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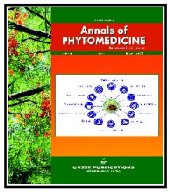

Review article: Open access

Fundamental of a comparative treatment in rheumatoid arthritis: A brief review

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Abstract

Rheumatoid arthritis (RA) is a debilitating chronic systemic autoimmune inflammatory disease, a long term condition and affects 1-3% of population worldwide that causes severe pain, inflamed bone erosion, unsteadiness, stiffness in the joints and deformity. It gradually deteriorates over the course of many years. The exact causes of RA are still unknown but genes, environmental factor, hormone, obesity, smoking; age may be involved in autoimmune development and progression. Pathophysiology of RA is usually due to synovial membrane inflammation, chemokine involvement leading to swollen joints. In the early hours, diagnosis and management can help to prevent damage to the joints. To understand the recent advances in physiology of RA, several biologics DMARDS include TNF-inhibitor, anti-CD20 antibody, IL-6 receptor antibody are implemented in current therapies and these advances are based on disease modifying therapy that includes with a goal where drug should reach targeted site and focused on pain relieving. Therapies are normally personalized with patients need including their general well-being. This review provides a modern appraisal from current literature on different RA treatment regimes.

1. Introduction

Rheumatoid arthritis (RA) is arising inflammatory asymptomatic disease, responsible for large amount of disability and morbidity. The second most common arthritis that affect world, the annual incidence of RA is approximately 1%. RA initially affects symmetric polyarticular swelling of synovial, often tiny junction like hands, wrists including feet and could influence interior organs so give rise to everlasting disorder in numerous cases. The inflammation result in pain, stiffness and swelling causes disability and erosion of bone (Michelle *et al*., 2011). The onset of disease usually affects 35-60 years adult, with repeal and aggravation. In youngster, prior to age of 16 years referred to as juvenile RA, where rheumatoid arthritis factor is not detected. RA is a chronic syndrome that is progressive and destructive as compared to osteoarthritis (Bullock *et al*., 2018).

The design of therapy for RA exist to lower articulation swelling as well as affliction, maximize intersection role and stop joint demolition including disproportion therapy regimen consist of combination of medication, aerobics, teach victim regarding diseases, natural medication as well as recline. Therapies are normally personalized with patients need including their general well being (Najm, 2016).

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This review provides a modern appraisal from current literature on different RA treatment regimes.

1.1 History

The word “Rheumatoid arthritis” is derived from Greek‘Rheum’ meaning that which flows and suffix ‘oid’ meaning like (Pouya Entezami *et al*., 2011). The earliest illustration of rheumatoid arthritis own before contemporary therapeutics established within thesis of Augustine Jacob Lander Beauvais from year 1800 and serve handful of cases with harsh rheumatism that are disqualified by other maladies to describe at the time such as “Rheumatism” or “osteoarthritis” Lawrence and Parish, (1963: Staff, 2012).

Alfred Garrod during 19th century is earliest to discriminate gout from additional arthritis. Archibald Garrod 4th son of Alfred Garrod over 1890, he authored a volume’ treatise and rheumatoid arthritis ‘and coined phrase RA (Lawrence and Parish, 1963).

1.2 Etiology

The exact causes of RA are still unknown but genes, environmental factor, hormone, obesity, smoking; age may be involved in autoimmune development and progression. Certain factors such as genetic especially human leukocyte antigen (HLA) class 2 genotype patients who are seropositive for anticitrullinated protein antibodies (ACPASs) or rheumatoid factor (RF) also have increased the risk of rheumatoid arthritis (Sana Bal, 2019).

Rheumatoid arthritis is conditions which involve 150 diseases usually progressive and relate with discomfort. Due to abnormality in cellular and humoral immunity leads to occurrence of antibodies like RF, ACPAS’s, AMPA (anti-modified protein antibodies), a CarP

(carbamylation), AAPA (acetylation) and also immigration of T and B-lymphocytes into synovium (Vander and Houwig, 2009).

The genome sequence such as protein tyrosine phosphate, non-receptor type 22(PTPN22), increases risk for development of type-1 diabetics, RA and systemic lupus erythematous (Hammer, 1995). This is characterized by HLA-DRB1 alleles (especially DR4 and DR1) that have 5 amino acid shared moti (QKRAA, QRRAA or RRRAA in positions 70-74 of DRB1 chain) which is encoded with positively charged P4 motif that known as shared epitope (Gregersen *et al*, 1987), HLA connect with 3 amino acid in beta chain of HLA-DR (11, 71 and 74), *i.e.*, one in HLA-B and one in beta chain HLA-DPB1 are associate with RA (Raychaudhuri, 2012). The self-protein like P4 when modified, they interact with RF, ACPA and anti-CarbP antibodies reinforce T-cell activation leads to epitope spreading finally leads to clinical disease (Tarcsa *et al.*, 1996).

