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SHORT REVIEW

Role of Natural Products in Combatting Rheumatoid Arthritis: Phytochemical Strategies and Antioxidant Defences

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Abstract

Rheumatoid Arthritis (RA) is a persistent inflammatory autoimmune illness that damages bones by causing joint discomfort, edema, and stiffness. In RA, inflammatory cell infiltration and synovial hyperplasia lead to the generation of proinflammatory cytokines like TNF-α and IL-1. To find phytochemical substances utilised in RA treatment, SciELO, Virtual Health Library, and PubMed databases were searched for rheumatoid arthritis, herbal remedies, and medicinal plants. One of the predominant transcription factors is NF-κB, in regulating inflammatory response. Translocation of active NF-κB into the nucleus leads to gene transcription that produces proinflammatory cytokines. Oxidative stress changes transcription factors, which affects inflammatory gene expression. Phytochemicals have treated various diseases, blocking NF-κB translocation mitigates proinflammatory cascade activation (Withanolides, Gugglosterone, Epigallocatechin-3-gallate, O-glucosylcimifugin, Andrographolide, Curcuminoids, and Resveratrol), Flavonoids (Quercetin, Hesperidin, Kaempferol, Liquirin). Their therapeutic potential aids in creating safe and effective medicines for NF-κB-driven immune-inflammatory disorders like RA. This study emphasises the involvement of NF-κB in a series of events of inflammation, highlighting the role of phytochemicals in regulating its activity. It also discusses the effectiveness of polyphenols in relieving RA by blocking the signalling pathways and suggests a further study to support their usage.

Keywords: Anti-inflammatory, Antioxidant, NF-κB, Phytocompounds, Rheumatoid Arthritis

1. Introduction

Rheumatoid Arthritis (RA) is indeed a chronic systematic autoimmune disease[1]. The most common system targets are skin- RA, which can cause skin conditions such as rheumatoid nodules and vasculitis. Eyes- May irritate the eyes, leading to conditions such as scleritis and uveitis. Lungs-RA can cause inflammation and damage lung tissue, known as rheumatoid arthritis. Heart- raises the chance of cardiovascular diseases such as heart disease and stroke. Kidneys-RA can irritate the kidneys, which can damage them. Salivary gland disease causes inflammation of the salivary glands, dry mouth, and other symptoms. Nerve tissue-RA can lead to nerve compression syndromes such as carpal tunnel syndrome. Bones- May affect bone function, resulting in decreased blood pressure. Bleeding-RA-related bleeding can affect blood vessels, leading to conditions such as vasculitis[2] — an important factor in the onset of RA progression and the release of inflammatory cytokines. TNF-α, for instance, is a pro-inflammatory cytokine that triggers the inflammation of the cells to activate and aggregate. This exacerbates the inflammatory response by releasing additional mediators of inflammation[3].

In RA joints, antigen-activated CD4+ T lymphocytes, monocytes, macrophages, and synovial fibroblasts start and maintain the inflammatory

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response. These cells release inflammatory mediators such as TNF-α, IL-1, and IL-6 (IL-6). These cytokines activate immune cells and increase inflammatory factors. In addition, chondrocytes, fibroblasts, and osteoclasts secrete metalloproteinases, resulting in Joint erosion, which dissolves cartilage and bone extracellular matrix[4].

Free radicals steal electrons, initiating a chain reaction. In addition to influencing cytoskeletal control, phagocytosis, flagging, separation, growth, development, and demise of cells, ROS preserves the redox conditions of cells. ROS can damage cell membrane fatty acids and phospholipids if they exceed solid values (chains of amino acids and nucleic acids). Antioxidants are chemicals that scavenge free radicals or inhibit cell oxidation. SOD, CAT, and GSH-related chemicals control cancer-suppressing responses, as do GPx, GR, and Thioredoxin Reductase (TR). It promotes ROS formation and oxidative phosphorylation and generates ongoing hypoxia cycles; the increased pressure factor inside the joints may cause persistent oxidative pressure in the synovial membrane. RA joints have hypoxia due to the inflammation reaction's rapid cell growth[5].

