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AN OVERVIEW ON USE OF HERBAL MEDICINES IN RHEUMATOID ARTHRITIS

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Abstract

Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease that is characterized by joint stiffness in the morning, symmetric joint swelling, and generalized fatigue, pain, deformities of small joints of fingers and functional impairment. This review article is an overview of rheumatoid arthritis, its symptoms, the historical background of treatment of RA, complementary and alternative medical remedies, safety issues in use of herbal medicines, different medicinal plants studied for the treatment of RA. Additionally, marketed preparations and compounds under research are tabulated.

Keywords: Rheumatoid arthritis, complementary and alternative medical remedies; CAM; herbal remedies;; inflammatory diseases; arthritis

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease, which affects 1% of the world's population. Patients with RA not only have a progressive and debilitating disease and severe functional impairment, but can also experience a reduced life expectancy due to frequent involvement of the major organ systems. There have been profound changes in research and patient management of Rheumatoid Arthritis over the last 5 years. Developments in molecular biology have dramatically increased insight into the inflammatory and destructive pathways of this complex disease. Over half a million patients have been successfully treated with biologic therapy and advances in imaging techniques have allowed increasingly early detection of disease onset. Rheumatoid factor is no longer the

unchallenged gold standard autoantibody but has competition from the anti-citrulline antibodies. Environmental factors influencing both susceptibility and progression have been sought, and smoking has emerged as a powerful factor. Steady progress in genetics is finally being made and one day it may be possible to predict RA before onset of symptomatic disease.[1]

Symptoms of Rheumatoid Arthritis

The symptoms of rheumatoid arthritis (RA)is as follows:

1) morning stiffness in and around joints lasting at least 1 hour before maximal improvement;

2) soft tissue swelling (arthritis) of 3 or more joint areas observed by a physician;

3) swelling (arthritis) of the proximal interphalangeal, metacarpophalangeal, or wrist joints;

4) symmetric swelling (arthritis);

5) rheumatoid nodules;

6) the presence of rheumatoid factor; and

7) radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints.

Rheumatoid arthritis is defined by the presence of 4 or more symptoms. [2]

History of Rheumatoid Arthritis

In the 1920s, rheumatoid arthritis was called chronic infectious arthritis. Other terms for rheumatoid arthritis used by various authors included proliferative arthritis and atrophic arthritis.[3]The idea that this disease was caused by a chronic infection was based on reports first by workers in Europe in the late 1800s, who found microbes in blood and joints from patients with various forms of arthritis.[4]

As time went by, more investigators were unable to identify bacteria in blood and joints from similar patients; it was suggested that earlier findings were due to contaminants and a second variant of the chronic infection idea was advanced. This hypothesis held that toxins liberated from extra joint foci of infection caused the arthritis or, alternatively, an allergy developed to the released bacterial products and caused the arthritis. Arthritis seen in patients with psoriasis and inflammatory bowel disease was suspected to have a similar pathogenesis.[3,5]

In the 1920s, basic treatment at for patients with chronic arthritis (probably both chronic infectious arthritis and poly articular osteoarthritis) included a well-balanced diet, rest, and physical therapy.[4]

Physical therapy was considered important. Exercises were aimed at improving the range of motion of affected joints, strengthening muscles, and preventing deformities. [3,6]

Analgesics, including aspirin, sodium salicylate, cinchophen, and aminopyrine, were prescribed but were not considered a major aspect of therapy. In the 1920s, dilute hydrochloric acid was given orally if gastric analysis showed low acid content. Fowler's solution (which contained potassium arsenate) was administered to some patients as a general tonic. By the early 1930s, these last 2 agents were no longer prescribed. [7]

Treatment of Rheumatoid Arthritis Between 1920 and 1960

a) Vaccines

Nonspecific vaccine (protein) therapy had been introduced as a treatment in 1916 and was increasingly used in many centers during the following decade.It was thought that using a vaccine made from cultures taken from one or more patients with chronic arthritis might be more effective because the bacteria could be directly related to the disease. [8]

The vaccine was usually given intravenously.A prodromal period followed the injection, during which the patient might experience chills. Three to 5 hours after the injection, fever developed, and patients often experienced malaise, headache, gastrointestinal upset, and increased musculoskeletal pain. The temperature reached a maximum of 39° to 40°C and subsided within 6 to 12 hours. A period of euphoria and reduced joint pains often followed for varying time frames.Serious adverse reactions occurred, even death, but were considered uncommon.[9]

b) Surgical Sympathectomy

During the 1920s, surgical sympathectomy was performed in selected patients with chronic infectious arthritis. The rationale for this procedure was based on the theory that development of arthritis was influenced by a neurogenic defect that limited the circulation to involved joints. This defect was corrected, at least in part, by sympathectomy. Patients considered the most suitable for sympathectomy were young individuals with rapidly progressive arthritis. Good candidates demonstrated alterations in vasomotor activity evidenced by cold, clammy, sweaty hands and feet. Sympathectomy was also performed in patients with scleroderma and Raynaud phenomenon in an effort to improve

circulation to involved areas.The results were not uniform, and in the 1930s sympathectomy was limited to patients with scleroderma with Raynaud phenomenon and hypertension.[10-14]

c) Fever therapy

Fever therapy for arthritis was introduced in the early 1930s. The use of fever in the treatment of syphilis led to its trial in other infections, or conditions suspected of being infectious. The rationale was that an elevated temperature that killed microorganisms was tolerated by humans.The suspected relationship of an infection, most likely streptococcal, was an important reason to try fever therapy for chronic atrophic arthritis, even though it became known that body temperatures achieved by fever therapy did not kill typical streptococci. [15-17]

The failure to produce sustained improvement led to less use, and by the end of the 1930s fever therapy was seldom used except in occasional cases of reactive arthritis. [18,19]

d) Nutritional and physiotherapy

By the 1930s, when the theory of systemic infection as a cause of rheumatologic diseases faded, the term atrophic arthritis became preferred. Also, more attention was paid to the general condition of patients.[20]

e) Gold salt injections

Gold salt injections had first been used for arthritis in France in the late 1920s.Results appeared promising, and gold became used widely in Europe. Early results in the United States were not as encouraging. Toxicity was common, perhaps due to higher doses used in early studies. [21]

f) Others

A variety of other medications included colloidal sulfur injections,[22] thyroid gland preparations,[23] blood transfusions,[24] radiation therapy to joints,[25] and colonic irrigations.

