OVERVIEW OF HERBALS USED IN RHEUMATOID ARTHRITIS

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ABSTRACT

Rheumatoid arthritis (RA) is a systemic inflammatory disorder which mainly affects the diarthrodial joint. It is very common auto immune inflammatory disease causing disability in old as well as young age group. Various drugs are useful in RA but longer term use of these drugs produce adverse effects. Because of the limitations and risks of conventional therapy, people are exploring alternative measures to treat the disease. Herbal medicine provides a foundation for various traditional medicine systems worldwide. Herbal therapies occupy a large section of alternative therapy. Herbal drugs are used single or in combination for treatment of RA.These plants are exhibiting active constituents which act by different mechanisms such as suppression of the immune system and control of inflammation to bring relief to painful conditions

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatorydisorder which mainly affects the diarthrodial joint. It hassocietal effect in terms of cost, disability, and lost productivity.However the pathogenesis of disease is not well understood.Efforts are being made to understand the cellular and molecularmechanism for the pathogenesis of RA. It has been reportedthat proinflammatory cytokines such as tumor necrosisfactor-α (TNF-α), interleukin (IL)-1β, and IL-6 are importantmediators of the disease perpetuation. Moreover, there arealso reports that free radical generation worsens the diseaseand contribute towards damage to bone and cartilage.Immune cells such as T cells also impart their role in theprogress of the disease. Apart from the conventionaltreatment strategies using nonsteroidal anti-inflammatorydrugs (NSAIDs), disease modifying antirheumatic drugs(DMARDs) and glucocorticoids newer and safer drugsare continuously being searched, as long term usage ofthese drugs have resulted in the hepatic and gastrointestinaldisorders. Alternative medicine is another therapeuticapproach for treatment of the disease, which include herbaland folklore medicines. Many plants and plant products areunder scientific exploration to develop a novel therapeuticagent. Here we have tried to review mainly various Indianancient Ayurvedic, Unani and Tibbi, as also some Chineseand Korean, medicinal plants for their potential to treat RA.

PATHOPHYSIOLOGY OF RHEUMATOID ARTHRITIS:

RA an autoimmune disease, whereby the body's immune system attacks its tissues as if it were a foreign invader[1] in which for some known reason, the immune system considers its joint tissues foreign. White blood cells that normally protect the body migrate to the joint cavity. The synovium becomes inflamed and engorged with fluid, causing synovitis. Lymphocytes, macrophages, continue to enter the joint cavity and multiply, differentiate and release inflammatory mediators, cytokines, leukotrienes and prostaglandins that initiate inflammation, attract other immune cells to the site, activate resident cells and cause excess synovial fluid production. Within weeks the synovium becomes thickened. The mass of synovial tissue that spreads over the top of cartilage in a rheumatoid joint is called a pannus, made of WBC's: macrophages, B and T cells, neutrophils, plasma cells, NK cells, and T Helper cells. These cells produce the Rheumatoid Factor, prostaglandins, cytokines, and other mediators. As the diseaseestablished, the chemicals from the cells damage cartilage, ligaments, tendons, and bone. B lymphocytes that involve the presence of CD19andCD20:lymphocytes are defined by the presence of CD3 and CD4 (T-helper cells) or CD8 (cytotoxic cells). TH1 cells T-helper 1 cells characteristically produce a series of proinflammatorymolecules (such as IL-2, interferon-γ, TNF-α, granulocyte-macrophage-colony-stimulating factor) that mediate delayed-type hypersensitivity reactions. In contrast, TH2 cells
produce a group of cytokines (IL-4, IL-5, IL-6, and IL-10), all of which affect B-cell differentiation and activation, shown in Table 1. The complex interactive control of the immune system is well illustrated by the observation that some of the cytokines produced by TH2 cells (IL-4, IL-5, IL-10 and transforming growth factor-β) also have potent antiinflammatory activity that can down-regulate TH1 immune responses [2]. The balance swings towards the pro-inflammatory cytokines in rheumatoid joints [3]. This can be up-regulated by the expression of cell adhesion molecules on endothelial cells by introducing IL-1 and TNF-α.

