DOI: https://doi.org/10.54393/pjhs.v4i05.792

PAKISTAN JOURNAL OF HEALTH SCIENCES

https://thejas.com.pk/index.php/pjhs

Volume 4, Issue 5 (May 2023)

Systematic Review

Campesterol: A Natural Phytochemical with Anti Inflammatory Properties as Potential Therapeutic Agent for Rheumatoid Arthritis: A Systematic Review

Sarwat Nazir[1*], Waqas Ashraf Chaudhary[2], Aishha Mobashar[1], Irfan Anjum[1], Saleha Hameed[3] and Sana Azhar[3]

[1]Faculty of Pharmacy, The University of Lahore, Lahore, Pakistan
[2]School of Biological Sciences, University of Leicester, Leicester, England
[3]School of Human Nutrition and Dietetics, Minhaj University, Lahore, Pakistan

ARTICLE INFO

Key Words:

Rheumatoid Arthritis (RA), Interleukin (IL), Campesterol (CAM), Tumor Necrotizing Factor (TNF), Disease Modifying Anti-Rheumatic Drugs (DMARDs), Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Anti-Citrullinated Protein Antibodies (ACPAs), Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP)

How to Cite:

Nazir, S. ., Chaudhary, W. A. ., Mobashar, A. ., Anjum, I. ., Hameed, S. ., & Azhar, S. . (2023). Campesterol: A Natural Phytochemical with Anti Inflammatory Properties as Potential Therapeutic Agent for Rheumatoid Arthritis: A Systematic Review: Campesterol: A Natural Phytochemical. Pakistan Journal of Health Sciences, 4(05). https://doi.org/10.54393/pjhs.v4i05.792

***Corresponding Author:**

Sarwat Nazir
Faculty of Pharmacy, The University of Lahore, Lahore, Pakistan
sarwat.alrai@gmail.com

Received Date: 14th May, 2023
Acceptance Date: 29th May, 2023
Published Date: 31st May, 2023

ABSTRACT

Rheumatoid Arthritis (RA) is a persistent inflammatory and autoimmune affliction, which results in significant impairment of mobility and a decline in the overall standard of living. The present therapeutic strategies for the management of RA are frequently associated with adverse reactions of notable severity. Medicinal plants containing Phytochemicals such as Campesterol, Crocetin, Nigella Sativa, and Ginkgolic Acid have been recognized as significant alternatives for the treatment of RA. This review article provides an overview of the bioactive constituent campesterol, which exhibits the capacity to regulate interleukins and immune modulation in vitro and in vivo experimental models. The current study aimed to obtain relevant academic literature about the utilization of natural products in the treatment of arthritic conditions. A systematic search strategy was employed, involving both electronic and manual efforts, to query prominent scholarly databases including PubMed, Embase, Scopus, and Web of Science. 76 publications were identified through this review, with 30 being deemed eligible for inclusion. Four researchers have reported their discoveries on the efficacy of natural constituents in the management of RA through investigations In Vitro & In Vivo. Scholarly reports investigated the role of bioactive constituents of phytochemicals for RA treatment, while 15 studies In Vivo evaluated the effectiveness of Campesterol, in alleviating arthritis symptoms through their inflammatory responses and modulation of interleukin production. This review presents notable findings suggesting that Campesterol appears to be particularly effective in the expression of pro-inflammatory modulation of cytokines, and anti-inflammatory cytokines, hence posing therapeutic potential in RA management.

INTRODUCTION

Rheumatoid Arthritis (RA) is a disorder of the auto-immune system that mostly affects joints of the body whereby all of them become inflamed [1]. The synovium of the joints is also affected and swells up. All of these occur in a complicated pattern where synovial cells proliferate and fibrosis occurs. Pannus are formed while the bone and cartilage undergo erosion [2]. Inflammation is caused by cytokines IL-6, IL-1, and TNF-a. RA is seen more frequently in women than men and there is a significant imbalance between males and females, where women show increased AIDs cases. In RA, the ratio of females to males is 3:1. RA patients also have a mortality rate of two times more than people without any autoimmune diseases [3]. The Global Burden of Disease 2010 study included the dissemination of an estimation regarding the global occurrence of RA. This study constituted a thorough endeavor to assess the

