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A REVIEW ON SOME SELECTED TRADITIONAL INDIAN MEDICINAL PLANTS OF IMMUNOMODULATORY POTENTIAL AND THEIR THERAPEUTIC USE IN RHEUMATOID ARTHRITIS

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ABSTRACT: Rheumatoid arthritis is a very common auto-immune inflammatory disorder, causing disability in developed and developing countries. Conventional drugs are not only costly but are also associated with very serious adverse effects. Several Indian medicinal plants have been traditionally used for their anti-arthritic effect since time immemorial. Present review focused on the immunomodulatory potentials and anti-inflammatory action of some selected medicinal plants in order to generate the experimental evidence of their therapeutic efficacy in this disease and thereby putting the base for the designing of advanced and safer drugs for this condition, thereby leading to the finding of alternative therapeutic process that can offer enhanced management of the disease. Further, these plants extent studies can result in an eco-friendly cost effective anti-arthritic herbal drug with anti-inflammatory properties contributing to the better maintenance of human society. This review summarizes the different studies performed using these medicinal plants screened for rheumatoid arthritis concerning the chemical constituents, screening methods and therapeutic moieties which will be a remarkable tool for the researcher who involves in the field of the research area.

INTRODUCTION: Rheumatoid arthritis (RA) is a most prevalent chronic inflammatory, autoimmune, progressive, disabling and incurable disease that leads to painful inflammation, often irreversible joint damage, and eventually to functional loss. Its etiology is still obscure [1]. However, to recognize the breakthrough in the pathogenesis of the disease has fostered the finding of new therapeutics with improved results.

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The consequent morbidity and mortality have a substantial socio-economic impact [2]. The prevalence of arthritis is higher in the West. In India the prevalence of RA is 0.75% of population [3], affecting females most to males at 3:1 ratio. According to the 2011 Census of India, with a population of 1.21 billion [4], an estimated 9 million people could be affected with RA.

Presently conventional treatments like nonsteroidal, steroidal and immunosuppressive drugs are used to control inflammatory symptoms and pain; they are associated with certain undesirable adverse effects. With these difficulties, the field of arthritis research has progressed exponentially towards herbal medicinal therapies as alternative medicine that has been considered safe and effective in all elevating

chronic pain associated with arthritis [5]. In Indian traditional medicines, Ayurvedic literature describes portions containing parts of certain plants for treating pain and inflammatory conditions like arthritis [6]. A large number of medicinal plants have been tested and found to contain active principles with curative properties against arthritis [7].

Inflammation is a universal host defense mechanism involving a complex network of cell, cell-mediated and tissue interactions. It occurs in response to a variety of harmful stimuli, physical, chemical, traumatic, antigen challenge, infections, and ionization, *etc*. The immune system gets activated, communication and coordination occur between different classes as well as the actions of immune cells to produce inflammation [8].

According to research inflammation is regulated by a large number of pro and anti-inflammatory mediators [9, 10]. World Health Organization (WHO) report, about 80% of the world's population relies on traditional medicine [11]. There are over 1.5 million practitioners of traditional medicinal system using medicinal plants in preventive, promotional and curative applications [12].

Pathophysiology of Rheumatoid Arthritis: RA an autoimmune disease, whereby the body's immune system attacks its tissues as if it were a foreign invader [13] 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 disease established, the chemicals from the cells damage cartilage, ligaments, tendons, and bone.

