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Potential Phytopharmaceuticals with their Randomized Trial for Management of Rheumatoid Arthritis

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ABSTRACT

Background: *Rheumatoid arthritis [RA] is a progressive inflammatory autoimmune condition that affects more women than men and is more often seen in the elderly. The pathophysiology of RA involves systemic inflammation of the synovial membrane, which may kill articular cartilage and juxta-articular tissue.*

Main Text: *The pathophysiology of RA involves systemic inflammation of the synovial membrane, which may kill articular cartilage and juxta-articular tissue. Although the exact cause of RA is unclear, its autoimmune growth and development may be influenced by dna, the climate, and hormones. RA usually begins steadily, with symptoms and signals appearing over many weeks or months. Rigidity, tenderness, and pain can be the first signs in at least one joint, particularly as the individual attempts to move the joint. Non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen and naproxen) were included as possible therapies for RA. This can reduce discomfort, inflammation, and rigidity, as well as improve muscle function, but it will have little effect on joint injury [i.e. NSAIDs are not DMARDs]. Herbal medicines are often used in RA, such as Evening primrose oil, Borage seed oil, Curcumin, Flaxseed oil, and others.*

Conclusion: *Rheumatoid arthritis [RA] is a progressive inflammatory autoimmune condition that affects more women than men and is more often seen in the elderly. Aspirin and colloidal gold were once used to treat RA. NSAIDs, DMARDs (Biological, Herbal), and other natural and synthetic medications are now used to manage RA. These drugs help the patient regulate or reduce RA symptoms.*

Keywords: *Rheumatoid Arthritis [RA], Pathophysiology, Systemic Inflammation, Synovial Membrane.*

INTRODUCTION

Rheumatoid arthritis [RA], an inflammatory condition that primarily affects the lining of synovial joints, may cause progressive weakness, premature death, and socioeconomic pressures, particularly in the elderly. Arthralgia, pain, redness, and even a restriction of mobility variety are all clinical signs of symmetrical joint engagement [1-2].

For improvement, it's important to get a diagnosis as soon as possible. The first 12 weeks following the onset of early signs was deemed the most cost-effective treatment window [3-4]. Rheumatoid arthritis [RA] is a persistent inflammatory

joint condition that affects about five out of every 1000 adults worldwide. The largest occurrence happened in the sixth decade. Prior to that, RA caused disabilities, work loss, and increased mortality. The findings have recently changed due to a greater understanding of RA pathophysiology and the development of better outcome measures and therapies [5]. The pathophysiology of RA involves systemic inflammation of the synovial membrane, which may kill articular cartilage and juxta-articular tissue. Recent discoveries of biologic processes have improved our understanding of events and their consequences. In the biological pathway, new molecules and cells have been identified and are targets for a treatment protocol [6]. This RA primer covers epidemiology, genetics, pathophysiology, diagnostics, clinical assessment, and RA management in depth. This Primer often looks at unmet needs and offers suggestions on how to solve the remaining issues so that everybody with RA has a brighter future.

EPIDEMIOLOGY

In the United States, RA affected nearly 1.3 million adolescents in 2005, with an estimated 1.5 million citizens affected two years later. In the literature, more recent details on the prevalence of RA in the United States is not yet accessible. RA will affect people of all races and ethnicities2. The prevalence of RA ranges from 0.5 to 1 percent [0.6 percent in the United States]. In developed countries, 5 to 7 women are two to three times more likely than men to become RA. Both breeds and ethnic groups are susceptible to RA [7, 8]. RA is most common in middle-aged and older people, although it may also affect children and young adults. Traumatic autoimmune rheumatic disease affects one out of every 12 women (8.3%) and one out of every 20 men (5%) throughout their lifespan. Females have a 1 in 28 [3.6 percent] lifetime risk of developing adult RA, whereas males have a 1 in 59 [1.7 percent] lifetime risk. The magnitude of RA has declined over time, owing to earlier diagnosis and effective drug regimens, but changes in the frequency, occurrence, and mortality of RA are dependent on the community studied [9-13].

