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Combination of DMARD & Glucocorticoids along with phytocompounds uses in the treament of Rheumatoid Arthritis

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A B S T R A C T

Rheumatoid arthritis (RA) is a very heterogeneous disease, the outcome of which is difficult to predict. The vast majority of the patients will have disease progression with bone erosions and cartilage breakdown resulting in joint destruction, functional impairment, and increased mortality. The management of RA to prevent and control disease progression has changed considerably in the past few years.. This review examines data on the risks for serious infections and other key infections of interest for the major classes of agents in use for RA: glucocorticoids, conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs), & phytochemicals which originate from herbs or plants, have been used in the clinical treatment of rheumatoid arthritis (RA) for many years.

Keywords: Rheumatoid arthritis, glucocorticoids, phytochemicals, immunosuppressive

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease, characterised by synovial hyperplasia, inflammatory cell infiltration, pannus formation and destruction of articular cartilage and bone matrix [1]. It is one of the most common and disabling forms of osteoarthritis. It is mainly manifested by redness, swelling, a hot sensation, pain, and other symptoms of the small joints of the extremities. The lesions develop symmetrically and destructively, which may eventually lead to joint deformity and loss of function, and can even affect the heart, lungs and nervous system [2]. In most developed countries, RA affects 0.3–1.0% of the adult population. At present, steroidal, non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying anti-rheumatic drugs (DMARDs), glucocorticoids, bacterial therapy and targeted treatment are used to relieve pain and control the disease [3]. Several genetic and environmental (microbiota, smoking, infectious agents) factors contribute to its pathogenesis. Although convention treatment strategies, predominantly Disease Modifying Anti Rheumatic Drugs (DMARDs) and Glucocorticoids (GC), are unchanged as the primary line of treatment; novel strategies consisting of biological DMARDs, are being developed and explored. Personalized approaches using biologicals target specific pathways associated with disease progression [4]. Currently, disease-modifying anti-rheumatic drugs (DMARDs) are the most commonly used drug for RA in clinic practices, including conventional synthetic DMARDs (csDMARDs), biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) [5]. Methotrexate, the representative of csDMARDs, is a cornerstone of treatment for RA; however, its clinical application is limited by slow onset and serious side-effects such as myelosuppression, nephrotoxicity and hepatotoxicity [6]. Biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) have a prompt and excellent effect on inhibiting inflammatory response, but potential risk of infections still exists [7]. Therefore, it is urgently necessary to discover more effective and safer drugs for treatment of RA [9]. Patients with severe joint involvement may suffer disability, and may even require joint repair or replacement [10].

The phytochemicals can form an alternative source to relieve symptoms in patients having RA as well as to the drawbacks associated with present treatment methods with synthetic drugs [10].

Epidemiology

The incidence of RA is approximately 1% to 2% of the world's population (about 60-120 million individuals) and 1% of the US population. Women are affected 3 times more commonly than men are. The disease can occur at any age but typically begins between the ages of 30 and 50 years. The severity of disease ranges from a self-limiting illness to a chronic, progressive disease causing joint destruction and deformity. Extra articular manifestations such as malaise and fatigue are common. With the advent of more effective therapies, less frequent extra articular manifestations such as pleurisy, pericarditis, episcleritis, vasculitis, and rheumatoid nodules have become rare. Total life span can be reduced by 3 to 18 years.3 In the United States the cost of medical care averages $5919 per case per year [11].

Sign & symptoms

These symptoms are RA:

- Joint pain, tenderness, swelling or stiffness that lasts for six weeks or longer.
- Morning stiffness that lasts for 30 minutes or longer.
- More than one joint is affected.
- Small joints (wrists, certain joints in the hands and feet) are typically affected first.
- The same joints on both sides of the body are affected [12].

Treatment of RA

Once RA is diagnosed in a patient, the overall treatment target is to either reach full remission or at least significantly lower disease activity within a span of approximately 6 months in order to prevent joint damage, disability, and systemic manifestations of RA [13, 14].

The importance of prompt and targeted RA treatment is underlined by the fact that 80% of insufficiently treated patients will have misaligned joints and 40% of patients will be unable to work within 10 years of disease onset [13, 15,16].

Currently, the available drug classes include NSAIDs, immunosuppressive glucocorticoids, and DMARDs. Drug treatment is typically supplemented by non-pharmacological treatment which includes physical therapy to sustain joint mobility and patient counselling to slowdown disease progression. Some secondary metabolites of crude drugs of phytochemicals used in the treatment of RA, NSAIDs like for example aspirin, diclofenac, or ibuprofen effectively reduce pain and swelling and improve joint function but are not disease-modifying since they do not prevent additional joint damage [4].

