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Evidence Based Targeting of Cytokines for Conventional and the Potential Phytotherapies in Management of Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis is an autoimmune disease that leads to chronic, systemic inflammatory reaction that primarily affects synovial joints. Current cytokine based therapies are effective and safe. However, they have a challenge of having short plasma half-life and even higher doses are required to manage the conditions. The processes involved in production using phage and viral technologies are expensive. Herbal medicines have been used for long and are considered safe and effective as medicines for many inflammatory related diseases. Many plants also posit as a potent anti-inflammatory agents. Evidence for use of herbal plants in both human and animal trials in studies suggest significant potential of application in herbal formulation in management of rheumatoid arthritis. Specifically, many studies suggest the direct effect of managing the agents of inflammation as a way of managing rheumatoid arthritis. Most evidence links the involvement of pro-inflammatory cytokines (interleukin-1, TNF-α, IFN-α, and NF-κB) to the long term. It has also been suggested that the use of protective cytokines such as (Interleukin-4, Interleukin-6, Interleukin-8). Key pathways involve cyclooxygenase 1 and 2, 5-Lipooxygenase, formations of metalloproteinases, and inhibition of formation of prostaglandin E2. Use of herbal medicines has potential of improving joint conditions in rheumatoid arthritis. Use of herbal extracts offers better, cheap and affordable solution for long term management of rheumatoid arthritis in patients. They also show potential of offering multifunctional approaches to the management of the conditions through their anti-oxidative and anti-inflammatory mechanisms. Further studies are required to demonstrate the mechanisms involved in activation of protective cytokines in the management of rheumatoid arthritis.

Keywords: Cytokine; Neutralization of cytokines; Rheumatoid arthritis; Herbal extracts; Cytokine based therapies; Anti-inflammatory cytokines

Introduction

Rheumatoid arthritis (RA) is a debilitating autoimmune disorder characterized by destruction of organs and joint tissues, including the synovium, cartilage and the underlying bone [1-5]. The mechanism of disease is still unclear. However, studies on the pathology and physiology of RA are widely studied. RA is affect three major parts of the body. The synovial lining is one part that is affected. It is normally one to about three cells thick. In RA, the cells in the synovial lining becomes greatly enlarged in inflammation (hypertrophied) to about 8-10 cells thick. The inflammatory cells population in the synovial fluid and lining includes fibroblasts and macrophages. Secondly, it also affects the sub-intimal area of the synovium [1,3,4]. They become heavily infiltrated with inflammatory cells mainly the lymphocytes, macrophages, mast cells and mononuclear cells that later become differentiated. Finally, the cartilage is also impaired in RA, leading to the distortion of the integrity, resilience and water content of cartilage. The cartilage is composed of type II collagen. It is associated with the production of the proteolytic enzymes collagenase, stromelysin [1,3]. At the same time, IL-1 and TNF are used to drive the formation of reaction oxygen and nitrogen species that cause damage leading to inflammatory reactions at the joints. The bone is also affected leading to its destruction in RA. The bone is composed of type I collagen. The formations of TNF-α, IL-1, and IL-17 have been isolated in inflammation at the joints. In the synovial cavity, RA leads to the formation of a viscous fluid believed to be derived from the hyaluronic acid and composed of a few cells [1,2]. In RA, the fluids are formed as exudates and are contain a high concentration of neutrophils. There are several causes of RA supported by various postulates. It is believed that RA is formed as a result of genetic defects. This is linked to the variation in the MHC class II antigens and its association with the HLA-DR4. The HLA-DR4 is now known as the highest genetic risk in the development of RA [3]. Inflammation is the main contributor to the development of RA [1,2]. Current therapies used in the management of RA focus predominantly on the reduction of symptoms through the suppression of the immune system. Even with the current therapies, many patients still experience incomplete relief from symptoms. Moreover, the currently potent immune suppressant therapies have a significant side effect profile; they make patients have a compromised quality of life, in the efforts of curbing RA exacerbations [6-10]. Therefore, there is a need for developing new treatments that will be able to modulate the effects of rheumatoid arthritis.

Role of Cytokines in RA

The cytokines are the mediators of the development of RA. The main cytokines generated in RA includes TNF-α, IL-1 and IL-6. They play a significant role as paracrine, autocrine and endocrine factors in the pathogenesis of the disease systemically. Other cytokines such as;

IL-8, GM-CSF, IL-15, IL-17 and IL-23 play different roles in the development of RA. It is shown that several chemicals are formed during the disease state in RA. They include: Prostaglandins, leukotrienes, glucocorticoids and proteinases [4]. Early detection of markers for inflammation play a significant role in detection of RA [5].

