Role of Natural Compounds in the Treatment of Rheumatoid Arthritis

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ABSTRACT: Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disease, affecting the joints. It is not just affecting the joints but also the internal organs. Arthritis tends to attacks in between ages of 20 and 40. There are three types of RA i.e seronegative, seropositive and juvenile idiopathic RA. There is no cure for this disease yet but some effective treatments were here to help the people with their pain. The main goal of the treatment is to minimise the pain and stop the progress of the disease. The treatment of RA is a combination of two or three methods like pharmaceutical drugs, weight exercises, improved lifestyle. Main focus is on pharmaceutical drugs with the anti-inflammatory properties because RA Is a inflammatory response of the body. There is a need of such drugs in the pharmaceutical industry. Dihydrohelenalin, Thiophenes, sulfonamides are natural compound which has the anti-inflammatory properties which makes them the potential for the development of the pharmaceutical drug for the treatment of RA. This review deals with Rheumatoid Arthritis, their causes and symptom in brief along with their role of natural compounds in the RA treatment.

KEYWORDS: Rheumatoid Arthritis, Anti-inflammatory, Autoimmune Disease, Dihydrohelenalin, Sulfonamides, Thiophenes, Pharmaceutical Drug

I. INTRODUCTION

Rheumatoid Arthritis is a disease that involves genetic predisposition and environmental components both [1,2,3,4,5]. There are 1.3 million people just only in United States affected by RA [6,7,8,9,10]. This disease affects the people in the age group between 20-40 years old and men are less likely to develop the RA as compare to women [7]. The common sign of RA is included redness of hands and feet [11], neck deformity [12]. Rheumatoid factor (RF) and anti-citrullinated protein/peptide antibodies (ACPA) are common serum biomarkers [13]. Oncoproteinsurvivin also known as the biomarker for the cancer were shown in one study [14] it was detected in 50.7% of RA patients but only 5.6% in controls, which indicates its high specificity.

It as disease which associated higher mortality rates as compare to the average of patient's population. The researchers found that RA was associated with a 32% excess risk for mortality but this risk was only 15% after 2006 [16]. There is need of new pharmaceutical drugs with Anti-rheumatic and anti-inflammatory properties to deal with the treatment of Rheumatoid. The risk of developing RA was three times higher in first-degree relatives of RA patients even though familial factors influence RA in men and women equally [21,22]. RA has four stages which get severe step by step. Diagnosis is important to prevent the further damage.

[1].Stages of Rheumatoid Arthritis
Stage 1: when body mistakenly attacks its own joint Tissues.
Stage 2: when body makes antibodies and joint start the swelling up
Stage 3: the joint start becoming bent and deformed, fingers become crooked.
Stage 4: If not treated, disease will progress to the last stage where there is no joint remaining at all and the joint is essentially fused.

Stage 1:
Triggering stage

Stage 2:
Maturation stage

Stage 3:
Targeting stage

Stage 4:
Fulminant stage

Figure 1: Stages of Rheumatoid Arthritis

Complications:
- Infections
- Chronic anemia
- Gastrointestinal cancers
- Pleural effusions
- Osteoporosis
- Heart disease
- Sicca syndrome

Figure 2: Complications of Rheumatoid Arthritis

[2].Types of Rheumatoid Arthritis

Seropositive, seronegative and juvenile idiopathic arthritis are three different types of RA which classified on the basis of the presence of the Ab/protein which produce when immune system is attacked. The diagnosis is based on the presence or absence of the Ab/protein in the body through different diagnostic tool kits. In seropositive and seronegative the factor known as rheumatoid factors (RF) is presence and absence respectively. RF factors is determined by the presence of the Ab/protein in the body. Juvenile idiopathic arthritis is the common among all three types of RA which found in children below the age of 17.

Rheumatoid Arthritis
- Seropositive
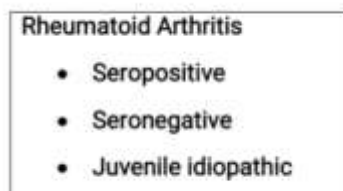- Seronegative
- Juvenile idiopathic

Figure 3: Types of Rheumatoid Arthritis

[3].Causes of Rheumatoid Arthritis

Rheumatoid Arthritis is a chronic condition in which body attacks itself due to lack of immunity that is autoimmunity. So If you have rheumatoid arthritis, your immune system mistakenly sends antibodies to the lining of your joints, where they attack the tissue surrounding the joint. That is the approach used in the diagnosis of the disease. There are several theories about the causes of the RA but not proven but there are some risk factors which may increase the risk of having the RA which are as follows: -

- Genes – According to some evidence, RA can be inherited from the family but with low chances because genes only play a small role in the rheumatoid Arthritis.
- Hormones – Women are more like to get rheumatoid arthritis as compare to the men; it definitely shows that hormones somehow play a role in the RA.
- Smoking – Those who do smoke are at high risk of getting infected with rheumatoid Arthritis that is the reason why doctor advice to avoid alcohol and smoking.

