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PHYTOTHERAPY IN THE TREATMENT OF ARTHRITIS: A REVIEW

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ABSTRACT: As the conventional treatment is associated with large number of side effects, herbal treatment is gaining popularity particularly in the treatment of chronic disease like jaundice, vitiligo, rheumatoid arthritis, asthma etc. Herbal treatment has been identified as safe and effective in treating such disease. The aim of this study was to review systematically the evidences and effectiveness of herbs used in the treatment of different forms of arthritis and their anti-inflammatory or anti-arthritic properties have been evaluated clinically. A number of plants have been identified as anti-inflammatory and anti-arthritic, but only few of them have evidence of clinical trial. We searched the following electronic database Cochrane Complementary Medicine Field Register; Cochrane Controlled Trials Register (CCTR); and MEDLINE for our study. The reviewed herbs appear relatively safe, further research is needed to examine their efficacy, safety and potential drug interactions.

INTRODUCTION: Medicinal plants have always been considered a healthy source of life for all people. Therapeutic properties of medical plants are very useful in healing various diseases and the advantage of these medicinal plants is being 100% natural. Phytotherapy (herbal remedies) is the study of the use of extracts from natural origin as medicines or health-promoting agents.

The popularity of phytotherapy has significantly increased over the last three decades in the U.S., a trend driven by a resistance to conventional therapy and its associated side effects. According to World Health Organization, about 80 percent of the population of Asia and Africa rely on traditional medicines, including herbal remedies.

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On an international level, herbal therapies represent the largest share of the traditional medicines market, with annual sales reaching billions of dollars in China and Western Europe. According to the University of Maryland Medical Center, about 70 percent of German physicians regularly prescribe between 600 and700 phytomedicines to their patients [1]. Motivating factors for use vary but frequently relate to the failure of conventional therapies in the treatment of chronic conditions. However, despite an increase in use, evidence for effectiveness and safety of many complementary therapies is limited.

Arthritis represents one of the most prevalent chronic health problems and is a leading cause of disability [2]. Arthritis affected 43 million U.S. adults [3] in 2002 and is the leading cause of disability in the United States [4]. By the year 2020, this number is expected to reach 60 million. In India also more than 20% of total population is suffering from arthritis. Arthritis is a condition where one or more joints are affected, featuring inflammation of those joints.

Joints are a location in the body where two different bones meet which allocate movement and endow with mechanical support [5]. In between the two bones there is cartilage which acts as a shock absorber when pressure is placed on the joint [6], when person walks or bear weight. In arthritis joints become swollen, tender and warm to touch or red [7] and movement become very painful because of damaged and narrowed cartilage, in some cases it may be lost by a degenerative process or by inflammation [8]. There are 100 different forms of arthritis; the most common is osteoarthritis [9] which is the result of injury or trauma to joints, infection or age.

Other forms are gout or pseudogout due to metabolic abnormalities [10] and misdirected immune system causes rheumatoid arthritis and psoriatic arthritis with autoimmunity [11]. Septic arthritis is the result of joint infection [12]. Arthritis can occur at any age [13] but usual age of onset is in between 25 and 50 with a peak in 40s and 50s [14]. The most common symptoms of arthritis are joint pain which occurs due to wear and tear of joints, muscle strain caused by vigorous movement against firm and throbbing joint. Before the treatment of arthritis it is important to understand the disorder and come across the solution to overcome from difficulty which prevents physical exercise [15].

Epidemiology of arthritis: Arthritis is most commonly affected elderly people but children can also be affected by the disease. At any age women are more likely to develop arthritis than men affect all races, ethnic groups and cultures. According to CDC survey in the year 2007-2009 in US, showed that 22.2 % (49.9 million) of adult aged >18 year had reported doctor diagnosed arthritis, and 9.4 % (21.1 million) had arthritic attributed activity limitation (AAAL). In elderly population, this number is expected to increase [16].

Types of Arthritis Many types of arthritis and rheumatism are in subsistence, some related to wear and tear (e.g. osteoarthritis) and few of them are result of an over-active immune system (e.g. rheumatoid arthritis) [17]. Every category of arthritis has its own characteristics symptoms and its own course. In addition, the mode of progress of disease differs from individual to individual.

Risk factors for Arthritis: Risk factor for arthritis means condition that does not seem to be direct cause of arthritis but may be associated in some way [18]. Risk factor for arthritis increases the chances of getting arthritis but it does not always lead to arthritis. The common risk factors for arthritis includes age, gender, obesity, infection, congenital factor, life style, environmental factor, and lack of physical activity.