TREATMENT STRATEGIES OF RA:

In the past decade, there has been a transformation in thetreatment of RA in terms of approach and choice of drugs too.Previous treatment strategies involved initial managementby NSAIDs for several years. NSAIDs have represented aneffective therapy for treating RA by eliciting their effectsby inhibiting cyclooxygenase activity and blocking thedownstream production of prostanoids and eicosonoids. Theadvantages of early management of rheumatoid arthritiswith DMARDs were not well recognized, until recently,and treatment options were limited to mono- or combinationtherapy with a relatively restricted therapeutic armament. DMARD therapy showed decrease in the markers of inflammation such as erythrocyte sedimentation rate andswollen joint counts. The combination therapy comprisesimmunosuppressives and DMARDs. This may exacerbatethe potential for hepatic enzyme disturbances. Additionalside-effects include weight loss, diarrhea, skin rash andalopecia [4].Although the recent years have brought new informationfor the researchers and clinicians, but the treatment of RAstill remains a challenge. Cytokine research has led to ideafor the use of anti-cytokine therapy for the treatment of RA.EtanerceptEtanercept (recombinant form of the p75 TNFR-II) andInfliximab (monoclonal antibody directed against TNF-α)were the first biological response modifiers approved forthe treatment of RA in the year 1992 [5,6]. Both drugshave been designed to bind with TNF-α and decrease itsbioavailability. Apart from all the above described treatmentapproaches scientists are now trying to cure RA using genetherapy, but it is still not fully explored.

OTHER APPROACHES

Because of the limitations and risks of conventionaltherapy, people are exploring alternative measures to treatthe disease. Commonly used alternative approaches includedietary modifications, nutritional supplements and botanicals.The response to these treatments varies from patient topatient. Alternative treatments have been used both asadjunct and an alternative to conventional therapy. Most ofthe treatments are relatively free of side effects[7].

HERBAL TREATMENT

Herbal medicine provides a foundation for varioustraditional medicine systems worldwide. Today, these herbscontribute approximately 25% of currently used crude drugsand another 25% is derived from chemically altered naturalproducts [8]. Herbal therapies occupy a large section ofalternative therapy. India, along with its wealth, is rich inwide variety of medicinal plants, a large number of popularremedies many of which are in common use even today.More than 2000 plants of medicinal value are mentionedin Indian ancient Ayurvedic, Unani and Tibbi systems ofmedicine [9]. We have also carried out a number of studieson possible intervention of herbal preparations with diabeticand arthritic conditions in experimental [10,11]

MEDICINAL PLANTS:

RA is a complex disease, combination drugs acting on several targets relevant to the disease may prove very effective and safe, rather than high doses of a single compound acting on a crucial target. In RA, hyperactivity of macrophages, T cells, B cells, etc. in the inflamed joint with concomitant elevation of cytokines such as IL-1 and TNF-α are occurring. Further, cartilage destruction, bone erosion, the proliferation of cells in the synovium, etc. are major pathological events. The medicine should contain chemical agents to counteract each of the pathological processes.

Medicinal plants contain herbal formulation with their essential phytoconstituents, such properties like Ginger which inhibits both cyclooxygenases and lipoxygenases. Boswelliaserrata inhibits lipopolysaccharide-mediated TNF-α induction in monocytes [12]. Therefore, a systematic approach should be made to find out the efficacy of plants against arthritis and inflammation to exploit them as herbal anti-arthritic agents and to use medicinal plant resources could result in the development of satisfactory medicines to treat RA patients.

1 . **Ashwagandha**

It is obtained from Dried roots and stem bases of Withaniasomnifera belongs tofamilySolanaceae .In traditional Indian systems of medicine, Ayurveda and Unani the roots of ashwagandha have been using.