[4].Pathogenesis of RA

There are two major subtypes of RA according to the presence or absence of anti-citrullinated protein antibodies (ACPAs). ACPAs can be detected in approximately 67% of RA patients and serve as a useful diagnostic reference for patients with early, undifferentiated arthritis [18,19]. The ACPA-positive subset of RA has a more aggressive clinical phenotype compared to ACPA-negative subset of RA [20]. The disease defined Based on validated scales which are obtained from the tender joint count, swollen joint count, global patient assessment, physician global assessment, and/or maker of inflammation which are as follows: -

- Simplified disease activity (SDAI) index: tender joint count, swollen joint count, patient global assessment, physician global assessment and c reactive protein in mg/dl.
- Clinical disease activity index (CDAI): tender joint count, swollen joint count, patient global assessment, physician global assessment

- DAS-Crp (disease activity score): tender joint count, swollen joint count, patient global assessment, and c reactive protein in mg/dl [23].

II. TREATMENT OF RHEUMATOID ARTHRITIS

Pharmacologic treatments of RA include NSAIDs, glucocorticoids, DMARDs, and biological agents [15]. There is no cure for this autoimmune disease, rather, symptoms are addressed on an individual basis. The goals of treatment for RA are to reduce joint inflammation and pain, maximize joint function, and prevent joint destruction and deformity. The treatment consists of Combinations of pharmaceuticals, weight-bearing exercise, educating patients about the disease, and rest. The treatment is customized according to the patient based on some factors like disease progression, the joints involved, age, overall health, occupation, compliance, and education about the disease [24].

NSAIDs- First Line Management Thus first line management is used to relieve pain and Reduce inflammation by using the drugs with anti-inflammatory properties. Such drugs are known as NSAIDs- nonsteroidal anti-inflammatory drugs and some examples of such drugs are shown in [Table 1]. First line management involves NSAIDs and Corticosteroids. Corticosteroids are a more potent anti-inflammatory medication than NSAIDs, but they come with greater side effects. Intra-articular injections of corticosteroids can be used for the local symptoms of inflammation [25].

DMARDs- Second Line Management The goal of second line management is to slowing or stopping the progression of joint destruction and deformity. Disease-modifying antirheumatic drugs (DMARDs) can also reduce the risk of developing lymphoma that can be associated with RA [26]. Over the last 20 years, the effectiveness of DMARDs has gained much attention as these can efficiently attenuate disease activity and substantially decrease and/or delay joint deformity[17]. Some examples of DMARDs are shown in the [Table: 1].

Types of Drugs	Drugs Function	Drugs Names
Anti inflammatory	Reduce inflammation	Ibuprofen (Advil, Motrin IB) and naproxen (Aleve, Naprosyn)
Corticosteroid	reduce	Prednisone

	inflammation and pain	(Deltasone, Sterapred, Liquid Pred) hydrocortisone (Cortef, A-Hydrocort) prednisolone.
Anti rheumatic or DMARDs	Slow the progression of the disease	hydroxychloroquine sulfate,leflunomide, methotrexate etc
Biological response modifiers	target specific parts of your immune system to stop inflammation	Abatacept, adalimubab, anakinra etc

Table 1: Drugs for Rheumatoid Arthritis treatment

III. ROLE OF CHEMICAL COMPOUNDS IN THE RHEUMATOID ARTHRITIS TREATMENT

1. Dihydrohelenalin

Helenalin can be found in several plants such as Arnica montana and Arnica chamissonis subsp. Foliosa. Helenalin possesses some in vitro anti-inflammatory and anti-neoplastic effects. Helenalin has a variety of observed effects in vitro including anti-inflammatory and antitumour activities [28]. Helenalin has been shown to selectively inhibit the transcription factor NF-κB, which plays a key role in regulating immune response, through a unique mechanism [29,31,32,]. Due to their anti-inflammatory properties this can be potentially use in the in vivo and in vitro study for the development of drugs against the rheumatoid Arthritis treatment if proper research held on.