1.3 Epidemiology

Epidemiology studies (www.who.int/chp/topics/rheumatic) suggest that rheumatism arise as long term intrinsic immunity disorders, stand up incessant in women than men (Qiang *et al.*, 2018). The prevalence of rheumatism is 0.5%-1% in female and male. In age 30 to 60 lies in ratio of 3:1, *i.e.*, 4 to 5 times high cases found in women less than 50 years but the ratio becomes approximately 2 to 1 after 60 years (Intriogo *et al.*, 2019) Therefore, the life time risk development of RA is 3.6% in women and 1.7% in men (Cynthia *et al.*, 2011). Lupus erythematous is about 1-10th common rheumatoid arthritis and common in especially in child bearing age (Inge-Margretne *et al.*, 2018). Lumbar vertebrae producing nerve irritation and ligamentous train result in low back pain affect commonly middle age men (Bao and Dai, 2011).

2. Plant natural products used in RA

Globally, plant based medicines are used for treatment of RA and achieved acceptance by wide-reaching capacity. Herbal products control inflammation through various pathway such as anti-inflammatory mediator (IL-4 and IL-10), osteo-immune cross talk (bone is bidirectional) and treg balance (essential for immunological tolerance).

Trpterygium wilfordii Hook F (TwHF) extract leads to suppression of COX-2 and reduces production of prostaglandin E2 (Tao *et al.*, 1998) (Guo W *et al.*, 2001). It targets the iNOS gene, *i.e.*, inducible nitric oxide synthetase and increase blocks the production of nitric oxide (Makrygiannakis, 2008). In synovial fibroblast of human, TwHF augmenting tissue inhibitor of metalloproteinase (TIMPs) and block MMP1&2, further blocks MMP 3. It suppresses numerous cytokine (TNFα) from T cells. TwHF conquer T/B unit boost and synovial fibroblast extension also induce T cell death.

Curcuma longa is an Indian indigenous plant, curcumin a secondary metabolite potent bioactive molecule possess broad range of anti-rheumatoid effect (Zdrojewicz *et al.*, 2017). In recent preclinical trials, curcumin shows effectiveness in treating arthritis by rat model and reduces extent of pro-inflammatory cytokines in serum as well as synovial fluids (Kim, 2008). It regulates COX and lipoxygenase enzyme, blocks various MMP 9 and MMP 13 and inhibit IL-1β, mitogen activated protein kinase (MAPK), peripheral blood mononuclear cell (PBMCs) in RA patient.

Camellia sinesis (green tea) originated in China, widely used in Asia and possesses some anti-rheumatoid effect (Ramadan, 2017; Haqqi *et al.*, 1999). Inducing green tea to AA rats reduced progression of arthritis and serum analysis shows reduced proinflammatory cytokine (TNFα and IL-1β) in rats (Bhumtia Pemba *et al.*, 2015). Epigallocatechin-3-gallate (EGCG), apolyphenol shows multiple inflammatory pathways (Hostetler GL *et al.*, 2017). EGCG can hinder RA with inhibition of IL-6 union and gesturing β-activated kinase (growth factor) in rat models. It shows increase in nuclear factor (Nrf2) and regulates indoleamine-2, 3 dioxegenase (IDO).

Flavanoids have been considered a powerful anti-inflammatory agent (Lee *et al.*, 2009). A surplus film of hexane fragment obtained from *Rhus verniciflua* decreased secretion of TNFα, IL-6, IL-8, MCP-1, VEGF, p-ERK, p-JNK and up regulation of p-p38-MAPK in animal model (Park *et al.*, 2016).

Reservatrol, a natural polyphenol potent antioxidant, antinflammatory agent obtained from stilbenes. *In vitro* studies of reservatrol shows decreased production of TNF-α, IL-1β in monocytes / macrophages (Zou *et al.*, 2013), inhibit T-cell activation; inhibit proliferation of fibroblast like synovicytes and decreased expression of MMP3 (Tian *et al.*, 2013; Masso Gonzalez *et al.*, 2010).

Boswellia serrata is used as ayurvedic medicine which includes chemical constituents like resin, terpinoid and oils. The extracts of this are used to treat chronic inflammatory disease (Kumar *et al.*, 1999). It act by inducing IL-6 which intern synthesis SGPT, SGOT enzymes in body (Chatterjee and Pal, 1984) which has capacity to stabilize lysosomal enzyme activity like alkaline phosphatase (ALP) (Mishra, 2011).