Signs and symptoms of Arthritis: Different types of arthritis have different symptoms. In general, people who have arthritis feel pain and stiffness in the joints. Arthritic pain, is generally worse in the morning and on initiating movement, and resolves in the cause of time. In elderly people and children, the pain may not be the main feature, and the patient simply moves less (elderly) or refuse to use the affected limb (children). Inflammation is involved in many forms of arthritis. The warning signs that inflammation presents are redness, swelling, heat and pain. Osteoarthritis does not generally cause any symptoms outside the joint. Symptoms of other types of arthritis may include fatigue, fever, a rash and the signs of joint inflammation. Arthritis and fever together are pointers towards septic arthritis. This is a medical emergency, and requires urgent referral to a rheumatologist.

Treatment of Arthritis: There is no cure for arthritis. Treatment depends on the type of arthritis which includes physical exercise, medication and surgery. The goal of treatment of arthritis is to manage the pain and inflammation and improve functioning of affected joints.

(1) **Physical Exercises:** In arthritis joint become stiff and movement is limited. Exercise of affected joint show necessary improvement in joint stiffness, reduces pain, and fatigue, improve muscle and bone strengthened reduces the need of surgery in advance cases. Exercises encourage maintaining the health of joint and overall body of the person.

(2) **Medications:** Treatment usually begins with medications that have lowest side effect, if it is not effective further medication is added. Medication is used to reduce pain and inflammation in mild to moderate cases of arthritis.

Drugs such as Analgesics (acetaminophene), non-steroidal anti-inflammatory drugs (NSAIDs) (ibuprofen and asprin) cox-2 inhibitor (rofecoxib and celecoxib) corticosteroid and cortisone injection (prednisone and hydrocortisone) are used as first line drugs to relive pain, inflammation and stiffness of joints [19]. Second line drug are used when first line drugs are no longer effective in the treatment of arthritis [20]. These are disease modifying anti-rheumatic drugs (gold salts, methotrexate and leflunomide) and biological response modifier (etanercept, adalimumab, abatacept). These drugs are also used in combination with first line drug. (http://www.niams.nih.gov).

The disadvantages of these drugs lie in their toxicity, side effects and reappearing of symptoms after discontinuation of therapy [21].

The most common side effects of these drugs are stomach irritation, kidney dysfunction, hepatic dysfunction, hematological abnormalities and serious gastrointestinal problems including ulcers, bleeding, heartburn, diarrhea, fluid retention and perforation of the stomach or intestine [22]. Therefore the use of herbal treatment is on rise and according to reports approximately 60-90% of dissatisfied arthritis patients are likely to seek the option of complementary and alternative medicine (CAM) [23].

(3) **Surgery:** It is the last treatment option. If the damage is severe and an individual does not respond to medication, the health care professional may recommend surgery. Surgeon may perform surgery to realign the joint, replace the damaged part of joint or to replace the total joint.

Advantage of Phytotherapy over Conventional Therapy: Ayurveda is the most ancient healing system in India. It is introduced near about 5000 year ago in India. Now a day it is challenged by modern medical system called allopathic. The aim of Ayurveda is to first find out the root cause of disease and then eradicate it completely from patient whereas allopathy gives instant relief from by destroying the organism that caused the disease but there is no guarantee that the disease is permanently cured. Ayurvedic treatment includes herbs which is associated with fewer side effects as compared to allopathic treatment. Treatment through Ayurveda is not fastest but surely the most effective one. Therefore, its popularity is continuously increasing in the western world in recent year. Inspite of being modern system of medical treatment, allopathy is unable to find permanent cure for disease like jaundice, vitiligo, rheumatoid arthritis, asthma etc. These diseases can be successfully managed by Ayurveda. Even world health organization has accepted Ayurveda as a system of medicine for treating all types of disease.

Herbs Used in the treatment of Arthritis: Following are the most commonly used herbs for the treatment of arthritis in Ayurveda:

1. **Evening primrose oil (*Oenothera blennis*):** Evening primrose is a biennial plant native to North America; it is also being cultivated in temperate countries. The seeds of evening primrose contain up to 25% essential fatty acids including linoleic acid (LA) and gamma-linolenic acid (GLA). Essential fatty acids carry out many important roles, GLA is a precursor of prostaglandin E1 which help inhibit or reduce inflammation, platelet aggregation, thrombosis, cholesterol synthesis, blood vessel tone, and the formation of abnormal cells.

Clinical evidence related to Arthritis:

i. In a 6-month trial of evening primrose oil (EPO), 40 patients were randomly assigned to receive 6 g/day of EPO (540 mg GLA/day) or placebo (olive oil, 6 g/day) [24]. Thirteen patients receiving EPO and 17 in the placebo group completed the trial. Reasons for withdrawal from the EPO group included nausea (*n*=2), joint surgery (*n*=2), deteriorating condition (*n*=1) and flu-like symptoms (*n*=1).