Indeed, antioxidants have been a focal point in exploring natural products for RA management. While the precise capacity of antioxidants in RA treatment remains a subject of debate due to conflicting evidence, their potential value in combating inflammation is well-documented. Antioxidants neutralize dangerous molecules called free radicals, which can cause tissue damage and inflammation in conditions like RA. Therefore, the antioxidant properties of natural products are often evaluated as a first step in research, preceding investigations into their anti-inflammatory effects. Despite conflicting evidence regarding the direct impact of antioxidants on RA symptoms, many patients report experiencing benefits from incorporating antioxidant-rich foods or supplements into their diet[6].

2. Methodology

A preliminary literature survey was performed to identify phytochemicals and their therapeutic actions in the treatment of rheumatoid arthritis. To gather relevant information regarding medicinal plants used in the context of RA. A thorough approach literature survey in the PubMed, Google Scholar, and Virtual Health Library databases.

3. Phytochemical Strategies of Rheumatoid Arthritis

3.1 Role of NF-κB in Inflammation

Nuclear factor-kappa B (NF-κB) is a vital transcription factor involved in expressing many genes in various cell types[7]. In RA patients, NF-κB activation is noticed in the synovial tissue at both early and later stages of the disease, suggesting its involvement throughout disease progression. The inflammatory process in RA is commenced by the interaction between Antigen-Presenting Cells (APCs) and T cells, which is a critical step in initiating an inflammatory response. The induction of NF-κB-dependent genes, and coordinated regulation of IFN-γ, IL-2, and IL-2R, are triggered by this interaction which promotes T-cell activation and proliferation. T cells that are activated generate molecules such as TNF, RANKL, and CD40 ligands, which interact with receptors on APCs, resulting in additional NF-κB activation. This amplifies the inflammatory response, supporting T-cell survival and multiplication. Activation of NF-κB is essential in the immune response towards a Th1 phenotype, releasing pro-inflammatory cytokines that sustain the inflammatory cascade in RA[8].

3.2 Inhibitory Actions of Bio-chemicals on NF-κB

Phytochemicals, natural substances derived from plants, have been extensively studied for their ability to inhibit the activation and deactivation of the transcription factor NF-κB (nuclear factor kappa B). Given the central role of NF-κB in modulating immune and immunological responses and its role in various pathological states, blocking its activity may provide therapeutic benefits[9] depicted in Figure 1.

Plant chemicals such as Triterpenes, thymoquinones, flavonoids, sesquiterpene lactones, steroids, terpenoids, sterols and phytoalexins have anti-inflammatory, anti-arthritic, and antioxidant properties (Figure 1).

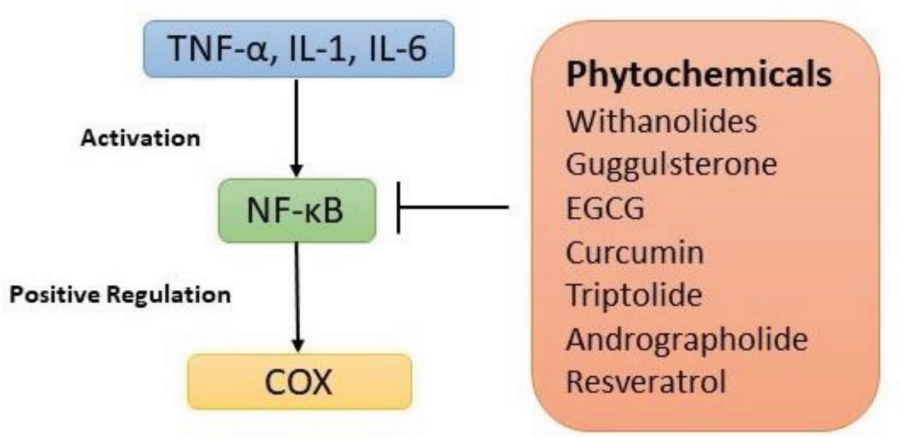

Figure 1. Mechanism of action of phytochemicals on inflammation.

