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Review Article

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Therapeutic potency of a Siddha formulation *Mudakkuvatha Legium* for Rheumatoid Arthritis: A Review

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Abstract

Siddha system of medicine with its evolution in the Pre-Christian era has always fascinated by the Practitioners and Researchers for its depth analytical approach and practical application. The medicines in the system are prepared from raw materials like herbs, minerals, metals and animal products. *Mudakkuvatha Legium* is a herbal formulation with eight ingredients. It is used for Rheumatoid arthritis, Flatulence and other type of Arthritis. This review is aimed to bring out scientific evidence for the therapeutic usage of *Mudakkuvatha Legium* and focussed on the pharmacological activity responsible for the curative nature of the drug. Most of the drugs have Anti-inflammatory, immunomodulator, anti-oxidant activity hence justifying its usage in above mentioned diseases.

Keywords: Siddha system, *Mudakkuvatha Legium,* Anti-inflammatory, immunomodulator, anti-oxidant, Rheumatoid arthritis.

Introduction

Siddha system is the foremost of all medical systems and is practised in South India, especially in Tamil Nadu. It is also called as Dravidian system of medicine, since it evolved along with Dravidian's culture. Tamil Nadu, the home of Siddhars, was a vast continent several millions of years ago. The term 'Siddhar' has derived from the world 'siddhi' which literally, means accomplished, achieved or perfected success; and so it refers to one who had attained his end in spiritual goal. They had investigated and studied fully the cause and effect of disease and all kinds of drugs; and thereby came realise what is beneficial and what was not to their existence in life. They also make use not only of certain special medicinal drugs, but also metallic preparations such as Sulphur, Mercury, Arsenic, Gold, Magnet, Mica etc[1].

In our siddha system of medicine, Medicines are classified into two types and each type consists of 32 forms:

1. Internal medicines (i.e. medicine for internal use)
2. External therapies (i.e. medicine for external application)[2]

Rheumatoid arthritis is the most common inflammatory arthritis. It is characterised by persistent cellular activation, autoimmunity and the presence of immune complexes at the sites of articular and extra-articular lesions. This leads to chronic inflammation, granuloma formulation and joint destruction. The typical clinical phenotype of RA is a symmetrical, deforming, small and large joint polyarthritis, often associated with

systemic disturbance and extra-articular disease features. The clinical course is usually life-long, with intermittent exacerbations and remissions. Up to 50% of the genetic contribution on susceptibility is due to genes in the HLA region. HLA-DR4 is the major susceptibility haplotype in most ethnic groups, for example of Caucasian patients[3].

The similarity of clinical features of rheumatoid arthritis and polyarthritis caused by infectious agents such as rubella, parvovirus B19 and Epstein Barr Virus, and reports of immune hyperactivity to their antigens in rheumatoid arthritis, continues to fuel interest in a potential role for such organisms in initiating rheumatoid disease. The rheumatoid disease process in the joints is characterised by synovitis, an inflammatory effusion and cellular exudate into the joint space, and by damage to tendons, ligaments, cartilage, and bone in and around articulating surfaces of the joint. Tendons, whose sheaths are lined by synovial membrane, such as in the palms, wrists, ankles, and feet, may also be involved by the inflammatory process and cause malfunction due to damage, rupture, and fibrosis[4].

RA can be difficult to diagnose because it may begin gradually with subtle symptoms. Blood tests and X-rays may be normal initially. The disease varies among individuals with respect to symptoms, joints affected, and the nature of other organs involved, such as eyes, lungs, or skin. Other types of arthritis may mimic RA. More than ever, skill and experience or essential to reach a precise diagnosis and to arrive at the most appropriate treatment. Around 60% to 70% of people with rheumatoid arthritis will test positively for a protein called 'Rheumatoid factor'. However some peoplewho do not have the disease also test positive for this protein and some of those who have the disease do not test positively initially. Therefore, although useful, this test does not confirm the presence or absence of the disease[5].

In Siddha concept:

According to Siddha system various text and authors denote the similar symptoms like rheumatoid arthritis. They are,

In the text book *Noi Naadal Noimuthal Naadal Thirattu – Vali Azhal Keel Vayu* is a chronic inflammation of the joints and other areas of the body characterized by pain, burning sensation, redness in wrist, ankle and phalangeal joints. Nodules are formed in joints, difficulty in flexion and extension, disturbed sleep and fever[6].