Cinnamomum zeylanicum is a shrub found in Asia, Australia and India. They are well known for non-volatility where essential oils extracted by distillation (Senanayake *et al.*, 1978). Type A-procyanidine polyphenols extracted from cinnamon used *in vitro* in AIA rat model (Anderson *et al.*, 2004). They act on C-reactive protein used in treating RA also found to be non-ulcerogenic and as no analgesic effect (Scott *et al.*, 1994)

Zingiber officinale is a ancient traditional medicine as anti-inflammatory effect and scientifically proved by Kiuchi in 1982 (Kiuchi, 1982). T-cell activity on vascular cellular adhension molecule (VCAM) in venules cause inflamed tissue (Feldmann and Steinman, 2005) where *Zingiber officinale* act by inhibiting prostaglandin and leukotriene biosynthesis catechol group of ginger played vital role which shows activity against 5-lipoxygenase (Thomson *et al.*, 2002).

Artemisia capillaris contains scoparone as major component, extracted using hot water (Barnes and Karin, 1997). When administered orally to mouse induce arachidonic acid and inhibit PGE2, iNOS, COX-2, TNF-α and stimulate macrophage (Kwon, 2011).

Coriandrum sativum (CS) is a perennial herb used in traditional system of medicine to treat RA (Evans, 2006). It is a potent antioxidant used in *in vitro* testing system (Krishnakantha and Lokesh, 1993). The anti-inflammatory activity is not clear whether CS contributes to antiarthritic activity or act as adjuvant for principle drug (Li *et al.*, 2008). Though, it is difficult to see activity of CS, the steroidal compounds present in high concentration in seeds are responsible for antiarthritic effect (Gupta *et al.*, 1980).

Jasminum lanceolarium is a traditional Chinese medicine (Wen *et al*., 2015). The stems and roots are used to treat RA which act by inhibiting membrane hydrolysis of membrane phospholipids which is involved in COX-2 production inhibit PGs (Sengar *et al*., 2015)

Hibiscuss platnifoliu is or species of a flowering tree, found in regions like India and Srilanka. It includes many active principle components like citric, tartaric and oxalic acid, sterol, cholesterol, fructose, glucose, sucrose, *etc*., which shows antiarthritic activity similar to aspirin (Paval *et al*., 2009).

Capsicum annum is a very popular antiarthritic remedy used both among local population and specialists practicing traditional medicine (Meghvansi *et al*., 2010). It interns reduce edema, decreases amount of alpa-1-acid glycoprotein in blood which mainly act by reducing the severity of non-specific inflammation (Setarch *et al*., 2018).

Table 1: Various plants used for the treatment of RA (Himanshu *et al*., 2019)

Plant name	Family	Constituents	Target	Inhibition	Action
Trpterygium wilfordii Hook F.	Celastraceae	Triptolide, Celastrol	iNOS gene	MMP1, MMP2, MMP3	Potent Anti-inflammator
Curcuma Longa	Zingiberaceae	Curcumin, Demethoxy curcumin, Bis demethoxy curcumin	Lipoxygenae enzyme	MMP9, MMP13, MAPK, PBMC's and IL-1β	Antidepressant Antioxidant
Camellia sinesis	Theaceae	Catechin, Epicatechin, Gallic acid	T-lymphocytes TH-17 kinase	IL-6, IL-17 B-activated	Antibacterial, Antiviral activity *in vitro*
Cissampelos pareira	Menispermaceae	Dicentrine, 5-Deoxy-inostiol	TH-1 Phenotype	Macrophage, TNF-α, IL-6, IFN-β	Analgesic, Antidiarrhea
Flavanoids	Zingerberaceae	Flavonol, Anthocyanin	Lipid and Gly-cogen enzyme	PI3K, MAPK, NFκB	Antagonistic effect
Reservatrol	*Bacillus cereus*	Stilbenetriol, Resorcinol, Benzene-1, 3-diol	Oxidative DNA damage	T-cell activation, Nuclear factor-κb ligang	Cardioprotective, Prevent ageing
Alpinia galanga	Zingiberaceae	Galangin, Beta-sitosterol	Human Chonddrocyte	IL-1β,MMP-2, MMP-9	CNS Stimulant, Antimicrobial
Glycyrrhiza glabra	Fabaceae	Glycyrrhizin, Glabridin	COX/TAX-2	Glutathione (GSH) expression	Hepatoprotective, Anticancer, Antiinflammatory
Moringa oleifera	Moringaceae	Kaempferol, Chlorogenic acid, Isothiocyanate	iNOS gene, COX-2	TNF-α,IL-β, IL-6	Regulate enzyme activity, Modulate blood glucose
Piper longum	Piperaceae	Piperine, Chavicine, Piper longuminine	IL-1β stimulated fibroblast	PGE2,IL-6, MMP's	Antimalaria, Antiasthma, Antigonorrhea
Aloe vera	Lillaceae	Barbaloin derivatives and resin	Growth factor	PGE2, Neutrophil	Purgative
Papaver somniferum	Papaveraceae	Morphine, Codeine	Brain and Spinal cord recptor	NFκB, TRPV 1COX-2,PGE2	Analgesic, Narcotic
Catharanthus roseus	Apocynaceae	Vincristine, Vinblastin	Immune cells	Anterograde and Retrograde Axonal transport	Antileukaemic, Anticancer