DOI: https://doi.org/10.54393/pjhs.v4i05.792

epidemiological status and patterns of 291 illnesses across 187 nations. The worldwide occurrence of rheumatoid arthritis (RA) among individuals aged 50 to 100 years in 2010 was ascertained to be 0.24% with a 95% confidence interval (CI) ranging from 0.23% to 0.25%. The present study discovered that the occurrence of rheumatoid arthritis (RA) in females was almost twice as common as in males, with a mean of 0.35% having a 95% confidence interval (CI) between 0.34% to 0.37%; while males had a mean of 0.13%, with a 95% CI ranging from 0.12% to 0.13% [4]. Most significant evidence suggests that autoimmune diseases are based on control of the genes and especially the ones in the sex chromosomes are most likely to support the female ratio being higher. Concomitantly, it has been substantiated that sex hormones exert a significant influence on the modulation of autoimmunity responses in both genders [5]. In RA, specifically, estrogens have been suggested to be contributors to autoimmune diseases such as RA. This is mostly seen in pregnant women where RA occurs in remission. This is also in relation to the immune system changing its response from Th1 to Th2 along with lesser inflammatory cytokines produced, due to the hormonal fluctuation in pregnant females. It is also suggested that to control this disease, anti-rheumatic drugs should be used safely, throughout pregnancy and the breastfeeding timeline [6]. Any other hormones taken for contraception or such are contraindicated if the patient has shown positive results for antiphospholipid antibodies due to the higher risk of thrombophilia. Hormone replacement therapy is also not recommended, in older women going through post-menopause osteoporosis with RA, since this increases the risk of cardiovascular disease [7]. To understand a disease like RA, live models such as animals are necessary so that drug trials and control groups can be created. Rodent models have been used to understand the pathogenesis of RA in humans but further testing, drug therapy, and their potency, efficacy, and safety are yet to be explored completely for human bodies [8]. To develop drugs, the study of the pathogenesis of RA will help researchers create other therapeutic targets aside from the available ones. The most common models used are arthritis induced by collagen, adjuvant-induced arthritis, and others less used such as proteoglycan and streptococcal cell wall-induced arthritis [9]. The root cause of RA is not known to this day, but it has been seen to be attributed to genetics, environmental factors, and hormones in combination with autoimmune development and progression. There exist various risk factors which are known to contribute to the onset and progression of rheumatoid arthritis (RA) under certain circumstances. These risk factors include but are not limited to advanced age, gender, genetic predispositions, tobacco use, past obstetric history, early life exposures, and obesity [10]. Offspring of individuals who tested positive for anti-citrullinated protein antibodies (ACPAs) or rheumatoid factors (RFs) exhibit an elevated susceptibility to rheumatoid arthritis (RA). Contrary to other factors of pregnant or lactating mothers, it is seen that women who breastfeed their children, lower the risk of developing RA on their own. Patients had a higher probability of earlier death due to premature atherosclerosis, cancer, and infection before disease-modifying anti-rheumatic drugs (DMARDs) and biological therapies were introduced [11]. The etiology of joint swelling in this particular condition results primarily from an inflammatory response within the synovial membrane, involving the participation of cytokines and chemokines. The key inflammatory components within the affected area include tumor necrosis factor (TNF), interleukin-6 (IL-6), and granulocyte-macrophage colony-stimulating factor [12]. Cytokines and chemokines contribute to the initiation or exacerbation of inflammation, by activating endothelial cells and promoting the accumulation of immune system cells within the synovial compartment. Activated fibroblasts, B cells, T cells, monocytes, and macrophages may ultimately induce osteoclast generation through the action of receptor activator of nuclear factor kappa-B ligand (RANKL), which is expressed on B cells, T cells, and fibroblasts [13]. The RANK receptor has been observed to be expressed in various cell types including macrophages, dendritic cells, and preosteoclasts [14]. Moreover, metalloproteinase and a range of other enzymes ultimately facilitate the degradation of the cartilage matrix within joints. Rheumatoid arthritis (RA) may exhibit signs and symptoms that bear similarity to those manifested by other rheumatic diseases, yet the utilization of classification criteria can expedite the diagnostic process. Patients can manifest symptoms such as weight loss, fever, fatigue, and/or weakness [15]. Furthermore, the laboratory diagnosis of rheumatoid arthritis (RA) has been refined through the discovery of specific biomarkers, which serve as measurable indicators of the disease. In addition to an augmented concentration of the C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), the existence of autoantibodies, such as anti-citrullinated protein antibody (ACPA) and rheumatoid factor (RF), commonly imply escalated joint deterioration and enhanced mortality in the affected individual [16]. It is noteworthy that rheumatoid factor (RF) plays a direct role in mechanisms of cytokine and macrophage activation. Furthermore, anti-citrullinated protein antibodies (ACPAs) generate immune complexes, which interact with RF, thereby intensifying the effects of inflammation and ensuing joint degradation. During the course of treatment for rheumatoid arthritis, it