TABLE 1: ROLE OF CD4+ (HELPER) T-CELL SUBSETS, CYTOKINES AND THEIR FUNCTIONS IN RHEUMATOID ARTHRITIS

T-Cell Subsets	Functions
TH1	Produces IL-2, interferon-γ, tumor necrosis factor-α, LT, IL-3, and granulocyte-macrophage-colony-stimulating factor
TH2	Produces IL-4, IL-5, IL-10, IL-3, and granulocyte-macrophage-colony-stimulating factor Cooperates with B cells to generate vigorous IgM, IgG1, IgA, and IgE responses
Cytokines	
Interleukin-1	Activates T cells; activates metalloproteinases that destroy cartilage
Interleukin-2	Stimulates proliferation of activated T cells and production of many other cytokines
Interferon-γ	Enhances expression of class II human leukocyte antigen on antigen-presenting cells; enhances intercellular adhesion molecule expression and favors TH1 cell growth
Interleukin-4	Anti-inflammatory, downregulates TH1 cytokine production; stimulates B-cell differentiation and antibody production
Interleukin-6	Causes B-cell differentiation and enhances antibody production; stimulates the production of acute-phase reactants by hepatocytes
Interleukin-8	Neutrophil chemotactic factor; attracts neutrophils to the synovial compartment
Interleukin-10	Anti-inflammatory; in concert with IL-4, inhibits interferon-induced expression of class II human leukocyte antigen
Interleukin-12	Activates and causes proliferation of natural killer cells; favors activation and growth of TH1 cells
Tumor necrosis factor-α	Enhances class II expression on antigen-presenting cells; enhances expression of intercellular adhesion molecules
Transforming growth factor-β	Profibrotic; enhances the production of tissue inhibitor of metalloproteinase, causing decreased production of collagenase and other destructive enzymes; possibly also responsible for late-stage fibrosis and ankylosis; suppresses the expression of class II major histocompatibility complex antigens induced by interferon-γ

Ig: immunoglobulin; IL: interleukin; LT: lymphotoxin; TH: T helper.

B lymphocytes that involve the presence of CD19 and CD20; T 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 proinflammatory molecules (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 anti-inflammatory activity that can down-regulate TH1 immune responses [14]. The balance swings towards the pro-inflammatory cytokines in rheumatoid joints [15]. This can be up-regulated by the expression of cell adhesion molecules on endothelial cells by introducing IL-1 and TNF-*α*.

Medicinal Plants of Immunomodulatory Potential: 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. *Boswellia serrata* inhibits lipopolysaccharide-mediated TNF-α induction in monocytes [16]. 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.

***Withania somnifera*:** 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 [17, 18].

***Zingiber officinale*:** Exhibit a vital role to lessen the unbearable pain and inflammation associated with RA [19, 20]. Ginger is obtained from rhizomes. It has been widely used as a medicinal herb and spice, since ancient times [21]. Anti-inflammatory effect of ginger was scientifically proved first by Kiuchi *et al*., in 1982. [22] They isolated four new different compounds 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 [23].

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 [24].

***Boswellia serrata*:** This is a promising antiarthritis plant with anti-inflammatory and other beneficial pharmacological properties with antiatherosclerotic, analgesic and hepatoprotective effect [25]. Resin derived from it used to treat arthritis associated with chronic inflammatory illnesses from centuries [26].