2.1 Abbreviation

iNOS, Induced Nitric oxide Synthase; MMP-1, Metaloproteinase-1; MMP-2, Metaloproteinase-2; MMP-9,Metaloproteinase-9; MMP-13, Metaloproteinase-13; MAPK, Mitogen Activated Protein Kinase; PBMC's, Peripheral Blood Mononuclear Cell; IL-1β, Interleukin-1β; IL-6, Interleukin-6; IL-17, Interleukin-17; IFN-Ò, Interferon-Ò; PI3K, Phosphatidylinositol-3-kinase; NFκB, Nuclear Factor Kappa-Chain-Enhancer of Activated B-cells; TNF-α, Tumor Necrosis Factor-α; TH-17, Helper cell T-17; COX-2, Cyclooxygenase-2; PGE2, Prostaglandin; VEGF, Vascular Endothelial Growth Factor; TRPV1, Transient Receptor Potential Vanilloid-1.

3. Convential drugs used in RA

Non-steroid anti-inflammatory drugs (NSAID's) help to lower the chronic pain, redness as well as swelling, thereby decreasing pain and improve function. They classified based on individual chemical structure, plasma half-life including cyclooxygenase. Commonly used class of NASID's drugs are acetyl salicylic acid, indomethacin, ketorolac, oxaprozin, ketoprofen, meclofenamate, phenlbutazone,

piroxicam, celecoxin, etoricoxib, lumaricoxib *etc*., are first line therapy. NSAID's based on plasma half-life tend to assemble in junction of joints remain shorter in plasma (Capone *et al*., 2010). Drugs with half-life more than 12 h. increases the plasma levels but remain constant between doses. The second isoform (COX2) is isoenzymes likely be important factor, express induced stimuli and result increased synthesis of PGs in neoplastic tissues. Specific pharmacologic factor associated with NASID's, might affect irregularity related to dose response, plasma half life, enantiomer change, secrete void as well as pharmacodynamics variations.

Today, prednisone is suggested at squat dose in RA and work as substitution therapy (Hinz and Brune, 2007). The exogenous synthetic glucocorticoids exerts a selected action, possess distinct plasma kinetic, metabolism and biologic half-life (mom-genomic at high dose compared to hydrocortisone). In long period, glucocorticoids may hinder with hypothalamus-pituitary-adrenal (HPA) function and effect endogenous cortisol production. In the era 1980-2004, long term glucocorticoid therapy was used, in former decade an ongoing depletion of mean initial low dose from 10.3 to 3.6 mg/day (prednisone) (Pincus *et al*., 2015) was prescribed.

3.1 Non biological disease modifying anti-rheumatoid drugs (DMARDs)

The non biological disease modifying anti-rheumatoid drugs (DMARDs) used in combination with low dose of glucocorticoids recommended for management of RA (Singh *et al*., 2016). In early morning hours, RA symptoms are maximum exaggerated, proinflammatory cytokines is relatively better to treat habitual signs in morning (Cutolo *et al*., 2005; Buttgereit *et al*., 2015). By accurate chronotherapy, many inflammatory pathways relating central nervous system, increase sleep quality and reduce depressive symptoms. Lot of research shows altered liberation of prednisone possesses healthier-efficacy for long term. Low dose glucocorticoid management shows a remarkable cutback in forenoon joint rigidity yet without any auxiliary repression of HPA axis (Hypothalamic-pituitary-adrenal axis) (Buttgereit *et al*., 2010; Atten *et al*., 2015).

3.2 Biological DMARD's

Biological DMARDs are suggested later to find break down after use of one or more standard DMARDs treatment. These are incompetent in mixture with one and all; trials are in progress to assess risk including satisfaction of combination therapy (Statkute and Ruderman, 2010). Biologic DMARDs drugs are infliximab, adulimumab, etanercept, golimumab and cetrolizumab. These biologics are efficient as monotherapy and satisfy in distant reaction and blockage of radiographic progression whether used in coexistence with a methotrexate (Breedveld *et al*., 2006).

Rituximab be illusive anti-CD20 monoclonal antibody used in RA and B-cell non-Hodgkin's lymphoma. In placebo controlled trials of rituximab showed slow radiographic progression with methotrexate after a year of treatment (Furst *et al*., 2007; Kevstone *et al*., 2009). Anakinra has accepted as a second line of therapy, is an IL-1 receptor antagonist is recommended with methotrexate as daily dose and shown improvement in patient function.