Current research into RA has led to the identification of two types of cannabinoid receptors that mediate the pathogenesis of the inflammatory diseases. This includes cannabinoid receptor 1 (CBR1) and Cannabinoid receptor 2 (CBR2) [2,6]. When activated, these receptors induce inflammation leading to increased formation of pro-inflammatory cytokines; TNF-α, IL-1, IL-6, MMP-3, and MMP-13 [5]. Besides, macrophage migration inhibitory cytokines are potent pro inflammatory cytokines which have potential impact of regulating the anti-inflammatory effects of the glucocorticoids. MIF is significant in acting in tandem with the endogenous glucocorticoids as a way of regulating the magnitude of inflammatory responses. Increase in the expression of MIF in blood and synovial fluid is associated with Rheumatoid arthritis. It also promotes progressive damage to the joint and enhances the pathology of the disease as demonstrated in experimental animals. In human subjects under study, CATT-tetra nucleotide with repeat polymorphism located at position-794 in the Mif gene affects the functioning of MIF promoter located in gene reporter assays experiments. Currently, there are four different types of genotypes comprising of 5, 6, 7 or 8 CATT repeat units. Moreover, it is now clear that 5-CATT repeat allele correlate with a very low disease severity in rheumatoid arthritis [7-9].

Markers for Improvement in RA

Common symptoms in RA include; fatigue, pain, tenderness, swelling, warmth and redness in the joints, hips. Severe conditions are characterized by increased joint stiffness, loss of a range of joint motions and are often characterized as polyarthritis. This is especially when several joints are involved in the loss motions or affected [10]. Improvement of these symptoms after administration of conventional medicines, herbal remedies and combined therapies has been reported in separate studies. The combined effects of use of novel therapies and new therapies are expected to modulate the effect of RA on the synovium, cartilage and the bone tissues [11]. The effectiveness use of subject drug can be measured by the reduction in absolute levels of pro-inflammatory cytokines and decline in the diagnostic markers for progression of RA. This is measured by decrease in the erythrocyte sedimentation rate (ESR) and C- reactive protein (CRP) which are significant indicators for the presence of inflammatory processes. In addition, screening for the presence of rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibodies will allow monitoring for improvement of RA [12].

Conventional Drugs

Cytokine targeted therapies for management of RA

The cascade mechanisms for the management of cytokine interaction are complex in nature; they involve a multiple number of cytokine targets. Moreover, tracking of the efficacy and toxicity of the cytokine interventions are a big challenge [4]. Currently, several cytokine based strategies have been developed in the treatment of inflammatory diseases. The all employ mechanisms that demonstrate the possibility of neutralizing the effect of the cytokines in the affected areas of the body, using either soluble receptors, monoclonal antibodies or receptor blockers that eventually inhibit the up regulation of mRNA for formation of the pro inflammatory cytokines using bioengineered versions of immunoregulatory cytokines [4].

Mechanism of cytokine targeted drugs

First, the cytokines can be neutralized using the soluble receptors. This takes advantage of the physiologic role of the soluble cytokine receptors when they bind to the cytokines. For example, TNF receptors will only bind to the TNF- α. The receptors are located on many of the surfaces of immune cells such as the monocytes, macrophages, T-cells, fibroblasts cells, osteoblasts, and endothelial cells. Currently, two types of receptors are known; p55 and p75. They are part of a big family of structurally related cell surface receptors [13,14]. The receptors have potential of activating different signal transduction pathways in the cytoplasmic space [15]. The additional function of p75 receptor involves the proliferation of the T cells and suppression of the inflammatory response initiated by TNF-α. On the other hand, p55 receptors trigger the host immune defense system and the inflammatory responses [16,17].

The soluble forms of TNF receptors (p55 and p75) make a feedback loop which has significant potential of regulating the inflammatory actions of the cytokine TNF-α. The membrane domains for the receptors are prone to lysis by proteases, such as TNF-α converting enzyme. These enable the production of the soluble forms of the receptors. These receptors are then released into the body fluids which can be detected. The soluble forms of the receptors are found in high concentrations in the synovial fluid and serum of RA patients [18]. However, in the presence of excess TNF- α relative to the concentration of soluble forms of TNF receptors. It causes a prolonged joint inflammatory condition.