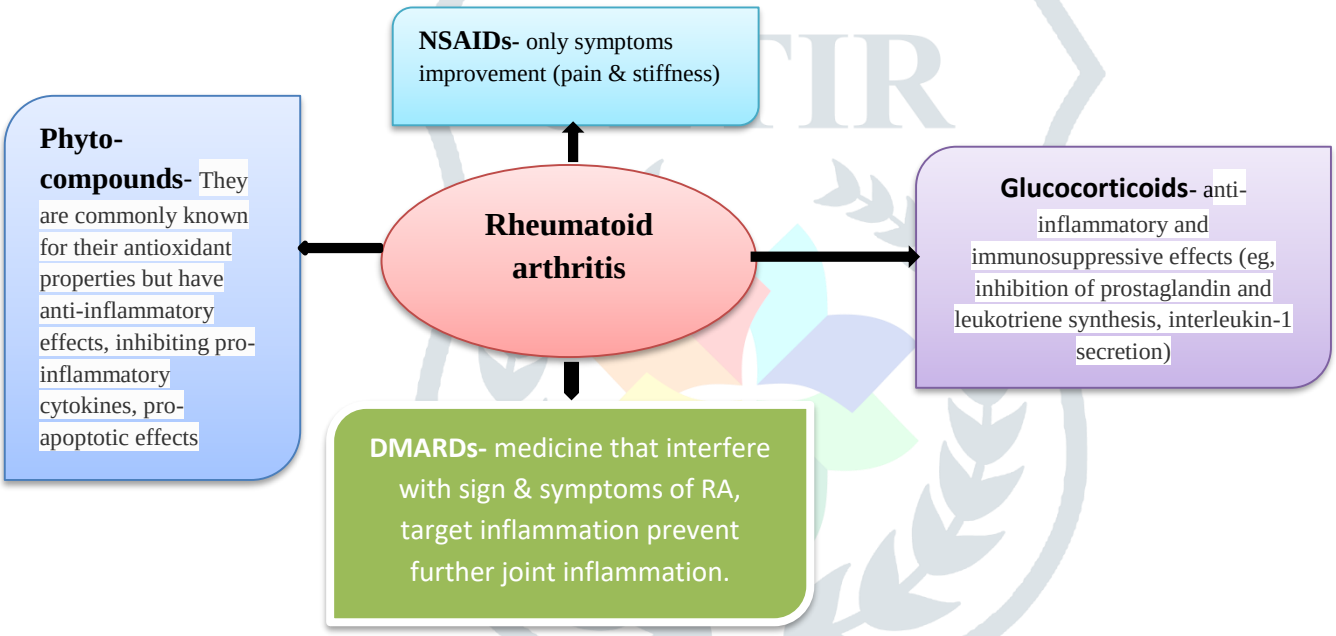
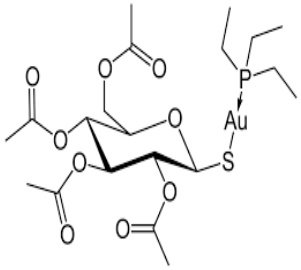
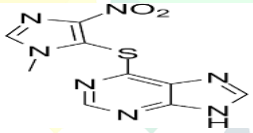
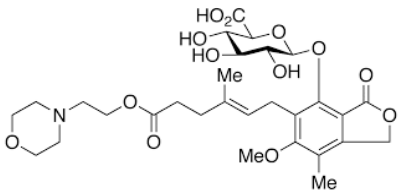
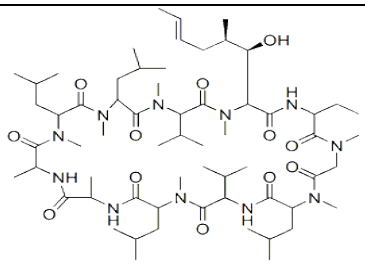
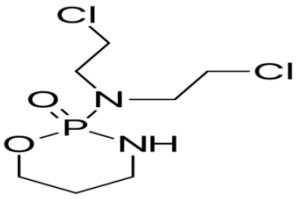
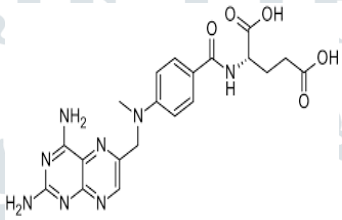
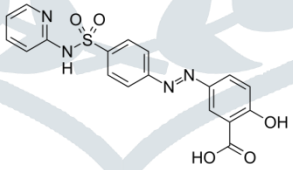
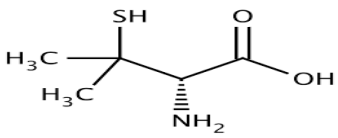
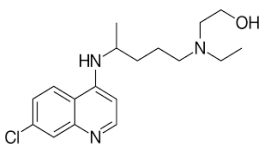
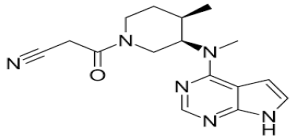
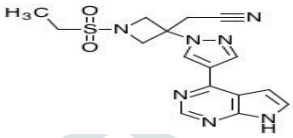


Table1.