ETIOLOGY

While the exact trigger of RA remains uncertain, the autoimmune development and progression of the disease may be influenced by chromosomes, the atmosphere, and hormones [7-8]. Any risk factors, such as age [highest prevalence of human leukocyte genotypes, as in the case of HLA-DRB1] seem to increase the incidence of RA: Tobacco [tobacco, cigarettes]; live birth experience [increased chance of null parity]; early childhood exposure; [increased risk of RA if mom smoked]; obesity [increased risk of increased body weight]. Patients of seropositive proteins [ACPAs] and rheumatoid factors [RFs] have an increased chance of RA. Surprisingly, the incidence of RA tends to be lower in patients that are breastfeeding their children. Before the advent of successful modifying antirheumatic medications [DMARDs] and biological treatments, patients with RA were more prone to suffer from early atherosclerosis, disease, and infection [9-13].

PATHOPHYSIOLOGY

The tumour necrosis factors [TNF], interleukin-6 [IL-6], and colony-stimulating factor for macrocyte granulation are the most appropriate elements of inflammation in the inflamed space. Synovial-membranial inflammation is common, with cytokine and chemical implications. By stimulating endothelial cells and promoting the accumulation of immune system cells in synovial cells,

cytokines and chemokines are responsible for causing or exacerbating the inflammatory response. The activated fibroblast, B cells, T cells, monocytes, and macrophages will activate if osteoclastic development is triggered by the receptor activator of the nucleic factor kappa-B ligand [RANKL] expressed on B cells, T cells, and fibroblasts. The RANK receptor is found in macrophages, dendritic cells, and preosteoclasts. Furthermore, metalloproteinase and other enzymes destroy the cartilage matrix in the joints in the long run [11].

SIGNS AND SYMPTOMS

RA usually begins steadily, with symptoms and signals appearing over many weeks or months. Rigidity, tenderness, and pain can be the first signs in at least one joint, particularly as the individual attempts to move the joint. Symptoms of tiny joints, such as the fingertips and toes, normally occur first. While the number of joints affected by RA varies, most people experience symptoms in at least five joints at the same time. A individual with RA who develops it suddenly can go to bed one night and wake up in excruciating pain the next morning. It's possible that you won't be able to get out of bed. RA normally impacts all sides of the neck, such as your knees and hands.

1) Effect on the joints
2) Morning stiffness
3) Fatigue
4) Low mood
5) A fever
6) A general feeling of unwell
7) Flare-up
8) Effect on organs –
9) Eye
10) Lungs
11) Pericardium
12) Nodular lesions
13) The voice box
14) Salivary gland
15) Sour tongue
16) Blood vessel

TREATMENT

The standard goal of RA therapy is to reduce inflammation, and without it, patients can develop permanent disabilities [7, 8]. Medicines, dietary improvements, and surgery are both options for treating RA and reducing joint damage, discomfort, and swelling. [1] is an example of a RA interference. For each strategy, a periodic reaction assessment [via disease activity] should be carried out, allowing for the development of adaptation strategies or the treatment of the targets [7]. Middle-to-moderate RA can be managed successfully in certain patients, with the condition being treated without flares [1]. In severe RA, the symptoms/signs will last for a long time [1]. Aspirin and colloidal gold were once used to treat RA [2]. These treatments improved effects but did not significantly delay or alter the course of the disease [2]. Steroids have rapid symptom relief and certain disease-modifying benefits, but long-term usage is associated with serious side effects [such as asthma, diabetes, osteoporosis, and cataracts] [2,7]. Cyclosporine has also been used, but it could be insufficient or unsuccessful in certain patients due to various side effects [2]. Non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen and naproxen) were included as possible therapies for RA. This will reduce discomfort, inflammation, and rigidity while also improving physical mobility, but it will have little effect on joint damage[NSAIDs are not DMARDs]. [number seven]. According to new recommendations [4,] these medications are no longer favoured. The most recent laws no longer support these medications. The mechanisms/pathways in RA that allow for site-specific drug development are now better understood [2]. There are two types of DMARDs: biological and

synthetic [see Table 1]. [number seven]. Conventional synthetic DMARDs are not site-specific and have unknown radiation-relieving pathways. On the other hand, for targeted, synthetic DMARDs [for example, Janus Kinase Inhibitors [JAK]], the emphasis is on the particular location. [number seven]. TNF, IL-6, IL-1, B or T cells are examples of site-specific biological MAIRs [2, 7].