g) Advent of cortisone

In 1949 the effect of cortisone was evaluated in acute rheumatic fever. In the first 3 patients, the symptoms of fever, tachycardia, and polyarthritis rapidly disappeared, and the erythrocyte sedimentation rate normalized, as did abnormalities on the electrocardiograms.[26]

During the next years, a number of cortisone analogues were developed with the hope of increasing the anti-inflammatory effect and reducing the adverse effects.[27 92]

The 40-year interval of 1920 to 1960 was a period of enormous advances in the care of patients with rheumatologic disorders. Between 1920 and 1940, rest, analgesics, and physical therapy were the main helpful treatments. However, the disease advanced, and many patients developed severe joint damage and disability and were confined to a chair or bed. By 1960, numerous medications were available. The improved understanding of most rheumatic diseases fostered better management and abandonment of unhelpful or even harmful therapies. Discarding the early concept of an infectious cause of rheumatoid arthritis and related conditions made the removal of "foci of infection," vaccine, and fever therapies unnecessary.[28]

Epidemiology of Rheumatoid Arthrits

Epidemiology is the study of the distribution and determinants of disease in human populations. Over the past decade there has been considerable progress in our understanding of the fundamental descriptive epidemiology (levels of disease frequency: incidence and prevalence, comorbidity, mortality, trends over time, geographic distributions, and clinical characteristics) of the rheumatic diseases. This progress is reviewed for the following major rheumatic diseases: rheumatoid arthritis (RA), juvenile rheumatoid arthritis, psoriatic arthritis, osteoarthritis, systemic lupus erythematosus, giant cell arteritis, polymyalgia rheumatica, gout, Sjögren's syndrome, and ankylosing spondylitis. These findings demonstrate the dynamic nature of the incidence and prevalence of these conditions – a reflection of the impact of genetic and environmental factors. The past decade has also brought new insights regarding the comorbidity associated with rheumatic diseases. Strong evidence now shows that persons with RA are at a high risk for developing several comorbid disorders, that these conditions may have a typical features and thus may be difficult to diagnose, and that persons with RA experience poorer outcomes after comorbidity compared with the general population. Taken together, these findings underscore the complexity of the rheumatic diseases and highlight the key role of epidemiological research in understanding these intriguing conditions. [29]

Biological Basis for Use Of Cam And Herbs In Ra: Treatment for RA are mostly symptomatic although recently it has been suggested that use of disease-modifying antirheumatic drugs (DMARDs) has led to important gains in our overall ability to treat RA patients, resulting in a better health status for patients with RA[30].

The value of DMARDs for treating OA or RA is also limited by their side effects and the fact that they are more expensive to use than traditional NSAIDs. The major side effects of NSAIDs are stomach ulcers, GI bleeding and perforations. Although a new class of NSAIDs—the specific inhibitors of COX-2—was developed, these drugs have similar efficacy as the general NSAIDs but are safer with respect to gastrointestinal toxicity.

However, some of these COX-2 inhibitors were recently withdrawn from the market or ordered by the United States Food and Drug Administration (FDA) to have a black box warning on the label because of concerns that their long-term use may increase the risk of stroke and heart attack. However, despite optimal use of currently available antirheumatic agents, most RA patients live with chronic pain and severe functional decline because these therapies focus primarily on preventing joint inflammation and soft tissue swelling, but are not effective in preventing cartilage breakdown and the joint destruction associated with RA.

Recently, efforts have been focused on using the class of drugs called biologics (antibodies or soluble receptors for IL-1, IL-6 and TNF-a) for the treatment of OA and RA. Although these agents reduce inflammation and joint destruction, their long-term risks and benefits are not yet clear. Additionally, higher costs and the findings that they are not effective universally and severe side effects such as life-threatening infections and increased risk of malignancies limit the use of such agents in many populations.[31-35]

Because of these and other limitations, the use of complementary and alternative medicine (CAM) therapies, such as acupuncture and extracts of medicinal herbs, is on the rise and according to reports _60–90% of dissatisfied arthritis patients are likely to seek the option of CAM therapy.[36,37]

Complementary and Alternative Medicines

They are defined by the World Health Organisation as: “A broad set of health care practices that are not part of the country’s own tradition and are not integrated into the dominant healthcare system[38]

"Complementary medicine" refers to use of CAM together with conventional medicine, such as using acupuncture in addition to usual care to help lessen pain. Most use of CAM by Americans is complementary.

"Alternative medicine" refers to use of CAM in place of conventional medicine.

"Integrative medicine" (also called integrated medicine) refers to a practice that combines both conventional and CAM treatments for which there is evidence of safety and effectiveness.[39]

Types of CAM[39]

CAM practices are often grouped into broad categories, such as natural products, mind-body medicine, and manipulative and bodybased practices. Although these categories are not formally defined, they are useful for discussing CAM practices. Some CAM practices may fit into more than one category.

Natural Products: This area of CAM includes use of a variety of herbal medicines (also known as botanicals), vitamins, minerals, and other "natural products." Many are sold over the counter as dietary supplements. (Some uses of dietary supplements—e.g., taking a multivitamin to meet minimum daily nutritional requirements or taking calcium to promote bone health—are not thought of as CAM.) CAM "natural products" also include probiotics—live microorganisms (usually bacteria) that are similar to microorganisms normally found in the human digestive tract and that may have beneficial effects. Probiotics are available in foods (e.g., yogurts) or as dietary supplements.They are not the same thing as prebiotics—nondigestible food ingredients that selectively stimulate the growth and/or activity of microorganisms already present in the body.

Mind-Body Medicine: Mind-body practices focus on the interactions among the brain, mind, body, and behavior, with the intent to use the mind to affect physical functioning and promote health. Many CAM practices embody this concept—in different ways.

Meditation techniques include specific postures, focused attention, or an open attitude toward distractions. People use meditation to increase calmness and relaxation, improve psychological balance, cope with illness, or enhance overall health and well-being.