DMARD Drug used in RA, its structure & mechanism.

S.N.	Agents	Class	Structure	Mechanism
1.	**Synthetic**	**Gold(Au)**	Auranofine  Na aurothiomalate	Auranofin inhibits activation of the transcription protein complex NF-kB and reduces expression of the inflammatory enzyme COX-2 Production of nitric oxide and the proinflammatory cytokines TNF-a, IL-1b and IL-6 are also reduced also reduce by these agents [17].
		Immunosuppressent	Azathiopurine  Luflunomide Mycophenolate mofetile  Cyclosporine	Azathioprine's active metabolite methyl-thioinosine monophosphate (MeTIMP) block the enzyme amido phosphor ribosyl transferase resulting in the inhibition of purine synthesis essential for the proliferation of T-cells and B-cells [18]. Leflunomide inhibit the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH), require for de novo synthesis of uridine monophosphate (rUMP), thus altering the synthesis of DNA and RNA for the rapidly dividing cells, especially lymphocytes. Its active metabolite Teriflunomide also inhibits several tyrosine kinases [19]. Mycophenolate is a prodrug of mycophenolic acid (MPA) an inhibitor of inosine-50-monophosphate dehydrogenase. MPA depletes guanosine nucleotides in T and B lymphocytes and inhibits their proliferation thereby suppressing cell-mediated immune responses and antibody formation [20]. Cyclosporin inhibits the

			 Cyclophosphamide 	dephosphorylation of nuclear factor of activated T-cells (NFATc) by binding to cytosolic protein (cyclophilin) of the T- cells as result block calcineurin, a protein responsible for dephosphorylation of NFATc under the normal condition [21]. Cyclophosphamide induces beneficial immunomodulatory effects by elimination of T regulatory cells (CD4 + CD25+ T cells) in naive and tumor- bearing hosts, induction of T cell growth factors, such as type I IFNs, enhanced grafting of adoptively transferred, tumor-reactive effector T cells by the creation of an immunologic space[22].
		Alkylating agent(nitrogen mustard)	Methotrexate 	Methotrexate inhibit dihydrofolate reductase (DHFR) but for anti-RA effects this mechanism is not the only mechanism but multiple mechanisms appear to be involved, including- i- Inhibition of enzymes involved in purine metabolism leading to accumulation of adenosine. ii- Inhibiting the activation of T-cells, their expression of intercellular adhesion molecules and increasing the sensitivity of activated T-cells to CD95 (FasR). iii- Selective down-regulation of B cells [23].
		Sulfa-drugs	Sulfasalazine 	Sulfasalazine is thought to work by directly inhibiting IkB kinases a and b resulting in the suppression of NF-kB. Its metabolite, sulfapyridine is also responsible for some of the anti-arthritic effects [24].
		Chelating agent	D-Penicillamine 	Penicillamine works by i- Reducing numbers of T-lymphocytes ii- inhibiting macrophage function and decreasing IL-1 production iii- Decreasing rheumatoid factor iv- Preventing collagen from cross-linking [25].
		Antimalarial drugs	Hydroxychloroqunine 	Hydroxychloroqunine interfere with lysosomal activity and autophagy, interact with the stability of cell membranes, and alter both signaling pathways and transcriptional activity. These processes interact with the production of cytokines and help to modulate co-