DOI: https://doi.org/10.54393/pjhs.v4i05.792

is expected that levels of anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF) will decline. Although it is uncommon for patients to attain ACPA seronegativity, it is plausible for them to achieve RF seronegative. In recent times, various scholars have brought to the forefront the precise mechanism underlying the onset of tissue damage in rheumatoid arthritis (RA) [17]. However, the etiological factors responsible for triggering this autoimmune response involving self-antigens and synovium, leading to inflammation and joint damage, continue to be predominantly attributed to genetic and environmental factors. Various populations have reported the presence of polymorphisms in genes, particularly in the locus of major histocompatibility complex II, which appear to be associated with susceptibility to RA [18]. The current inquiry is focused on the identification of Human Leukocyte Antigens (HLAs), specifically HLA-DR1, HLA-DR4, HLA-DR6, and HLA-DR10, which are closely linked to the predisposition towards Rheumatoid Arthritis (RA). Given individuals possessing a genetically vulnerable background, environmental factors such as infections and smoking have been postulated as significant instigating factors. A comprehensive survey encompassing the pathological features and etiological mechanisms underlying the development of arthritis is presented. Following the onset of vasculitis, the synovial membrane undergoes infiltration by T and B cell populations. A higher prevalence of CD4+ T cells relative to CD8+ T cells has been observed among T cells. Moreover, there exists a presence of activated cytotoxic T cells and natural killer cells (NK cells). The migration of lymphocytes is facilitated by adhesion molecules. The process of lymphocyte homing results in a structural transformation of the synovial membrane, whereby it acquires morphological features that resemble those of a secondary immune organ. The current study supports the notion that activated CD4+ cells associated with macrophages through MHC class II molecules are responsible for an increase in pathogenic humoral and cellular immune responses. The production of rheumatoid factors and antibodies targeting type II collagen precipitate the formation of cytotoxic immune complexes. "The formation of the pannus is triggered by cellular interactions that result in the upregulation of pro-inflammatory cytokines and growth factors." The degree of invasiveness exhibited by the pannus is contingent upon the specific HLA configuration [19]. In 70% of cases, synovial tissue enriched with T cells is found to be positive for HLA-DR4, whereas only 15% of B cell-enriched membranes exhibit this particular HLA phenotype, as reported in reference [20]. The T-cell abundant phenotype exhibits a heightened propensity towards aggressive behavior. The pathological condition known as pannus is responsible for the destruction of both the articular cartilage and the subchondral bone. The categorization of cells present in the invasion site of the pannus exhibits variegation. The predominant categorization offered by investigators is that of macrophages, while alternative characterizations have arisen from some investigators labeling them as activated fibroblasts. The aforementioned perspective is bolstered by scientific investigations conducted on severe combined immunodeficiency (SCID) mice. Rheumatoid arthritis (RA) is distinguished by three distinct pathogenic mechanisms: the persistent inflammatory reaction of the synovial membrane. The present study investigates the augmented immune-reactive responses of pathogenic T and B cells, which are associated with the emergence of autoimmune phenomena. The phenomenon of increased cellular proliferation resulting in the expansion of synovial tissue is commonly referred to as synovial tissue hyperplasia. The inquiry on the initiating mechanism that subsequently elicits the remaining mechanisms is presently unresolved within academic discourse. The pathogenesis of rheumatoid arthritis (RA) is critically influenced by the pivotal role of macrophages and CD4+ cells, which are associated through the medium of major histocompatibility complex (MHC) class II molecules. In recent times, various scholars have brought to the forefront the precise mechanism underlying the onset of tissue damage in rheumatoid arthritis (RA) [17]. However, the etiological factors responsible for triggering this autoimmune response involving self-antigens and synovium, leading to inflammation and joint damage, continue to be predominantly attributed to genetic and environmental factors. Various populations have reported the presence of polymorphisms in genes, particularly in the locus of major histocompatibility complex II, which appear to be associated with susceptibility to RA [18]. The current inquiry is focused on the identification of Human Leukocyte Antigens (HLAs), specifically HLA-DR1, HLA-DR4, HLA-DR6, and HLA-DR10, which are closely linked to the predisposition towards Rheumatoid Arthritis (RA). Given individuals possessing a genetically vulnerable background, environmental factors such as infections and smoking have been postulated as significant instigating factors. A comprehensive survey encompassing the pathological features and etiological mechanisms underlying the development of arthritis is presented. Following the onset of vasculitis, the synovial membrane undergoes infiltration by T and B cell populations. A higher prevalence of CD4+ T cells relative to CD8+ T cells has been observed among T cells. Moreover, there exists a presence of activated cytotoxic T cells and natural killer cells (NK cells). The migration of lymphocytes is facilitated by

DOI: https://doi.org/10.54393/pjhs.v4i05.792

adhesion molecules. The process of lymphocyte homing results in a structural transformation of the synovial membrane, whereby it acquires morphological features that resemble those of a secondary immune organ. The current study supports the notion that activated CD4+ cells associated with macrophages through MHC class II molecules are responsible for an increase in pathogenic humoral and cellular immune responses. The production of rheumatoid factors and antibodies targeting type II collagen precipitate the formation of cytotoxic immune complexes. "The formation of the pannus is triggered by cellular interactions that result in the upregulation of pro-inflammatory cytokines and growth factors." The degree of invasiveness exhibited by the pannus is contingent upon the specific HLA configuration [19]. In 70% of cases, synovial tissue enriched with T cells is found to be positive for HLA-DR4, whereas only 15% of B cell-enriched membranes exhibit this particular HLA phenotype, as reported in reference [20]. The T-cell abundant phenotype exhibits a heightened propensity towards aggressive behavior. The pathological condition known as pannus is responsible for the destruction of both the articular cartilage and the subchondral bone. The categorization of cells present in the invasion site of the pannus exhibits variegation. The predominant categorization offered by investigators is that of macrophages, while alternative characterizations have arisen from some investigators labeling them as activated fibroblasts. The aforementioned perspective is bolstered by scientific investigations conducted on severe combined immunodeficiency (SCID) mice. Rheumatoid arthritis (RA) is distinguished by three distinct pathogenic mechanisms: the persistent inflammatory reaction of the synovial membrane. The present study investigates the augmented immune-reactive responses of pathogenic T and B cells, which are associated with the emergence of autoimmune phenomena. The phenomenon of increased cellular proliferation resulting in the expansion of synovial tissue is commonly referred to as synovial tissue hyperplasia. The inquiry on the initiating mechanism that subsequently elicits the remaining mechanisms is presently unresolved within academic discourse. The pathogenesis of rheumatoid arthritis (RA) is critically influenced by the pivotal role of macrophages and CD4+ cells, which are associated through the medium of major histo-compatibility complex (MHC) class II molecules.