Consequently, it is theorized that managing patients with a recombinant soluble form of cytokine receptors could be a great solution for suppression of inflammation. The only challenge with this management strategy is the short half-life of the soluble receptors in the body fluids. Moreover, administration of repetitive doses can only lead to the neutralization of the effect of the cytokines in the body fluids. It is suggested that the problem can only be solved with conjugation of TNF receptors to the human Fc which is the proteolytic section of the immunoglobulin G. This allows for the extension of the receptors half-life compared to the immunoglobulin [19]. The other strategy is to complex the anti-TNF-α or TNF receptors with polyethylene glycol. This is believed to extend the half-life of the receptors in circulation. The use of this strategies are not well understood, the safety and efficacy of this strategies are yet to be determined.

Use of antibodies as a way of neutralizing the effects of cytokines is the other approach for managing the pathological changes in RA. The use of antibodies is widely known to be very effective. Use of murine monoclonal antibodies promotes antigenic responses leading to the formation of anti-mouse antibodies in most of the recipients [20]. However, the use of chimeric or human monoclonal antibodies does not trigger any immunological response. Hence, it is considered to be less immunogenic compared to the murine monoclonal antibodies. They are therefore preferred as therapeutic agents [21]. The cost of processing is expensive and the therapies themselves are not affordable due to the technologies involved in the preparation of the therapies.

Another approach is to block the binding of the cytokines to their specific receptors as a way of interfering with the signal transduction

process. This involves the use antagonists on receptors such as IL-1 receptor [4]. Antibodies against the cytokine receptors may also serve as an alternative method. The only challenge with this is the possibility of determination of the concentration of the receptors in circulation. Moreover, it is also not easy to determine the amount of the antagonists to be administered to the patients. In order to sustain long term effects, the concentration of the antagonists need to be high enough to competitively bind to most of the receptors for longer durations [4].

Use of anti-inflammatory mechanisms has also been contemplated as a strategy for suppressing the development of inflammation. This involves the use of anti- inflammatory cytokines such as IL-10, and IL-4 [22-24]. Despite their known effect, no evidence of effectiveness was established, moreover, their effects are pleiotropic; evidence of increased expression of cell surface and soluble TNF receptors with administration of IL-10 is an effect that has the potential of making cells more responsive to TNF-α and its pro inflammatory effect to the joints [25]. The cytokines are also proteins with very low molecular weights and very short half-life. It is therefore be a challenge to sustaining serum concentrations of the anti-inflammatory cytokines besides the very expensive and cumbersome production and purification processes involved.

It is recommended that gene therapy is the best alternative approach for managing RA. It supports continuous up regulation of the production of the mRNA for production of the anti-inflammatory cytokines in the joints. In animal models studies transfected with IL-10 and IL-4 using viral vectors into synovial fibroblasts performed in *in vitro* studies, found that it led to the suppression of inflammation and destruction of joints [26,27].

Cytokine Targeted Drugs and Their Challenges

Human cytokine-receptor proteins are used as cytokine drugs. Several drugs are currently in the market as human cytokine receptor protein drugs. Etanercept is designed as a complex protein for p75 receptor fused with human Fc segment of the Immunoglobulin G. It is a dimeric protein and is very effective and efficient just as the monomeric soluble p75 TNF receptors [28]. In different placebo controlled studies for RA involving the sub cutaneous injections of 25 mg of etanercept resulted in the improvement of the RA condition evaluated by the decrease in the number of swollen joints after a period of six months [28-30]. Moreover, the drug was well tolerated and had minor drug related reactions at the site of injection. Gross pathology of the synovial biopsies showed a significant decrease in the number of plasma cells, vascular adhesions molecules, T-cells, and IL-1 expression after a month of etanercept administration [31]. Similarly, no major adverse related reactions were recorded for a period of 33 months. Efficacy was also established [32]. Combinatorial therapies involving etanercept and methotrexate showed that it was more effective than methotrexate alone in a controlled trial involving 89 patients with RA [33]. Other studies suggest efficacy of etanercept in patients with juvenile RA [34]. In this study, a randomized placebo controlled trial involving 51 patients with juvenile RA. Each patient was administered with 0.4 mg/kg bw etanercept subcutaneously two times weekly for a period of four months. The number of joints with arthritis decreased by 58% while the range of motion of the affected subjects was increased by 80% compared to the baseline group. Further evidence suggested that etanercept is a well-tolerated and effective drug compared to methotrexate in patients suffering from RA. Moreover, there was less radiographic evidence for progression of RA among the patients using etanercept compared to methotrexate [35].