Tocilizumab is a recombinant humanized monoclonal antibody that binds to IL-6 receptor. Monthly infusion of tocilizumab refine consequence and standards of patient who meet cut out control of accepted DMARD' or anti-TNF therapy (Emery *et al*., 2008; Old *et al*., 2009).

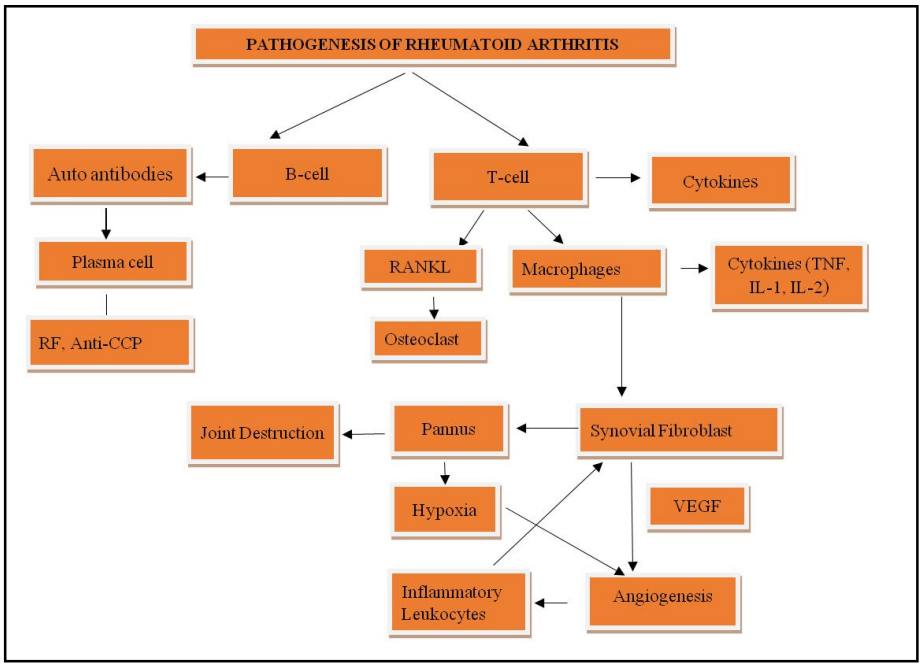
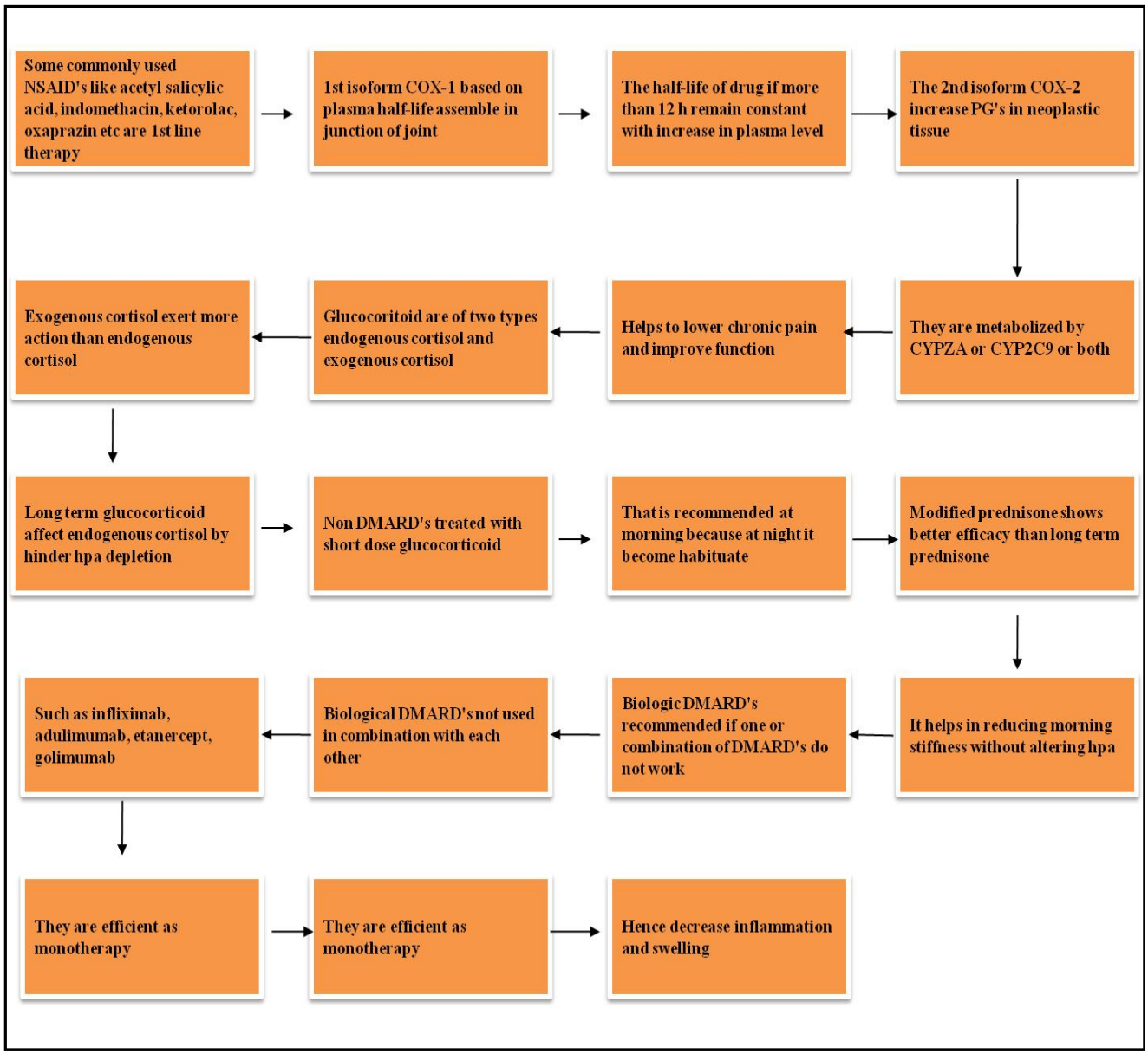