3.2.1 *Withania somniferum*

Withania somnifera (*Ashwagandha*, WS), a potent herb inhibiting NF-κB activation, is used to treat RA[10]. Withanolides fall under the ergostane-type steroid group, where C-22 and C-26 atoms are linked to the C-1 oxide and the d-lactone functional group. A strong withanolide called withaferine A inhibits NF-κB activity[11,12].

3.2.2 *Tripterygium wilfordii*

Tripterygium wilfordii Hook f (TWHF), referred to as Thunder God Vine, is a popular herb in Chinese herb. TWHF is effective in the treatment of several infectious diseases[13]. TWHF extract includes over 70 components, including glycosides, β-sitosterol, dulcitol, triterpenoids, sesquiterpenoids, and diterpenoids. TWHF extract's medicinal benefits come from triptolide, a diterpene triepoxide. Recent research indicates that TWHF inhibits transcription factors like NF-AT, AP-1, and NF-κB (Nuclear factor of activated T cells)[14].

3.2.3 *Commiphora mukul*

Plant sterol Guggulsterone (4,17(20)-pregnadiene-3,16-dione) is obtained from the gum resin(guggulu) of *C. mukul*. This plantin Ayurvedic therapy is believed to be responsible for hyperlipidemia, arthritis and obesity. Considerable anti-inflammatory properties of guggulsterone are mediated by inhibition of NF-κB signaling[15-17].

3.2.4 *Camellia sinensis*

Epigallocatechin-3-gallate (EGCG) found abundantly in *C. sinensis* (green tea) contributes to the antioxidant and anti-inflammatory response extracted. EGCG interferes with the suppression of NF-κB pathway, lowering its quantity and translocating to the nucleus, which prevents RA from binding DNA and is also known to inhibit nuclear translocation of NF-κB[18].

3.2.5 *Saponshnikovia divaricata*

Saposhnikovia divaricata, an Indian plant of Mexican origin known as "*fangfeng*" in China, contains sesquiterpene lactones, that exhibit anti-inflammatory effects, commonly used to treat arthritis. Essential oils, coumarin, mannitol, glycosides, polyacetylene, and bioactive chromate are found in the dried root[19,20].

3.2.6 *Andrographis paniculata*

Andrographis paniculata (AP), belongs to family Acanthaceae, treats inflammation, digestive issues, and more. The aerial section of the plant contains andrographolide, a labdane diterpene with medicinal effects that prevents NF-κB activation by preventing binding to its consensus sequence[21].

3.2.7 *Curcuma longa*

Curcumin, indeed a component found in the rhizome of turmeric, has been documented to possess anti-arthritic properties. Curcumin a diarylheptanoid, is one of the three major curcuminoids that comprises up to 3-4 % of total composition. Curcuminoids are a group of phenolic components that impart turmeric its characteristic yellow colour. Curcumin's inhibitory effects on NF-κB have been thoroughly studied[22-24].

3.2.8 *Vitis vinifera*

Resveratrol (trans-3,4′hydroxystilbene) is a polyphenolic phytoalexin available in the skin of red grapes (*Vitis vinifera*) and demonstrates antioxidant, anti-inflammatory, immunomodulatory, and anti-arthritic properties[25] and exhibited chondroprotection by Reactive Oxygen Species (ROS) production and inhibition of IL-1β. It modulates the translocation of nuclear NF-κB by regulating IκB[26,27].

4. Role of Polyphenols and Flavonoids in RA

Antioxidants include polyphenols like flavonoids, phenolic acids, and stilbenes like resveratrol. They directly scavenge and reduce oxidative stress and safeguard lipids, proteins, and DNA by neutralising free radicals and Reactive Oxygen Species (ROS). Polyphenols initiate antioxidant enzymes glutathione, peroxidase, catalase, and Superoxide Dismutase (SOD). Strengthening the body's antioxidant defences. Polyphenols in plants can influence inflammatory pathways and signalling cascades, including NF-κB suppression, which affects pro-inflammatory gene expression. These drugs inhibit COX and lipoxygenase enzymes to lower cytokines, prostaglandins, and leukotrienes. Polyphenols can also reduce macrophage and neutrophil synthesis of inflammatory mediators and migration to inflammation sites[28-30].