Monoclonal antibodies are also in use in the market. Infliximab is a chimeric monoclonal IgG1 antibody that acts against the effect of TNF-α. In a double blind clinical trial with 73 patients suffering from RA: A single dose of 10 mg/kg body weight reduced the number of inflamed and swollen joints and concentration of serum C-reactive proteins [36]. Improvement in clinical presentation of patients was observed within a week after start of treatment. The number of T-cells, vascular cell adhesions molecule-1 and E-selectin was significantly reduced in synovial biopsy specimens four weeks after start of treatment when compared to those before treatment [37]. In other randomized placebo controlled trial involving 101 patients with RA, both the placebo and infliximab was administered repeatedly with or in the absence of methotrexate [38]. Antibodies against infliximab were produced in most of the patients. Moreover, a dose of 3 mg/kg body weight of infliximab combined with methotrexate was effective as a single dose of 10 mg/kg with or without methotrexate. These finding is a further confirmation of the effectiveness of combination therapies on a clinical trial that lasted about 30 weeks and involving a higher number of patients (428) [39]. D2E7 is a human antibody designed to fight TNF-α in RA. It was developed using the phage display technology as vectors [40]. On the other hand, Nerelimomab is a monoclonal antibody designed to protect against the inflammatory effects promoted by TNF-α. It consists of a hyper variable region of the murine monoclonal antibody against TNF-α. However, it is crafted into the human κ light chain and IgG4 heavy chain [41]. Both of these antibodies are effective from evidence collected in the preliminary studies in randomized, placebo controlled trials in patients with RA [42,43]. Monoclonal antibodies against IL-6 receptors have potential anti-inflammatory effects in RA. The formation of an antibody against the receptor for IL-6 has shown efficacy in collagen induced arthritis [42]. They are able to protect the cells from production of IL-6.

Cytokine receptor blocking technique is also employed in the regulation of cytokine synthesis and generation in arthritis. Interleukin-1–receptor antagonist is a recombinant therapy designed to work as a cytokine receptor blocker. In a randomized double blind placebo controlled clinical trial involving 472 patients suffering from RA, and managed with a human IL-1 receptor antagonist. The recombinant drug was able to moderately improve the clinical symptoms of the joints and decreased the erosion of the joints when evaluated using radiographic techniques [43,44]. The only adverse events occurred at the site of injection. The effectiveness of combining IL-1 receptor antagonist with methotrexate has not been tested and it is still on going. The only challenge with this treatment is as a result of its short plasma half- life of about 6 hours in the plasma [45]. Hence, it requires repeated treatment with higher doses to sustain the therapeutic effect. It also requires large concentration of IL-1 antagonists of between 10-1000 fold) for effective management of RA *in vitro* and *in vivo* [46]. Gene therapy is suggested as a better method of managing this challenge [47], it is anticipated to produce copious levels of IL-1 receptors agonist in the synovial fluids. First, the synovial fibroblasts will be transfected with the human interleukin-1-receptors antagonist and then re-injected into the joints to produce interleukin-1-receptor antagonist in the synovium providing for improvement in the clinical symptoms in the patients with RA [48]. Moreover, *ex-vivo* gene transfers for interleukin-1-receptor antagonist into the joints for patients with RA before they were subjected to total joint replacement. Tissue biopsies from the joint showed that there was

increased expression of intra articular expression for interleukin-1-receptor antagonist gene [47].

Similarly, recombinant therapies for both IL-10 and IL-4 have been tested in patients with RA [49,50]. The study was not a success due to the lack of efficacy in the recombinant therapies. It is suggested that this may be as a result of the short half-life of the IL-10 and IL-4 in body fluids.

Herbal Remedies with Potential Anti-Arthritic Activities

Herbal materials have always been in use in the management of various inflammatory conditions since time immemorial. It is on this basis that bioscreeening and bio-prospection for new remedies from herbal plant material is based. It is known that herbal plant materials are safe, affordable and effective in management of various medical conditions including Rheumatoid arthritis.

Urtica dioica is a possible therapy for the management of arthritis and other inflammatory conditions and is established as a possible symptom mitigating therapy [51]. *Urtica dioica* has potent anti-inflammatory, antioxidant and immune-regulatory functions [52]. *Urtica dioica* extracts contains coumarins, formic acid, chlorophyll, flavonoids, terpenoids, lignans, mineral salts and vitamin C. The Flavonoids and polyphenols are important in the reduction of the reactive oxygen species and the nitrogen species reducing through the anti-oxidative species [53].