TABLE 2: ACTIVE COMPOUNDS OF MEDICINAL PLANTS WITH THEIR PHARMACEUTICAL AND BIOLOGICAL IMPORTANCE

Botanical/ Family Name	Common Name	Plant Parts / Solvents	Chemical Constituents	Properties/Screening methods	First author, year
Withania somnifera / Solanaceae	Ashwagandha, winter cherry, withania root, Indian ginseng	Root extract/95% ethanol; 2% gum acacia, 50% aqueous alcohol, aqueous hot water; leaves / *n*-hexane	Withanolides, alkaloids, withanine, pseudowithanine, tropine, pseudo-tropine, somniferine, somnine, somnine-alkaloids 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	Antibacterial, antitumoral, anti-inflammatory, antiarthritic, antioxidant, immunomodulating; Increase total WBC count, bone marrow cellularity, circulating antibody titer, plaque forming cells in the spleen, phagocytic activity of macrophages	Budhiraja, 1987[42]; Mirjalili, 2009[17]; Patwardhan, 2010[18]; Kumar, 2015[43]; Singh, 2007[44]; Ghosal, 1989[45]; Grover, 2010[46]
Vitex negundo / Verbenaceae	Nirgundi, sambhalu, mewri	Fresh berries, seeds, leaf (oil form), roots, bark & flowers /ethanol, petroleum ether extract, water	Carbohydrates, sterols, C-glycosides, flavanoids, polyphenolic compounds, terpenoids, glycosidic iridoids and alkaloids, casticin, essential oil, benzoic acid, vitamin c, flavones; 3*β*-Aceto-xyolean-12-en-27-oic acid, 2*α*, 3*α*-dihydroxyleana-5, 12-dien-28-oic acid; 2*β*, 3*α*-diacetoxyolean-5, 12-dien-28-oic acid and 2*α*, 3*β*-diacetoxy-18-hydroxy-olean-5, 12-dien-28-oic acid isolated from seeds	Antiseptic, ophthalmic, anti-gonorrhoeic, depurative, anti-inflammatory; Control pain and inflammation; useful in dispersing swellings of the joints from acute rheumatism; A tincture of fresh berries are used for treatment of paralysis, pain in limbs, rheumatic disorder, weakness, *etc*./ CFA induced rat model, Carrageenan induced hind paw edema, anti-adjuvant induced arthritis in rat	Ramesh petchi, 2011[47]; Rose, 2011[48]; Subramani, 2009[49]; Vishwanathan, 2010[50]; Dharamasiri, 2003[51]; Chawla, 1992[52]
Boswellia serrata/ Burseraceae	Shallaki, salai guggul, Indian frankincense, salallai	Oleogum resin, bark, whole plant/ *n*-hexane, petroleum ether	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	Shows-anti-inflammatory, immuno-modulatory and anti-arthritic activities. Inhibits passive paw anaphylaxis reaction and mast cell protection; Bowellic acid Showed anti-inflammatory and complement inhibitory activities in rats; down-regulation of TNF-*α* and IL-1/CFA induced (rat) model, anti-adjuvant induced arthritis in rats	Mishra, 2011[53]; Sharma, 1998[28]; Kumar, 2010[54]; Reddy, 2014[55]; Kapil, 1994[56]; Manjula, 2006[57]
Zingiber officinale/ Zingiberaceae	Shunthi, sonth, dry ginger, adrak	Dry ginger extract powder, rhizome (dry), root poultice/ethanol, Hydroxy-methoxyphenyl compounds	Terpenes, monoterpene hydrocarbon, sesquiterpene hydrocarbons and oxygenated monoterpinecineol, borneol, citral, camphene, phelandrene, ginerol, shogaol, zingefone, zinziberin, Phenylpropanoids, 6- Shogaol, Gingerdiols and sesquiterpenoids, with (-) zingiberene	Anti-arthritic, antiseptic, anticarcinogenic, antifungal, anti-microbial, as a stomachic, an aromatic, a carminative, stimulant, flavoring agent, analgesic activity; Inhibition of prostaglandin and leukotriene bio-synthesis	Rehman, 2011[58]; Nievergelt, 2011[59]; Shimoda, 2010[60]; Park, 1998[61]; Subramoniam, 2004[62]
Pluchea lanceolata/ Asteraceae	Rasna	Leaf, stem, root, callus, tuber/ethanol (50%), 90% alcohol, methanol	Moretenol, moretenol acetate, neolupeol, neolupenol, octacoanoic, hexacosanoic and tetracoanoic acid, tetrcosanol, hexacoanol, triacontanol, stigmasterol andbeta-Sitosterol-DGlucoside (leaves and stems) quercetin & isorhamnetin (air-dried leaves); triterpenoids sorghumol, sorghumol acetate, boehmerol acetate from the roots, psi-taraxasterol acetate	Anti-inflammatory, Immunosuppressive, anti-oxidant activity, and anti-arthritic activity/ inhibition protein denaturation and HRBC	Goyal, 2013[63]; Srivastava, 1990[64]; Feroz, 1982[39]; Arya, 2013[65]; Srivastava, 2012[66]

WBC: White blood cells; CFA: Complete Freund's adjuvant; IL-1: Interleukin-1; HRBC: Human red blood cell