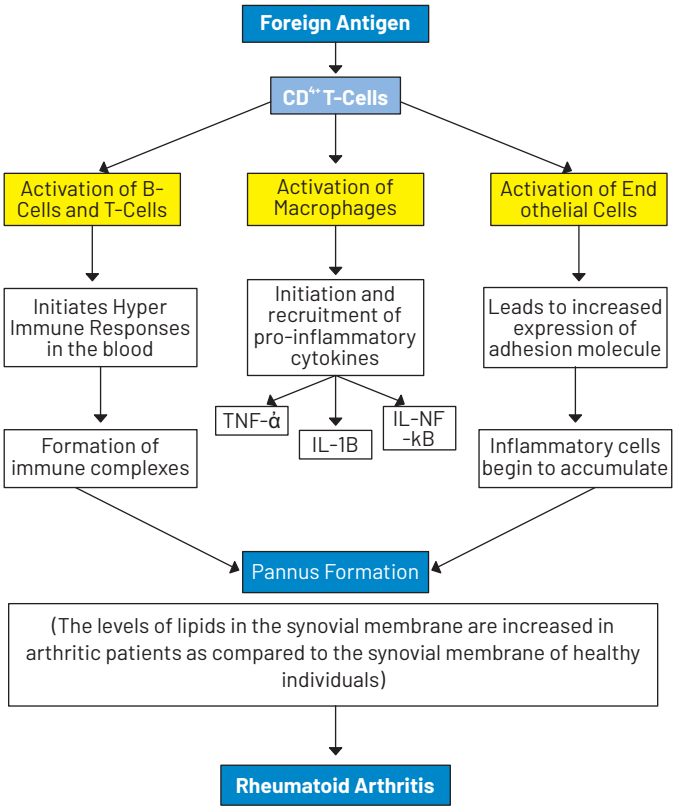

Figure 1: Pathogenesis of Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an affliction characterized by inflammation, for which the initial course of treatment typically involves the administration of medications with anti-inflammatory qualities, including glucocorticoids (GCs) and non-steroidal anti-inflammatory drugs (NSAIDs), by conventional practice. This therapeutic modality offers expeditious relief of pain and amelioration of inflammation among patients diagnosed with rheumatoid arthritis. Disease-modifying anti-Rheumatic drugs (DMARDs) commonly utilized in the management of rheumatoid arthritis include Methotrexate, Sulfasalazine, Leflunomide, and (HCQ) Hydroxychloroquine. Disease-Modifying anti-Rheumatic Drugs (DMARDs) are agents with a slow onset of action that exhibit beneficial effects in ameliorating both the symptoms and radiographic progression of the disease [21]. The standard objective of therapy for Rheumatoid Arthritis (RA) is the reversal of inflammatory processes. Failure to implement appropriate treatment measures may culminate in the onset of permanent disabilities in patients. Therapeutic measures for rheumatoid arthritis encompass pharmacological interventions, modifications in lifestyle, and surgical procedures, which collectively have the potential to mitigate the degeneration of joint structures and alleviate symptoms such as pain and inflammation. It is imperative that in every management approach, a systematic evaluation of response based on

DOI: https://doi.org/10.54393/pjhs.v4i05.792

disease activity should be conducted regularly. This enables an adaptation strategy or treating to target approach to be implemented. Mild-to-moderate rheumatoid arthritis (RA) can potentially be effectively managed in select patients, as the disease may be controllable without instances of exacerbation. In contrast, severe rheumatoid arthritis (RA) may present with persistent indicators and manifestations, as reported in the literature [22].A fundamental form of sterol called Campesterol contains a hydroxyl group situated at position C-3 in its steroid skeleton. The sterol structure is fully-saturated, except for the presence of a 5-6 double bond in the B ring. Campesterol (CAS 474-62-4) is classified as a member of Phytosterols, which is characterized as a 3beta-sterol, a 3beta-hydroxy-Delta (5)-steroid, and a C28-Steroid [23]. The substance in question serves as a metabolite in mice. The aforementioned substance originates from a hydride of campestane, denoted by the molecular formula C28H48O, molecular weight 400.7 g/mol and IUPAC name is (3S,8S,9S,10R,13R,14S,17R)-17-[(2R,5R)-5,6-dimethylheptan-2-yl]-10,13-dimethyl 2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol)[24].