Three withdrew from the control group because of nausea and the other moved from the area. Between-group comparisons were not reported. However, within-group comparisons showed a significant reduction in morning stiffness in the EPO group, with no change in the Ritchie articular index (AI) or pain.

In contrast, olive oil produced a significant reduction in AI and pain but no change in morning stiffness. Neither group demonstrated a change in well-being or Health Assessment Questionnaire scores.

ii. Another study of EPO [25] involved 49 patients with mild RA, who were randomly assigned to receive EPO, EPO/fish oil combination or placebo (liquid paraffin). EPO capsules provided 540 mg GLA and EPO/fish oil capsules provided 450 mg GLA and 240 mg essential fatty acids. Using intent-to-treat analysis at the end of 12 months, researchers found no significant change for any of the groups in the clinical measurements.

However, a significantly greater percentage of patients in the treatment groups reported subjective improvement compared with the placebo patients (94 *vs* 30%) and 73% of EPO and 80% of EPO/fish oil patients had reduced or stopped their non-steroidal anti-inflammatory drugs (NSAIDs) compared with only 33% of placebo patients ($P < 0.05$).

Eighteen patients participated in a 3-month trial [26] in which EPO (20 ml/day) was compared with olive oil (20 ml/day). Patients were permitted to continue on long-term anti-rheumatic drugs throughout the study and to use paracetamol for pain if necessary; NSAIDs were not allowed. At the end of the trial, no significant changes were observed in the clinical variables. In the treatment group, four patients were considered better, for the same, and one worse; in the control group, five patients were better and four were worse.

2. **Blackcurrant seed oil (*Ribes nigrum*):** Black currant oil is obtained by crushing the seeds of the black currant plant. It contains high levels of GLA (gamma-linolenic acid), a beneficial fatty acid that our body converts to prostaglandin E1 (PGE1), and a hormone-like substance that works as an anti-inflammatory.

Clinical evidence related to Arthritis: In a 6-month study, 34 patients received either blackcurrant seed oil (BCSO) (n=20) or placebo (n=14) [27]. The daily dose of BSCO was 10.5 g (2.0 g GLA); identically appearing placebo capsules contained soyabean oil. Throughout the study, patients were asked to continue their pretrial doses of NSAIDs and/or corticosteroids. Among those who completed the study, the treated group showed significant improvement in joint tenderness count [ES=1.73, 95% confidence interval (CI) 0.519, 2.93)] and tenderness score (ES=1.51, 95% CI 0.339, 2.68) compared with the placebo group. Intent-to-treat analysis confirmed that these results were not due to bias from dropouts. One patient in the BCSO group experienced meaningful improvement while six had no meaningful change; in the placebo group none of the seven had meaningful change.

3. **Flaxseed oil (*Linum usitatissimum*):** It is rich in Omega-3 fatty acids like alpha-lipoic acid, which have anti-inflammatory properties.

Clinical evidence related to arthritis: Twenty-two patients received 30 g/day of either flaxseed oil or safflower oil for a 3-month period [28]. All patients also took NSAIDs. On the basis of within-group comparisons, none of the clinical parameters changed in either group.

4. **Ginger (*Zingiber officinale*):** Ginger is well known natural spice having medicinal properties. Recent studies conducted in university of Miami recently suggested that ginger is effective in the treatment of arthritis as it contains anti-inflammatory properties. Its roots contains active compound like zingiberon and zingirol that are important antioxidant that clears the impurities of joints.

Clinical evidences related to Arthritis:

(a) In a controlled double blind, crossover study, ginger extract was compared to placebo and ibuprofen in patient with osteoarthritis of hip and knee. Trial is performed with wash out period of one week followed by three treatment period in randomized sequence each of three weeks duration. A ranking of efficacy of three treatment periods: ibuprofen> ginger extract> placebo was found for visual analogue scale of pain. In this study, no significant difference was found between placebo and ginger extract but the treatment period show better effect of both ibuprofen and ginger extract than placebo [29].

(b) In an another study, 156 patients out of which 28 with rheumatoid arthritis, 18 with osteoarthritis and 10 with muscular deformities received powdered ginger against their afflictions. Arthritis patient experienced relief in pain and swelling with no adverse effect during the period of study which is ranged from three months to 2.5 years. Possible mechanism by which ginger share its effect could be related to prostaglandin and leucotrine biosynthesis so it works as a dual inhibition of eicosanoid biosynthesis [30].