The various styles of yoga used for health purposes typically combine physical postures, breathing techniques, and meditation or relaxation. People use yoga as part of a general health regimen, and also for a variety of health conditions.[39]

Summary of complementary and alternative system of medicine[40]

• Homeopathy • Naturopathy • Traditional Chinese medicine • (including acupuncture) • Ayurveda	Complete systems of theory and practice
Mind–body interventions • Meditation • Hypnotherapy • Creative therapies, e.g. art, music, dance	Techniques to enhance the mind's capacity to affect bodily function
Biologically based therapies • Herbalism • Dietary manipulation and supplements • Vitamins	Use of naturally occurring substances
Manipulative and body-based • Chiropractice • Osteopathy • Reflexology • Massage	Based on movement or manipulation of one or more parts of body
Energy therapies • Biofield, e.g. Reiki • Bioelectromagnetic field therapy	Unconventional use of magnetic and electromagnetic fields

"Acupuncture" is a family of procedures involving the stimulation of specific points on the body using a variety of techniques, such as penetrating the skin with needles that are then manipulated by hand or by electrical stimulation. It is one of the key components of traditional Chinese medicine, and is among the oldest healing practices in the world. Ex. deep-breathing exercises, guided imagery, hypnotherapy, progressive relaxation, qi gong, and tai chi.

Manipulative and Body-Based Practices: Manipulative and body-based practices focus primarily on the structures and systems of the body, including the bones and joints, soft tissues, and circulatory and lymphatic systems. Two commonly used therapies fall within this category: Spinal manipulation and massage therapy. [39]

Herbal Medicines

Herbal medicine, in which plants (dried or in extract form) are used as therapeutic substances, is one of a number of practices encompassed by the term "complementary and alternative medicine" (CAM). [41]

Traditional medicine using herbal drugs exists in every part of the world. The major areas are Chinese, Indian and European traditions. The philosophies of these traditional medicines have some resemblance to each other but differ widely from modern Western medicine. In view of the progress of Western medicine not only new synthetic drugs but also herbal drugs have to fulfill the international requirements on quality, safety and efficacy. Herbal drugs have the advantage of being available for patients in the geographical area of the special traditional medicine. The development procedure of herbal drugs for world-wide use has to be different from that of synthetic drugs**.[41]**

Practically every country develops its own medical system, which includes the ancient civilization of China, Egypt and India. Thus, the Indian Medical System-Ayurveda came into existence. The raw materials for Ayurvedic medicines were mostly obtained from plant sources in the form of crude drugs such as dried herbal powders or their extracts or mixture of products. Also, Siddha, Unani and Tibb are traditional health care systems have been flourishing for many centuries. Apart from these systems there has been a rich heritage of ethnobotanical usage of herbs by various colorful tribal communities in the country**[42]**.

Vast ethnobotanical knowledge exists in India from ancient time. Our work over four decades, both in the field and literary studies, has resulted in a dictionary of Indian folk-medicine and ethnobotany that includes 2532 plants. India has about 45,000 plant species; medicinal properties have been assigned to several thousand. About 2000 figure frequently in the literature; indigenous systems commonly employ 500. Despite early (4500-1500 BC) origins and a long history of usage, in the last two centuries Ayurveda has received little official support and hence less attention from good medical practitioners and researchers. Much work is now being done on the botany, pharmacognosy, chemistry, pharmacology and biotechnology of herbal drugs. The value of ethnomedicine has been

realized; work is being done on psychoactive plants, household remedies and plants sold by street drug vendors. Statistical methods are being used to assess the credibility of claims. Some recent work in drug development relates to species of *Commiphora* (used as a hypolipidaemic agent), *Picrorhiza* (which is hepatoprotective), Bacopa (used as a brain tonic), *Curcuma* (anti-inflammatory) and *Asclepias* (cardiotonic). A scrutiny of folk claims found 203 plants for evaluation. Less well known ethnomedicines have been identified that are used to treat intestinal, joint, liver and skin diseases[43].

SAFETY ISSUES IN USE OF HERBAL MEDICINES

Although it is widely perceived that "natural" products are safe, the evidence suggests that CAM use is not without risk. Of 90 patients with rheumatoid arthritis, 82% had tried more than one form of alternative medicine or therapy, including dietary modification, and 31% of these patients had experienced at least one adverse effect.[44]

Intrinsic effects are those of the herb itself and are characterised, as for pharmaceuticals, as type A (predictable, dose-dependent) and type B (unpredictable, idiosyncratic) reactions.[45]

Extrinsic effects are not related to the herb itself, but to a problem in commercial manufacture or extemporaneous compounding. Potential failures to adhere to a code of Good Manufacturing Practice, while not specific to herbal medicine, can occur, particularly in developing countries where such a code is not in place.

1: Classification of adverse effects associated with herbal medicine

Intrinsic

Type A reactions: Predictable toxicity, overdosage, interaction with pharmaceuticals

Type B reactions: Idiosyncratic reactions (e.g., allergy, anaphylaxis)

Extrinsic

Failure of good manufacturing practice:

- Misidentification
- Lack of standardisation
- Contamination
- Substitution
- Adulteration
- Incorrect preparation and/or dosage; and
- Inappropriate labelling and/or advertising.

Adapted from Bensoussan and Myers.[14]

Misidentification: It is difficult to track and identify adverse effects of herbal ingredients, as the plants can be named in four different ways -- the common English name, the transliterated name, the latinised pharmaceutical name, and the scientific name.It is essential that plants are referred to by their binomial Latin names for genus and species; misidentification can occur when other names are used.[46]

Lack of standardization: The therapeutic/toxic components of plants vary depending on the part of the plant used, stage of ripeness, geographic area where the plant is grown, and storage conditions. Therefore, batch-to-batch reproducibility of plant material should be assessed in the production of marketed products, but, in practice, product variation in herbal medicines can be significant.

Contamination: During growth and storage, crude plant material can become contaminated by pesticide residues, microorganisms, aflatoxins, radioactive substances and heavy metals;lead, cadmium, mercury, arsenic and thallium have been reported as contaminants of some overseas herbal preparations.[47]

Substitution:

Adulteration: The intentional use of pharmaceutical adulterants has been reported.

Incorrect preparation/dosage: The processing of crude plant material carried out by a manufacturer, CAM practitioner or the patient is a major determinant of the pharmacological activity of the finished product.

Inappropriate labeling/advertising.

BOSWELLIA SERRATA

Family: Herbal medicine of the burseracea family.