TABLE 3: LIST OF MEDICINAL PLANTS USED IN THE TREATMENT OF RHEUMATOID ARTHRITIS

Medicinal plant	First author, year	Study purpose	N (experiment/ control/ Age (years))	Plant part/Solvent used/Dosage, no. of days/ Control drug	Screening methods/ Model/ Active compound	Method of diagnosis	Key findings
Withania somnifera	Anbalagan[67], 1981	Studied on anti-inflammatory properties of WS in an animal model	info not provided	WS root extract suspended in 2% gum acacia / 50 mg/ mL) orally administered, 3 days/ Phenylbutazone (100 mg/kg) to positive control	FCA induced rat model	Acute phase reactants of the blood monitored by crossed immunoelectrophoresis showed changes in the concentration of many serum proteins (α2-glycoprotein, major acute phase α1- protein and pre-albumin) in the WS group. The α2-glycoprotein found only in inflamed rat serum was decreased to undetectable levels in the WS group. Phenylbutazone, on the other hand, caused a considerable increase in the α2- glycoprotein in both arthritic and healthy rats. Another acute phase protein (peak 2, α-1 major acute phase) which increased by approximately 200 percent by inflammation was brought back to normal levels by WS treatment but only to 132 percent of normal by phenylbutazone. WS influenced several modulator proteins in normal rats, suggesting that several plant chemicals in WS possibly interact with the liver protein synthesis process	Observed inflammation in rats and decreasing to undetectable levels the α2-glycoprotein found only in inflamed rat serum
	Somasundaram[68], 1983	Studied on the mechanism of action for the anti-inflammatory properties of WS in the animal model	Not clear	WS extract	Rats injected with 3.5-percent from a line in the hind leg footpad showed a decrease in absorption of 14C-glucose in rat jejunum	Glucose absorption was maintained at the normal level by both WS and the cyclooxygenase inhibitor oxyphenbutazone. Both drugs produced anti-inflammatory effects	The study observed rats injected with formalin in the hind leg footpad showed decreased absorption of 14 C-glucose in rat jejunum, glucose absorption is maintained at the normal level by *Withania* extracts, which produced an anti-inflammatory effect
	Anbalagan[69], 1984	The study investigates the role of a primary prostaglandin. PGE1, on α2M during the inflammatory process in the animal model	6-8 rats in each test group	WS root/ethane/dose of 500, 1000, 1500, or 1200 mg/kg oral suspension, 3-4 hours/ PGE1 ethanol suspension(10 mg/ml)	Carrageenan-induced model (Male Wistar rats)	After doses of WS root powder administered induction of inflammation, paw edema (volume) was measured at a different time interval, and blood samples were collected	WS caused dose-dependent suppression of α2-macroglobulin (an indicator for anti-inflammatory drugs) in the serum of rats inflamed by

					by heart puncture. Electro-immuno-assay of α2M was performed followed by administration of PGE1, *in-vitro*-studies with liver slices, Effect of PGE1 to detect α2M protein	sub-plantar injection of carrageenan suspension maximum effect (about 75%) was seen at 1000 mg/kg
Begum[70], 1988	Study effect of WS on FCA rat model following physical and radiological methods	Not clear	WS root extract powder/ 1000 mg/kg, orally daily for 15 days/ hydrocortisone (15 mg/kg)	Freund's complete adjuvant-induced rat model	Physical (paw swelling), Biochemical and radiological (bony degenerative changes) methods performed	The extracts exhibited a significant reduction in both paw swelling and bony degenerative changes in FCA arthritis as observed by radiological examination
Ziauddin[71], 1996	Immuno-modulatory study in an animal model	-	Root extract	Three myelosuppression models in mice: cyclophosphamide, azathioprine, or prednisolone	Hemoglobin concentration, red blood cell count, white blood cell count, platelet count, and body weight were observed in WS-treated mice compared to untreated control mice	Observed significant increases in hemolytic antibody responses toward human erythrocytes which indicated immunostimulatory activity
Dhule[72], 1997	Studied on the functions of macrophages obtained from mice treated with the carcinogen OTA	male albino mice	WS root and leaves extraction/80% ethanol/crude 100 mg/kg, orally once daily for 17 weeks/control OTA received DW 10 ml/kg	Carcinogen OTA induced model / Alkaloid and Steroids	The phytochemical study, Macrophage culture, and determination of macrophage chemotaxis, macrophages obtained from mice treated with OTA and Indian herbs were cultured, and the supernatant was obtained for further cytokines analysis (IL-1 and TNF-α)	A significant decrease in the chemotactic activity of the macrophages was seen. Interleukin-1 and TNF-α production was also markedly decreased
Ichikawa[73], 2006	WS employed in the treatment of arthritis and are known to be potent inhibitors of angiogenesis, inflammation and oxidative stress using cell lines	-	Leaf/ *n*-hexane	Cell Lines KBM-5 (human chronic myeloid leukemia) cultured in Iscove's modified Dulbecco's medium with 15% fetal bovine serum, A293 (human embryonic kidney carcinoma) cultured in DMEM, MCF-7 (human breast adenocarcinoma) cultured in RPMI 1640 and RAW 264.7 (murine monocytic cell) cultured in DMEM/F-12 supplemented with 10% fetal bovine serum and 100 units/mL penicillin and 100 Ag/mL streptomycin/ isolation of withanolides	Electrophoretic Mobility shift assays, Western blot analysis, IKK Assay, NF-nB-dependent reporter gene expression assay was done to observe effects of withanolide on TNF-α, TNFR associated death domain, The effect of withanolide on the nuclear translocation of p65 was examined by immunocytochemistry, live and dead assay	This paper shows that those withanolides inhibit activation of NF-kB and NF-kB-regulated gene expression, which might explain the ability of withanolides to enhance apoptosis and inhibit invasion and osteoclastogenesis
Singh[44], 2007	Shows anti-inflammatory properties in PBMCs from RA patients and Healthy	PBMC and SFMC from RA patients/ Healthy donor (n=	The dried and powdered roots/ ethanol (95%)	Cell culture for isolation of PBMC from healthy and RA patients and SFMC were isolated from synovial	Culture supernatants and cells were harvested for ELISA and RNA extraction. Cell viability, cytokines analysis;	This study demonstrated that the WS crude ethanol extract suppressed the production of proinflammatory molecules