2. Sulfonamides

Sulfonamides are the functional group basis of various drugs. Sulfasalazine, in addition to its use as an antibiotic, is also used in the treatment of inflammatory bowel disease[30]. It is also a sulfonamides derivatives and it shows the anti-inflammatory action in the treatment of bowel disease. In this way this compound can be used in the computational studies against the rheumatoid Arthritis.

3. Thiophenes

Thiophenes are important heterocyclic compounds that are widely used as building blocks in many agrochemicals and pharmaceuticals[27]. The benzene ring of a biologically active compound may often be replaced by a thiophene without loss of activity[33]. This is seen in examples such as the NSAID lornoxicam, the thiopheneanalog of piroxicam, and sufentanil, the thiopheneanalog of fentanyl.
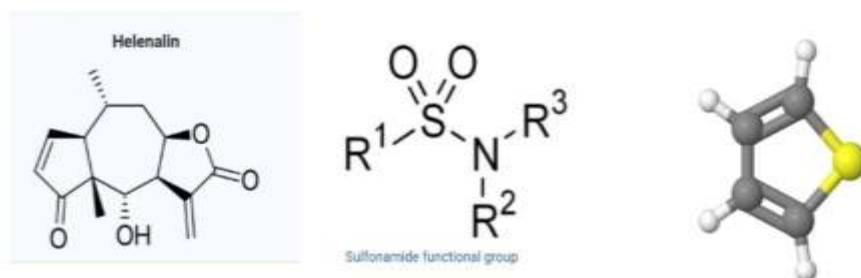
Figure 5: Structure of helenalin, Sulfonamide and Thiophenes

Protein Tyrosine Phosphatase (PTPs)

In RA, these cells aggressively invade the extracellular matrix, producing cartilage-degrading proteases and inflammatory cytokines. The behaviour of FLS is controlled by multiple interconnected signal transduction pathways involving reversible phosphorylation of proteins on tyrosine residues [34]. Fibroblast Like Synoviocytes (FLS) plays an important role in the mediating the action of inflammation and joint destruction in the body of RA patient. The FLS cells enter through the extracellular matrix which further produce cartilage degrading proteases and inflammatory cytokines [35]. The behaviour of FLS is controlled by multiple interconnected signal transduction pathways involving reversible phosphorylation of proteins on tyrosine residues.

If we use the PTPs as a target protein and use the Dihydrohelenalin, sulfonamides and Thiophenes as Ligands. With the help of tools and software of molecular docking we can find the potential protein-ligand complex for the development of drug for the Rheumatoid Arthritis treatment.

IV. CONCLUSION

In this study, Rheumatoid Arthritis disease which is a chronic and autoimmune disorder found in the people of age group 20-40 years old has been discussed in detail. But according to a study woman are more likely to affected by this disorder as compared to the men. The cause of this disorder is not still proven even though they have many theories about their causes. The treatment is a combination of one or two methods like drugs and exercises and physiotherapy also. We need drugs with the property of anti-inflammatory and anti-rheumatic to deal with the rheumatoid treatment. It can be concluded that the Dihydrohelenalin,

sulfonamides and Thiophenes can be used in the further study for the drugs for the rheumatoid treatment. In future, this can be prove potentially helpful in the treatment of RA after the getting in vitro and in vivo research.

REFERENCES

[1]. Du Montcel S.T., Michou L., Petit-Teixeira E., Osorio J., Lemaire I., Lasbleiz S., Pierlot C., Quillet P., Bardin T., Prum B., et al. New classification of HLA-DRB1 alleles supports the shared epitope hypothesis of rheumatoid arthritis susceptibility. Arthritis Rheumatol. 2005;52:1063–1068. Doi: 10.1002/art.20989. [PubMed] [CrossRef] [Google Scholar]

[2]. Fugger L., Svejgaard A. Association of MHC and rheumatoid arthritis. HLA-DR4 and rheumatoid arthritis: Studies in mice and men. Arthritis Res. 2000;2:208–211. Doi: 10.1186/ar89. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[3]. Makrygiannakis D., Hermansson M., Ulfgren A.K., Nicholas A.P., Zendman A.J., Eklund A., Grunewald J., Skold C.M., Klareskog L., Catrina A.I. Smoking increases peptidylarginine deiminase 2 enzyme expression in human lungs and increases citrullination in BAL cells. Ann. Rheum. Dis. 2008;67:1488–1492. Doi: 10.1136/ard.2007.075192. [PubMed] [CrossRef] [Google Scholar]

[4]. Snir O., Widhe M., von Spee C., Lindberg J., Padyukov L., Lundberg K., Engstrom A., Venables P.J., Lundeberg J., Holmdahl R., et al. Multiple antibody reactivities to citrullinated antigens in sera from patients with rheumatoid arthritis: Association with HLA-DRB1 alleles. Ann. Rheum. Dis.