The phenylpropanoid metabolic pathway produces flavonoids[31,32]. Besides being antioxidants, flavonoids can reduce inflammation. They inhibit NO, eicosanoids, pro-inflammatory cytokines, and Nuclear factor-κB transcription[33,34].

4.1 Phytocompounds in the Treatment of RA

Quercetin, a flavonoid, reduced IL-17 A and IL-21 production and helped treat RA[35]. Hesperidin explored potential protective activity against RA with a significant decrease in joint degradation and serum TNF-α levels[36]. The traditional plants *Oroxylum indicum* and *Scutellaria baicalensis* and contain abundant baicalin and aglycone (*baicalin-2*). They possess antioxidant and anti-inflammatory qualities by reducing ROS formation, NF-kB activity, cyclooxygenases, and TNF-α. This makes it possible for RA therapy targets[37]. Gentakwanin, Hydroxygenkwanin, luteolin, and apigenin from *Daphne genkwa* were anti-inflammatory and immunomodulatory. RA was effectively countered by reducing levels of ROS, NO, TNF-α, IFN-γ, IL-6, and IL-2[38]. *Glycyrrhiza uralensis* roots contain a flavonoid compound called liquiritin, which reduces inflammation by causing alterations in the mitochondrial membrane, inducing apoptosis in the synovial membrane, and encouraging DNA fragmentation[39]. *Oroxylin A*, an anti-inflammatory flavonoid, lowered TNF-α, IL-6, IL-1β, and IL-17 levels in the serum. T-cell assay demonstrated increased regulatory T cells, indicating strong anti-inflammatory activity[40]. Kaempferol reduces TNF-α production and inhibits fibroblast-like synoviocyte migration, invasion, and proliferation, which are crucial for cartilage degradation. It significantly reduces synovial inflammation and cellular infiltration in RA[41,42].

3.2 Stilbenes

Stilbenes group of polyphenolic non-flavonoid compounds usually found in red wine, peanuts, berries, grapes, etc., are antioxidants and anti-inflammatory. Resveratrol, a stilbene found in grape skin, also slows ROS and MDA expression and also inhibits NF-κB expression[43].

4. Conclusion

Plants provide many substances that are effective in the treatment of diseases. Phytochemical that inhibit NF-κB activity, transactivation, and DNA binding may be helpful anti-inflammatory medicines. New RA medicines are enhancing the quality of life. Why natural RA treatments need studies is inexplicable. Plant polyphenols and flavonoids have the potential to delay or improve RA progression through their enzymatic, immunomodulatory, anti-inflammatory, and antioxidant qualities. Thus, these secondary metabolites may help create RA medications that enhance quality of life. This review summarised herbs and herbal compounds that treat RA models *in situ* and *in vitro*. RA treatment with these substances focuses on anti-inflammatory and antioxidant properties. Many chemicals have drug-like characteristics worth studying. Some chemicals' pharmacological behaviour demands optimization.

