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EFFICACY OF AYURVEDIC INTERVENTION OF ANTI-INFLAMMATORY ANTI-RHEUMATOID ARTHRITIC (RA) AND ANALGESIA: A COMPREHENSIVE REVIEW

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ABSTRACT

Inflammation not a disease it is a symptoms of our immune system. Due to intervention of any infectious organism our body produced pro-inflammatory and inflammatory cytokines which leads to inflammatory reaction. The inflammation can be acute of chronic. In both the cases some immunes cells mediates complex of reaction. Any damage in our phospholipid layer activates phospholipid-lipase breaks arachidonic acid (AA), which also synthesized prostaglandin and leukotriene by activation of cyclooxygenase (COX) and lypooxygenase (LOX) enzyme. The Rheumatoid Arthritics (RA) is chronic inflammatory disorder due to over expression of immune system. In RA mainly joints are affected more. Due to activation of T-lymphocyte by antigen dependent activation trigger synovial lining proliferation activation of cytokine production like IL-1, IL-6, IL-8 and Tumor necrosis factor- α (TNF-α). Main pathophysiological hallmark of RA is inflammation in synovium. The proliferation of synovium formed pannus, which migrates to subchondrial bone and cartilage mainly articular

cartilage that's leads to damage of bone cartilage and tendons. The analgesics are the substances which relives from pain. There are numerous allopathic drugs, NSAIDs are available for anti-inflammatory, anti-rheumatoid arthritis and analgesia but main disadvantages of these drugs is liver damage. The immune's suppressant drugs are used for the treatment of RA and main dis-advantages of those drugs leads to other infection. That's why these review paper discussed about the Ayurvedic plants which are also effective as anti-inflammatory, anti-rheumatoid arthritis and analgesic

KEYWORDS: COX, IL-1, IL-6, IL-8, pannus, synovium.

INTRODUCTION

Inflammation is an immune reaction to tissue due to any injuries. Inflammation can be caused by infective agents, immunological, physical and chemical agents.[1] Inflammation is a complicated biochemical reaction in different tissues which involves specific of responses of leukocytes with blood vesicles. Inflammation is characterized by five cardinal signs.[2,3]

rubor (redness);

tumor (swelling);

calor (heat); and

dolor (pain).

function laesa (loss of function)

The common steps of inflammations involve, adhesion and margination, transmigration and chemotaxis, and last phagocytosis by WBC.[4] Another mechanism of inflammation of the formation of prostaglandin and leukotriene from its precursor of arachidonic acid through cyclooxygenase (COX) and lipooxygenase (LOX) pathways during injuries of phospholipid. The Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder, it not only affects the joints but also affects different organs like organs—skin, blood vessels, heart, lungs, and muscles. Immune system ailments happen when the body's insusceptible framework assaulted its own cells as an antigen and coming about obliterate those cells. Rheumatoid arthritis (RA) is autoimmune inflammatory disorder not one affect the joint but also affect multiple organ like lungs, heart, muscles, blood vessels and skin. The RA is characterized by synovitis leads to inflammation which developed to damage of the articular cartilage and ankylosis of the joints.[5] Many factor may influenced RA such as intervention of any infectious organism, genetic factor mainly Human Leukocyte antigen DR4 (HLA-DR4) which is important diagnostic marker for RA. Anticitrullination (arginine to citrulline)

of proteins is highly explicit for RA patients. Due to activation of T-lymphocyte by antigen dependent activation trigger synovial lining proliferation activation of cytokine production like IL-1, IL-6, IL-8 and Tumor necrosis factor- α (TNF-α). Main pathophysiological hallmark of RA is inflammation in synovium. The proliferation of synovium formed pannus, which migrates to subchondrial bone and cartilage mainly articular cartilage that's leads to damage of bone cartilage and tendons.[6] The word pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". The word analgesic is derived from Greek word "an" means without and "algos" means pain.[7] Analgesics are the agents which are used to relieve pain without loss of consciousness.[7] The main of pain is due to activation of prostaglandin biosynthesis from damaged cell due to excessive secretion of cyclo-oxygenase-2 enzyme through activation of cAMP pathways.[8]