Scientific name: Boswellia serrata.

Other names: Resin, olibanum, salai guggal,11-keto ß-boswellic acid, acetyl-11-keto ß-boswellic acid (AKBA), African elemi, Arabian incense (Bakhour), Boswellia serrata gum resins, boswellic acids, boswellic, Sallaki®, S-compound®.5-LOXIN®.[48-49.]

Description: Indian frankincense is a plant extract which is used as an Ayurvedic remedy for the treatment of a number of diseases. In the ancient ayurvedic medical texts of india, the gummy exudates from the Boswellia tree is grouped with other gum resins and referred to collectively as guggals. Historically, the guggals were recommended

for a variety of conditions including arthritis, diarrhea, dysentery, pulmonary disease, and ringworm. Salai guggal is very effective in osteoarthritis, juvenile rheumatoid arthritis, soft tissue fibrositis and spondilytis without any side effect.[50]

Mechanism of action: Gum resin of Boswellia serrata, which were demonstrated to act as antiinflammatories in vivo animal models, were studied in a set of in vitro experiments in order to elucidate the mechanism of their beneficial effects. Boswellic acids were isolated from the gum resin of Boswellia serrata and identified as the active principles. Boswellic acids inhibited the leukotriene synthesis via 5- lipoxygenase and the cycloxygenase activities. Boswellic acids did not impair the peroxidation of arachidonic acid by iron and ascorbate. The data suggest that boswellic acids are specific, non-redox inhibitors of leukotriene synthesis either interacting directly with 5-lipoxygenase or blocking its translocation.[51]

Safety and toxicity: As it is a emmenagogue, may cause abortion.[52]

BLACKCURRENT SEED OIL[53,54]

Family: Herbal medicine of the Saxifragaceae family.

Scientific name: Ribes nigrum.

Other names: Quinsy Berries, squinancy berries, cassis, red currant, European black currant, mustaherukka, grosellero negro, siyah frenkuzumu.

Description: Ribes nigrum is a plant native to northern parts of Europe and Asia. The fruit of this plant is formed from a very dark purple berry containing seeds. The berries and leaves of this plant are used medicinally for maintaining health and treating several diseases. Blackcurrant seed oil is rich in both omega- 3 and 6-fatty acids that are important for maintaining joints cell structure and function and can fight joint inflammation. This dietary supplement is available over-the-counter as capsules and as bottled oil. It is considered to be a relatively safe medication. However, the little available evidence suggests that blackcurrant seed oil may not be effective in treating RA.

Mechanism of action: Oil derived from blackcurrant seeds is rich in both omega-3 alpha-linolenic acid (ALA; 13 per cent) and omega-6 gamma-linolenic acid (GLA; 17 per cent). These essential fatty acids are also important for

maintaining joints' cell structure and function. Both ALA and GLA are converted in the body to hormone-like substances, called prostaglandins, which regulate the immune system and fight joint inflammation. GLA might also suppress inflammatory responses by directly acting on some inflammatory cells.

BORAGE SEED OIL[55, 56]

Family: Herbal medicine of the Boraginaceae family.

Scientific name: Borago officinalis.

Other names: Star flower oil, bee bread, tailwort, common bugloss, echiun amoenum

Description: Borago officinalis is an annual herb native to the Mediterranean region, but cultivated in other countries.The MedicInal product is derived from the plant seed oil.

Mechanism of action: In addition to its content of tannic, oleic and palmetic acid, the oil derived from borage seed contains very high levels of two types of polyunsaturated omega-6 essential fatty acids: linolenic acid (LA; converted in the body to GLA) and gammalinolenic acid (GLA; 20 per cent - 26 per cent). GLA is a vital precursor of hormone-like molecules in the body called prostaglandins which regulate the immune system and fight joint inflammation. GLA might also suppress inflammatory responses by directly acting on some inflammatory cells. Sunflower oil and other oils generally used in normal diet contain only LA. Several factors can interfere with the production of GLA from LA in the body. These include aging, dietary deficiencies, viral infections
and some diseases. Borage seed oil is the richest source of pure GLA.

Safety and toxicity: Reported adverse effects include nausea, indigestion, headache and skin rash.

CAPSAICIN[57]

Family: Solanaceae

Scientific name: Capsicum annum

Description: an active component derived from the fruit of capsicum annum .this substance has been used to relieve pain ,improve circulation and to treat psoriasis topically becouse of its pungent nature ,capsaicin is thought to have carcinogenic activities, however a study in rats demonstrated that topical application of capsaicin does not induce tumors.[58]

Mechanism of action: Capsaicin is believed to cause depolarization pf c-fiber polymodal nociceptors and release of substance p,which is a neurotransmitter that relays pain signals to the brain .this action may actually increase pain sensation after initial use .however ,

Interactions:repat applications deplete the reserves of substance p at the afferent neurons leading to pain relief.[59]

Safety and toxicity: Adverse effects include burning, urticaria,and contact dermatitis.

The acute toxicity of capsaicin shows a large variation depending on the route of administration. In male mice , the ld 50 varies from 0.56 mg/kg (i.v.)to 60-75 mg/kg body weight (in ethanol) and 190 (122-294) mg/kg b.w body weight. (in dimethyl sulfoxide), following iktragastric intubation. The possible cause of death was considered to be due to respiratory paralysis36 intraduodenal and intragastric administration of 10% caosaicum as well as 0.014% capsaicin in 0.85% saline to msle rats produce morphological damage in the duodenal mucosa.[60]

CURCUMA LONGA

Family: A member of the Zingiberacea family

Scientific name: Curcuma Longa

Other names: Turmeric, Haldi, haridra. [61]

Description: Turmeric is a widely used spice and coloring/flavoring agent that comes from the root of the plant C. longa, The FDA classified turmeric among substances 'generally recognized as safe'. In Ayurveda, turmeric has been used for various medicinal conditions including rhinitis, wound healing, common cold, skin infections, liver and urinary tract diseases and as a 'blood purifier' [62-65]. Turmeric was found to be effective even when given by different routes including topical, oral or by inhalation, dependent on the intended use. The major constituent of turmeric is curcumin (diferuloylmethane), which constitutes up to _90% of total curcuminoid content, with demethoxycurcumin and bis-demethoxycurcumin comprising the remainder.[63]

Mechanism of action: NSAIDs may act via single or combination of any of the mechanism involving inhibition of arachidonic acid metabolism, inhibition of cycloxygenase (COX) inhibition of the PG synthesis, inhibition of lipoxygenase (LOX), inhibition of cytokines (IL, TNF, etc) release of steroidal hormones from the adrenals, stabilization of lysosomal membrane and uncoupling of oxidative phosphorylation etc.