Extracts from *Uncaria tomentosa* (UT) has potential anti-arthritic effect in patients with rheumatoid Arthritis. In a clinical trial study involving the use of sulfasalazine or hydroxycloroquine in treating patients for a period of 52 weeks, divided in two phases in a randomized controlled study. In the first phase, a double blind placebo controlled study among the patients was performed with UT extracts or placebo treatment for 24 weeks. In the second phase for 28 weeks, all the patients received the plant extract. There was significant improvement in the number of painful joints when compared to the placebo group. In the second phase, the number of painful joints, swellings and Ritchet index were highly significant different compared to the values recorded in the first phase for 24 weeks of placebo. Minor side effects were observed in this case. It was demonstrated that UT was safe with modest efficacy in the management of tender joints in rheumatoid arthritis using sulfasalazine or hydroxycloroquine [53].

Use of a combination of herbs and mineral formulation (harbomineral) in a randomized double blind placebo controlled study has also been evaluated for effect in the management of Osteoarthritis. The herbal plant extracts were derived from *Withania somnifera*, *Boswellia serrata*, and rhizomes of *Curcuma longa.* Zinc complex was used in this study. The efficacy of the herbomineral or placebo groups were determined using the severity of pain, morning stiffness, Ritchet articular index, disability and joint score, grip strength. The study also evaluated the erythrocyte sedimentation rate and use of radioactive techniques monthly. There was a significant decrease in the severity of pain and disability using the techniques employed in this study. The tissue radiology evaluation did not find any significant change in the treatment for both of the groups. This study did not find any toxic effects in the herbal formulation or placebo to warrant the withdrawal of the treatment [54].

In china, several vine herbal plants have been identified with potential anti-inflammatory activities. Either the stem or root of *Spatholobus suberectus*, *Trachelospermum jasminoides*, *Tripterygium wilfordii*, *Sinomenium acutum*, *Piper kadsurai*, *Polygonum multiflorum*, *Tinospora sagittata*, *Tinospora sinensis*, and *Clematis chinensis* was used as the source of the extracts. The activity of these plants was evaluated through the comparative effects on key enzymes associated with inflammation such as: cyclooxygenase 1 and 2 (COX-1 and COX-2), phospholipase A2 (PLA2), 5-lipoxygenase (5-LO) and 12-lipoxygenase (12-LO). It was established that each of the stem or root extracts used in the management of inflammation had activity in at least a single enzymes with varying degrees depending with the concentration of the dosages applied. The stem extract from *Spatholobus suberectus* had inhibitory activities against all the enzymes except the COX-2. Moreover, *Trachelospermum jasminoides* had inhibitory activities against COX-1 and PLA2. The most effective inhibitory activity on both Cyclooxygenases s and 5-Lipoxygenases was by the root extracts from *Tripterygium wilfordii*. This study was able to justify the potential effect and social value in the use of vines in the management of inflammatory conditions. These similar effects are potential in the management of rheumatoid Arthritis's [55].

In a study dubbed the 'gold mine' for management of arthritis, several medicinal pathways and herbal materials with potential medicines effects have been suggested. This study has suggested a possible connection between the inflammatory conditions in arthritis with the pro inflammatory cytokines TNF-α, Interleukin -1β and pro inflammatory cytokines that mediate the formation of prostaglandins such as cyclooxygenase-2 and leukotriene's by the Lipooxygenases. The processes are also linked to the expression of metalloproteinase and hyper proliferations of the synovial fibroblasts. All this factors are connected through the regulation of transcription factor nuclear factor-kB. Hence, it is postulated that suppression of TNF-alpha, IL-1, COX-2, Lipooxygenases and metalloproteinases or suppress the formation of NF-kB have potential in the management of arthritis. It was demonstrated that herbal plant agents have potential in the suppression of the cell signaling intermediates such as curcumin, red grapes. Cranberries, peanuts, tea polyphenols, genistein, soy, quercetin in onions, silymarin, boswellic acid and withanolides. These plants have also been verified in various clinical trials for potential effects in the management of arthritis. The use of herbal materials that are safe and effective in the management of arthritis through the modulation of the inflammatory cytokines was the basis for the definition of gold mines in management of arthritis [56].

White willow bark is considered the oldest remedy for the management of pain and inflammation used by the ancient Egyptians, Romans, Greek and Indians both as an antipyeric and analgesic. It is demonstrated that the mechanism of action involved in the use of white willow back is same as that of aspirin. It is also known to be an inhibitor of both COX-1 and COX-2 which are key pathways for the prevention of the production of inflammatory prostaglandins [57]. This was verified in randomized placebo controlled trials comparing the use of white willow bark with non-steroidal agents and aspirin. The white willow bark is demonstrated to contain a chemical compound salicin that is converted to salicylic acid in the liver and which is demonstrated to have fewer side effects compared to aspirin. However, it comes with a few challenges: it is expensive compared to aspirin, it is also not recommended for use in children since it is responsible for Reye's syndrome. Moreover, it can also not be used by people suffering from peptic ulcers, diabetics and people suffering from hepatic and renal dysfunctions. It is also suggested that it should not be used in many other conditions on which aspirin is contraindicated. The

effective dose of 240 mg/day for white willow bark is recommended [58-65].