There are numerous studies that report regarding treatments of inflammation, rheumatoid arthritis (RA) using systemic as well as herbal remedies. NSAIDs are first-line medications for all inflammation, RA can only reduce tissue inflammation, analgesia, and swelling but main disadvantage of analgesic and NSAID is liver toxicity, gastrointestinal disorder like ulcer. The corticosteroids to stop dynamic harm to ligament, bone, and neighboring delicate tissues for arthritic treatment. Methotrexate has picked up prevalence among specialists as an underlying second-line tranquilize due to the two its adequacy and moderately rare symptoms of arthritics. The Gold salts have been used to treat rheumatoid joint but main disadvantages is skin rash, mouth bruises, kidney harm with spillage of protein in the pee, and bone marrow harm with weakness and low white cell check. Therefore need for searching alternative approach to treat inflammation RA and analgesic.

METHODOLOGY

Information was collected from different offline, online peer-review journals, and online database like PubMed, Medline Plus, Soddhganga and Google Scholar etc. of preclinical efficacy on anti-arthritic, anti-inflammatory and analgesic activities of different ayurvedic plants on chemically induced rheumatoid arthritics in animal model. Ayurveda traditional textbook, like the Charaka Samhita and Sushruta Samhita, were also look over to make valuable decision from traditional facts.

RESULT AND DISCUSSION

After reading of some paper related to review and research paper we are discussing the following plants having anti-inflammatory, anti-rheumatoid arthritics and analgesic activity

Haritaki (*Terminalia chebula* Retz.)

Fig. 1: *Terminalia chebula* Retz.

The haritaki is one of the main constituents of ayurvedic polyherbal formulation like 'Triphala'. The dried fruit of T. chebula contains high amounts phenolic intensifies that comprise of ellagic acid, gallic acid and chebulic acid.[9] Yang et al. announced the anti-activity of 12 bioactive mixes from the concentrate of T. chebula organic products through restraint of COX-2 and iNOS exercises.[10] Triphala treatment was appeared to repress the paw volume, lipid peroxidation stages, lysozymes and TNF-α, a middle person of aggravation. Ethanolic extract of T. chebula, dose of 400 and 600 mg/kg body weight (b.w), p.o single administration for the period of 3 hour significantly deceased the number of wriths in acetic acid induced mice and increased in the mean reaction time to heat stimuli in hot plate in rat.[11] The Oral administration of watery extract of T. chebula dose of 150 ,300, and 600 mg/kg,bw significantly inhibit the licking response in the early and late phases in 1% formalin induced right dorsal hind paw edema in mice and carrageenan induced paw edema in rats due to inhibition of prostaglandins and other mediators at the peripheral pain sites Topical administration of T. chebula, dose of 1, 2 and 4 mg/ear significantly inhibit EPP (ethyl phenylpropiolate) induced ear edema but not on the AA-induced ear edema in rats.[12]

The methanolic extract of T. chebula at the dose of 1000 mg/kg, bw, oral administration showed highest reduction 63.1% of writhing from 14.1 to 5.2 than the 300, 500 mg/kg, bw oral in acetic acid induced writhing in rats by inhibits cyclooxygenase enzyme (COX) which is rate limiting enzyme for prostaglandin biosynthesis.[13] This anti-arthritic activity of T. chebula due to the inhibition of both COX & LOX pathway by chebulagic acid, as a result decreased generation of inflammatory mediators.[14] The Hydro-alcoholic extract of T. chebula significantly decreased joint swelling by reducing the level of TNF-α in serum and expression of TNF-R1, IL-6 and IL-1β in synovium in formaldehyde and Freund's adjuvant induced arthritis in rats.[15]

Bellerica (*Terminalia bellerica* Roxb*)*

Fig. 2: *Terminalia bellerica.*

The *Terminalia bellerica* Roxb. (Combretaceae) is universally used plants in traditional medicine system in India. The fruit rind one of the important component of "Triphala" (three fruits).[16] It containing various phytochemicals like tannins, chebulinic acid, gallic acid, ethyl gallate and glycoside.[17] There are verious studies has been done on T. bellerica. The Aqueous extract of T. bellerica decreased decreased total number of writhing at the dose of 9, 18 and 36 mg/kg, bw, oral in acetic acid induced Swiss albino mice with the significance of $p<0.045$, $p<0.024$, $p<0.019$.[18] The Methanolic extract of T. bellerica reduced paw edema 50%, 55.88% and 61.76% at the respective dose of 50, 12 and 300 mg/kg, bw, oral in carrageenan induced paw edema in rats.[19] The T. bellerica extract (TBE) showed anti-inflammatory activity at the dose of 100–400µg/mL in lipopolysaccharide (LPS) induced