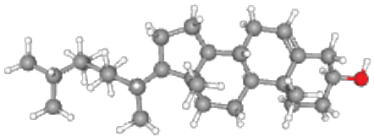

Figure 2: 3D model Campesterol

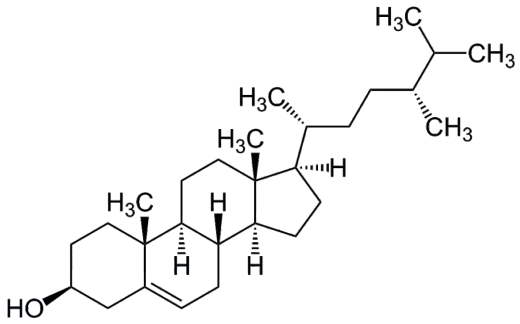

Figure 3: Structure of Campesterol

Literature Review

Historical therapies for rheumatoid arthritis encompassed the use of medications such as Aspirin and colloidal Gold. The aforementioned therapies demonstrated a relief in symptoms; however, they lacked significant impact in terms of deceleration or modification of the progression of the disease. The use of steroids is known to facilitate prompt relief from symptoms and in some cases exhibit properties of disease modification. However, prolonged utilization of Steroids is commonly associated with severe negative consequences such as Hypertension, Diabetes, Osteoporosis, and Cataracts. Cyclosporine has been employed as a treatment modality; nonetheless, it may prove to be inadequate or ineffectual for specific patients, whilst manifesting an array of adverse consequences [25]. Nonsteroidal anti-Inflammatory Drugs (NSAIDs), such as Ibuprofen and Naproxen, were deemed potential treatment options for rheumatoid arthritis (RA). The utilization of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) has been established to mitigate symptoms of musculoskeletal conditions, such as pain, swelling, and stiffness, as well as enhance physical functionality. Nevertheless, it should be noted that NSAIDs do not exhibit any perceptible impact on the impairment of joints, and therefore cannot be classified as Disease-Modifying anti-Rheumatic Drugs (DMARDs). As per current guidelines, the use of NSAIDs is not preferred [26]. Currently, there exists a more comprehensive comprehension of the pathophysiological mechanisms and pathways implicated in rheumatoid arthritis (RA). Such an understanding has facilitated the potential for pharmacological development targeting specific anatomical locations. There exist two primary classifications of disease-modifying anti-rheumatic drugs (DMARDs), namely biological and synthetic. The conventional synthetic DMARDs (csDMARDs), despite their therapeutic efficacy in the management of rheumatoid arthritis (RA), lack site-specificity and indeterminate mechanisms of action for alleviating the aforementioned disease. In contrast, focused and synthetic Disease-Modifying anti-Rheumatic Drugs (DMARDs) are designed to act on a particular therapeutic target, such as the Janus kinase (JAK) enzyme. On the other hand, biological DMARDs operate at a site-specific level, by targeting various molecules such as TNF, IL-6, IL-1, B cells, or T cells [27, 28]. During the process of angiogenesis, the generation of new blood vessels within the synovial tissue heavily relies on endothelial cells, which serve as an essential source [29]. This study posits that Vascular Endothelial Growth Factor (VEGF) is a fundamental activator that regulates various phases of angiogenesis, whilst Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) is the main mediator responsible for VEGF-controlled endothelial signaling [30]. The vascular endothelial growth factor (VEGF) exhibits binding affinity for its cognate receptor, VEGFR2, thereby triggering phosphorylation events at two specific tyrosine residues, namely Y1173 and Y949, that are conserved in homologous sequences of VEGFR2. The process of phosphorylated Y1173 binding with phosphorylated phospholipase C γ (PLCγ) and subsequent activation is well documented in the scholarly literature [31]. This activation, in turn, leads to the activation of the ERK1/2 pathway, which ultimately leads to changes in gene transcription. These changes influence critical biological processes such as cell migration, proliferation, and homeostasis. The process of