The pharmacological activity of the root shows the presence of alkaloids and steroidal lactones. Among the alkaloids, withanine, withanine, pseudowithanine, tropine, pseudo-tropine, somniferine, somnine are mainly present. Oral administration of ashwagandha, root powder exhibit the anti-arthritic effect in adjuvant-induced arthritic rats and helps in providing progressive, long lasting results for various health concerns like aging, anemia, arthritis, fatigue, and stress-disorders[13,14]

Fig 1 :- Ashwagandha roots

echin-3-gallate exhibited inhibitory effect on the biomarkers namely TNF-α, TFN-γ, NFKβ, iNOS and COX those are responsible for rheumatic diseases. In India, in traditional medicine, many plants are used as a single drug or combination of one or two medicinal plants of herbal formulations to treat RA and other inflammatory diseases. In India, in traditional medicine, many plants are used as a single drug or combination of one or two medicinal plants of herbal formulations to treat RA and other inflammatory diseases.Numerous plants were tested for their anti-arthritis and anti-inflammatoryactivities using experimental animal models.

2 . Indian frankincense

Frankincense resin is obtained from trees of the genus Boswelliaserrata ,(family Burseraceae) This is a promising antiarthritis plant with anti-inflammatory and other beneficial pharmacological properties with antiatherosclerotic, analgesic and hepatoprotective effect [15]. Resin derived from it used to treat arthritis associated with chronic inflammatory illnesses from centuries[16] Alcohol extract of salaiguggul (B. serrata) displayed marked anti-inflammatory activity in carrageenan-induced paw edema in rats and mice. It was equally effective in adrenal-itemized rats [17].Alcohol extract of salaiguggul strongly inhibited antibody production and the infiltration of polymorphonuclear leukocyte; it decreased the volume of pleural exudates [18].The plant extract has antihyperlipidemic activity also [19,20]. The compound also protected mice against galactosamine / endotoxin-induced hepatitis in mice [21]. The protection was interpreted in terms of its ability to inhibit the formation of leukotrienes. Acetylboswellic acids inhibit lipo- polysaccharide-mediated TNF-α induction in monocytes by direct interaction with IκB kinases [22] Besides, acetyl-keto-β-boswellic acid inhibits cellular proliferation through a p21-dependent pathway in colon cancer cells [23].

Fig 2 :- Boswelliaserrata

3. Zingiber officinale:

Ginger Exhibit a vital role to lessen the unbearable pain and inflammation associated with RA [24,25] Ginger is obtained from rhizomes. It has been widely used as a medicinal herb and spice, since ancient times [26]. Anti-inflammatory effect of ginger was scientifically proved first by Kiuchi et al., in 1982. [27] They isolated four new differentcompounds from ginger, and all showed the potential inhibitory effect to reduce prostaglandin synthesis, which is the key to inflammation. Active components include gingerols, gingerdiols and gingerdiones and their dehydration products,, the shogaols[28]. Z. officinale blocks inflammatory prostaglandins and thromboxane. The volatile and essential oils, beta-phellendrene and zingiberine, decompose on drying. The warming gingerol principle transforms into shogaols on drying making it more centrally heating.Fresh ginger is more peripherally active while dry ginger is more centrally stimulating and warming; it is considered as effective as acetylsalicylic acid in reducing carrageenan-induced paw swelling in rats. It is thought that these anti-inflammatory actions are the result of inhibition of prostaglandin release and hence ginger may act similarly as NSAID, which interfere with prostaglandin biosynthesis. It is found that 6-gingerol and 6-shagol have analgesic and antipyretic activities.[29]

Fig 3 :- zingiberofficinale

4. Rasna:

In an indigenous system of medicine all parts of the plant are broadly used. It shows anti-inflammatory and analgesic activity and is significantly used in rheumatoid arthritis, neurological diseases, sciatica, edema, bronchitis, dyspepsia, cough, psoriasis and piles [30,31].The plant involves different secondary metabolites viz. flavonoids (quercetin, isorhamnetin, daidzein), triterpenes, sitosterols, taraxosterols, pluchine, etc. which contribute it anti-inflammatory and analgesic properties[32,33,34] In Albino rats, the water-soluble fraction of the 90% alcohol extract showed significant anti-inflammatory activity in induced formalin arthritis and granuloma pouch. The decoction of the plant has been used in arthritis. The leaves are aperients and used as a laxative, analgesic and antipyretic.[35]