RAW264 murine macrophage cells by MAPK/NF-kB pathway and enhance antioxidant defense capacity via Akt/AMPK/Nrf2 pathway.[20]

Garlic (*Allium sativum*; Liliaceae)

Fig. 3: *Allium sativum.*

Garlic is a significant components of Indian traditional medication. As Garlic has lots of medical property, used in the treatment of some diseases.[21] Garlic containing important phytochemicals like phytomolecules, including organosulfur compoundA. sativum is rich in several sulfur-containing phytoconstituents such as alliin, allicin, ajoenes, vinyldithiins, and flavonoids also containing quercetin.s, phenolic acids, allyl thiosulfinates, flavonoids, and vitamins.[21, 22] The allcin the main active constituent of garlic significantly reduced the knee joint diameter in turpentine induced arthritic rats at the dose level of 100 mg/kg, bw, oral.[23] Oral administration of aqueous extract of A. sativum at the dose of 100 and 200 mg/kg,bw significantly decreased paw edema in rats in carrageenan and histamine induced paw edema by inhibit the synthesis of prostaglandin by cyclooxygenase pathway.[24] The M. Ali et al. suggested that mechanism of anti-inflammatory activity of Allium sativum is due to noncompetitive inhibition of cyclooxygenase with respect to arachidonic acid (AA).[25] The aqueous extract of A. sativum at the dose of 250, 500 mg/kg, bw, p.o significantly decreased writhing in 4% NaCl induced writhing also prolonged the reaction time 60 mintute and 90 minute in hot plate and tail-clip method in mice.[26]

Turmeric (*Curcuma longa*)

Fig. 4: *Curcuma longa.*

Turmeric is usually used herb in house hold cooking and Ayurvedic medicines. Curcumin is the main active component of this herb, and exhibits anti-inflammatory and antioxidant properties.[27] Significant improvement in morning stiffness, walking time and joint swelling have been observed as anti-arthritic effects after regular curcuma consumption by RA patients.**[28]** The oral administration of ethanolic extract of **C**. longa, at the dose of 100, 200 and 400mg/kg, bw significantly increased time interval of pain response in Wister rats in Eddy's hot plate induced pain.[29] The ethanolic and aqueous extract of C. longa at the dose of 100, 200 mg/kg, bw significantly increase mean reaction time in tail immersion method in Wistar rat after seven days treatment.[30] Two clinical trial was performed to determine anti-inflammatory activity od C. longa. First one conducted by taking 25 subjects with the dose level of 8000 mg for 3 month doesn't showed any toxicity during the treatment.[31] Other human trial has been done by taking 1125-2500 mg of dose of curcumin in per day also did not showed any toxicity. The result of the study suggested that curcumin have anti-inflammatory activity by inhibiting cyclooxygenase, lipooxygenase pathway which are responsible for biosynthesis of prostaglandin and leukotriene, it also inhibit tumor necrosis factor (TNF) and interleukin-12 (IL-12).The essential oil of C. longa showed anti-arthritic activity at the dose of 250-500 mg/kg oral or IP.[32]

The curcumionids showed central pain activity at the dose of 5, 20, 80 mg/kg/day for 12 days and low dose have higher centrally acting analgesic activity in hot plate induced pain model in mice.[33] After 14 days oral administration of ethanolic extract of turmeric at the dose of 300 mg/kg, bw, showed 54 % inhibition of foots thickness by improvement in plasma

malondialdehyde (MDA) level as oxidative stress marker and tumor necrosis factor-α (TNF-α) as inflammatory marker in adjuvant induced arthritic rats.[34]

Cinnamomum zeylanicum L.

Fig. 5: Cinnamomum zeylanicum.