5. **Turmeric (*Curcuma longa*):** It has been used in Indian systems of medicine for a long time. In India it is popularly known as "Haldi". It is said that use of Curcuma longa for numerous medicinal problems ranging from constipation to skin disease goes back to 600 BC as mentioned in literature. Polyphenolic compound curcuminoid gives turmeric its yellow color. Curcumin is the man curcuminoid found in turmeric. Other curcuminoid found in turmeric are bisdimethoxycurcumin, 5'-methoxycurcumin and dihydrocurcumin. Evidence shows that curcumin may have anti-inflammatory and anti-cancer activity.

Clinical evidence related to Arthritis: Clinical trials have examined the efficacy of curcumin as anti-inflammatory in the treatment of arthritis. In a clinical trial efficacy of curcumin was compared with a non-steroidal anti-inflammatory drug. In these study 18 patients with rheumatoid arthritis receives oral curcumin 1200mg/day. It was found that there were improvement in morning stiffness, walking time and joint swelling after two weeks which were comparable to those experienced after two weeks of phenylbutazone (NSAIDS) therapy (300mg/day). Larger clinical trials are needed to determine the efficacy of curcumin in the treatment of rheumatoid arthritis [31].

6. **Stinging nettle (*Urtica dioica*):** Stinging nettle (Urtica dioica) is a perennial, flowering, stalk-like plant that is found in the United States, Canada, Asia, and Europe. Its medicinal history goes back to medieval Europe when it was used as a diuretic and to relieve joint pain.

Clinical evidence related to Arthritis: Twenty-seven patients with OA pain at the base of the thumb or index finger were randomized to receive topical treatment with stinging nettle leaf (*Urtica dioica*) followed by placebo treatment using white deadnettle (*Lamium album*) leaf or vice versa in a double-blind crossover RCT [32]. White deadnettle leaf looks like a stinging nettle leaf but has no sting. Stinging nettle leaf was applied daily for 1 week to the painful area. After a 5-week washout period, the placebo treatment was applied for a 1-week period. After 1 week of treatment with nettle sting, reductions in both pain (VAS) and disability (Stanford Health Assessment Questionnaire) were significantly larger than with placebo (P=0.026 and P=0.0027 respectively). No significant differences in either score were observed following the 5-week washout period. There was a non-significant decline in daily use of analgesic and anti-inflammatory drugs following 1 week of treatment with stinging nettle.

7. **Ashwagandha (*Withania somnifera*):** It contains steroidal alkaloid, steroidal lactones such as withanolides, bitter alkaloid 'somniferin' having hypnotic property and other content like, phytosterol, mixture of saturated and unsaturated acid. It has been used in the disease like rheumatism, asthama, leprosy and arthritis.

Clinical evidences related to Arthritis:

a. In an animal study, it was found that ashwagandha was more effective than phenylbutazone in controlling inflammation. Ashwagandha treated group showed reduced inflammatory protein whereas phenylbutazone had increased inflammatory protein. In another study Ashwagandha showed better result in reducing inflammation as compared to hydrocortisone [33].

b. In another study, 46 patients of rheumatoid arthritis had received ashwagandha root powder with dose of 4, 6 or 9gms for 3-4 weeks. 14 patients showed excellent response with ashwagandha root powder as pain and swelling completely disappeared in these patients, 10 patients showed considerable improvement and 12 patients showed moderate improvement in pain and swelling.

In a double blind placebo control study, combination of ashwagandha, turmeric and zinc showed significant improvement in pain and inflammation [34].

8. **Boswellia (*Boswellia serrata*):** Historically *Boswellia serrata* is recommended for osteoarthritis, juvenile rheumatoid arthritis, soft tissue fibrositis and spondilytis without any side effect. It possesses analgesic and anti-inflammatory properties. It also acts as cox-2 inhibitor and reduces pain and inflammation without affecting gastric mucosa. It soothes the joints and also helps to improve the level of synovial fluid making entire structure lubricated and easy to move. Bark of boswellia yield a gummy oleoresin. The gum is used as an anti-inflammatory when applied externally or internally. One of the principal constituent of gum resin is boswellic acid which exhibit anti-inflammatory activity.

Clinical evidences related to Arthritis:

(a) To assess the efficacy, safety and tolerability of boswellic acid, a randomized double blind placebo control crossover study was conducted in a group of 30 patients with osteoarthritis of knee. Group of 15 patients each received boswellia extract or placebo for eight weeks. After the first intervention, washout was given and then the groups were crossed over to receive the opposite intervention for eight weeks. All patients receiving boswellia extract reported reduced knee pain, increased knee flexion and decrease in frequency of swelling in knee joint.