DOI: https://doi.org/10.54393/pjhs.v4i05.792

phosphorylating Y949 results in the stimulation of the sarcoma gene (c-SRC) situated at intercellular junctions, thereby determining the subsequent signaling pathways that affect cell morphology, viability, and the permeability of blood vessels [32]. In contemporary times, it has been observed that the utilization of anti-VEGF/VEGFR2 therapies presents beneficial outcomes in animal models of rheumatoid arthritis (RA). Moreover, such therapies hold significant therapeutic potential for individuals with RA. Particularly noteworthy among these therapies are Avastin (Bevacizumab), a VEGF Humanized Monoclonal Antibody, and Sorafenib, a Proangiogenic Receptor Tyrosine Kinase Inhibitor, which primarily impedes the expression of VEGFR2 [33]. CAS, a bioactive Phytosterol with broad applications in nutritional complements and pharmaceutical products, has a rich historical provenance and can be extracted from a diverse array of plant species. The element is frequently used in the creation of functional foods and pharmaceutical materials due to its capacity to reduce inflammation, combat oxidative stress, and lower cholesterol levels. These beneficial properties make it a valuable ingredient in producing pharmaceutical raw materials, as affirmed by [34]. The participation of Phytosterols in multiple physiological mechanisms has been documented in the literature. These mechanisms include suppressing the growth of cancer cells, inhibiting angiogenesis, and facilitating apoptosis of cancer cells [35]. It is widely accepted within the scientific community that the characteristics exhibited by synovial angiogenesis bear a striking resemblance to those displayed by tumor angiogenesis, as reported by Fearon *et al.,* in 2016. Thus, it is postulated that CAM has the potential to impede synovial angiogenesis in Rheumatoid Arthritis (RA) by exerting a modulatory influence on endothelial cells (ECs), consequently mitigating the extent of joint inflammation and damage. In a recent study [36] Fearon et al, utilized the GSEA method to examine the transcriptome of synovial endothelial cells (ECs) in individuals with Rheumatoid Arthritis (RA). Notably, findings exhibited were that ECs exhibited significant enrichment in terms of proliferation and migration. Subsequently, the study revealed that the (VEGF)Vascular Endothelial Growth Factor [37], the (PI3K) Phosphatidylinositol 3-kinase-Protein kinase B (AKT)-the mechanistic target of rapamycin (mTOR), and the transforming growth factor-beta (TGF-β) cascades, which are associated with angiogenesis (the formation of new blood vessels), were stimulated in endothelial cells (ECs). Consequently, in this investigation, the author employed human umbilical vein endothelial cells (HUVECs) and collagen-induced arthritis (CIA) mice as model systems to investigate the impact of CAM on synovial angiogenesis, along with its plausible mechanism. The management of RA has incorporated therapeutic interventions with a primary emphasis on the modulation of the immune system and suppression of synovial inflammation [38]. The currently available therapeutic medications for rheumatoid arthritis (RA), encompassing a range of pharmaceuticals such as NSAIDs (Non-Steroidal Anti-inflammatory Drugs), Corticosteroids, Immuno-Suppressants, Biologicals & Regenerative Therapies, have demonstrated efficacy but are accompanied by notable adverse effects. An increased risk of developing infections and certain malignancies has been observed among individuals diagnosed with rheumatoid arthritis (RA) who receive extended biological agent therapy [39]. Moreover, individuals diagnosed with Rheumatoid Arthritis who are undergoing treatment with Methotrexate and low-dose Prednisone are at a heightened risk of developing opportunistic infections, as evidenced by research conducted by Dudics *et al.,*[40]. Consequently, there exists a pressing need for the development of novel Rheumatoid Arthritis (RA) therapeutics that are both efficacious and devoid of any deleterious side effects. In consideration of this matter, natural products exhibiting potent antioxidant and anti-inflammatory properties pose as auspicious complementary agents or substitutes to rheumatoid arthritis therapeutics.

CONCLUSIONS

Despite the efficacy of current treatments for Rheumatoid Arthritis (RA), their prolonged application frequently results in notable adverse effects. For centuries, natural products have been employed in CAM (Complementary Alternative Medicine), Traditional Chinese Medicine (TCM), Homeopathy, and Tibb for managing Rheumatoid Arthritis (RA). The present review yields findings indicating that utilizing natural compounds for the management of Rheumatoid Arthritis may bring about a more secure, safe, and effective therapeutic approach, as it is associated with a lower incidence of undesirable outcomes or potential adverse effects.

Authors Contribution

Conceptualization: SN, AM
Methodology: SN, IA
Formal analysis: SH, SA, SN, WAC
Writing-review and editing: WAC, SN, AM, IA, SH, SA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflicts of interest.

Source of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

DOI: https://doi.org/10.54393/pjhs.v4i05.792

REFERENCES

[1] Gupta M. Natural products in treatment of rheumatoid arthritis. International Journal of Green Pharmacy(IJGP). 2017 Oct; 11(03): S356-63.

[2] Ito H, Ogura T, Hirata A, Takenaka S, Mizushina K, Fujisawa Y, Katagiri T, Hayashi N, Kameda H. Global assessments of disease activity are age-dependent determinant factors of clinical remission in rheumatoid arthritis. InSeminars in Arthritis and Rheumatism. WB Saunders. 2017 Dec; 47(3): 310-4. doi: 10.1016/j.semarthrit.2017.04.008.

[3] van der Linden MP, van der Woude D, Ioan-Facsinay A, Levarht EN, Stoeken-Rijsbergen G, Huizinga TW, *et al*. Value of anti-modified citrullinated vimentin and third-generation anti-cyclic citrullinated peptide compared with second-generation anti-cyclic citrullinated peptide and rheumatoid factor in predicting disease outcome in undifferentiated arthritis and rheumatoid arthritis. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 2009 Aug; 60(8): 2232-41. doi: 10.1002/art.24716.

[4] Paschke S, Weidner AF, Paust T, Marti O, Beil M, Ben-Chetrit E. Technical advance: inhibition of neutrophil chemotaxis by colchicine is modulated through viscoelastic properties of subcellular compartments. Journal of Leukocyte Biology. 2013 Nov; 94(5): 1091-6. doi: 10.1189/jlb.1012510.

[5] Gabriel SE, Crowson CS, Kremers HM, Doran MF, Turesson C, O'Fallon WM, *et al*. Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. Arthritis & Rheumatism. 2003 Jan; 48(1): 54-8. doi: 10.1002/art.10705.

[6] Monu, Agnihotri P, Biswas S. AGE/non-AGE glycation: An important event in rheumatoid arthritis pathophysiology. Inflammation. 2022 Apr; 45(2): 477-96. doi: 10.1007/s10753-021-01589-7.