	Target	Pan JAK Inhibitor	Tofacitinib 	stimulatory molecules [26]. Tofacitinib inhibits the phosphorylation and activation of JAK, thereby preventing the phosphorylation and activation of STATs, and thus the activation of gene transcription This leads to decreased cytokine production and modulation of the immune response [27].
		JAK 1/2 Inhibitor	Barcitinib 	Baricitinib altered the expression of genes involved in immune pathways, including multiple genes for key cytokines (STAT 1, 2 and 4), cytokine receptors, T cells, regulatory cells and cytokine regulators that are associated with the immune pathogenesis of SLE [28].
	Biologic al	TNF Inhibitors	Infliximab Chimeric mouse/human IgG1 anti-TNF monoclonal antibody [29].	Infliximab inhibits the biological activities of TNF-α include the induction of the cytokines involved in inflammation such as interleukin-1 (IL-1) and IL-6, promotion of leukocyte migration, induction of eosinophil and neutrophil activity, as well as the stimulation of acute-phase reactants and tissue degrading enzymes [30].
			Etanercept Soluble fusion protein of two 75kD TNF receptors each linked to human IgG1 Fc tail [29].	Etanercept acts as a soluble TNF receptor and binds TNF-alpha and TNF-beta [30]. TNF is a cytokine that can bind to TNF receptor 1 (TNFR1) or TNF receptor 2 (TNFR2) and is involved in inflammation and the immune response [31].
			Adalimumab Fully human IgG1 anti-TNF monoclonal antibody [29].	Adalimumab is the first fully human recombinant immunoglobulin G1 monoclonal antibody that binds and neutralizes soluble and membrane-bound tumor necrosis factor (TNF), so that it cannot interact with p55 and p75 cell-surface TNF receptors [32, 33].
			Golimumab Fully human IgG1 anti-TNF monoclonal antibody [29].	Golimumab binds with high affinity to both the soluble and transmembrane bioactive forms of human TNF-α, thereby preventing the binding of TNF-α to its receptors [34].
		IL-6 Inhibitor	Tocilizumab Humanized antibody against membrane-bound and soluble IL6 receptorα (IL6Rα) [29].	Tocilizumab is a novel monoclonal antibody that competitively inhibits the binding of interleukin-6 (IL-6) to its receptor (IL-6R). Inhibiting the entire receptor complex prevents IL-6 signal

		B- cell depletion Inhibitor of T-cell co- stimulation	Sarilumab Fully human monoclonal antibody against membrane bound and soluble IL6Rα [29]. Rituximab Chimeric human/mouse antiCD20 monoclonal antibody [29]. Abatacept Fusion protein of the extracellular domain of human CTLA-4 and human IgG1 Fc tail [29].	transduction to inflammatory mediators that summon B and T cells [35]. Sarilumab is an interleukin-6 (IL-6) receptor antagonist. Sarilumab binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6-mediated signaling through these receptors [36]. The mechanism of action of rituximab in autoimmune disease is thought to be due to disruption in B cells' function in the immune system or a decrease in plasma cell production as CD20+ B cells are intermediates in the process of maturation [37]. Abatacept binds to the costimulatory molecules CD80 and CD86 on antigen-presenting cells (APC), thereby blocking interaction with CD28 on T cells, the prevention of T-cell activation by interfering with signaling via CD28 still represents the main mechanism of action [38, 39].

Table2. Glucocorticoids Drug used in RA, its structure & mechanism.

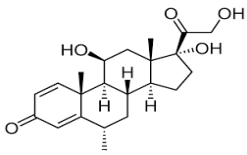
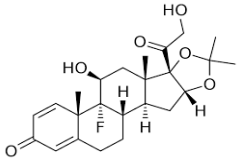
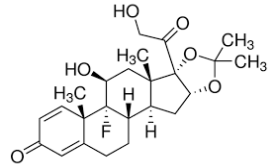
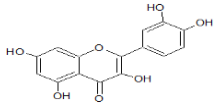
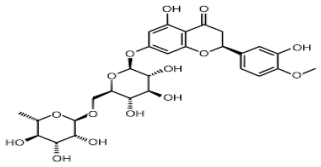
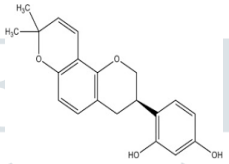
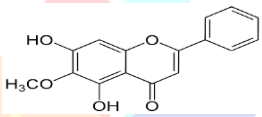
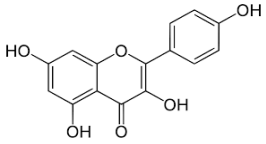
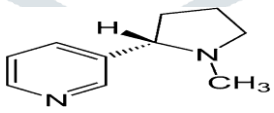
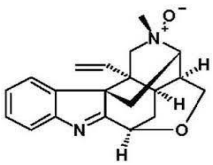
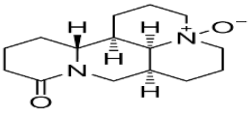
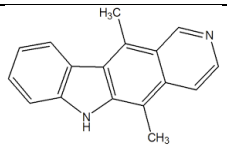
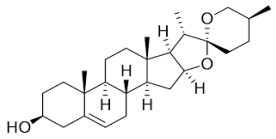
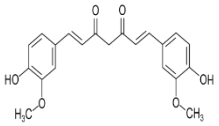
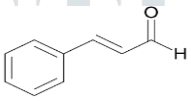
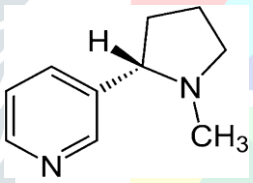
S.N.	Agents	Class	Structure	Mechanism
1.	**Glucocorticoids**	glucocorticoid	Methyl Prednisolone  Prednisolone Triamcinolone acetonide  Triamcinolone hexa acetonide 	Methylprednisolone diffuses passively across the cellular membrane and binds to the intracellular glucocorticoid receptor. This complex translocates into the nucleus, where it interacts with specific DNA sequences, resulting in either enhancement or suppression of transcription of particular genes [40, 41, 42]. Triamcinolone acetonide inhibit phospholipase A2 on cell membranes, preventing the breakdown of lysosomal membranes of leukocytes, which in turn prevent the formation of arachidonic acid [43, 44, 45, 46, 47].