2009;68:736–743. Doi: 10.1136/ard.2008.091355. [PubMed] [CrossRef] [Google Scholar]

[5]. Van der Helm-van Mil A.H., Verpoort K.N., Breedveld F.C., Huizinga T.W., Toes R.E., de Vries R.R. The HLA-DRB1 shared epitope alleles are primarily a risk factor for anti-cyclic citrullinated peptide antibodies and are not an independent risk factor for development of rheumatoid arthritis. Arthritis Rheumatol. 2006;54:1117–1121. Doi: 10.1002/art.21739. [PubMed] [CrossRef] [Google Scholar]

[6]. Alamanos Y., Drosos A.A. Epidemiology of adult rheumatoid arthritis. Autoimmun. Rev. 2005;4:130–136. Doi: 10.1016/j.autrev.2004.09.002. [PubMed] [CrossRef] [Google Scholar]

[7]. Crowson C.S., Matteson E.L., Myasoedova E., Michet C.J., Ernste F.C., Warrington K.J., Davis J.M., III, Hunder G.G., Therneau T.M., Gabriel S.E. The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. Arthritis Rheumatol. 2011;63:633–639. Doi: 10.1002/art.30155. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[8]. Helmick C.G., Felson D.T., Lawrence R.C., Gabriel S., Hirsch R., Kwoh C.K., Liang M.H., Kremers H.M., Mayes M.D., Merkel P.A., et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheumatol. 2008;58:15–25. Doi: 10.1002/art.23177. [PubMed] [CrossRef] [Google Scholar]

[9]. Silman A.J., Pearson J.E. Epidemiology and genetics of rheumatoid arthritis. Arthritis Res. 2002;4:S265–S272. Doi: 10.1186/ar578. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[10]. Symmons D., Turner G., Webb R., Asten P., Barrett E., Lunt M., Scott D., Silman A. The prevalence of rheumatoid arthritis in the United Kingdom: New estimates for a new century. Rheumatology. 2002;41:793–800. Doi: 10.1093/rheumatology/41.7.793. [PubMed] [CrossRef] [Google Scholar

[11]. Harris E.D., Jr. Rheumatoid arthritis. Pathophysiology and implications for therapy. N. Engl. J. Med. 1990;322:1277–1289. [PubMed] [Google Scholar]

[12]. Eberhardt K., Johnson P.M., Rydgren L. The occurrence and significance of hand deformities in early rheumatoid arthritis. Br.

J. Rheumatol. 1991;30:211–213. Doi: 10.1093/rheumatology/30.3.211. [PubMed] [CrossRef] [Google Scholar]

[13]. Gavrila B.I., Ciofu C., Stoica V. Biomarkers in Rheumatoid Arthritis, what is new? J. Med. Life. 2016;9:144–148. [PMC free article] [PubMed] [Google Scholar]

[14]. Chun-Lai T., Murad S., Erlandsson M.C., Hussein H., Sulaiman W., Dhaliwal J.S., Bokarewa M.I. Recognizing rheumatoid arthritis: Oncoproteinsurvivin opens new possibilities: A population-based case-control study. Medicine. 2015;94:e468. Doi: 10.1097/MD.0000000000000468. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[15]. Treatment of rheumatoid arthritis Angelo Gaffo et al. Am J Health Syst Pharm. 2006. https://doi.org/10.2146/ajhp050514

[16]. https://www.rheumatologyadvisor.com/home/rheumatoid-arthritis-advisor/rheumatoid-arthritis-mortality-rate-declining-but-still-prevalent/

[17]. Grennan DM, Gray J, Loudon J, Fear S. Methotrexate and early postoperative complications in patients with rheumatoid arthritis undergoing elective orthopaedic surgery. Ann. Rheum. Dis. 2001;60:214–217. [PMC free article] [PubMed] [Google Scholar]

[18]. Nishimura K, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann. Intern. Med. 2007;146:797–808. [PubMed] [Google Scholar]