Cinnamon is a common spice that has been used with different food items for several centuries by different cultures around the world. It is obtained from different parts of a tropical evergreen tree. The cinnamon bark essential oil mainly contains cinnamaldehyde (55%–76%), eugenol (5%–18%) and saffrole (up to 2%).[35] The Oil of C. zeylanicum showed anti-inflammatory activity at the dose level of 200 mg/kg, bw, oral in carrageenan induced paw edema in Wistar rats.[36] The hydro-alcoholic extract of C. zeylanicum significantly increased in the tail-flick latency and latency to reaction time in hot plate test in mice at the dose level of 100, 200, and 400 mg/kg, per orally (p.o) in tail flick, hot plate method, and formalin test.[37] The hydroalcoholic extract (CCHE) of C. zeylanicum bark at the dose level of 50, 100 and 200 mg/kg CCHE (p.o) significantly decreased MDA levels and joint swelling in dose dependently also significantly decreased malondialdehyde (MDA) and joint swelling and reduced glutathione levels were elevated in formaldehyde-induced and CFA induced arthritic rat by joint swelling as well as IL-1β and TNF-α.[38] Extracted Type-A procyanidine polyphenols (TAPP) from C. zeylanicum showed significant anti–inflammatory activity at dose of 4, 8 and 25mg/kg, bw in carrageenan induced paw edema in rats. Oral administration of TAPP at the dose of 8mg/kg showed anti-arthritic activity in rats after 9days treatment.[39]

Ginger (Zingiber officinale)

Fig. 6: *Zingiber officinale.*

It is scientifically profound that *Zingiber officinale* Roscoe (Zingiberaceae) has a crucial role to minimize the unendurable pain and inflammation associated with RA.[40, 41] Helpful effects of *Zingiber officinale* on Arthritis Associated Symptoms. Facts described that intake of ginger aids in releasing pain of joints connected with rheumatoid arthritis. Anti-inflammatory effect of ginger was systematically shown first by Feng,T et al. in 2011.[42] The ginger exhibited anti-inflammatory activity by inhibiting biosynthesis of prostaglandin and leukotriene.[43] Three main constituents of Zinger is diarylheptanoid, yakuchinone and proanthocyanidin; between them two shows anti-inflammatory activity; diarylheptanoid shows anti-inflammatory activity by inhibiting 5-lipooxygenase, rate limiting enzyme leukotriene biosynthesis in the other hand yakuchinone inhibit cyclooxygenase, rate limiting enzyme of prostaglandins biosynthesis.

The aqueous extract of zinger shows anti-inflammatory activity during 4 week of oral as well as intraperitoneal administration 58-90.Ethanolic extract of rhizome of Z. officinale reduced paw edema and reduced number of writhing in carrageenan induced paw edema and acetic acid induced writhing in mice at the dose of 50 and 100 mg/kg bw oral.[44] The hydro-alcoholic extract of rhizome of Z. officinale significantly decreased paw volume in carrageenan induced paw edema in rats at the dose of 62, 186 and 310 mg/kg bw, oral.[45]

Aloe (Aloe barbadensis)

Fig. 7: *Aloe barbadensis*.

Aloe vera showed one important role in traditional medicine. The main constituent of aloe is anthraquinone, anthracene, cinnamic acid and anthranilic acid, between these anthraquinone responsible for anti-arthritic activity. The main anti-inflammatory mechanism of aloe is not only inhibits cyclooxygenase enzyme, which is responsible for prostaglandin (PGE2) biosynthesis but also increase breakdown of bradykinin.[46,47] The Aqueous extract and chloroform extract of aloe significantly decreased paw volume from 130 µl to 75 and 60 µl in carrageenan induced paw edema in rats at the dose of 200 and 400 mg/kg, bw oral by inhibiting cyclooxygenase and decreasing migration of neutrophils into the peritoneal cavity.[48] The ethanolic extract of aloe also showed anti-inflammatory activity at the dose of 50, 200, 600 mg/kg, bw oral by decreased number of neutrophils.[48] The aqueous leaf extract of aloe showed chronic anti-inflammatory activity by decreasing carrageenan and formaldehyde induced paw edema, and inhibiting percentage granuloma formation at the dose of 100, 200, 400, 600 mg/kg bw i.p after 7 days consecutive treatment.[49] Aqueous extract of aloe showed analgesic activity at the dose of 100, 200, 400, 600 mg/kg bw i.p by increasing the reaction time of central pain produced by Ugo Basile hot plate method and tail immersion method in rats also reduced number of writhing in acetic acid induced writhing method.[49] The aqueous extract of aloe vera gel showed analgesic activity after at the dose of 300 mg/kg bw oral for 14 days treatment in radiant heat and hot plate method and also inhibit 51.17 % writhing in acetic acid induced writhing methods.[50] The aqueous extract of Aloe