5. References

1. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet. 2016; 388:2023-38. https://doi.org/10.1016/S0140-6736(16)30173-8 PMid:27156434
2. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011; 365(23):2205-19. https://doi.org/10.1056/NEJMra1004965 PMid:22150039
3. Kany S, Vollrath JT, Relja B. Cytokines in inflammatory disease. Int J Mol Sci. 2019; 20(23):6008. PMid:31795299 PMCid:PMC6929211
4. Zhao X, Kim YR, Min Y, Zhao Y, Do K, Son YO. Natural plant extracts and compounds for rheumatoid arthritis therapy. Medicina (*Kaunas*). 2021; 57(3):266. https://doi.org/0.3390/medicina57030266 PMid:33803959 PMCid:PMC8001474
5. Behl T, Upadhyay T, Singh S, Chigurupati S, Alsubayiel AM, Mani V, *et al*. Polyphenols targeting MAPK mediated oxidative stress and inflammation in Rheumatoid Arthritis. Molecules. 2021; 26(21):6570. https://doi.org/10.3390/molecules26216570 PMid:34770980 PMCid:PMC8588006
6. Arulselvan P, Fard MT, Tan WS, Gothai S, Fakurazi S, Norhaizan ME, *et al*. Role of antioxidants and natural products in inflammation. Oxid Med Cell Longev. 2016; 2016:5276130. https://doi.org/10.1155/2016/5276130 PMid:27803762 PMCid:PMC5075620
7. Roman-Blas JA, Jimenez SA. NF-κB as a potential therapeutic target in osteoarthritis and Rheumatoid Arthritis. Osteoarthr Cartil. 2006; 14:839-48. https://doi.org/10.1016/j.joca.2006.04.008 PMid:16730463
8. Makarov SS. NF-κB in Rheumatoid Arthritis: A pivotal regulator of inflammation, hyperplasia, and tissue destruction. Arthritis Res. 2001; 3:200-6. https://doi.org/10.1186/ar300 PMid:11438035 PMCid:PMC128895
9. Aravilli RK, Vikram SL, Kohila V. Phytochemicals as potential antidotes for targeting NF-κB in rheumatoid arthritis. 3 Biotech. 2017; 7(4):253. https://doi.org/10.1007/s13205-017-0888-1 PMid:28721679 PMCid:PMC5515733
10. Mishra LC, Singh BB, Dagenais S. Scientific basis for the therapeutic use of *Withania somnifera* (ashwagandha): A review. Altern Med Rev. 2000; 5:334-46.
11. SoRelle JA, Itoh T, Peng H, Kanak MA, Sugimoto K, Matsumoto S, Levy MF, Lawrence MC, Naziruddin B. Withaferin A inhibits pro-inflammatory cytokine-induced damage to islets in culture and following transplantation. Diabetologia. 2013; 56:814-24. https://doi.org/10.1007/s00125-012-2813-9 PMid:23318585
12. Grover A, Shandilya A, Punetha A, Bisaria VS, Sundar D. Inhibition of the NEMO/IKKβ association complex formation, a novel mechanism associated with the NF-κB activation suppression by *Withania somnifera's* key metabolite withaferin A. BMC Genom. 2010; 11:1-11. https://doi.org/10.1186/1471-2164-11-1 PMid:21143809 PMCid:PMC3005936
