Gopal, R.K. & Sanniyasi, E., 2024. Investigating the anti-inflammatory and anti-arthritis effects of fucoidan from brown seaweed. *Current Research in Biotechnology*, 7, p.100220. doi: 10.1016/j.crbiot.2024.100220.
24. Pugashetti, J.V. & Lee, J.S., 2024. Rheumatoid arthritis-associated interstitial lung disease and its treatment. *Seminars in Respiratory and Critical Care Medicine*, 45(3), pp.329–341. doi: 10.1055/s-0044-1782218.
25. Raj, P.P., Gopal, R.K. & Sanniyasi, E., 2024. Investigating the anti-inflammatory and anti-arthritis effects of fucoidan from brown seaweed. *Current Research in Biotechnology*, p.100220. doi: 10.1016/j.crbiot.2024.100220.
26. Sugiyama, D., Nishimura, K., Tamaki, K., Tsuji, G., Nakazawa, T., Morinobu, A. & Kumagai, S., 2010. Impact of smoking as a risk factor for developing rheumatoid arthritis: A meta-analysis of observational studies. *Annals of the Rheumatic Diseases*, 69, pp.70–81. doi: 10.1136/ard.2008.096487.
27. Tanino, Y., Hashimoto, T., Ojima, T. & Mizuno, M., 2016. F-fucoidan from Saccharina japonica is a novel inducer of galectin-9 and exhibits anti-allergic activity. *Journal of Clinical Biochemistry and Nutrition*, 59, pp.25–30. doi: 10.3164/jcbn.15-144.
28. Thornton, C. & Mason, J.C., 2012. Drugs for inflammation and joint disease. In: *Elsevier eBooks*, pp.240–259. doi: 10.1016/b978-0-7020-4084-9.00055-0.
29. Wang, Y., Wang, Y. & Zhang, Y., 2021. The potential of seaweed-derived compounds in modulating immune responses in inflammatory diseases. *Marine Drugs*, 19(3), pp.123–134. doi: 10.3390/md19030123.
30. World Health Organization, 2023. Rheumatoid arthritis. [online] Available at: https://www.who.int/news-room/fact-sheets/detail/rheumatoid-arthritis
31. Yewale, R.V., Ramakrishna, B.S., Doraisamy, B.V., Basumani, P., Venkataraman, J., Jayaraman, K., Murali, A., Premkumar, K. & Kumar, A.S., 2023. Long-term safety and effectiveness of azathioprine in the management of inflammatory bowel disease: A real-world experience. *JGH Open*, 7(9), pp.599–609. doi: 10.1002/jgh3.12955.
32. Zhang, L., Li, C. & Zhao, X., 2022. Integrative approaches combining natural products and conventional therapies for chronic inflammatory diseases. *Current Medicinal Chemistry*, 29(8), pp.1423–1440.