Fig 4:- pluchealancolata

5. Chinese chaste tree:

Vitexnegundo L.: Also known as “nirgundi” (Blue flowered plant). It is a hardy plant, flourishing mainly in the Indian region. It has analgesic, anti-bacterial and anti-inflammatory properties. It is useful in the treatment of fever, arthritis, headaches, swelling, digestion problems and mouth related problems. The sub-effective dose of nirgundi potentiated the anti-inflammatory activity of phenylbutazone and ibuprofen significantly in carrageenin-induced hind paw edema and cotton pellet granuloma models. The synergy of anti-inflammatory activities phenylbutazone andibuprofen by nirgundi indicates that it may be useful as an adjuvant therapy along with standard anti-inflammatory drugs. One of a study done by Yunos et al., and Jana et al., who investigated anti- inflammatory properties of nirgundi extracts in acute and sub-acute inflammation which are attributed to prostaglandin synthesis inhibition[36,37].

Fig 5:- vitex negundo

6. Strychnospotatorum (Linn.)

Strychnospotatorum (Linn.) belongs to family Loganiaceae, commonly known as Katakam in Ayurvedic system of medicine, is a moderate–sized tree found in southern and central parts of India, Srilanka and Burma. According to Ayurveda, its seeds are acrid, alexipharmic, lithotriptic and cure strangury, urinary discharges and head diseases. In Unani system of medicine, seeds are used in liver and kidney complaints, gonorrhea and for colic. The ripe seeds are used for clearing muddy water.Biswas et al.studied on the diuretic and antidiarrhoeal activities of Strychnospotatorum Linn. Seed extract in albino rats and found it quite worthy. Due to polysaccharide gum its seeds are utilized in paper and textile industries. Roots cure leucoderma, whereas fruits are useful in eye diseases, thirst, poisoning and hallucinations. Its seeds are used to purify water for drinking. In traditional system of medicine, Strychnospotatorum (Linn.) seeds were used for various ailments including inflammation, diabetes etc. Although Strychnospotatorum Linn is widely used in traditional medicine, there existsa controversy on its toxic effect as expected with another species Strychnosnuxvomica

Fig 6 :- Strychnospotatorum L

7.Liquorice:

Glycyrrhizaglabra (liquorice) is a herb belonging to the pea and bean family, liquorice is cultivated for its underground stems that are used to flavour confectionery; it is also valued for its medicinal qualities. In the traditional system of medicine, the roots and rhizomes of Glycyrrhizaglabra (Family: Leguminosae) have been employed clinically for centuries for their anti–inflammatory, antiulcer, expectorant, antimicrobial and anxiolytic activities. In modern medicine, liquorice extract has been used for peptic ulcer and as an alternative to bismuth that has a protective role against acid and pepsin secretions by covering the site of lesionand promoting the mucous secretion. There are many useful compound in liquorice root such as, glycyrrhizin and its aglycone, glycyrrhetinic

acid wich are clinically used for hyperlipidemia. Liquorice flavonoid constituents mainly include flavones, flavonals, isoflavones, chalcones, bihydroflavones and bihydrochalcones. A pharmacological investigation indicates that they have antioxidant, antibacterial and anti–inflammatory activities.[38,39]

Fig 7 :- Liquorice

Sr No	Name	Botanical name	Family	Part used	Chemical constituents
•	Ashwagandha	Withania somnifera	Solanaceae	Dried roots & stems	Withanolides, alkaloids, withanine, pseudowithanine, tropine, pseudotropine, somniferine, somnine, somninealkaloids and steroidal lactones; 2-acyl glucosides viz sitoindoside-7 &sitoindoside-8 (isolated from root); Withaferin A and 3- b- hydroxy-2, 3-dihydro-withanolide F
2.	Indian frankincense	Boswellia serrata	Burseraceae	Dried resins	Carbohydrates, Terpenoids, gums, mucilages, β-boswellic acid in resin portion (acetyl-β-boswellic acid, keto-β-boswellic acid and acetyl-11-keto-β-boswllic acid), volatile oil & sugar
3.	Ginger	Zingiber officinale	Zingiberaceae	Roots & Rhizomes	Terpenes, monoterpene hydrocarbon, sesquiterpene hydrocarbons and oxygenated monoterpinecineol, borneol, citral, camphene, phelandrene, ginerol, shogaol,