Table.3 Phytocompounds used in RA, its structure & mechanism.

S.N.	Agents	Class	Structure	Mechanism
1.	Phytocompounds	Flavonoids	Quercetine 	Decreased expression of IL-17 A, IL-21, and TNF-α. Decreased migration of Th17 lymphocytes. Increased expression of IL-10 [48].
			Hespiridine 	Decreased expression of TNF-α. Decreased osteoclastogenesis [49].
			Liquiritin 	liquiritin significantly inhibits the expression of IL-6 and IL-8 via inhibition of JNK, p38 MAPK, AP-1, AMPK and NF-κB signaling in IL-1β-induced SW982 cells [50].
			Oroxylin A 	OA decreased the secretion of IL-1β and IL-6 from TNFα-stimulated RA FLS in a dose-dependent manner. TNFα-induced p38 MAPK, ERK1/2 and NF-κB signaling pathways were suppressed by OA [51]
			Kaempferol 	kaempferol dramatically suppressed tumor necrosis factor (TNF)-α-induced MAPK activation without affecting the expression of TNF-α receptors [52].
		Alkaloids	Nicotine 	Nicotine reduced the levels of IL-17A and RORc, induced the phosphorylation of ERK1/2[53].
			Koumine 	KM blocked apoptosis-associated speck-like protein containing a CARD (ASC) speck formation and its oligomerization and hampered the NLRP3-ASC interaction [54].
			Oxymatrine 	Oxymatrine has the ability to regulate lymphocytes cellular response, decreasing the population of circulating Th17 lymphocytes and increasing the population of regulatory T lymphocytes [55].
			Ellipticine	Ellipticine inhibits the proliferation of fibroblast-like synoviocytes in a dose-dependent manner [56].

				
		Saponins Terpenes	Hecogenin  Curcumin  Cinnamaldehyde  β-Elemene 	It inhibits the migration of fibroblast-like synoviocytes and stimulating cell apoptosis by increasing the expression of caspases 3, 8, and 9 [57]. Curcumin from CLR can reduce Complete Freund's Adjuvant (CFA)-induced glial cell and inflammatory mediator levels IL-1_, monocyte chemotactic protein-1 (MCP-1), and monocyte inflammatory protein in the spinal cord-1 (MIP-1) [58,59,60]. CA is a potential therapeutic compound that can inhibit RA progression by suppressing IL-1β by modulating the succinate/HIF-1α axis and inhibiting NLRP3 [61]. β-Elemene effectively induces mitochondrial apoptosis in fibroblast-like synoviocytes, and this effect is mediated via induction of ROS formation and p38 mitogen-activated protein kinase (MAPK) activation [62].

Conclusion

Combination of DMARD, Glucocorticoids & Phyto-compounds used in the treatment RA, produces mixed results: some cause undesirable side effects, while others can worsen the disease. Even a low-occurring side effect needs to be carefully considered against the drug's therapeutic potential. DMARDs drugs that not guarantee complete relief in RA cases. Phyto-compounds from plants can delay or improve RA due to its antioxidant, anti-inflammatory, immunomodulatory, and enzymatic effects. These secondary metabolites can that minimize the disease & alternative to the development of therapies capable of improving life quality in patients affected by RA. In this review, we summarized phyto-compounds isolated from plants DMARDs & Glucocorticoids that have therapeutic effects on RA models in vitro and in vivo. The mechanisms of action of these compounds in RA treatment mainly include anti-inflammatory, immunomodulatory, antioxidant activities. Most of the compounds possess good drug-like properties, valuable for further research.

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