Curcumin reduces pro-inflammatory leukotriene synthesis via inhibition of LOX enzyme.

Various diaryl-heptonoids, including curcumin,were found to be potent inhibitors of 5-HETE productions by intact human meutrophils with IC 50 values ranging from 4 to 8 µm.[66]

Safety and toxicity: Because of the possibility of antiplatelet activity, caution shoul be taken with respect to concurrent use of curcumin with anticoagulants and with medications and dietary supplemensts known to have antiplatelet activity.

Contraindications: Curcumin act as a menstrual stimulant so avoided in pregnancy, it shoul be avoided in patients with bleeding disorder and bile duct obstruction.[67]

CAT'S CLAW[68]

Family: Rubiaceae family.

Scientific name: Uncaria tomentosa.

Other names: Life-giving vine of Peru, una de gato.

Description of the compound: Cat's claw is extracted from the stem and root of some woody vines native to South and Central America. Cat claw (Cat's claw is a Peruvian vine with medicinal properties that are well-documented in alternative medicine literature. Extract of cat's claw has been shown to possess antioxidant, anti-inflammatory and immunomodulating properties.The chemical composition of the aqueous extract of U. tomentosa vine includes oxindole alkaloids (virtually absent in U. guianensis) tannins, quinovic acid, glycosides, flavonoids and sterols. The most investigated of the active constituents in U. tomentosa extract for immunomodulating and anti-inflammatory effects are pentacyclic oxindole alkaloids, which are reported to induce a yet unknown immune regulating factor. The use of an extract of cat's claw from the part of the vine that is rich in pentacyclic alkaloids (roots) showed a reduction in the number of painful joints when compared to placebo in patients with RA. Since no adverse effects were reported, this small preliminary study demonstrated the relative safety and modest benefit to the tender joint count of a highly purified extract from the pentacyclic chemotype of U. tomentosa in patients with active RA taking sulfasalazine or hydroxychloroquine.

Safety and toxicity: In some cases, mild nausea may occur upon ingestion of crude extracts or teas (perhaps due to micropulverized bark in some preparations), and diarrhea may occur.

Mechanism of action: Studies in the laboratory have found that cat's claw can prevent the activation of several inflammatory substances in the body. Studies have also shown that cat's claw has anti-oxidant properties (i.e. can prevent cell damage in the body by interacting with harmful molecules produced within cells known as free radicals). Studies on animals have also confirmed these anti-inflammatory properties.

Interactions: Cat's claw may increase the effect of drugs used to treat hypertension, so should be taken with caution in patients receiving treatment for hypertension. Laboratory studies have also found that cat's claw can stimulate the production of certain immune hormones called cytokines. These cells are important for immunity. For that reason patients who are on medicines that suppress the immune system should be cautious when taking this compound.

EVENING PRIMROSE OIL[69, 70]

Family: Plant family of Onagraceae.

Scientific name: Oenothera biennis.

Other names: Tree primrose, fever plant, night willow herb, King's-cure-all, scabish, scurvish, sun drop, suncups.

Description of the compound: EPO is a North American native biennial plant, but now found all over the world. The medicinal product is derived from the plant's seeds. EPO is rich in polyunsaturated omega- 6 fatty acids that can help in the regulation of pain and inflammation with no major safety problems. Products containing this compound are available in most pharmacies, health food shops and supermarkets. Evidence for the effectiveness of EPO in reducing joint pain in RA patients is not conclusive. However, there is some evidence for effectiveness in improving morning stiffness. EPO does not seem to modify long-term disease activity, so, if used, should be taken along with conventional therapy.

Mechanism of action: EPO is a rich source of two types of polyunsaturated omega-6 essential fatty acids: linolenic acid (LA; 70 per cent; converted in the body to GLA) and gamma-linolenic acid (GLA; two–15 per cent). GLA is a vital precursor of hormone-like molecules in the body called prostaglandins which are important for the regulation of pain and inflammation. GLA might also suppress inflammatory responses by directly acting on some inflammatory

cells. Sunflower oil and other oils generally used in normal diet contain only LA. Several factors can interfere with the production of GLA from LA in the body. These include aging, dietary deficiencies, viral infections and some diseases. EPO is one of the richest sources of pure GLA.

Safety and toxicity: The compound, if taken in the correct dose, has no major safety problems. Common adverse effects include nausea, diarrhoea and skin rash. Patients with epilepsy or seizure disorder should not take this product as it can induce seizures.

Interactions: Not well studied, but interactions with anti-inflammatory drugs (e.g. cortisone) and anticoagulants (e.g. aspirin, warfarin) are possible.

FEVERFEW[71, 72]

Family: Perennial plant in the family Compositae (sunflower family).

Scientific name: Chrysanthemum parthenium, (or tanacetum parthenium).

Other names: Bachelor's buttons, featherfew, Santa Maria, Mother-herb, altamisa, featherfoil, flirtwort, midsummer Daisy, febrifuge plant.

Description of the compound: Chrysanthemum parthenium or feverfew is a perennial, originally native to Eastern Europe and Asia Minor, but is now cultivated throughout Europe and America. Medicinally-used compounds are prepared from the leaves of the plant. Feverfew, reputed by folklore to be effective in arthritis, has in vitro properties that could be beneficial in the control of inflammatory disease. Forty one female patients with symptomatic rheumatoid arthritis received either dried chopped feverfew (70-86 mg) or placebo capsules once daily for six weeks. Allocation was random and not known by patient or observer. Variables assessed included stiffness, pain (visual analogue scale), grip strength, articular index, full blood count, erythrocyte sedimentation rate, urea, creatinine, C reactive protein, complement breakdown products (C3dg), rheumatoid factor titre, immunoglobulins (IgG, IgA, IgM), functional capacity, and patient and observer global opinions. Feverfew is believed to have anti-inflammatory and analgesic properties.