Figure 1: Pathogenis of RA; Inflammation in RA is due to activation of B-cells and T-cells. Activated in synovium leads macrophages activation and pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 cause joint damage this futher leads to increased MMP's production and activates osetoclast. TNF-α, IL-1β and IL-6 due to over production forms pannus which induce state of relative hypoxia and promote angiogenesis thus pannus invade into cartilage and bone leading to joint destruction. Production of vascular endothelial growth factor (VEGF) stimulate angiogenesis that identifies inflammation recruting more inflammatory leukocytes. (Branimir, 2014).



Flow chart 1: Various treatment used in RA.

4. Nanotherapy in RA

Nanotherapy is highly striking as diagnostic agents, the targeted nanocarrier sustained drug delivery system in RA increase solubility of certain drugs and protect them against degradation in circulation, further increase bioavailability and reduce unwanted off-target side effect (Christine, 2011). The anti-inflammatory therapeutics are quite toxic in both inflamed cell and normal cell, however, implementing passive and active targets of anti-inflammatory drugs in to nanoparticles can improve specificity of inflamed cell and tissue (Kapoor *et al*., 2014; Yang *et al* ., 2017). Nanotechnology enables redesign of already effective rheumatologic medications in to nanoformulation that confer better specificity long therapeutic effect and safe profile such as nanoencapsulated NASID's, liposomal and polymeric preparation of glucocorticoids and nanosystem that directly inhibit angiogenesis are considered as nanotherapies (Jasenka, 2019). To improve specificity and efficacy, nanoparticles like micells and liposome mixed with an antibody, peptide or polysaccharide (act on specific receptor) reduce unwanted toxicity and side effect. Nanoparticles permeate through endothelial cell of synovial tissue and retained in extravascular space releases drug slowly, improved permeability and retention (Metselaar *et al*., 2004; Hofkens *et al*., 2011)

Folic acid with albumin nanoparticles used to enhance specific in an *in vitro* model methotrexate with PLGA nanoparticles against macrophage specific receptor CD64 are effective than free drug in treating RA (Moura *et al*., 2014). The folic acid targeted PLGA nanoparticles significantly increase cellular uptake of dexamethasone in activated macrophage and decrease production of proinflamma-