Turmeric (Curcumin) occurs naturally as a yellow pigment extracted from *Curcuma longa*. *Curcuma longa* is a natural flowering plant classified with the ginger family. It is widely used as a flavoring, coloring spice for food traditionally. It was also used in traditional medicines as an ayurvedic and Chinese as an anti-inflammatory agent for the management of the digestive disorders and to manage the healing of wounds. Various studies demonstrate that curcumin have an antioxidant, anti-inflammatory, and has antineoplastic effects. Evidence of efficacy in the management of cystic fibrosis is as a result of its anti- inflammatory effects in also available [28]. It is also demonstrated that it inhibits activators for NF-kB suppressing the formation of NF-kB while also keeping in check its expression. Its involvement in the management of colitis, neurodegenerative diseases, arthritis and cancer is available. Its main mechanism of action involves the regulation of several key enzymes and cytokines by targeting the inhibition of both COX-1 and COX-2. Further research also shows possible involvement of NF-kB, COX-1, and COX-2 as key anti-inflammatory mechanisms. This evidence thus suggests the potential of *Curcuma longa* in the management of the inflammatory RA. None of the studies have indicated possible adverse side effects following the use of *Curcuma longa* extracts except when used in high doses for longer duration leading to stomach upsets and ulcers. It is probably also the best alternative to the non-steroidal drugs used for the treatment of inflammation. A dose of curcumin powder of 400-600 mgs taken 3 times every day is recommended [51]. It can also be combined with low doses of non-steroidal medications [66-73].

Green tea is known for its rich antioxidant capacity and for a long time, it is used in the management of cardiovascular and cancer treatment traditionally. Recently, its role in the management of arthritis due to its anti-inflammatory potential was recognized. It is rich in polyphenols, catechins and epigallocatechin-3 galate as the most prevalent catechin in green tea. It is known that Epigallocatechin-3 galate strongly inhibits IL-1 induced proteoglycan release and degradation of the type 2 collagen in cartilage explants [74]. It also inhibits and suppresses the formation of IL–1b and hinders the activation of the transcription factor NF-kB in *in vitro* studies. Similarly, it inhibits the aggrecanes which can be able to degrade cartilage. Use of green tea confers chondroprotective effects besides the anti-inflammatory effects. As a result, it is theorized that increased consumption of green tea can lead to cardiovascular, neurone damage protection and cancer prevention [75]. It is recommended that 3-4 cups of the green tea be consumed daily. Similarly, a dose of 300-400 mg/day is permitted. However, it can lead to stomach irritation as a result of its caffeine content. Currently, the decaffeinated varieties of the green tea are available. The polyphenol contents in the green tea are not known [76-81].

Maritime pine bark has been in use since the ancient times. Pycnogenol is a derivative of the maritime pine tree *Pinus maritime*. It has been in use for more than 2000 years. It was used in the management of scurvy, wounds, and ulcers and in the management of the vascular inflammatory conditions. These effects are associated with high levels of polyphenols, catechins, taxifolin, procyanidins and phenolic acids. It is among the most potent antioxidant compounds [58,82]. The mechanism of actions of pycnogenol involves the inhibition of TNF-α–induced NF-kB activation and the expression of adhesions molecules which are expressed in the endothelium. Inhibition of NF-kB activation has also been recorded in polysaccharide stimulated monocytes in decreasing the inflammatory responses. It also inhibits the matrix metalloproteinase-9 [83]. Involvement of the matrix degrading enzymes in inflammatory reactions is known to be the main mechanism of pathogenesis in chronic inflammatory diseases [84]. Comparative studies on the potency of pycnogenol to vitamin E revealed that it is 50 to 100 times more potent as an antioxidant for free radicals and significantly helps in the recycling and elongation of the activity of vitamin C and E. It is also effective in lowering blood pressure and risks of nervous thrombosis as a result of its effects in vascular endothelium. The most effective dose recommended for use is 100-200 mg/day. It has few gastrointestinal side effects associated with diarrhea and stomach upsets. Moreover, it is contraindicated for patients using immunosuppressants or corticosteroids. This is because the use of pycnogenol enhances the functioning of the immune system. There is also potential interaction with drugs that can suppress the immune system [57,84,85].