[7] Ghisletti S, Meda C, Maggi A, Vegeto E. 17β-estradiol inhibits inflammatory gene expression by controlling NF-κB intracellular localization. Molecular and Cellular Biology. 2005 Apr; 25(8): 2957-68. doi: 10.1128/MCB.25.8.2957-2968.2005.

[8] Rubtsov AV, Rubtsova K, Kappler JW, Marrack P. Genetic and hormonal factors in female-biased autoimmunity. Autoimmunity Reviews. 2010 May; 9(7): 494-8. doi: 10.1016/j.autrev.2010.02.008.

[9] Liu Y, Zhang Z, Jin Q, Liu Y, Kang Z, Huo Y, *et al*. Hyperprolactinemia is associated with a high prevalence of serum autoantibodies, high levels of inflammatory cytokines and an abnormal distribution of peripheral B-cell subsets. Endocrine. 2019 Jun; 64: 648-56. doi: 10.1007/s12020-019-01896-y.

[10] McInnes IB and Schett G. The pathogenesis of rheumatoid arthritis. New England Journal of Medicine. 2011 Dec; 365(23): 2205-19. doi: 10.1056/NEJMra1004965.

[11] Pradhan VD, Dalvi H, Parsannavar D, Rajadhyaksha A, Patwardhan M, Ghosh K. Study of PTPN22 1858C/T polymorphism in rheumatoid arthritis patients from Western India. Indian Journal of Rheumatology. 2012 Sep; 7(3): 130-4. doi: 10.1016/j.injr.2012.06.003.

[12] Mahabadi M, Faghihiloo E, Alishiri GH, Ataee MH, Ataee RA. Detection of Epstein-Barr virus in synovial fluid of rheumatoid arthritis patients. Electronic Physician. 2016 Mar; 8(3): 2181-6. doi: 10.19082/2181.

[13] Scher JU, Littman DR, Abramson SB. Microbiome in inflammatory arthritis and human rheumatic diseases. Arthritis & Rheumatology (Hoboken, NJ). 2016 Jan; 68(1): 35. doi: 10.1002/art.39259.

[14] Lahiri M, Morgan C, Symmons DP, Bruce IN. Modifiable risk factors for RA: prevention, better than cure?. Rheumatology. 2012 Mar; 51(3): 499-512. doi: 10.1093/rheumatology/ker299.

[15] McInnes IB and Schett G. The pathogenesis of rheumatoid arthritis. New England Journal of Medicine. 2011 Dec; 365(23): 2205-19. doi:10.1056/NEJMra1004965.

[16] Guo Q, Li L, Zheng K, Zheng G, Shu H, Shi Y, *et al*. Imperatorin and β-sitosterol have synergistic activities in alleviating collagen-induced arthritis. Journal of Leucocyte Biology. 2020 Aug; 108(2): 509-17. doi:10.1002/JLB.3MA0320-440RR.

[17] McInnes IB and Schett G. The pathogenesis of rheumatoid arthritis. New England Journal of Medicine. 2011 Dec; 365(23): 2205-19. doi:10.1056/NEJMra1004965.

[18] Najm A, Masson FM, Preuss P, Georges S, Ory B, Quillard T, *et al*. MicroRNA-17-5p reduces inflammation and bone erosions in mice with collagen-induced arthritis and directly targets the JAK/STAT pathway in rheumatoid arthritis fibroblast-like synoviocytes. Arthritis & Rheumatology. 2020 Dec; 72(12): 2030-9. doi:10.1002/art.41441.

[19] Elshabrawy HA, Chen Z, Volin MV, Ravella S, Virupannavar S, Shahrara S. The pathogenic role of angiogenesis in rheumatoid arthritis. Angiogenesis. 2015 Oct; 18: 433-48. doi:10.1007/s10456-015-9477-2.

[20] Fraile L, Crisci E, Córdoba L, Navarro MA, Osada J, Montoya M. Immunomodulatory properties of beta-sitosterol in pig immune responses. International Immunopharmacology. 2012 Jul; 13(3): 316-21. doi: 10.1016/j.intimp.2012.04.017.

[21] Nirmal SA, Pal SC, Mandal SC, Patil AN. Analgesic and anti-inflammatory activity of β-sitosterol isolated

DOI: https://doi.org/10.54393/pjhs.v4i05.792

from Nyctanthes arbortristis leaves. Inflammopharmacology. 2012 Aug; 20: 219-24. doi:10.1007/s10787-011-0110-8.

[22] Zhang F, Liu Z, He X, Li Z, Shi B, Cai F. β-Sitosterol-loaded solid lipid nanoparticles ameliorate complete Freund's adjuvant-induced arthritis in rats: involvement of NF-κB and HO-1/Nrf-2 pathway. Drug Delivery. 2020 Jan; 27(1): 1329-41. doi:10.1080/10717544.2020.1818883.

[23] Woyengo TA, Ramprasath VR, Jones PJ. Anticancer effects of phytosterols. European Journal of Clinical Nutrition. 2009 Jul; 63(7): 813-20.doi:10.1038/ejcn.2009.29.