Mechanism of action: Feverfew is believed to have a range of properties, including anti-inflammatory and analgesic. It has been postulated that it reduces the release of an inflammatory substance, serotonin, from blood cells

and slows down the production of a chemical transmitter in the body called histamine. Both serotonin and histamine play an important role in migraine headache.

Safety and toxicity: No major safety problems have been identified in short-term use. The long-term safety is not known. Reported adverse effects from previous studies (mainly on migraine patients) include mouth ulceration, indigestion, heartburn, colicky abdominal pain, dizziness and skin rash.

FISH OIL[75-79]

Family: Dietary supplements; omega-3 essential fatty acids.

Scientific name: Fish oil (fish body oil and/or fish liver oil).

Description of the compound:

Fish body oil: These are dietary supplements derived from tissues of fatty fish like sardines, sprat, salmon, and mackerel.

Fish liver oil: These are dietary supplements derived by pressing cooked liver of cod (most commonly), halibut or shark.

Fish body oil and fish liver oil (cod-liver oil) are rich in omega-3 essential fatty acids which can regulate the body's immune system and fight joint inflammation. Cod-liver oil is also a rich source of vitamin A (a strong anti-oxidant) and vitamin D (important for maintaining healthy joints). Evidence suggests that both fish body and liver oils are safe with no major adverse effects if taken at therapeutic doses. There is good evidence that fish body oil can result in improvement in the symptoms associated with RA. There is also some unconfirmed evidence that the combined treatment of fish body and liver oils might be of longterm benefit to patients with RA, particularly in reducing daily requirements of NSAIDs.

Mechanism of action: Fish body and/or liver oils are rich in omega-3 essential fatty acids. These fatty acids have strong anti-inflammatory properties. Firstly, they significantly reduce the release of several proinflammatory elements from white blood cells. Secondly, they form the building blocks for the production of anti-inflammatory substances in the blood called prostaglandins. Prostaglandins are hormone-like substances that regulate the immune system and fight joint inflammation. Omega-3 fatty acids also play a role in lowering cholesterol and triglyceride

levels in blood, hence reducing the risk of heart disease and stroke in patients with inflammatory types of arthritis. Fish liver oil (cod-liver oil – see below) also contains high levels of vitamin A and D. Vitamin A is a strong anti-oxidant (i.e. can prevent cell damage in the body by interacting with harmful molecules produced within the cells known as free radicals). Vitamin D, in addition to its role in maintenance of a healthy musculoskeletal system, plays an important part in the production of proteoglycan in joint cartilage.

Safety and toxicity: Fish body and fish liver oils are considered to be safe at therapeutic doses. The most common adverse effect is stomach upset. However if these oils are consumed in very high doses there is concern about potential environmental contaminants such as methyl mercury and polychlorinated biphenyls (PCBs). These compounds can also accumulate in people eating fish frequently. Adverse effects, at therapeutic doses, which are usually minor and uncommon, include stomach upset, flatulence and diarrhoea. It is important not to consume large amounts of fish liver oil (codliver oil), so as not to exceed recommended dietary allowance of vitamin A. Excess intake of vitamin A can lead to liver problems and hair loss. Excess vitamin A may also harm unborn babies and therefore cod liver oil and vitamin A supplements should be avoided in pregnancy.

Interactions: Fish body or liver oils can interfere with blood clotting, so should not be taken together with other medications which prevent clotting (e.g. aspirin and warfarin).

FLAXSEED OIL[80]

Family: Herbal medicine of the Linaceae plant family.

Scientific name: Linum usitatissimum (or flax plant).

Other names: Linseed, brown, golden flaxseed.

Description of the compound: The flax plant is native to Egypt, but cultivated in many places, including Europe and the United States. Oil extracted from the plant seeds is used medicinally for treating several diseases.

Mechanism of action: Flaxseed oil contains alpha linolenic acid (ALA), which is an omega-3 essential fatty acid. ALA is converted into two important compounds within the body – DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid). Both DHA and EPA play a significant role in the production of anti-inflammatory substances in the blood called prostaglandins. These hormone-like substances regulate the immune system and fight

joint inflammation. Flaxseed oil also contains some chemicals called lignans, which have anti-oxidant properties and hence have been used to prevent cardiovascular disease.

Safety and toxicity: Adverse effects include stomach discomfort, rash and breathing difficulties. In theory, flaxseed may increase the blood sugar level and increase the risk of bleeding.

Interactions: Flaxseed might increase the risk of Bleeding if taken with other medications which affect blood clotting like aspirin, heparin and warfarin.

T. WILFORDII HOOK F[81-84]

Family: The botanical family "Celastraceae".

Scientific name: Tripterygium wilfordii Hook.

Other names: T Wilfordii Hook F (TWHF), Lei gong teng, Lei-kung teng, Huang-teng ken, Tsao-ho-hua, yellow vine root, early rice flower, three-wing nut.

Description of the compound: Tripterygium is a perennial vine which grows in the mountains of China, Taiwan and Myanmar. With the exception of its root pulp (which is used medicinally), all other components of the vine are poisonous. In China, extracts from the vine's roots made with ethyl acetate and chloroform-methol are packaged into capsules and have been used to treat a broad spectrum of autoimmune and inflammatory diseases including RA. Extracts made with chloroformmethol are also named T2. T. wilfordii Hook F (TwHF) is a perennial vine-like plant that grows in Southern China and Taiwan and is also known as 'Thunder God Vine'. The medicinal extract is derived from the root and has been used for the treatment of various autoimmune and inflammatory diseases including RA, systemic lupus erythematosus, nephritis, psoriasis and asthma for several centuries. An ethanol/ethyl acetate extract of TwHF showed therapeutic benefit in patients with treatmentrefractory RA. At the dosages used, the TwHF extract was well tolerated by most patients in this study. A prospective, double blind, placebo-controlled study of TwHF ethanol/ ethyl acetate extracts with RA patients has also been reported[34]. With a two-dose regimen, (180 and 360 mg day_1) used for 20 weeks, patients at the higher dose achieved a rapid ACR-20 response with 50% of patients improving during the first 4 weeks of treatment. Both treatment groups showed a significant decrease in the number of tender and swollen joints and improvement in the physician's global assessment. In another phase-I

study, eight out of nine patients treated with TwHF extract (>360 mg day_1) showed improvements in both clinical manifestations and laboratory findings[35]. One patient met American College of Rheumatology criteria for remission. Based on these data it was concluded that the extract of TwHF at dosages up to 570 mg/day, appeared to be safe, and doses >360 mg/ day, were associated with clinical benefit in patients with RA. In both of these studies, no toxic or adverse effects other than diarrhea were observed in patients receiving the highest dose. Topical application of TwHF was also tested in a randomized, double-blind, placebo-controlled trial using 61 patients with RA and the authors concluded that topical application of TwHF was efficacious in improving ACR-20 score. In these and other studies, the most common side effects of TwHF were vomiting, hair loss, diarrhea, headaches, dryness, abdominal pain and vaginal spotting. TwHF usage can also lead to the development of amenorrhea, which is reversible if present for <2 years in patients <40 years of age but irreversible in perimenopausal women patients.