	donors	not mentioned)		fluid of RA patients (All patients fulfilled the ACR criteria)/ HPLC for sample preparation, Chromatography for standardization withaferin A from WS	TNF-α, IL-1β, IL-6, and IL-12p40 by sandwich ELISA, nitric oxide measurement, EMSA, and Western blotting	*in-vitro*. This activity is partly through the inhibition of transcription factors NF-κB and AP-1 by the constituent withanolide.
Khan[74], 2009	The first study demonstrated that WSL activate the immune system in an animal model	BALB/c mice	Leaf extract / aqueous alcoholic (50%, v/v) /orally, 2 weeks	Ovalbumin-FCA induced animal model/ withanolides /glucowithanolides	Prepared and treated murine splenocytes *in-vitro*, measured Th1/Th2 cytokines by ELISA, Determined IgG2a and IgG1 isotypes by ELISA, Isolated, treated and estimate cytokines in mouse peritoneal macrophages, FCA and IFA immunization, Isolated splenic macrophages for cell supernatant for FACS analysis for surface markers and co-stimulatory molecules	The withanolide 2, 3 dihydro- 3- sulphonile with anyone is a major constituent of WSL responsible for skewing to Th1 immune polarization by stimulating the expression of IFN- γ and B cell switch over to secrete IgG2a while simultaneously enhancing the expression of co-stimulatory molecules and integrins
Kuma[43], 2015	This study evaluates the efficacy and safety for treatment in RA patients	n= 125 (86 patients satisfied inclusion criteria)/ no control taken	5g of ashwagandha powder, twice a day for three weeks with lukewarm water or milk was given to RA patients	The follow up of patients was carried out every two weeks. The primary efficacy endpoint was based on the ACR 20 response. Secondary endpoints were ACR50, ACR70 responses, change from baseline in DAS 28 score and ACR parameters	Biochemical assessments hepatic function (ALT, AST, ALP, bilirubin and ß2 microglobulin), renal function (urea and creatinine and NGAL) tests and urine mercury level through ELISA	This study completed by 90.7 percent (78/86) patients. Patients with moderate and high disease activity were 57.7 percent (45/78) and 42.3% (33/78), respectively. Ashwagandha treatment decreased RA factor. A significant change in post-treatment scores of tender joint counts, swollen joint counts, physician global assessment score, patient global assessment score, pain assessment score, patient self-assessed disability index score and ESR level was observed as compared to baseline scores. ACR20 response was observed in 56.4 percent (44/78) patients and moderate response in 39.74% (31/78) patients Ayurvedic treatment for seven weeks in RA patients showed normal kidney and liver function tests. However, increased urinary mercury levels were was observed after treatment