[24] Pan D, Li N, Liu Y, Xu Q, Liu Q, You Y, *et al*. Kaempferol inhibits the migration and invasion of rheumatoid arthritis fibroblast-like synoviocytes by blocking activation of the MAPK pathway. International

[25] Immunopharmacology. 2018 Feb; 55: 174-82. doi:10.1016/j.intimp.2017.12.011.
Karaman S, Leppänen VM, Alitalo K. Vascular endothelial growth factor signaling in development and disease. Development. 2018 Jul; 145(14): dev151019. doi:10.1242/dev.151019.

[26] Carpentier G, Berndt S, Ferratge S, Rasband W, Cuendet M, Uzan G, *et al*. Angiogenesis analyzer for imagej—A comparative morphometric analysis of "endothelial tube formation assay" and "fibrin bead assay". Scientific Reports. 2020 Jul; 10(1): 11568. doi:10.1038/s41598-020-67289-8.

[27] Du HX, Xiao WH, Wang Y, Zhou X, Zhang Y, Liu D, *et al*. Engineering Yarrowia lipolytica for campesterol overproduction. PLoS One. 2016 Jan; 11(1): e0146773. doi: 10.1371/journal.pone.0146773.

[28] Farzaei MH, Farzaei F, Abdollahi M, Abbasabadi Z, Abdolghaffari AH, Mehraban B. A mechanistic review on medicinal plants used for rheumatoid arthritis in traditional Persian medicine. Journal of Pharmacy and Pharmacology. 2016 Oct; 68(10): 1233-48. doi: 10.1111/jphp.12606.

[29] Leblond A, Allanore Y, Avouac J. Targeting synovial neoangiogenesis in rheumatoid arthritis. Autoimmunity Reviews. 2017 Jun; 16(6): 594-601. doi: 10.1016/j.autrev.2017.04.005.

[30] Simons M, Gordon E, Claesson-Welsh L. Mechanisms and regulation of endothelial VEGF receptor signalling. Nature reviews Molecular Cell Biology. 2016 Oct; 17(10): 611-25. doi: 10.1038/nrm.2016.87.

[31] Sakurai Y, Ohgimoto K, Kataoka Y, Yoshida N, Shibuya M. Essential role of Flk-1 (VEGF receptor 2) tyrosine residue 1173 in vasculogenesis in mice. Proceedings of the National Academy of Sciences. 2005 Jan; 102(4): 1076-81. doi:10.1073/pnas.0404984102.

[32] Liu L and Shi GP. CD31: beyond a marker for endothelial cells. Cardiovascular Research. 2012 Apr; 94(1): 3-5.doi:10.1093/cvr/cvs108.

[33] Zhai S, Jacob DJ, Wang X, Shen L, Li K, Zhang Y, *et al*. Fine particulate matter (PM< sub> 2.5</sub>) trends in China, 2013–2018: separating contributions from anthropogenic emissions and meteorology. Atmospheric Chemistry and Physics. 2019 Aug; 19(16): 11031-41. doi: 10.5194/acp-19-11031-2019.

[34] Babu S and Jayaraman S. An update on β-sitosterol: A potential herbal nutraceutical for diabetic management. Biomedicine & Pharmacotherapy. 2020 Nov; 131: 110702. doi: 10.1016/j.biopha.2020.110702.

[35] Shahzad N, Khan W, Shadab MD, Ali A, Saluja SS, Sharma S, *et al*. Phytosterols as a natural anticancer agent: Current status and future perspective. Biomedicine & Pharmacotherapy. 2017 Apr; 88: 786-94. doi: 10.1016/j.biopha.2017.01.068.

[36] Fearon U, Canavan M, Biniecka M, Veale DJ. Hypoxia, mitochondrial dysfunction and synovial invasiveness in rheumatoid arthritis. Nature Reviews Rheumatology. 2016 Jul; 12(7): 385-97. doi:10.1038/nrrheum.2016.69.

[37] Sorenson WR, Sullivan D, Collaborators: Baugh S, Collison M, Das R, Erickson A, *et al*. Determination of campesterol, stigmasterol, and beta-sitosterol in saw palmetto raw materials and dietary supplements by gas chromatography: collaborative study. Journal of AOAC International. 2007 May; 90(3): 670-8. doi:10.1093/jaoac/90.3.670.

[38] Yap HY, Tee SZ, Wong MM, Chow SK, Peh SC, Teow SY. Pathogenic role of immune cells in rheumatoid arthritis: implications in clinical treatment and biomarker development. Cells. 2018 Oct; 7(10): 161. doi: 10.3390/cells7100161.

[39] Simon TA, Boers M, Hochberg M, Baker N, Skovron ML, Ray N, *et al*. Comparative risk of malignancies and infections in patients with rheumatoid arthritis initiating abatacept versus other biologics: a multi-database real-world study. Arthritis Research & Therapy. 2019 Dec; 21: 1-9. doi: 10.1186/s13075-019-1992-x.

[40] Dudics S, Langan D, Meka RR, Venkatesha SH, Berman BM, Che CT, *et al*. Natural products for the treatment of autoimmune arthritis: their mechanisms of action, targeted delivery, and interplay with the host microbiome. International Journal of Molecular Sciences. 2018 Aug; 19(9): 2508. doi: 10.3390/ijms19092508.