B. serrata extract was well tolerated, except for minor gastrointestinal adverse drug reactions. Fan et al. examined the effects of an acetone extract of *Boswellia carterii* gum resin on adjuvant-induced arthritis in Lewis rats. The results show that *B. carterii* extract had significant anti-arthritic and anti-inflammatory properties, and suggest that these effects may be mediated via the suppression of pro-inflammatory cytokines. Further studies are needed to fully realize the potential of this agent in the treatment of arthritis [35].

(b) A double-blind, placebo-controlled, cross-over study involving treatment of osteoarthritis with a herbomineral formulation containing *Boswellia serrata* showed that the formulation produced a significant drop in severity of pain and disability score proving its effectiveness in osteoarthritis.

Studies revealed that the Boswellic acids isolated from the *Boswellia serrata* are the active principles responsible for its anti-inflammatory activity. Boswellic acids exert specific inhibition of leukotriene synthesis which is one of the key intermediate leading to inflammatory response. 5-lipoxygenase is an enzyme catalyzing leukotriene synthesis pathway in the body leading to inflammatory reaction. By inhibition of the 5-lipoxygenase either by direct interaction or by blocking its translocation, boswellic acids exert anti-inflammatory response by preventing leukotriene synthesis (agroinfotech).

(c) Its anti-inflammatory and antiarthritic activities have been mainly attributed to a component in the resin containing [beta]-boswellic acid. In an animal-model study boswellic acids significantly reduced the infiltration of leukocytes into the knee joint, in turn significantly reducing inflammation causing immune white blood-cell response [36].

9. **Guggul (*Comoiphora mukul*):** Guggul act as anti-inflammatory agent that reduces joint pain, inflammation morning stiffness and other related symptoms. Guggulsteron is the gum resin of *C. mukul*, this sterol can inhibit NF-kB activation and downregulate the expression of inflammatory gene product such as cox2 and MMP9 which are major players in the development of arthritis.

Clinical evidences related to Arthritis:

(a) Guggul showed significant improvement in osteoarthritis in both clinical and pre-clinical studies conducted in South Carolina University of Health Sciences, USA. The study data suggested that there is significant reduction in joint pain inflammation, stiffness and improved mobility.

It was due to new triterpene Myrrhanol A found in *C. mukul* (www.holistic-herbalist. com/guggul.html).

(b) The anti-arthritic and anti-inflammatory activities of gum guggul were first demonstrated by Gujral *et al*., in 1960 [37]. Subsequently, the anti-inflammatory activity of *C. mukul* (guggul) has been compared with that of NSAIDs, namely phenylbutazone and ibuprofen. In this clinical study, inflammatory syndrome which resembles rheumatoid arthritis in human was induced in albino rat by injecting mucobacterial adjuvant in liquid paraffin and development of arthritic syndrome was studied for period of five month with and without drug treatment.

Anti-inflammatory agents such as phenylbutazone, ibuprofen and fraction 'A' of gum-guggul from *C. mukul* were administered orally at a daily dose of 100 mg/kg, 100 mg/kg and 500 mg/kg, respectively, for a period of five months. The result showed the beneficial effect of all three drugs in reducing pain and inflammation in experimental animal [38].

(c) In another study conducted to determine the efficacy of guggul in reducing the symptoms of osteoarthritis and its tolerability in older patients. There are significant improvements of symptoms in patient during trial. For assessment purpose both Western Ontario and McMaster Universities (WOMAC) and visual analogues scale (VAS) has been used. Guggul appears to be safe and effective and no side effect has been reported during trial [39].

10. **Devil's claw (*Harpagophytum procumbens*):** Traditionally it has been used for itspurgative action and as a bitter tonic for digestive disturbances. It has also been used to treat migraine, arthritis and rheumatism. Principal constituent of Devil's claw is Iridoid glycosides – harpagoside, harpagide, procumbide, other constituent are flavonoids-kaempferol and luteolin, phenolic acid triterpene etc.

Clinical evidences related to Arthritis:

(a) Anti-rheumatic effect of Devil's claw was conducted by European scientist professor Zorn in 1957. In this clinical study, arthritis has been induced in white rat with formaldehyde. These experimental animals received Devil's claw extract orally and subcutaneously and showed significant improvement in swelling of arthritic joints. Healing process is continued even after the treatment has ceased. Thus Zorn concluded that Devil's claw contained potent anti-inflammatory and anti-rheumatic substances.

(b) Intraperitoneal pre-treatment of rats with a dried aqueous extract (2.2% harpagoside) of Devil's Claw, 30 min before oedema provocation, significantly reduced carrageenan-induced hind paw oedema in a dose-dependent manner. Doses of 400 and 1200 mg/kg, corresponding to 665 and 2000 mg/kg, of Devil's Claw, as powdered drug, reduced oedema by 43 and 64%, respectively, three hours after administration. The efficacy of the 1200 mg/kg dose was similar to that of indomethacin 10 mg/kg [40].