Table 1. Biological and Synthetic Drugs

Conventional Synthetic DMARDs
Hydroxychloroquine Leflunomide Methotrexate Sulfasalazine
Targeted Synthetic DMARDs
Baricitinib Tofacitinib
Biological DMARDs
TNF alpha inhibitors
Adalimumab Certolizumab pegol Etanercept Golimumab Infliximab
Anti-B-cell[CD20]
Rituximab
Anti-T-cell costimulation[CD80,CD86]
Abatacept
Anti-IL-6
Sarilumab Tocilizumab
DMARD:disease-modifying antirheumatic drug; IL: interleukin; RA: Rheumatoid arthritis; TNF: tumor necrosis factor. Source: Reference 7,8

HERBAL DRUGS FOR RHEUMATOID ARTHRITIS

□-Linolenic acid [GLA]

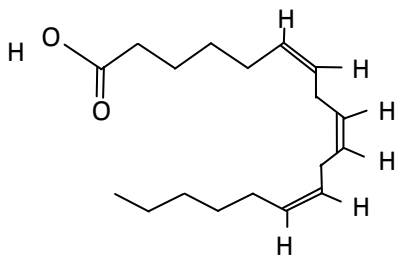

Fig 1.Structure of Gamma-Linolenic acid

Borage Seed Oil, *Borago officinalis*.

Fig 2. Images for this profile are taken

from the Maltese Islands at or after the year 2000 [27].

Two studies looked at the efficacy of borage seed oil for RA. To begin, 1.4 g of GLA per day in the form of borage seed oil was compared to placebo capsules containing cottonseed oil [14]. Patients treated with borage seed oil saw significant improvements in joint tenderness counts and ratings, joint inflation, medical worldwide diagnosis, and discomfort after six months of treatment as compared to patients in the placebo community. In the treatment community, no patient was remission, while seven patients [36.8%] saw major gains and seven patients [36.8%] did not. In the placebo group, one patient [5.6%] progressed and 12 patients [63.2 percent] did not.

Evening Primrose Oil, Oenothera Blennis

Fig 3. Evening primrose oil, Oenothera blennis[28]

During the 6-month EPO experiment, 40 patients were randomly assigned to either 6 g/day [540 mg GLA / day] or placebo [olive oil, 6 g / d] for EPO and 17 patients were randomly assigned to placebo. The procedure was completed by 13 EPO patients and 17 EPO patients, respectively. The causes for removal from the EPO Community involved nausea [n=2], joint procedure [n=2], deteriorating condition [n=1], and flu-like symptoms [n=1].

Three people dropped out of the control group due to nausea, and one moved out of the region. There were no reports of intergroup comparisons. The morning rigidity of the community EPO, on the other hand, was significantly reduced without affecting the Articular Index [AI] or Ritchie discomfort. Olive oil, on the other hand, greatly decreased AI and discomfort while having little impact on morning rigidity. There was no change in fitness evaluation or health assessment ratings in either category [15,16,17].

Blackcurrant seed oil, *Ribes nigrum*

Fig 4. Blackcurrants [ribes Nigrum] is a photograph by Maria Mosolova/science Photo Library which was uploaded on September 28th, 2018.[29]

During a six-month study, 34 patients were randomly assigned to either BCSO [n=20] or placebo [n=14]. The daily dosage of BSCO was 10.5 g [2.0 g of GLA], and the placebo capsules included soybean oil. NSAID and/or corticosteroid pre-trial doses were maintained during the trials.

As comparison to the placebo community, the treated group reported significant improvements in joint pain count [ES=0.73, 95 percent confidence interval [CI] 0.519, 2.93] and pain score [ES=1.51, 95 percent CI 0.339, 2.68] among students who completed the survey.

The analysis of purpose to care confirmed that such results did not result in medication discontinuation. One patient in the BCSO community changed dramatically, while six others did not [18]. There were no major

differences in the placebo group of seven patients.

OTHER HERBAL PREPARATIONS

Capsaicin

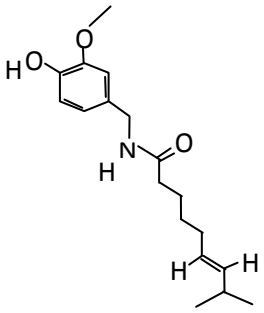

Fig 5.-Structure of Capsaicin

For four weeks, patients with mild to severe knee pain who met at least three of the criteria for definite or probable RA were randomly assigned to capsaicin [0,025 percent] or car cream [19]. During the study, 94 percent of patients and all placebo patients took oral arthritis medications that had been stabilised prior to the procedure; 88 percent and 80 percent were on nonsteroidal anti-inflammatory drugs (NSAIDs). Corticosteroid injections into the knees, on the other hand, were not permitted. Due to negative experiences, two of the 16 nurses in the treatment community withdrawn from the protocol; none of the nurses in the monitoring group withdrew. The mean average medical doctor's assessment outcomes did not differ between institutions at the end of the four weeks [SE=0.5693, 95 percent CI 20.17, 1.31], however there was a significant difference in decreases in patient VAS pain scores between the therapy and control classes. Mild burning was recorded by 44% of those in the therapy community at the site of capsaicin application, raising concerns about whether patients might be deemed blinded [19]. Topical capsaicin prescriptions accounted for over 120,000 of the 4.5 million rubefacient and other anti-rheumatic drug prescriptions written in England in 2002 (total costs £ 2.2 million) [60, 61].