13. Bao J, Dai SM. A Chinese herb *Tripterygium wilfordii* Hook F in the treatment of rheumatoid arthritis: Mechanism, efficacy, and safety. Rheumatol Int. 2011; 31:1123-9. https://doi.org/10.1007/s00296-011-1841-y PMid:21365177
14. Matta R, Wang X, Ge H, Ray W, Nelin LD, Liu Y. Triptolide induces anti-inflammatory cellular responses. Am J Transl Res. 2009; 1:267-82.
15. Xiao D, Singh SV. z-Guggulsterone, a constituent of ayurvedic medicinal plant *Commiphora mukul*, inhibits angiogenesis *in vitro* and *in vivo*. Mol Cancer Ther. 2008; 7:171-80. https://doi.org/10.1158/1535-7163.MCT-07-0491 PMid:18202020
16. Patel SS, Shah PV. Evaluation of anti-inflammatory potential of the multidrug herbomineral formulation in male Wistar rats against rheumatoid arthritis. J Ayurveda Integr Med. 2013; 4:86-93. https://doi.org/10.4103/0975-9476.113869 PMid:23930040 PMCid:PMC3737452
17. Shishodia S, Aggarwal BB. Guggulsterone inhibits NF-κB and IκB Kinase activation, suppresses expression of anti-apoptotic gene products, and enhances apoptosis. J Biol Chem. 2004; 279:47148-58. https://doi.org/10.1074/jbc.M408093200 PMid:15322087
18. Wu PH, Lin SK, Lee BS, Kok SH, Wang JH, Hou KL, *et al*. Epigallocatechin-3-gallate diminishes cytokine-stimulated Cyr61 expression in human osteoblastic cells: A therapeutic potential for arthritis. Rheumatol. 2012; 51:1953-65. https://doi.org/10.1093/rheumatology/kes174 PMid:22843790
19. Bork PM, Schmitz ML, Kuhnt M, Escher C, Heinrich M. Sesquiterpene lactone containing Mexican Indian medicinal plants and pure sesquiterpene lactones as potent inhibitors of transcription factor NF-κB. FEBS Lett. 1997; 402:85-90. https://doi.org/10.1016/S0014-5793(96)01502-5 PMid:9013864
20. Hehner SP, Heinrich M, Bork PM, Vogt M, Ratter F, Lehmann V, *et al*. Sesquiterpene lactones specifically inhibit activation of NF-κB by preventing the degradation of IκB-α and IκB-β. J Biol Chem. 1998; 273:1288-97. https://doi.org/10.1074/jbc.273.3.1288 PMid:9430659
21. Burgos RA, Hancke JL, Bertoglio JC, Aguirre V, Arriagada S, Calvo M, *et al*. Efficacy of an *Andrographis paniculata* composition for the relief of rheumatoid arthritis symptoms: A prospective randomised placebo-controlled trial. Clin Rheumatol. 2009; 28:931-46. https://doi.org/10.1007/s10067-009-1180-5 PMid:19408036
22. Basnet P, Skalko-Basnet N. Curcumin: An anti-inflammatory molecule from a curry spice on the path to cancer treatment. Molecules. 2011; 16:4567-98. https://doi.org/10.3390/molecules16064567 PMid:21642934 PMCid:PMC6264403
23. Sharma RA, Gescher AJ, Steward WP. Curcumin: The story so far. Eur J Cancer. 2005; 41:1955-68. https://doi.org/10.1016/j.ejca.2005.05.009 PMid:16081279
24. Funk JL, Oyarzo JN, Frye JB, Chen G, Clark R, Jolad SD, *et al*. Turmeric extracts containing curcuminoids prevent