Boswellia is a resin and an extract from the *Boswellia* species of trees. They are also referred to as olibum. *Boswelina serrate* is found in India, Somalia, Ethiopia, and Arabian Peninsula. The resin is demonstrated to possess anti-inflammatory, anti-arthritic and analgesic properties. It is known to inhibit the leukotriene's involved in the biosynthesis of neutrophilic granulocytes through the inhibition activity on 5-LOX. Consequently, it has a significant effect on a number of inflammatory diseases promoted by the production of the leukotriene's [86]. It is also use clinically in the treatment of degenerative and inflammatory joint disorders. It is shown to lower the white blood cell counts in the joint fluids and inhibit the activity of leucocyte elastase in RA. After 8 weeks of treatment with B. serrate at a dose of 333 mg taken three times a day, there was significant improvement in the condition of arthritis. The function of the joints also improved, however, there was no change in the affected joints when determined radiographically. It is possible to combine *Boswellia* with other extracts such as curcumin. A combination of curcumin and *Boswellia* indicated greater efficacy, tolerability when compared to the non- steroidal pain killer drug diclofenac used in the management of osteoarthritis. *Boswellia* is administered as an extract containing about 30-40% of boswellic acid (300-500 mg twice or thrice a day. It is well tolerated though mild side effects have been reported in the form of stomach discomfort, nausea, acid reflux and diarrhea [57,86-91].

Resveratrol is found in various concentrations in different plants. However, higher concentrations are believed to be derived from Japanese Knot weed or *Polygonum cuspidatum*, and from the skins of red wine grapes. In plants, it is often located in the plant skin which serves as a phytoalexin in the protection of the plant from infection, excessive UV radiation and general plant defense system. It is known to possess anti-mutation, antioxidant and anti-inflammatory and DNA protection activities when consumed by both animals and humans. Many of the studies have been demonstrated in neuro and cardioprotection. This is used in the management of RA in management of arthritic joint pain. Study findings using intra articular injections of resveratrol showed protective abilities on the cartilage through the reduction of the inflammatory reactions caused by the osteoarthritis in the knees. This has also been justified with the reduction of the paw edema in experimental animal models believed to be linked to the inhibition of production of the prostaglandins [92]. It is also a potent inhibitor of the TNF-α and IL-1b-induced NF-kB activation. Similarly, the anti-inflammatory activities seem to suppress the COX -2 pathway through the blocking of NF-kB activation in the joints. Resveratrol is extracted from many sources. However, when

administered, it is converted to trans-resveratrol which is the active form. A dose of 50-500 mg/day can be administered. No significant side effects have been recorded and no safety issues have also been indicated in many of the studies involving use of resveratrol. Possible anti-platelet effect is suggested, hence, there is need for proper care when using other key prescription drugs or coagulation interfering products [93-98].

Capsicum annum fruit is used traditionally by the native of the American tropics for many centuries. It was originally grown in the tropics of the United States of America. It is known to contain high chemicals that cause highly selective anesthesia by the breakdown of the capsaicin sensitive nociceptive nerve endings. It is known to be potent in the activation of the receptor potential for vanilloid-1. This is believed to be the main receptor for nociception. It is also suggested to have potential in the inhibition of NF-kB activation as a mechanism of action for generating the ant-inflammatory effect. The herb is often mixed with other natural anti-arthritic herbal preparations. It is also used for peripheral neurone disorders and chronic musculoskeletal pain [99-105].

Oils from animal have also proved to be effective as herbal remedies for the management of RA [106-113]. The summary of key pathways and mechanisms involved and the possible side effects associated with use of these herbs studied (Table 1).