Capsaicin preservation creams are the most commonly researched therapeutic type of capsaicin (Zostrix, Zostrix-HP, and Axsain). Rheumatoid arthritis, osteoarthritis, diabetic neuropathy, postherpetic neuralgia, postmastectomy pain syndrome, cluster headache, and reflex muscular dystrophy [62-70].

Curcumin [Diferuloyl methane]

Curcumin can suppress pro-inflammatory pathways linked to most chronic disorders and prevent TNF and TNF-mediated cell signaling both in different cell types. In in vitro and in vivo studies, curcumin may be a TNF blocker directly connecting to TNF [71-73].Curcumin is one of NSAIDs with both *in vivo* and *in vitro* anti-inflammatory and anti-oxidant activity [74].As an agent of potential use in RA treatment, curcumin has been of increased interest with the regulatory function of the associated antioxidant inflammatory factors [75].Curcumin can be the most successful candidate for RA therapy with overall improvement in Disease Activity Score and the American College of Rheumatology (testing of RA and RA disease symptoms in clinical practice and in clinical trials) in all three categories [76].

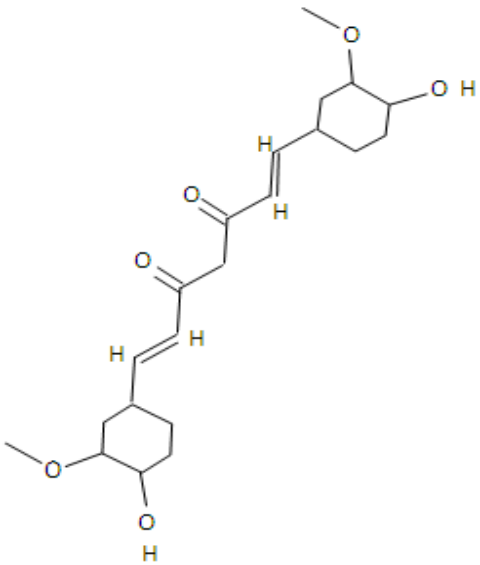

Fig 6. Structure of Curcumin

A crossover trial comparing 1200 mg per day curcumin to 300 mg per day curcumin included 18 patients. Curcumin is a part of the turmeric rhizome [Curcuma longa Linn.] that has anti-inflammatory properties. Morning

pain, walking time, and joint swelling were all greatly reduced in each category. Although the authors claim that "curcumin's anti-rheumatic action is persuasive," no distinctions were made between the curcumin and phenylbutazone classes [20].

Feverfew *[Tanacetum parthenium]*

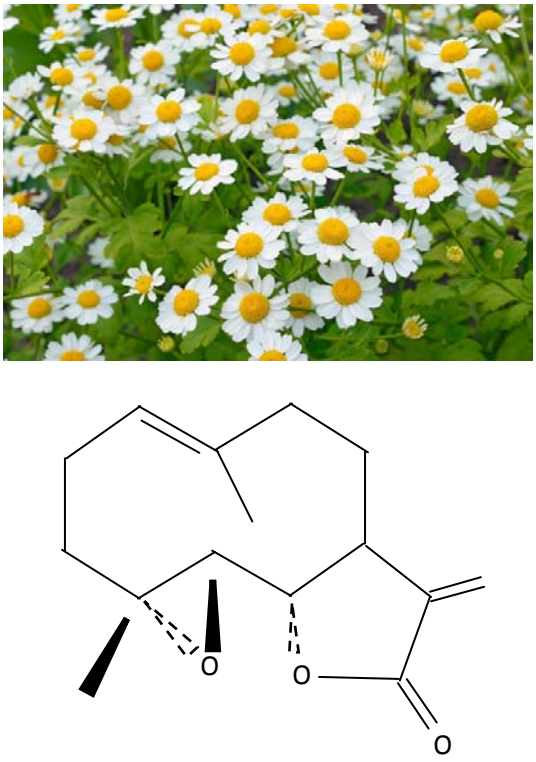

Fig 7. Photo and Structure of Tanacetum Parthenium.