(c) Two double blind placebo controlled studies shows that Devil's claw is effective as an anti-rheumatic agent and its effectiveness is similar to potent NSAIDs such as phenylbutazone and indomethacin and its analgesics effects is comparable to acetylsalicylic acid [41, 42].

11. **Feverfew (*Tanacetum parthenium*):** The feverfew herb has a long history of use in traditional and folk medicine, especially among Greek and early European herbalists. The plant contains a large number of natural products, but the active principles probably include one or more of the sesquiterpene lactones known to be present, including parthenolide. Other potentially active constituents include flavonoid glycosides and pinenes.

Clinical evidence related to arthritis: In a study of 41 women with symptomatic RA, half received 70–86 mg/day of dried, powdered feverfew and half received identically treated cabbage [43]. Subjects maintained their current NSAID and analgesic treatment throughout.

At the end of 6 weeks, treatment and placebo groups showed a significant difference in the change in grip strength (ES=0.915, 95% CI 0.265, 1.57). Other clinical assessments demonstrated no significant change. The authors concluded that, perhaps at larger doses or over a longer period of time, feverfew might have some benefit for RA.

12. **Guduchi (*Tinospora cardifolia*):** *Tinospora cardifolia* is most widely used plant in folk and Ayurvedic system of medicine. It is found throughout India. The principal constituents are alkaloids, diterpinoid lactones, glycosides steroid, sesquiterpenoid, phenolic, aliphatic compound and polysaccharides.

    Medicinal properties of *T. cardifolia* has been reported by scientific research which includes anti-diabetic, antipyretic, anti-inflammatory, anti-arthritic, anti-oxidant, anti-malarial immuno-modulator and anti-neoplastic activities.

Clinical evidences related to Arthritis:

(a) It is traditionally used in compound form for the treatment of rheumatoid arthritis. Its alcoholic extract has been found to exert anti-inflammatory action in experimental model with acute and sub-acute inflammation[44].

(b) Carrageenan induced inflammatory response in experimental model is significantly inhibited by aqueous extract of *T. cardifolia* when given in dose of 50mg/100g administered orally and intraperitoneally. A significant inhibition of primary and secondary phase of inflammation was observed in a model of adjuvant-induced arthritis [45].

(c) In cotton-pellet granuloma and formalin induced arthritis model, the aqueous extract of *T. cardifolia* showed significant anti-inflammatory effect which was comparable to indomethacin and mode of action appeared to resemble non-steroidal anti-inflammatory agent. *T. cardifolia* was found to be more effective than acetylsalicylic acid in acute inflammation but in sub-acute inflammation it was inferior to phenylbutazone [46].

(d) In both cotton-pellet induced granuloma and formalin induced arthritis in rat model, aqueous extract of *T. cardifolia* showed significant anti-inflammatory effect [47].

13. **Rasna (*Pluchea lanceolata*):** It is used to prevent the swelling of joints in arthritis, inflammations, rheumatism, bronchitis, cough, psoriasis, piles and neurological diseases. The stem and leaves contain moretenol, moretenol acetate, neolupenol, octacosanoic, hexa-cosanoic and tetracosanoic acid, tetracosanol, hexaco sanol, triacontanol, stigmasterol and beta-sitosterol-D-glucoside.

Clinical evidences related to arthritis: Anti-inflammatory and anti-arthritic activity of pluchine has found to reduce inflammation in experimental animal (albino rat) in which inflammation is induced by both immunological and non-immunological method [48]. It was found that in comparison with betamethasone, pluchine not only suppress the acute inflammation induced by carrageenan, histamine and formaldehyde but also effectively suppress both primary and secondary phases of adjuvant arthritis (induced by a suspension of dead tubercle bacilli, human DT, in liquid paraffin) like metamethasone. In experimental animal (albino rat) acute sensitivity reaction produced by purified tuberculin has been significantly suppressed by pluchine and was less toxic than betamethasone. These properties of pluchine or betaine hydrochloride of *Pluchea lanceolata* can account for the use of drug for the treatment of rheumatism in Ayurvedic system of medicine.

14. **Willow bark (*Salix alba*):** White willow has been used to combat fevers and pain for thousands of years. Willow bark may be the oldest herb known to treat pain and inflammation. The inner bark of the white willow tree contains salicin, which is changed to salicylic acid in the body. The compound in aspirin, acetylsalicylic acid, is derived from salicylic acid.