[19]. Bizzaro N, et al. Anti-cyclic citrullinated peptide antibody titer predicts time to rheumatoid arthritis onset in patients with undifferentiated arthritis: results from a 2-year prospective study. Arthritis Res. Ther. 2013;15:R16. [PMC free article] [PubMed] [Google Scholar]

[20]. Malmstrom V, Catrina AI, Klareskog L. The immunopathogenesis of seropositive rheumatoid arthritis: from triggering to targeting. Nat. Rev. Immunol. 2017;17:60–75. [PubMed] [Google Scholar]

[21]. Schiff MH, et al. Long-term experience with etanercept in the treatment of rheumatoid arthritis in elderly and younger patients: patient-reported outcomes from multiple controlled and open-label extension studies. Drugs Aging. 2006;23:167–178. [PubMed] [Google Scholar]

[22]. Kuo CF, et al. Familial aggregation of rheumatoid arthritis and co-aggregation of autoimmune diseases in affected families: a nationwide population-based study. Rheumatology. 2017;56:928–933. [PMC free article] [PubMed] [Google Scholar]

[23]. Rheumatoid Arthritis Chauhan K, Jandu JS, Goyal A, et al.

[24]. Staheli LT. Lower extremity management. In: Staheli LT, Hall JG, Jaffe KM, Paholke DO, editors. Arthrogryposis: A Text Atlas. Cambridge: Cambridge University Press; 1998. Pp. Pp. 55–73. [Google Scholar]

[25]. Combe B, Landewe R, Daien CI, Hua C, Aletaha D, Álvaro-Gracia JM, et al. 2016 update of the EULAR recommendations for the management of early arthritis. Ann Rheum Dis. 2017 Jun;76((6)):948–59. [PubMed] [Google Scholar]

[26]. Smolen JS, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis. 2010 Jun;69((6)):964–75. [PMC free article] [PubMed] [Google Scholar]

[27]. Swanston, Jonathan (2006). "Thiophene". Ullmann's Encyclopedia of Industrial Chemistry. Weinheim: Wiley-VCH. Doi:10.1002/14356007.a26_793.pub2. ISBN 3527306730..

[28]. Powis G, Gallegos A, Abraham RT, Ashendel CL, Zalkow LH, Grindey GB, Bonjouklian R (1994). "Increased intracellular Ca2+ signaling caused by the antitumor agent helenalin and its analogues". Cancer Chemotherapy and Pharmacology. 34 (4): 344–50. Doi:10.1007/BF00686043. PMID 8033301. S2CID 22818483.

[29]. Tornhamre, Susanne; Schmidt, Thomas J.; Näsman-Glaser, Barbro; Ericsson, Inger; Lindgren, Jan Åke (2001). "Inhibitory effects of helenalin and related compounds on 5-lipoxygenase and leukotriene C 4 synthase in human blood cells". Biochemical Pharmacology. 62 (7): 903–911. Doi:10.1016/S0006-2952(01)00729-8. PMID 11543725.

[30]. Lackie, John (2010). A Dictionary of Biomedicine. Oxford University Press. P. 543. ISBN 978-0199549351.

[31]. Huang PR, Yeh YM, Wang TC (September 2005). "Potent inhibition of human telomerase by helenalin". Cancer Letters. 227 (2): 169–74. Doi:10.1016/j.canlet.2004.11.045. PMID 16112419.

[32]. Hall IH, Starnes CO, Lee KH, Waddell TG (May 1980). "Mode of action of sesquiterpene lactones as anti-inflammatory agents". Journal of Pharmaceutical Sciences. 69 (5): 537–43. Doi:10.1002/jps.2600690516. PMID 6247478

[33]. Daniel Lednicer (1999). The Organic Chemistry of Drug Synthesis. 6. New York: Wiley Interscience. P. 187. ISBN 0-471-24510-0.

[34]. Protein tyrosine phosphatase expression profile of rheumatoid arthritis fibroblast-like synoviocytes: a novel role of SH2 domain-containing phosphatase 2 as a modulator of invasion and survival M Stanford et al. Arthritis Rheum. 2013 May. PMCID: PMC3636201DOI: 10.1002/art.37872

[35]. Protein tyrosine phosphatase expression profile of rheumatoid arthritis fibroblast-like synoviocytes: a novel role of SH2 domain-containing phosphatase 2 as a modulator of invasion and survivalStephanie M Stanford et al. Arthritis Rheum. 2013 May. PMCID: PMC3636201DOI: 10.1002/art.37872