	Kiran[75], 2016	This study compared the acute and chronic anti-inflammatory effect of *Withania somnifera* with a corticosteroid (Hydrocortisone) in the animal model	Albino rats of either sex, 4 groups (n=6)	Roots/ ethanolic extract/ 12mg/kg & 25 mg/kg p.o./ Hydrocortisone as standard control	Carrageenan and CFA rat model	Maximum percentage inhibition of edema exhibited with 12 mg/kg & 25 mg/kg of ethanolic extract of *WS* at 3 h were 36.36 % and 61.36 % with compare to Hydro-cortisone (40 mg/kg s.c.) 65.91%. Inthe CFA model, on 3rd day hydrocortisone percentage inhibition of paw edema is 31.58% as compare to WS *i.e*. 21.83%	Ethanolic extract of WS elicited significant dose dependent acute and chronic anti-inflammatory activity in carrageenan comparable to hydrocortisone
Zingiber officinale	Srivastava[76], 1992	This study shows the effect of ginger in arthritis and muscular discomfort and suggests a possible mechanism of action	n=56 (28 RA, 18 OA and 10 with muscular discomfort)	Dry ginger powder for three months	The analysis was based on questionnaires by patients	Bioactive components of ginger may act as dual inhibitors of cyclooxygenase and lipoxygenase pathways and may act by inhibiting PGE2 and leukotriene B4 synthesis	Majority of patients experienced some level of relief from pain and swelling
	Tripathi[77], 2008	This study examined the effect of ginger extract on macrophage activation in the presence of LPS stimulation in an animal model	Male and female C57Bl and Balb/C mice (6-8 weeks)	Ginger extract	Murine animal model	Murine peritoneal macrophages were stimulated by LPS in the presence or absence of ginger extract and production of pro-inflammatory cytokines (TNF-*α*, IL-12, and IL-1β) and chemokines (RANTES, MCP-1, IP-10) by ELISA. Also studied the effect of ginger extract on the LPS induced expression of MHC II, B7.1, B7.2, and CD40 molecules. The function of the antigen presenting of ginger extract treated macrophages by primary mixed lymphocyte reaction	Ginger extract inhibits macrophage activation and APC function and indirectly inhibits T cell activation
	Ribel-Madsen[78], 2012	This study aimed at determining if synovial cell cultures from RA, OA, and HC differ and are suitable disease models in pharmacological studies, and tested their response to some anti-inflammatory drugs	OA n= 12; males 0, females 12, RA n= 10; males 2, females 8, HC n=6; males 6, females 0	EV.EXT77extraction of the rhizomes of the herbs *Zingiber officinale* and *Alpinia galanga*, both of which belong to the ginger family/ betamethasone-base, ibuprofen as control drug 77/15 was 100 µg/mL in the cell culture medium	Synovial cells were isolated from the synovial membrane or joint fluid. Cells were cultivated and exposed to no or TNF-α stimulation without, or in the presence of, betamethasone, ibuprofen, or a standardized ginger extract	Concentrations of a panel of cytokines, growth factors and chemokines were mapped for each culture and condition	Cells secreted an increased amount of the cytokines IL-1*β*, IL-6, and IL-8 in response to TNF-*α* stimulation in all conditions. OA cells showed a higher IL-6 and IL-8 and a lower IL-1*β* production, when not stimulated than RA and HC cells, which were similar. TNF-*α* stimulation caused similar IL-1*β*, IL-6, and IL-8 release in all groups. Ibuprofen showed no effect on cytokine production, while ginger