experimental rheumatoid arthritis. J Nat Prod. 2008; 69:351-5. https://doi.org/10.1021/np050327j PMid:16562833 PMCid:PMC2533857
25. Shakibaei M, Csaki C, Nebrich S, Mobasheri A. Resveratrol suppresses interleukin-1β-induced inflammatory signaling and apoptosis in human articular chondrocytes: Potential for use as a novel nutraceutical for the treatment of osteoarthritis. Biochem Pharmacol. 2008; 76:1426-39. https://doi.org/10.1016/j.bcp.2008.05.029 PMid:18606398
26. Csaki C, Keshishzadeh N, Fischer K, Shakibei M. Regulation of inflammation signaling by resveratrol in human chondrocytes *in vitro*. Biochem Pharmacol. 2008; 75:677-87. https://doi.org/10.1016/j.bcp.2007.09.014 PMid:17959154
27. Zhu X, Liu Q, Wang M, Liang M, Yang X, Xu X, *et al*. Activation of Sirt1 by resveratrol inhibits TNF-α induced inflammation in fibroblasts. PLoS One. 2011; 6:11. https://doi.org/10.1371/annotation/60addd69-bd2d-4ecf-8369-6a5a1bf2cd04 PMid:22069489 PMCid:PMC3206084
28. Oliviero F, Scanu A, Zamudio-Cuevas Y, Punzi L. Anti-inflammatory effects of polyphenols in arthritis. J Sci Food Agric. 2018; 98(5):1653-9. https://doi.org/10.1002/jsfa.8664 PMid:28886220
29. Ansari MY, Ahmad N, Haqqi TM. Butein activates autophagy through AMPK/TSC2/ULK1/mTOR pathway to inhibit IL-6 expression in IL-1β stimulated human chondrocytes. Cell Physiol Biochem. 2018; 49:932-46. https://doi.org/10.1159/000493225 PMid:30184535
30. Ansari MY, Khan NM, Haqqi TM. A standardized extract of *Butea monosperma* (Lam.) flowers suppresses the IL-1β-induced expression of IL-6 and matrix-metalloproteases by activating autophagy in human osteoarthritis chondrocytes. Biomed Pharmacother. 2017; 96:198-207. https://doi.org/10.1016/j.biopha.2017.09.140 PMid:28987943
31. De Villiers A, Venter P, Pasch H. Recent advances and trends in the liquid-chromatography-mass spectrometry analysis of flavonoids. J Chromatogr A. 2015; 1430:16-78. https://doi.org/10.1016/j.chroma.2015.11.077 PMid:26718188
32. Jackson JK, Higo T, Hunter WL, Burt HM. The antioxidants curcumin and quercetin inhibit inflammatory processes associated with arthritis. Inflamm Res. 2006; 55(4):168–75. https://doi.org/10.1007/s00011-006-0067-z PMid:16807698
33. Burda S, Oleszek W. Antioxidant and antiradical activities of flavonoids. J Agric Food Chem. 2001; 49(6):2774-9. https://doi.org/10.1021/jf001413m PMid:11409965
34. Cao G, Sofic E, Prior RL. Antioxidant and prooxidant behavior of flavonoids: Structure-activity relationships. Free Radic Biol Med. 1997; 22(5):749-60. https://doi.org/10.1016/S0891-5849(96)00351-6 PMid:9119242
35. Yang Y, Zhang X, Xu M, Wu X, Zhao F, Zhao C. Quercetin attenuates collagen-induced arthritis by restoration of Th17/Treg balance and activation of Heme Oxygenase 1-mediated anti-inflammatory effect. Int Immunopharmacol. 2018; 54:153-62. https://doi.org/10.1016/j.intimp.2017.11.013 PMid:29149703
36. Ahmad S, Alam K, Hossain MM, Fatima M, Firdaus F, Zafeer MF, *et al*. Anti-arthritogenic and cardioprotective action of hesperidin and daidzein in collagen-induced Rheumatoid Arthritis. Mol Cell Biochem. 2016; 423(1-2):115-27. https://doi.org/10.1007/s11010-016-2830-y PMid:27704466
37. Dinda B, Dinda S, DasSharma S, Banik R, Chakraborty A, Dinda M. Therapeutic potentials of baicalin and its aglycone, baicalein against inflammatory disorders. Eur J Med Chem. 2017; 131:68-80.https://doi.org/10.1016/j.ejmech.2017.03.004 PMid:28288320
38. Jiang CP, He X, Yang XL, Zhang SL, Li H, Song ZJ, *et al*. Anti-rheumatoid arthritic activity of flavonoids from *Daphne genkwa*. Phytomedicine. 2014; 21(6):830-7. https://doi.org/10.1016/j.phymed.2014.01.009 PMid:24561028
39. Zhai KF, Duan H, Cui CY, Cao YY, Si JL, Yang HJ, *et al*. Liquiritin from Glycyrrhiza uralensis attenuating rheumatoid arthritis via reducing inflammation, suppressing angiogenesis, and inhibiting MAPK signaling pathway. J Agric Food Chem. 2019; 67(10):2856-64. https://doi.org/10.1021/acs.jafc.9b00185 PMid:30785275
40. Wang Y, Gao J, Xing LZ. Therapeutic potential of Oroxylin A in rheumatoid arthritis. Int Immuno Pharmacol. 2016; 40:294-9. https://doi.org/10.1016/j.intimp.2016.09.006 PMid:27643663
41. Lee CJ, Moon SJ, Jeong JH, Lee S, Lee MH, Yoo SM, *et al*. Kaempferol targeting on the fibroblast growth factor receptor 3-ribosomal S6 kinase 2 signaling axis prevents the development of rheumatoid arthritis. Cell Death Dis. 2018; 9(3). https://doi.org/10.1038/s41419-018-0433-0 PMid:29540697 PMCid:PMC5851988
42. 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. Int Immuno Pharmacol. 2018; 55:174-82. https://doi.org/10.1016/j.intimp.2017.12.011 PMid:29268189
43. Zhang Y, Wang G, Wang T Cao W, Zhang L, Chen X. Nrf2–Keap1 pathway–mediated effects of resveratrol on oxidative stress and apoptosis in hydrogen peroxide–treated rheumatoid arthritis fibroblast-like synoviocytes. Ann N Y Acad Sci. 2019; 1457:166-78. https://doi.org/10.1111/nyas.14196 PMid:31475364