Feverfew may inhibit the activity of platelet medicines (a blood-blood-flavored substance) to consult a health care provider before taking this herb for people taking blood-thinning medications such as aspirin and warfarin [57].

Feverfew may alter the effects of some prescription and non-prescription medications. If you are currently being treated with any of the following medications, you should not use feverfew without first talking to your health care provider [58, 59].

Half of 41 RA-symptomatic females were given dried powdered feverfew, half were given 70–86 mg/day, while the other half were given handled cobweed. Things are also being treated with NSAIDs and analgesics. At the end of six weeks, there was a significant grip gap between the treatment and placebo groups [ES=0,915, 95 percent CI 0,265, 1,57]. Some psychiatric reviews revealed no significant changes. The authors discovered that feverfew could help with RA, perhaps at higher doses or for a longer period of time [21,30].

Flaxseed Oil

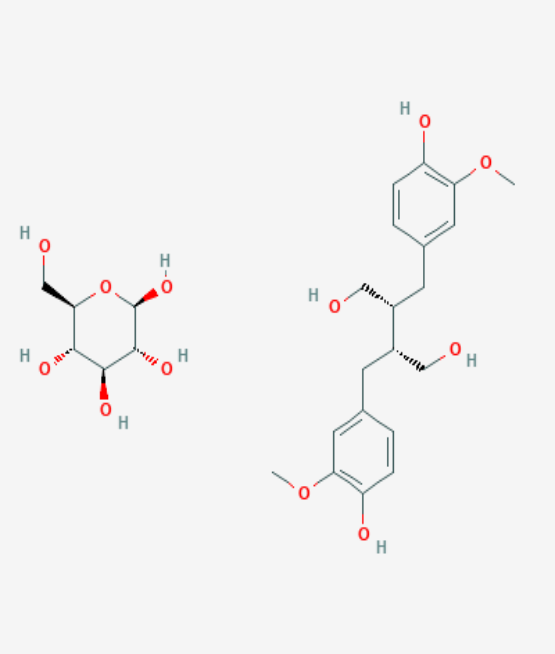

Fig 8. Structure of Flaxseed oil

Flaxseed is one of the best herbal suppliers of ALA (33-36), as well as lignans (phytoestrogens) (37, 38). Brown flax is a common ingredient in paints, coatings, cloth, and cattle feed (39-44). Linens are gluten-free and have a soybean-like amino acid profile (45-48).

Flaxseed is also thought to have anti-arrhythmic properties (49, 50). Flaxseed includes bioactive peptides including cyclolinopenopeptide A, which have a strong immunosuppressive and antimalarial effect in cultured Plasmodium falciparum (51, 52).

Twenty-two patients were given 30 g of flaxseed or safflower oil a day for 30 months. Any of the patients were given NSAIDs. Internal patient comparisons revealed that

neither group changed any therapeutic parameters [22, 31].

H15 [Extract of *Boswellia serrata, olibanum*]

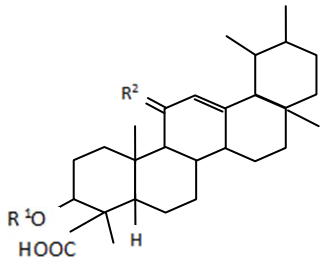

Fig 9. Photo and Structure of four pentacyclic txiterpenic acids[Boswellic acids]

Ayurvedic Traditional Medicine uses Boswellia serrata resinous extracts. Terpenes, b-sistotherin, and phlobaphene, as well as Arabinose, Galactose, and Sylose, are all contained in H15. Patients in the treatment community [n=18] received 1200 mg in the first week, and either 3600 mg or 2400 mg a day over the following 11 weeks; patients in the monitoring group [n=19] received no medication. Concurrent medications were permitted during the study if they had been taken three months prior.

Two patients in the therapy group tended to undergo oral steroids, although one patient in the therapy group and three patients in the placebo group received corticosteroid injections after six weeks. At the conclusion of the 12 weeks, the researchers saw no meaningful or clinically significant baseline improvements or discrepancies in the discomfort and swelling types. The usage of NSAIDs has declined by an estimate of 5.8% in the treatment community relative to 3.1 percent in the control group [23, 32].