							extract was similar to betamethasone. Ginger extract was as effective an anti-inflammatory agent as betamethasone in this *in-vitro* model
Boswellia serrata	Etzel[79], 1996	Studied special extract of *Boswellia serrata* (H15) in the treatment of rheumatoid arthritis	n=260/Control not clear (placebo)	H15, a standardized extract of the gum resin of BS. A tablet of 400 mg of the dried extract (lipophile)/Dose of 3x2 or 3x3 of the tablet to RA patients,6 month	Clinical study / TLC and HPLC of the $CHCl_3$ extract of H15	The criteria for assessment were mainly joint swelling, pain, ESR, stiffness, additional use of NSAID, side effects and tolerance	H15 produced a significant reduction in swelling and pain compared to the placebo, ESR and morning stiffness was often reduced. The patients often could considerably reduce their intake of NSAID during treatment. The patients' general health and well-being improved
	Kapil[56] 1994	This study evaluated the influence of BA on complement-related inflammation in the experimental animal models of inflammation	n=30, male albino rats	Boswellic acid/100 mg/kg twice a day, 5 days/ control drug ibuprofen injected IP	Arthritis induced by CFA and carrageenan-induced paw edema in rats / Boswellic acid	Inflammatory assays: measurement of left hind foot thickness before and over 5 days after adjuvant induced; Complement activity and the immuno-haemolysing effect of the test samples *via* the classical pathway was determined spectrophotometrically	In both the rat model, BA was found to possess significant anti-inflammatory and complement inhibitor activities. Significantly reduced footpad thickness of experimental animal models and simultaneously also reduced complement activity
	Sharma[80], 2010	The study was designed to investigate the anti-inflammatory and analgesic effect of different fractions of *Boswellia serrata* in an animal model	Albino rats	Oleo-gum-resin/ petroleum ether (100 mg/kg)	Carrageenan-induced paw edema /5-lipoxygenase enzyme	Anti-inflammatory and analgesic activity by the acetic acid-induced writhing response, formalin-induced pain, hot plate, and tail flick method	The different fractions of *B. serrata* showed prompt anti-inflammatory and analgesic activity due to the inhibition of 5-lipoxygenase enzyme
	Sengupta[81], 2011	Studied anti-inflammatory properties of gum resin extracts of *B. Serrata* in an animal model	n=5, Not clear	BE-30 [30% 3-O-acetyl-11-keto-boswellic acid (AKBA)] / 20 mg orally and Aflapin 30 mg for 14 days	Freund's adjuvant-induced inflammation model of rat	TNFα ELISA, Cell culture (HCH), Cell proliferation assay, cartilage matrix production assay, MMP-3 ELISA	Both the *Boswellia* products, BE-30 (5-Loxin) and Aflapin, exhibit powerful anti-inflammatory efficacy and anti-arthritic potential.
	Ismail[82], 2016	Studied the efficacy of anti-inflammatory potential of *B. serrata* in experimental rats	30 Male wistar rats, 5 groups n= 6	Whole plant extract/ normal saline/ low dose (50 mg/kg/ bw), mid dose (100 mg/kg/ bw) and high dose (200 mg/kg /bw) of *B. serrata* through oral gavage/ Indomethacin (10 mg/kg/bw)	Carrageenan-induced rat model	Performed physical parameters such as paw edema measurement, percentage of paw edema inhibition, Histopathological analysis	Treatment of *B. serrata* inhibited the edema and decreases the cellular infiltrates probably by inhibiting the inflammatory mediators. *B. serrata* has high anti-inflammatory activity and suggests as herbal anti-inflammatory medicine
Pluchea lanceolata	Srivastava[64], 1990	Studied anti-inflammatory activity in an animal model	5 groups of mice and rats	Aerial parts extract/ethanol/ indomethacin (2 mg/kg/po) to mice, phenylbutazone (30 mg/kg/po) to rats	Acute carrageenan-induced edema model in both mice and rats / Ψ-taraxasterol acetate	Performed physical parameters such as paw edema measurement, percentage of paw edema inhibition	The ethanol extract of *P. lunceolata* has anti-inflammatory activity in mice as well as rats

	Bhagwat[83], 2010	Investigated the immune-suppressive properties of PL extract and its corresponding chloroform fraction PLC, as also its plausible role in relieving the inflammatory conditions of the body	Male Balb/c mice (Mus musculus) n=6	Leaves extract/50% ethanol, chloroform and *n*-butanol/ PL extract in doses of 50, 100, 200, 400, 600, and 800 mg/kg and PLC fraction in doses of 25, 50, 100, and 200 mg/kg in 1% w/v gum acacia/ Standard control; Cyclophosphamide 250 mg/ kg and cyclosporine-A 5 mg/kg administered orally, once daily	Immunomodulation model for humoral antibody response, cell-mediated immune response	hemagglutination antibody titers, delayed-type hypersensitivity, skin allograft rejection test, *in-vitro* (*C. albicans* method), and *in-vivo* phagocytosis (carbon clearance test), Extraction and fractionation with chloroform, *n*-butanol, and water, fractions were employed for flow cytometry to study the T-cell specific immunosuppressive potential of these fractions	*P. lanceolata* causes immunosuppression by inhibiting Th1 cytokines
	Arya[65], 2013	Comparative analysis of *in-vitro* anti-arthritic and anti-inflammatory activities in methanolic extracts of *in-vivo* and *in-vitro*	Not clear	Leaves, root stem and callus in powdered form/methanol/ 100,250,500 and 1000 µg/ml/ standard, diclofenac sodium	HRBC (human red blood cell)/ flavonoids (quercetin, isorhamnetin, daidzein), triterpenes, sitosterols, taraxosterols, pluchine	*In-vitro* anti-inflammatory activity by HRBC membrane stabilization method; *In-vitro* anti-arthritic activity by inhibition of protein denaturation method	1000µg/ml dose of leaves extract exhibited notable anti-inflammatory activity. Active constituents from *in-vivo* and *in-vitro* plant parts of *P. lanceolata* support in treating inflammation and rheumatism
	Chokshi[84], 2012	Studied anti-inflammatory activity in an animal model	7 groups of Albino Wistar rats/6 rats in each group	Plant parts/combination of different organic solvents: methanol, ethanol, chloroform and petroleum ether/1ml/kg/ mahanarayan oil as a standard control for 24 hours	Carrageenan-induced rat paw edema	After topical application and Sub-cutaneous administration of respective formulation, Paw Volume was evaluated at a different time interval (1, 2, 3 h) up to 24 h	The main aim of the study was to replace water by different organic solvents and obtain oil which has much better efficacy than the traditionally extracted oil. The ethanolic extract has shown to be having high extract yield in the literature on comparison to control
Vitex negundo	Ramesh[47], 2011	Studied anti-inflammatory property in an animal model	Not clear	Fresh berries, leaves (oil form)/ethanol	CFA induced rat model/ Carbo-hydrates, sterols, alkaloids, glycosides, flavonoids, phenolic compounds	-	Plant extract controls pain and inflammation in RA