Name	Anti-arthritic mechanism of action	Phytochemical compounds listed	Side effects
Urtica dioica [51,52]	Anti-inflammatory, antioxidant and immune-regulatory.	Coumarins, formic acid, chlorophyll, flavonoids, terpenoids, lignans, mineral salts and vitamin C	None recorded
Uncaria tomentosa (UT) [53]	Significant improvement in the number of painful joints when compared	None suggested	Minor side effects
Harbomineral (*Withania somnifera*, *Boswellia serrata*, and rhizomes of *Curcuma longaZinc complex*			None
Spatholobus suberectus, *Trachelospermum jasminoides*, *Tripterygium wilfordii*, *Sinomenium acutum*, *Piper kadsurai*, *Polygonum multiflorum*, *Tinospora sagittata*, *Tinospora sinensis*, and *Clematis chinensis* [55].	*Inhibitory activities against COX-1, PLA_2, 5-Lipoxygenases*.	None suggested	None Observed
curcumin, red grapes. Cranberries, peanuts, tea, and soy [56].	Inhibits cyclo oxygenase-2, leukotriene's formation, lipo-oxygenase, metalloproteinases and hyperproliferations of the synovial fibroblasts, activation of transcription factor NF-kB, suppression of TNF-alpha, IL-1, COX-2, and Lipooxygenases	Polyphenols, Quercetin, silymarin, boswellic acids, withanolides	None observed
White willow barks [57-65].	Inhibitor of both COX 1 and COX-2	Salicin	Avoid use in children, peptic ulcers, diabetic, hepatic and renal dysfunctions
Curcumin (turmeric) [66-73].	Anti-inflammatory, antioxidant, anti-inflammatory, antineoplastic effects. Inhibits activators for NF-kB; suppress formation of NF-kB and its expression. regulation of several key enzymes and cytokines by targeting the inhibition of both COX-1 and COX-2	Turmeric (curcumin)	
Green tea [75-81].	Inhibits IL-1 induced proteoglycan release and degradation of type 2 collagen in cartilage, inhibits and suppress the formation of IL – 1b, hinders activation of transcription factor NF-kB, inhibits aggrecanes which degrades cartilage.	polyphenols, catechins and epigallocatechin-3 galate	None suggested
Maritime pine bark [58,82-85].	Inhibition of TNF-α, induced NF-kB activation and expression of adhesions molecules. Inhibits NF-kB activation in polysaccharide stimulated monocytes in decreasing the inflammatory reaction, it also inhibits the matrix metalloproteinase-9	levels of polyphenols, catechins, taxifolin, procyanidins and phenolic acids	Diarrhea and stomach upsets.
Boswelina serrate [86-91].	The resin possesses anti-inflammatory, anti-arthritic and analgesic properties. They inhibit leukotriene's involved in the biosynthesis of neutrophilic granulocytes by inhibiting the activity of 5-LOX.	Resins	Stomach discomfort, nausea, acid reflux and diarrhea
Capsicum annum [97-105]	inhibition of NF-kB activation as a mechanism of action for generating the ant-inflammatory effect	None mentioned	None suggested

Fish Oil (Omega-3 fatty acids) (eicopentaenoic acid (EPA) and docosahexaenoic acid (DHA) [106-113].	Catalyze conversion of COX to prostaglandin E3. Inhibit formation of prostaglandin E2, inhibits synthesis of pro-inflammatory cytokines; TNF-α and IL-1b. EPA and DHA competitively inhibit the 5-LOX pathway that converts arachidonic acid to the inflammatory leukotriene's.	EPA and DHA	Steatorrhea, belching occasionally

Table 1: Medicinal plants with potential anti-arthritic activities.

Challenges for Use of Herbal Remedies

It is a challenge to prepare herbal derived compounds, determine their quantities and concentrations [114-116]. Similarly, the processes involved in the preparation of herbal extracts are often not standardized. Consequently, the method used for extraction of the herbal materials and type of plant used influence the concentration of the end product. Moreover, there is always no uniformity in the process of manufacturing of the herbal preparations. Even though herbal extracts are classified as dietary supplements, they are regulated as food products. Contamination of the extracts is also a great challenge: More recently, lead content was found in Ayurvedic preparations from India and exported to the US [114-118]. On the other hand, herbal drug manufacturers may make claims without citing possible side effects and drug interactions. For instance, evidence for involvement of drugs such as white willow in bleeding complication needs to be clearly indicated in the packages white willow bark extracts [118]. Despite these challenges, herbal remedies have demonstrated potential for management of RA compared to conventional therapies.

Conclusion

The understanding of pathogenesis of rheumatoid arthritis is still inconclusive. Possibly, inflammatory reactions are the main cause of the tissue damage which is associated with pain and swelling at the joints. Evidence for involvement of cytokine in inflammatory mechanism is well known. As a result, targeting for regulation of cytokines as direct target molecules and their receptors involved in the inflammatory pathways in RA, has given way to the innovation of cytokine based therapies. Herbal extracts are effective, less toxic and preferable in short and long term targeted treatment of RA. However, use of these medicines requires confirmatory tests for effectiveness of anti-inflammatory cytokine based therapies using radiographic tests so as to indicate their effects on disease progression. There is good potential for application of plant herbal formulation in the management of the RA in the near future with increasing research better working alternatives in herbal phytotherapy's. The multifunctional approach of herbal extracts makes them even more preferable for management of RA by targeting the cytokine anti inflammation and reduction of the oxidative potential of the reactive of oxygen and nitrogen species in the body. It is possible that these herbal remedies will offer solution for the sustained need to find better, effective, non-toxic and affordable chemotherapeutics for management of arthritis and associated conditions.

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