Mechanism of action: Studies in the laboratory and on animals show that thunder god vine reduces the production of the proteins responsible for inflammation of joints. These studies have also found that thunder god vine has an immunosuppressive activity (i.e. it is capable

of reducing the activity of the body's immune system.

Safety and toxicity: Well documented adverse effects include stomach pain, diarrhoea, nausea, headache, skin rash, hair loss, infertility in men and amenorrhea (failure to menstruate) in women. The herb can also be extremely poisonous if it is not extracted properly.

TCM[85]

Family:

Scientific name: Tong luo kai bi.

Other names: Tong Ren Da Huo Luo Wan.

Description of the compound: A mixture of traditional Chinese medicines for RA. Tong luo kai bi is a Chinese herb being used by some patients with RA. The mechanism of action and safety of these pills is still largely unknown, and there is little evidence available at present on which to judge whether or not this Chinese herb is effective in the treatment of RA. One RCT conducted in China evaluated the potential beneficial effects of this

Chinese herbal compound in patients with RA. A total of 120 patients were randomly assigned to either tong luo kai bi tablets or placebo tablets. Moderate improvement and marked improvement was achieved by 43 per cent and 45 per cent, respectively, of patients taking the active treatment. Moderate improvement and marked improvement was achieved by 55 per cent and 27 per cent of patients on the placebo treatment. Tong luo kai bi is a Chinese herb being used by some patients with RA. The mechanism of action and safety of these pills is still largely unknown, and there is little evidence available at present on which to judge whether or not this Chinese herb is effective in the treatment of RA.

WITHANIA SOMINIFERA [86]

Family: Solanacea

Scientific name: Withania sominifera

Other names: Withanolide

Description: Withanolides, which are extracted from Withania somnifera, are employed in the treatment of arthritis and are known to be potent inhibitors of angiogenesis, inflammation and oxidative stress. Our group showed for the first time that withanolides can indeed inhibit the activation of NF-κB and NF-κB-regulated gene expression which could explain their anti-arthritic actions. Begum and Sadique showed for the first time the long-term effects of W. somnifera on adjuvant-induced arthritis in rats. More recently, Rasool and Varalakshmi investigated the effect of W. somnifera root powder on paw volume and serum lysosomal enzyme activities in rats in which arthritis was induced with MSU crystal. In addition, the levels of β-glucuronidase and lactate dehydrogenase were measured in MSU crystal-incubated polymorphonuclear leucocytes. Significant increases in both paw volume and the levels of serum lysosomal enzymes were observed in rats with MSU crystal-induced arthritis. Increased β-glucuronidase and lactate dehydrogenase levels were observed in untreated polymorphonuclear leucocytes incubated with MSU. Upon treatment with W. somnifera root powder (500 mg/kg to 1000 mg/kg), β-glucuronidase and lactate dehydrogenase levels reverted to near normal. W. somnifera also displayed potent analgesic and antipyretic effects, without any sign of gastric damage, at different doses in experimental rats; the NSAID indomethacin was used as a standard. These

results provide evidence for the suppressive effect of W. somnifera root powder on arthritis by reducing amplification and propagation of the inflammatory response, without causing any gastric damage.

WILLOW[87, 88]

Family: Herbal medicine of Salicaceae (Salix) family.

Scientific name: Willow.

Other names: Salix spp., basket willow, bay willow, beta-salicin, black willow, brittle willow, crack willow, daphne willow, populin, purple willow, salicin, salicortin, salicoylsalicin, salicyl alcohol, salicylate, salicylic acid, salicyluric acid, salidroside, saligenin, salipurposide, Salix alba, Salix daphnoides, Salix fragilis L., Salix pentandra, Salix purpurea, white willow, white willow bark, willow tree, willowprin.

Description of the compound: The bark of some, but not all, species of Salix trees has been used for treating inflammatory and arthritis related conditions since ancient times. Extracts from the following species of Salix trees have been used as sources of willow: Salix purpurea (purpule willow), Salix fragilis (crack willow), Salix alba (white willow), Salix daphnoides (violet willow) and Salix pentandra (bay willow). These Salix species are also considered the natural source of acetylsalicylic acid (also known as aspirin).

There are many salicin-containing plants, including willow, meadowsweet, cottonwood, aspen, poplar, and wintergreen. Some people may not get the pain relieving effect of willow (Salix spp), since the conversion of salicin to the more active salicylic acid seems to be genetically predetermined and influenced by gut flora. Studies on willow bark are few, methodologically poor, and provide mixed results for acute back pain and OA (15, 16). One issue with willow bark products is that the level of salicin can vary dramatically across various willow species, from 2% to 11% depending upon the species and the time of year it was harvested. It is probably advisable, if using willow bark, to use a standardized extract that provides a daily dose of 240 mg salicin. A full dose of willow extract, 240 mg/day, has less of an inhibitory effect on platelet aggregation than 100 mg/day of aspirin, so it may offer a safer alternative for some patients (17).

Mechanism of action: Willow bark contains an ingredient called salicin, which is transformed in the body into another chemical substance called salicylic cid. Similar to acetylsalicylic, salicylic acid inhibits the production of

certain prostaglandins in the nerves and this effect relieves pain and discomfort. Willow bar showed anti-inflammatory activity in several laboratory based studies.

Safety and toxicity: Willow bark should be used with caution in patients with gastrointestinal problems, liver problems and diabetes. Common adverse effects include stomach upset, increased blood pressure and allergic reactions. Overdose can lead to serious consequences including stomach ulcers and bleeding.