ferox showed anti-inflammatory and analgesic activity at the dose of 400 mg/kg bw oral, by reducing 78.2 and 89.3% of carrageenan and formalin induced paw edema also reduced 88.2% of writhing in acetic acid induced writhing method in Wister rats.[51] Oral administration of crude aloe gel anti-inflammatory properties by reducing carrageenan induced paw edema 58.69% and 74.09% with the respective dose of 25 gm. wet gel/kg body weight (20 mg dry weight/kg body weight) 50 gm wet gel/kg body weight (40 mg dry weight/kg body weight) in rats.[52] Aqueous extract of aloe barbadensis significantly decreased formalin-induced paw edema as well as reduced 66.49 and 57.59 % of 0.6% acetic acid induced writhing at the dose of 25, 50 and 100 mg/kg bw oral, compared with control group at the beginning of 3 hour in rat.[53] Isolated constituents of aloe, aloe emodin (AE) showed anti-inflammatory and anti-arthritic properties by reduced paw edema induced by carrageenan after 6 hour treatment and Complete Freund's adjuvant (CFA) after 28days treatment at the dose in rats by inhibit inducible nitric oxide (iNO) and PGE2 via on murine macrophages.[54] Lyophilized succulent Aloe vera (AVS) significantly reduced tail-flick latency and number of writhes by radiant heat and acetic acid induced writhing methods at the dose of 200 and 300 mg/kg, bw, oral in mice.[55]

Ashwagandha (*Withenia somnifera* Linn.)

Fig. 8: *Withenia somnifera* Linn.

Another name of ashwagandha is Indian ginseng family Solanaceae which have important role in Ayurvedic medicine.[56] The main chemical constituents of ashwagandha which is responsible for anti-inflammatory activity are withaferin A and 3-b-hydroxy-2, 3-dihydrowithanolide. queous extract of W. somnifera showed anti-arthritic activity by significantly reduced level of pro-inflammatory cytokines, TNF-α (0.44 fold) and IL-1β (0.53 fold) in Collagen Induced Arthritic rats at the dose of 300mg/kg, bw, oral.[57] The aqueous

extract of root powder of *W. sornnifera* showed acute inflammatory activity at the dose of 1000 mg/kg, bw, oral in carrageenan induced paw edemic rats. Ethanolic exract of W. somnifera significantly inhibit 36.36% and 61.36% of paw volume in carrageenan and Freund adjuvant induced paw edema in rats at the dose level of 12 and 25 mg/kg bw, oral compare with hydrocortisone.[58] The hydro-alcoholic extract of W. somnifera (HAWS) revealed concentration dependent protein (albumin) denaturation at the concentration range of 3125 to 1000 µg/ml in egg albumin induced edema in rats.[59] The watery suspension of root powder of W. somnifera showed anti-arthritic activity by significantly decreased the severity of arthritis by effectively suppressing the symptoms of arthritis and improving the functional recovery of motor activity and radiological score in collagen induced arthritic rats after 45 days treatment at the dose of 600 mg/kg, bw, oral.[60]

Guggul (*Commiphora mukul)*

Fig. 9: *Commiphora mukul.*

The guggul plays important role in Indian traditional medicine. The Guggulu contains lots of phytochemicals like steroid, aliphatic sterols, ferulates, di and triterpenoids, diterpenoids, triterpenoids, steroids, long chain. The main constituents of guggul is guggulosterone-I, II &III which is responsible for the anti-arthritic activity.[61] Oral administration of aqueous resin and stem bark extract and methanolic extract of Commiphora wightii showed anti-inflammatory activity by decreasing carrageenan induced paw edema period of 5hours at the dose level of 500 mg/kg bw, oral.Oral administration of fraction of C.mukul significantly decreased joint swelling of mycrobacterial adjuvant induced arthritic rats at the daily dose of 100 and 500 mg/kg bw, for 5 month. During 6 hour treatment of C. mukul at the dose of 500mg/kg significantly reduced paw edema, induced by carrageenan**.**

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