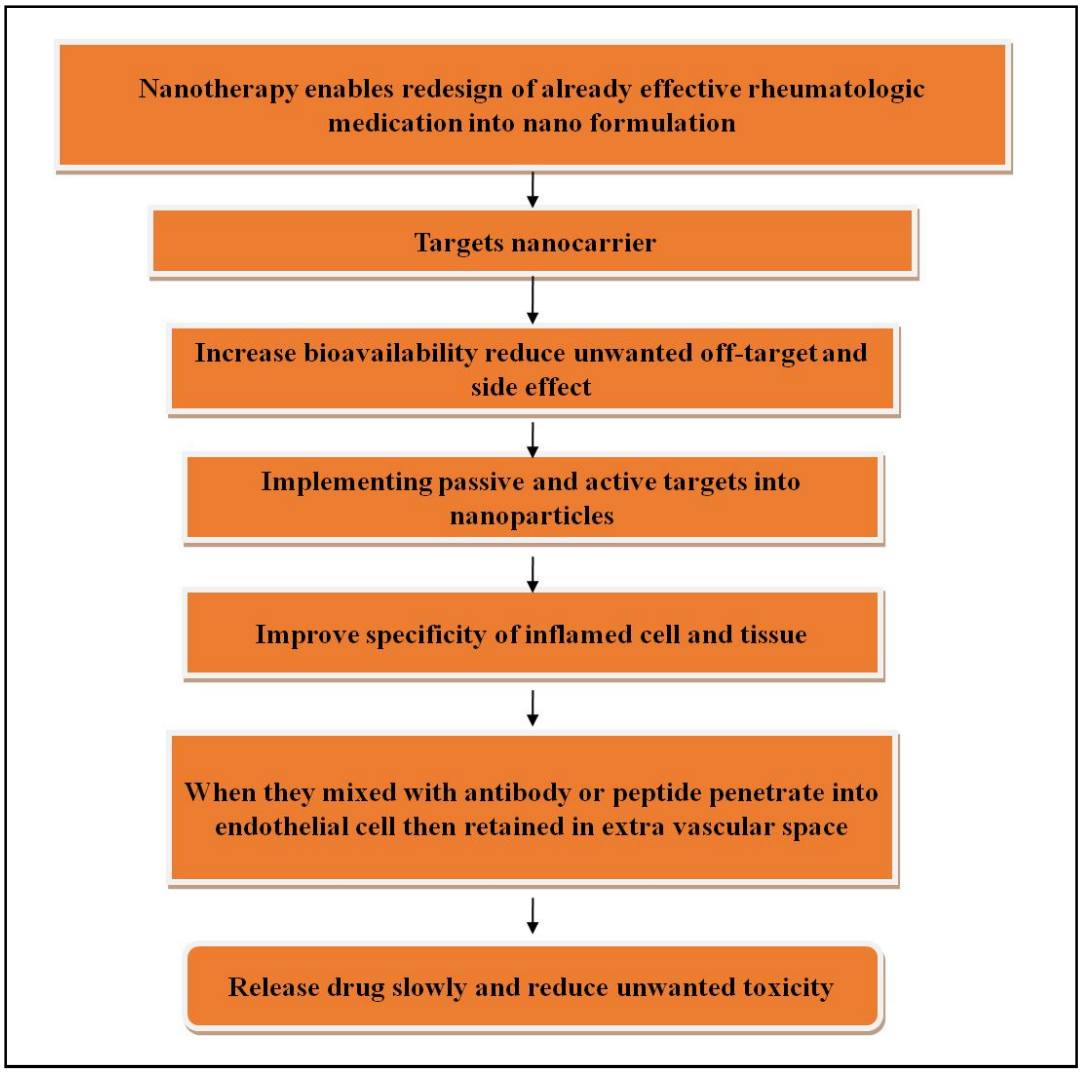
tory cytokinase (TNF-α, IL-1, IL-6) and nitric oxide from activated macrophage (Put *et al*., 2013) . Folic acid with albumin nanoparticles used to enhance specific delivery of etoricoxib also showed remarkable success in delivery of etoricoxib in tissue sac of inflamed joint compared to free drug and non-targeted nanoparticles due to strong affinity of folic acid (Gerlag *et al*., 2001).

Table 2: Conventional classification of target carriered RA drugs

Classification	Drugs	Carriers	Size	Target	Refrences
NASID's	Indomethacin Aceclofenac	Polymericmiscellies Lysine-liposomes	240 -	EPR EPR	(Bernardi *et al*., 2009) (Sharma *et al*., 2017)
Glucocorticoid	Dexamethasone Methylprednisone	Liposomes Cyclodextrin polymeric	96 27	EPR EPR	(Quan *et al*., 2014) (Hwang *et al*., 2008)
DMARD's	Methotrexate Clodronate	Stealth-type polymeric Liposomes	51-116 120-160	EPR Macrophages	(Ishihara *et al*., 2009) (Barrera *et al*., 2000)
BIOLOGIC DMARD's	Etanercept Anakinra	TMN Complex Folate-chitosan DNA	250 110	EPR Macrophages	(Jung *et al*., 2012) (Femand *et al*., 2018)

Abbrevation: Enhanced permeability and retention (EPR)

Flow chart 2: Nanotherapy used in RA.