Clinical evidence related to Arthritis: Schmid *et al*., performed a randomized 78 hospital in-patients suffering from OA of the knee or hip joints to receive two tablets twice daily of either willow bark extract (corresponding to 240 mg salicin per

day) or placebo tablets for a 2-week period [49]. Drug effectiveness was measured primarily by the pain dimension of the WOMAC OA index [50]. All patients also received regular physical therapy following standard procedures. A statistically significant advantage of the active treatment over placebo was observed (P=0.047). Secondary outcome measures of physical function were better in the treatment group compared with placebo, although this was not statistically significant and no differences in stiffness were observed between the two groups during the study period.

A significant positive effect of the active medication was confirmed by overall assessments both by the physician and by the patients (P<0.01). No significant correlation was observed between the different physical therapy methods and the primary outcome measure, suggesting that the observed medication effect was not influenced by the physical therapy. No relevant differences between outcomes were observed in knee and hip OA.

15. **Nirgundi (*Vitex nigundo*):** It has anti-inflammatory, analgesic, anti-arthritic**,** and antioxidant actions. The leaves contain iridoid glycosides, isomeric flavanones and flavonoids, besides casticin and the glucosides, luteolin-7-glucoside and alpha-D-glucoside of a tetrahydroxy monomethoxy flavone. Dried powder of roots contains hentriacontane, beta-sitosterol and its aetat & Stigmasterol Two pentacyclic triterpenoids, betulinic acid and ursolic acid, along with an aliphatic alcohol, n-hentriacontanol, beta-sitosterol and p-hydroxybenzoic acid have been isolated from leaves. The seeds contain p-hydroxybenzoic acid, 5-oxyisophthalic acid, glucose and the triterpene, vitextriterpene. Several anti-inflammatory triterpenoids and flavonoids have also been isolated from the seeds

Clinical evidences related to Arthritis:

(a) Anti-inflammatory properties of *Vitex nigundo* extracts in acute and sub-acute inflammation. Anti-inflammatory and pain suppressing activities of fresh leaves of *Vitex nigundo* are responsible for inhibition of prostaglandin synthesis, antihistamine, membrane stabilizing and antioxidant activities [51].

(b) In a clinical study, to demonstrate the anti-inflammatory activity of ethanol extract of *Vitex nigundo* leaves was conducted on carrageenan-induced rat paw oedema. Three groups of six animals (Albino rat) of each were considered for the study. The test group received the dose of 200mg/kg of ethanolic extract of Vn leaves, standard group received 150mg/kg of diclofenac sodium and control group received vehicle only. All the treatment was given orally 30min prior to the injection of carrageenan. The extract had very consistent anti-inflammatory activity. The greater degree of inhibition in oedema formation was observed in extract at 3hr onward as compared to standard drug (diclofenac sodium) at the same time interval.

(c) The mechanism of anti-inflammatory action was explored by observing its effect on oxytocin induced contractions in rat uterus and oxidative stress. VN extract was administered orally in graded doses (100, 250 and 500 mg kg^{-1}) as single dose therapy and twice daily for 7 day in respective inflammatory experimental models. The effects were compared with phenylbutazone (100 mg kg^{-1}) orally in carrageenan induced hind paw edema method and ibuprofen (200 mg kg-1.B.DX 7 days) orally in cotton pellet granuloma test as standard controls, respectively. The test drug showed significant anti-inflammatory activity in dose dependent manner in both experimental models.

Vitex negundo inhibited oxytocin induced contractions of rat uterus and plasma MDA (malondialdehyde) levels significantly. These observations suggest that *Vitex negundo* possesses anti-inflammatory activity against acute as well as sub-acute inflammation, which appear to be due to prostaglandin inhibition and reduction of oxidative stress respectively, which needs to be substantiated by further study (www. banlab.com/Healingherbs/nirgundi.htm).

16. **Pippali (*Piper longum*):** Black pepper (*Piper nigrum*) is commonly used as a spice in human diets, but it is also used as a medicine, a preservative, and a perfume in many Asian countries.

    An extract of the active phenolic component, piperine, is well known to provide beneficial physiological effects [52]. It stimulates the digestive enzymes of pancreas, protects against oxidative damage, lowers lipid peroxidation, and enhances the bioavailability of a number of therapeutic drugs. In addition, its anti-inflammatory activities have been demonstrated in rat models of carrageenan-induced rat paw edema, cotton pellet-induced granuloma, and a croton oil-induced granuloma pouch [53].