CFA: Complete freund's adjuvant; PGE: prostaglandins; α2M: α2-macroglobulin; OTA: Ochratoxin A; NF-kB: Nuclear factor-kappaB; DMEM: Dulbecco's Modified Eagle's Medium; RPMI: Roswell Park Memorial Institute; IKK: IκB kinase; TNFR: TNF receptor; PBMC: Peripheral blood mononuclear cells; SFMC: Synovial fluid mononuclear cells; EMSA: Electrophoretic mobility shift assay; GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase; HPLC: High Performance Liquid Chromatography; WSL: *Withania somnifera* leaf; IFA: Incomplete Freund's Adjuvant; Th: T helper; ELISA: Enzyme-linked immunosorbent assay; RA: Rheumatoid Arthritis; ACR: American College of Rheumatology criteria; EULAR: European League Against Rheumatism criteria; DAS: Disease activity score; ESR: Erythrocyte sedimentation rate; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; NGAL: Neutrophil gelatinase associated lipocalin; PGE2: prostaglandin E2; APCs: antigen presenting cells; LPS: lipopolysaccharide; FITC: Fluorescein isothiocyanate; MHC II: Major histocompatibility complex class II; MCP-1:Monocyte chemoattractant protein-1; RANTES: regulated on activation, normal T cell expressed and secreted; CD-40: Cluster of differentiation 40; NSAID: nonsteroidal anti-inflammatory drugs; BS: *Boswellia serrata*; ESR: erythrocyte sedimentation rate; TLC: Thin-layer chromatography; AKBA: 3-O-acetyl-11-ketob-boswellic acid; CMC: Carboxymethyl cellulose; HCH: Human primary Chondrocytes; TCA: Trichloroacetic Acid; TNF-α: Tumor necrosis factor alpha; MMp-3: Matrix metalloproteinase; PL: *Pluchea lanceolata*; PLC: *Pluchea lanceolata* chloroform; SRBC: Sheep red blood cells.

Alcohol extract of salai guggul (*B. serrata*) displayed marked anti-inflammatory activity in carrageenan-induced paw edema in rats and mice. It was equally effective in adrenal-itemized rats [27]. Alcohol extract of salai guggul strongly inhibited antibody production and the infiltration of polymorphonuclear leukocyte; it decreased the volume of pleural exudates [28].

The plant extract has antihyperlipidemic activity also [29, 30]. The compound also protected mice against galactosamine / endotoxin-induced hepatitis in mice [31]. 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 [32]. Besides, acetyl-keto-β-boswellic acid inhibits cellular proliferation through a p21-dependent pathway in colon cancer cells [33].

***Pluchea lanceolata*:** 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 [34, 35]. The plant involves different secondary metabolites *viz*. flavonoids (quercetin, isorhamnetin, daidzein), triterpenes, sitosterols, taraxosterols, pluchine, *etc*. which contribute it anti-inflammatory and analgesic properties [36, 37, 38]. 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 [39].

***Vitex negundo* 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 and ibuprofen 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 [40, 41].

Therapeutic Potential 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 in **Table 2**.

These plant is 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 as shown in **Table 3**. A systematic literature review was carried out using Pubmed, Google Scholar; Medicinal plants database, as well as the journals.

CONCLUSION: 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. Although many studies were carried out, the studies were not concentrating on the expansion of therapeutic agents against RA. Most studies are preliminary.

However, plants such as *Boswellia serrata*, *Withania somnifera*, and *Zingiber officinale* are promising for further studies leading to possible growth of satisfactory medicine for arthritis. From the above review, it should be evident that these medicinal plants which exert anti-arthritic activity, anti-inflammatory and immunomodulatory property at a particular dose. This review attempts to give a scientific account of the use of valuable medicinal plants extracts in rheumatoid arthritis.

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