5. Chemotherapy in RA

In numerous studies showed development of rheumatologic symptoms in patients include those with lung cancer, ovarian cancer, and Hodgkin's lymphoma as well as patients with hematologic malignancies (Amir and Jaferian, 2012). Slow acting anti-RA drugs (SAARD's) help slowly the progression and reduce joint damage and other serious complication. Some studies showed depletion in sequence of erosion is temporary with gold, sulphasalazine, cyclophosphamide and methotrexate but aggregate work cut out to convey notable affect of SAARD's working as radiologic progress (Scott *et al*., 1983; Spector Seoff, 1988). Chemotherapy treatment for RA involves DMARD's take medication from of pill, injection or intravenous infusion. RA chemotherapy often involves a combination therapy to improve the efficacy and minimize side effect (Elizabeth Hanes, 2019; Schwarzer *et al*., 1990). The patient with multiple myeloma treated with melphalan, dexamethasone with allopurinol in chemotherapy regimen. Numerous rheumatologists forsaken the conventional therapeutic pyramid or undo this with stand down overpass appeal of combination in disease control.

6. Nutraceuticals (Food extracts)

Nutraceutical are a blend of nutritional supplements and pharmaceutical medication and its outcome change in c-reactive protein (CRP), seromucoids, fibrinogen, TNF-α, prostaglandin E2, oxidative stress, erythrocyte sedimentation rate (ESR), antioxidant status (Sahar and Al-Akbi, 2012). Some of the nutraceuticals phenolic compound, polyunsaturated fatty acid, phytosterols and carotenoids used in joint pathology includes glucosamine, chondroitin, fish oil, capsaicin, turmeric, *etc*. (Vista and Lau, 2014). Glucosamine is a key component in biosynthesis of prostaglandin and inhibits activity of catabolic enzyme such as phospholipase A2, aggrecanases then reduce regulated IL-1 level in synovial fluid (Chan *et al*., 2006; Calamia *et al*., 2010).

Chondroitin sulphate controls high level of proteogly, thus help preventing inflammation and break down of joint cartilage (Uebelhart *et al*., 1998). Topical capsaicin acts in the skin and causes hypersensitivity and also activates nonneuronal TRPV1 which release IL-8, IL-6, PGE2, thus reduces by a process defuntionalization of nociception (Masoumeh *et al*., 2019). Fish oil contains omega-3-fatty acid which is natural anti-inflammatory mediator which helps in slow blood cloting and decreases joint tenderness and morning stiffness (Bethany, 2015).

7. Gene therapy in RA

Gene transfer may be alternative approach targeted sustain delivery of inhibitor of inflammatory cytokinines. Recently gene therapy for RA has entered clinical trials. TNF-α inhibition playd vital role in gene therapy, either single or combination gene therapy, TNF-α is found at high level in synovial fluid of patients with RA (Tak *et al*., 1997). Hence, TNF-α blockade result in amelioration of joint destruction and local expression of anti-TNF-α single chain antibody blocks disease development which is observed in mice with CIA (Smith *et al*., 2003). Because of complex pathology combination of TNF-α and IL-1 blockade by adenoviral gene therapy in rabbits is more effective than cytokines alone (Ghivizzani *et al*., 2001). Using this approach, it is possible to obtain 20% improvement in about 60-70% of RA patients (Flendrie *et al*., 2005).

Inhibition of NFκB activation which is highly activated in synovium and as ability to induce pro-inflammatory mediators like cytokines and inducible nitric oxide which also act as protecting factor of synovial cell from apoptosis (Didonato *et al*., 1997). Hence, NFκB inhibition increase synovial cell apoptosis in RA patients so phosphorylation inhibition of κB (IκB) protein is a major step in NFκB inhibition. The use of potent NFκB inhibitor, result in decrease joint swelling in mice with CIA (Gerlag DM *et al*., 2000). Treatment for RA patient in NFκB inhibition also had done by over expression of IκBα in human synovial tissue reduces production of pro-inflammatory cytokines without affecting anti-inflammatory mediators (Miagkov *et al*., 1998).

8. Conclusion

Taken together, in last decades a major revolution has seen in treatment of RA patients. The current treatment principle includes symptomatic management and disease modification. NSAIDs can be recommended for RA patients for immediate relief of pain, swelling and stiffness of joint at risk of adverse effects. DMARDs therapies appear to be both patient and physical dependent. Early treatment with DMARDs can retard disease progression more efficiently but decreases ability to fight infection. Biological DMARDs are with fast onset of action and high. Rate of responses but interfere with immune system and increase risk for infection. Herbal medicines outcome are inconsistent, so can be used as complimentary medicines. *Curcuma longa* and TwHF have most clinical evidence to treat RA. Further defining mechanism of action and significant validation of plant products will be more widely accepted. Nanotherapy is designed to improve the therapeutic properties and ensure controlled release of drugs. Despite the increasing number of new drugs, complete long term remission is not achieved. A new retroviral mediated adoptive cellular gene therapy is used for RA. The main challenge in gene therapy is to provide cost effective long term safe treatment.

In conclusion, new combined improved therapeutic approach will dramatically improve the current therapeutic outcomes.

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Conflict of interest

The authors declare that there are no conflicts of interest relevant to this article.

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