					zingefone, zinziberin, Phenylpropanoids, 6-Shogaol, Gingerdiols and sesquiterpenoids, with (-) zingiberene
4.	Rasna	Pluchea lanceolata	Asteraceae	Roots, stem , leaves	Moretenol, moretenol acetate, neolupeol, neolupenol, octacoanoic, hexacosanoic and tetracoanoic acid, tetrcosanol, hexacoanol, triacontanol, stigmasterol&beta-Sitosterol-DGlucoside (leaves and stems) quercetin &isorhamnetin (air-dried leaves); triterpenoidssorghumol, sorghumol acetate, boehmerol acetate from the roots, psitaraxasterol acetate.
5.	Chinese chastetree	Vitex negundo L	Lamiaceae	Fresh barries, seeds, leaves	Carbohydrates, sterols, C-glycosides, flavanoids, polyphenolic compounds, terpenoids, glycosidiciridoids and alkaloids, casticin, essential oil, benzoic acid, vitamin c, flavones; 3β-Acetoxyolean-12-en-27-oic acid, 2α, 3α-dihydroxyleana-5, 12-dien-28-oic acid; 2β, 3α-diacetoxyolean-5, 12-dien-28-oic acid and 2α, 3β-diacetoxy-18-hydroxyolean-5, 12-dien-28-oic acid isolated from seeds.
6.	Strychnospotatorum	Strychnos potatorum (Linn.)	Loganiaceae	Seeds, Fruits, Leaves	Diaboline (major alka-loid) and its acetate, brucine, loganin, strych-nine, mannose, sucrose, β-sitosterol, stigmasterol, oleanolic acid, and saponim are reported from the seeds. Isomotiol, mixture of sitosterol, stigmasterol, and campesterol have been isolated from leaves and bark.

7.	Liquorice	Glycyrrhiza glabra	Fabaceae	Dried roots & Rhizomes	Glycyrrhizic acid (major glycoside) , Glycyrrhitic acid (aglycone), Glucoronic acid , Liquuritoside:, isoLiquuritoside, liquiritin, isoliquiritin, Sugar : mannitol, glucose,resin , Starch , volatile oils

Therapeutic Activity of Traditional Medicinal Plants against RA:

Ayurveda, a traditional system of medicine, emphasized the use of medicinal plants in the form of various formulations for the treatment of arthritis. Present review elaborates the isolated constituents from plant origin, which showed promising activity against RA .These plantsare exhibiting active constituents which act by different mechanisms such as suppression of the immune system and control of inflammation to bring relief to painful conditions. Here are some key findings validating the therapeutic approach against arthritis by using these alternative potential medicinal plants . A systematic literature review was carried out using PubMed, Google Scholar; Medicinal plants database, as well as the journals.

CONCLUSIONS:

In recent decades, 45 % rheumatic diseases patients are having comorbidities such as hypertension, hypothyroidism and diabetes mellitus. There are various synthetic drugs available for the management of Rheumatoid Arthritis but on long term use of these drugs produce fatal side effects. There are various medicinal plants which contains bioactive phytochemicals exhibited potential respons on this auto immune disease. Epigallocatechin-3-gallate exhibited inhibitory effect on the biomarkers namely TNF-α, TFN-γ, NFKβ, iNOS and COX those are responsible for rheumatic diseases. In India, in traditional medicine, many plants are used as a single drug or combination of one or two medicinal plants of herbal formulations to treat RA and other inflammatory diseases. In India, in traditional medicine, many plants are used as a single drug or combination of one or two medicinal plants of herbal formulations to treat RA and other inflammatory diseases.Numerous plants were tested for their anti-arthritis and anti-inflammatory activities using experimental animal models.

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