Interactions: Similar to aspirin, willow bark interacts with the following drugs: anticoagulants (e.g. heparin, aspirin); acetazolamide; drugs for hypertension; anti-inflammatory drugs (e.g. cortisone and NSAIDs) and beta blockers (e.g. propranolol).

ZINGIBER OFFICINALE [89-91].

Family: Herbal medicine; Zingiberaceae (ginger family).

Scientific name: Zingiber officinale.

Other names: Gan Jiang, zingiber, EV.EXT35, African ginger, black ginger, chayenne ginger, Zinaxin®.

Description: Ginger is a plant native to China, Southeast Asia, West Africa and the Caribbean. The herbal preparation is extracted from the rhizome which is part of the stem of the plant.

Mechanism of action: Some studies in the laboratory and on animals have found that extracts from ginger can reduce the production of several chemical substances (including leukotrienes) that promote joint inflammation. Ginger also contains salicylates, which is transformed

by the body into a chemical substance called salicylic acid. Salicylic acid inhibits the production of certain prostaglandins in the nerves and this effect relieves pain and discomfort.

Safety and toxicity: Ginger is a relatively safe herbal remedy with minor adverse effects. The most commonly reported adverse effects are stomach upset and irritation of the mouth.

Interactions: Treatment with ginger might increase the risk of bleeding if taken with other medications which affect blood clotting like aspirin, heparin and warfarin.

Conclusion

Rheumatoid arthritis is a chronic disease therefore it becomes preferable to use medicines with long term safety. Although there are many plants which are effective in treatment of RA they have limitations such as lack of efficacy, excessive side effects and high cost. However, much of the current research is focused on the identification, isolation and characterization of active principle(s) from crude extracts of known medicinal plants or herbs, often overlooking the fact that strong synergism of several constituents in the crude drug may prove more potent and effective than any single purified compound and this may help to nullify the toxic effects of individual constituents. Their long-term safety and efficacy of most of the herbal preparations commonly promoted as anti arthritic have not been established by placebo-controlled randomized trials in patients and indeed some of these may even interfere with the ongoing treatments. Therefore, it is imperative that scientific evidence regarding the safety and efficacy of herbal preparations commonly used by arthritis patients be studied and presented.

List of herbal marketed preparations for rheumatoid arthritis.

PREPARATIONS	BRAND NAMES
Capsaicin gel	Axsain®, Zacin®, chilli, pepper gel, cayenne.
Traditional Chinese medicine.	Biqi Jiaonang.
Blackcurrant seed oil	Quinsy Berries, squinancy berries, cassis, red currant, European black currant, mustaherukka, grosellero negro, siyah frenkuzumu.
Borage seed oil	Star flower oil, bee bread, tailwort, common bugloss, echiun amoenum
Cannabis oral spray.	Cannabis sativa, Sativex®.
Cat's claw	Life-giving vine of Peru, una de gato.
Collagen hydrolysate.	Hydrolyzed collagen, purified gelatin, HCP, Collagen type 2.
Eazmov	Ginger, purple nutsedge, guduchi, picrorrhiza and costus.
Evening primrose oil (EPO).	Tree primrose, fever plant, night willowherb,
Feverfew	King's-cure-all, scabish, scurvish, sun drop, suncups. Bachelor's buttons, featherfew, Santa Maria, Mother-herb, altamisa, featherfoil, flirtwort, midsummer Daisy, febrifuge plant.
Fish oil	Fish liver oil:, Fish body oil:
Flaxseed oil	Linseed, brown, golden flaxseed.
	Resin, olibanum, salai guggal, Sallaki®,

Indian frankincense	S-compound®.5-LOXIN®.
100mg of white willow bark, 40mg guaiacum resin, 35mg black cohosh, 25mg of sarsaparilla and 17mg of poplar bark.	Reumalex
Clematis mandshurica, Trichosantes kirilowii and Prunella vulgaris.	SKI 306X. CarathronQ®, JOINS®.
Tripterygium wilfordii Hook.	T Wilfordii Hook F (TWHF), Lei gong teng, Lei-kung teng, Huang-teng ken, Tsao-ho-hua, yellow vine root, early rice flower, three-wing nut.
traditional Chinese medicine (TCM).	Tong Ren Da Huo Luo Wan., Tong luo kai bi.
Willow.	Salicylate, salicylic acid, salipurposide, Salix alba, pentandra, Salix purpurea,white willow bark, willow tree, willowprin.

List of Herbals for treatment of RA under research

PLANTS	OTHER NAMES
1.Aloe vera	Lily of the desert, plant of immortality, medicine plant
2.Artrosilium	Organic silica, currant and Queen of the Meadow meadowsweet
3. Basil	Holy basil, tulsi, ocimum sanctum
5. Bee stings	bee venoms, Nectar Ease
6. Black cohosh	Actaea racemosa
7. Chlorella pyrenoidosa	Green algae
8. Cider vinegar	Apple cider vinegar
9. Co-enzyme Q10	CellSparc 360 combined with fish oil and Tocotrienolsvit E
10. Curcuma longa	Curcumin, Turmeric
11. Echinacea	
12. Emu oil	Emuline
13. Garlic	Allium sativum
14. Gingko biloba	
15. Ginseng	Siberian ginseng
16. Green tea	
17. Guaicum resin	
18. Kava kava	Piper methysticum
19. Melatonin	
20. Milfoil	Yarrow, Achiliea millefolium
21. Nicotinamide adenine dehydrogenase (NADH)	
22. Noni juice	Morinda citrifolia
23. Organic silica	Bambusa vulgaris
24. Phosphatidyleserine	
25. Poplar bark	American aspen, white poplar

26. Qianggu	
27. Sarsaparilla	Smilax
28. Serum dehydroepiandrosterone sulphate	DHEAS
29. Solidago virgaurea	Solidago canadensis; goldenrod
30. St John's wort	Hypericum perforatum
31. Tipi	Indian ginseng, Indian frankincense and turmeric)
32. Valeriana officinalis	Valerian
33. White royal jelly	
34. Wintergreen oil	Methyl salicylate
35. Withania somnifera	Ashwagandha, Indian ginseng, winter cherry

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