RA-1 [standardized Ayurvedic formulation]

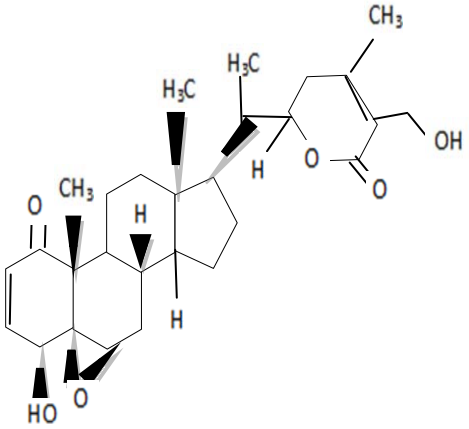

Fig 10. Structure of RA-1

RA-1 is a standardised solution produced from plant extracts of Withania somnifera (ashwagandha), Boswellia serrata (gugulla), Zingiber officinale (adrak or ginger), and Curcuma longa (haldi or circumin). RA-1 consists of 182 patients with active-on-chronic RA or placebo pills, with 80 active patients and 85 placebo patients having completed a four-month study. The patients were recruited from free 'arthritis testing and recovery camps,' which were held as part of a community-based government-wide RA advertising programme. The total regular alcohol dose was 444 mg, but in the event that the health condition worsened, the researcher was able to increase the dosage. Their dose rose from 28 out of 80 (35%) in the RA-1 sample to 44 out of 85 (52%) in the placebo group.

Though NSAIDs were prohibited during research, oral paracetamol in 500 mg tablets was permitted as a rescue analgesic if required. There was no statistically meaningful discrepancy between the RA-1 and placebo groups in improvements in therapeutic effectiveness or laboratory

efficacy variables at the end of the trial. However, in the therapeutic community, a higher proportion of patients recorded a reduction in joint pain of over 50% compared to the placebo group [P 0.5] [24].

Reumalex

100 mg powdered white willow bark BHP, 40 mg powdered guaiacum resin BHP, 35 mg powdered black cohosh BHP, 25 mg powdered ecstasy Sarsaparilla 4:1, and 17 mg powdered ecstasy bark 7:1 are included in this herbal blend. 502 patients with arthritis and 20 patients with RA were given two tablets of Reumalex or placebo [calcium phosphate] a day for two months. Subjects were able to hold whatever previously self-prescribed opioid doses they like, even analgesics, with little difference made between counselling groups. In each party, four patients completed the survey, but they did not decide if they had osteoarthritis or RA [25].

***Tripterygium wilfodii* Hook F [TWH]**

A herbal plant that grows predominantly in South China is described in ancient Chinese medicinal texts and is widely used for the treatment of joint pain in China. Tripterygium has been used in China for several decades to cure arthritis, and its toxicity is mainly intestinal (53, 54). In vitro HIV symptoms were shown in Tripterygium triptonin, diterpene lactone, and sesquiterpene alkaloids (55, 56). For three months, 70 patients with active symptoms who had not responded to NSAIDs for at least two months were given either 60 mg/day TWH or equivalent placebo tablets. As opposed to placebo, all metrics changed significantly at the end of the treatment: softened score, swelling count, morning rigidity, and grip power. The number of patients in the TWH division increased significantly, with a cumulative efficiency rate of more than 90%. These health improvements were shown in the first four weeks of treatment [26].

CONCLUSION

Rheumatoid arthritis [RA] is a progressive inflammatory autoimmune condition that affects more women than men and is more often seen in the elderly. RA is most common in middle-aged and older people, although it may also affect children and young adults. Although the exact cause of RA is unclear, its autoimmune growth and development may be influenced by DNA, the climate, and hormones. By stimulating endothelial cells and promoting the accumulation of immune system cells in synovial cells, cytokines and chemokines are responsible for causing or exacerbating the inflammatory response. RA usually begins steadily, with symptoms and signals appearing over many weeks or months. Rigidity, tenderness, and pain can be the first signs in at least one joint, particularly as the individual attempts to move the joint. Symptoms of tiny joints, such as the fingertips and toes, normally occur first. It's possible that you won't be able to get out of bed. Both sides of the body, both feet, and both hands are commonly affected by RA. The traditional goal of RA therapy is to reduce inflammation, because without it, patients can develop permanent disabilities. Aspirin and colloidal gold were once used to treat RA. NSAIDs, DMARDs (Biological, Herbal), and other natural and synthetic medications are now used to manage RA. These drugs help the patient regulate or reduce RA symptoms.

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