    Constituents of the piper species have shown *in vitro* inhibitory activity against the enzymes responsible for leukotriene and prostaglandin biosynthesis, 5-lipoxygenase and COX-1, respectively [54]. These effects of piperine seem to be beneficial for inflammatory diseases that are accompanied by severe pain; for example, rheumatoid arthritis. Two alkaloid piper-longumine, and piperlonguminne, sesqui-terpenes; piperine, piplartine, triacontane, glycosides, sesamin The fruit contains 1% volatile oil, resin, alkaloids Piperin and piper-longuminine, a waxy alkaloid N-isobutyl deca-trans-2-trans-4-dienamide and a terpenoid substance**.**

Clinical evidences related to Arthritis:

(a) To demonstrate the analgesic effect of piperine carrageenan-induced paw hyperalgesia test is performed on rat model. It has been found that in paw pressure tests on rats treated with piperine could tolerate higher pressures on the affected paw).The efficacy at 100 mg/kg was better than that of celecoxib, and at a dose of 20 mg/kg, piperine showed a mild analgesic effect [55].

(b) To demonstrate the *in vivo* anti-arthritic effect of piperine, the efficacy of piperine was tested in a rat model of carrageenan induced arthritis. The piperine (100 mg/kg) group showed a significant reduction in paw volume compared to the vehicle treated arthritic group. At this dose, piperine showed almost the same efficacy as prednisolone (10 mg/kg), which was used as a positive control.

    Piperine also provided a mild anti-edema effect at 20 mg/kg, although it was not statistically significant. The vocalizations caused by flexion or extension of the inflamed ankle reached a maximum point on day 1 after the carrageenan injection and was sustained at a maximum level in untreated rats through the end of the experiment. In the100 mg/kg piperine treated group, the number of vocalizations started to decrease at 5 days post-carrageenan injection. At 20 mg/kg, piperine exhibited little analgesic effect [56].

17. **Cayenne pepper (*Capsicum minimum*):** Cayenne pepper has been used for centuries as a spice, but also as a natural remedy. Cayenne pepper contains a chemical called capsaicin, which helps to reduce inflammation in the body and to reduce platelet stickiness. By reducing inflammation in the body, capsaicin can decrease pain, making cayenne pepper a natural addition to any arthritic person' diet.

Clinical evidence related to Arthritis:

(a) Capsaicin (*trans*-8- methyl-*N*- vanillyl-6-nonenamide) is derived from hot chilli peppers. It is used as a topical analgesic for a variety of conditions characterized by pain. A meta-analysis of three double-blind, placebo-controlled RCTs [57, 58, 59] (192 capsaicin patients, 190 controls) for the treatment of primary OA with topically applied capsaicin has been published [60]. Trials were abstracted for response data and analyzed using both a fixed effects model and a random effects model.

    The odds ratio (OR) of the response rate of subjects receiving topical capsaicin relative to that of the subjects on placebo was determined and used as the main outcome measure. The response rate difference (RD) was used as the response variable under the random effects model.

The results in all three trials favored capsaicin cream for improvements in pain and articular tenderness, although only one of these trials reached the usual statistically significant level (*P*=0.05).

The meta-analysis showed that capsaicin cream was better than placebo in the treatment of OA [OR=4.36 (95% confidence interval [CI]=2.77, 6.88); RD=0.29 (95% CI=0.2, 0.37)].

(b) An additional RCT not included in this meta-analysis was located [61]. Altman *et al*, performed a double-blind, parallel, vehicle-controlled, six-center study with a mixed population of 113 patients suffering from OA of the knee, ankle, elbow, wrist or shoulder. Randomly selected 113 patients receive 0.025% capsaicin cream or vehicle cream as placebo. Cream was applied to affected joints four times daily for 12 weeks. At the end of the study there is significant reduction in pain in capsaicin-treated patients as compared to vehicle-treated patients (*P*=0.03), while pain severity as measured by VAS was found to be significantly decreased (*P*=0.02).

Overall, capsaicin-treated patients had significantly greater improvement in tenderness on passive range of motion (4-point scale) (*P*=0.03) and physician palpation (*P*=0.01) than vehicle-treated patients. A 5-point severity scale for 'today's pain' and secondary outcome measures of morning stiffness using a two-question method and a modified health assessment questionnaire showed no significant differences.

CONCLUSION: Conventional treatments are associated with various drawbacks such as excessive side effects, lack of efficacy and their high cost. These drawbacks are significant because arthritic patient requires treatment for their entire life. Long-term safety data are largely missing for any of the included herbal medicines. Good tolerance of most of the herbal remedies was demonstrated although caution is warranted in interpreting safety due to small sample size in some of the studies. The current available evidence for herbal treatment of arthritis is generally sparse and reliant on small sample sizes and is therefore insufficient for reliable assessment of efficacy to be made. Non-clinical studies are required to determine the toxicity profiles of almost all herbal medicines in common use for the treatment of arthritis.

Available data suggests that the extracts of most of these herbs or compounds derived from them may provide a safe and effective adjunctive therapeutic approach for the treatment of arthritis.

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