In the text book Siddha *Maruthuvam-Pothu* – The clinical features of *Uthiravathasuronitham* is pain, swelling in phalangeal, ankle, knee joints, Loss of appetite and confusion[7].

In the text book of *Yugima Vaithiya Sinthamani 800* – The clinical features of *Paithiyavathasuronitham* is severe pain in knee, elbow, phalanges, forehead, cheek and other articulate joint, anaemia, fever and body pain[8].

According to the "*Saambasivapillai" Mudakuvatham* is painful information affecting the muscles and small joints accompanied by calculi. Chronic inflammation of a joint with deformity is arthritis deformans[9].

The rationale behind the selection of *Mudakuvatha Legium* for this study is that most of the ingredients are used in inflammatory joint diseases. So, the medicine is expected to give cure to arthritis patients.

Table 1. Method of preparation of Mudakkuvatha Legium[59]

S.No.	Tamil name	Botanical name	Part used[10]	Quantity
1	Parangipattai	*Smilax china*	Root Bark	18 grams
2	Kodiveli	*Plumbago zeylanica*	Root Bark	18 grams
3	Sangan	*Azima tetracantha*	Root Bark	18 grams
4	Chukku	*Zinziber officinale*	Root tuber	18 grams
5	Milagu	*Piper nigrum*	Fruit	18 grams
6	Thippili	*Piper longum*	Unripe fruit	18 grams
7	Seeragam	*Cuminum cyminum*	Seeds	18 grams
8	Elam	*Eletaria cardamomum*	Seeds	18 grams

Table 2. Information on herbal ingredients as per the text Gunapadam Mooligai Vaguppu[60]

S.No.	Botanical name	Vernacular names				Part used
		Tamil	English	Hindi	Sanskrit	
1	*Smilax china*	Parangipattai, Mathusmeegam, Seenapattai.	China root	Chobchini	madusnuhi	Root Bark
2	*Plumbago zeylanica*	Kodiveli, Chithramoolam, Chithiram, Vanni, Karunaagam.	Ceylon leadwort	Chitrak	Angi-shika	Root Bark
3	*Azima tetracantha*	Sangan	Mistletoeberry thorn	Kalangur-kanai	Kundali	Root Bark
4	*Zinziber officinale*	Chukku, Arukkan, Adhagam, Vidamoodiyaamirtham.	Dried ginger	Sonth	Naagaram	Root tuber
5	*Piper nigrum*	Milagu, Kalinai, Kari, Malayali, Thirangal. Maasam	Black pepper	Kali-mirch	Maricha	Fruit
6	*Piper longum*	Thippili, Aargadhi, Ambu, Aadhimarunthu, Saram, Kolagam	Long pepper	Pipal, pippli	Pippali	Unripe fruit
7	*Cuminum cyminum*	Seeragam, Asai, Seeri, Pithanaasini, Posanakudori	Cumin seeds	Zira	Jirakams	Seeds
8	*Eletaria cardamomum*	Elam, Aanji, Thudi, Korangam	Cardamom seeds	Elachi	Ela	Seeds

Purification of the drugs:

All the raw drugs were purified as per the methods mentioned in Siddha literature.

Standard operative procedure for preparation of *Mudakkuvatha legium:*

The purified raw drugs mentioned in table 1 were made into fine powder. Ghee, Honey and Sugar are mixed together and heated. Then the powder added to the above mixture and mixed well until it becomes legium consistency.

Pharmacological activities of the ingredients of *Mudakkuvatha legium:*

Smilax china

Smilax china has anti-inflammatory activity. Its decoction (90 and 180 mg/kg; p.o) could significantly inhibit inflammatory swelling on adjunctive arthritis mouse[11.] Shu *et al* 2006 has studied the anti-inflammatory activity[12]. Sieboldogenin, isolated from ethyl acetate fraction of *Smilax china* has potent anti-inflammatory activity[13]. In traditional chinese medicine, it is used in the management of chronic pelvic inflammatory disase[12], syphilis, acute bacterial dysentery and chronic nephritis[14]. The methanol extract of Smilax china exhibit antimicrobial activity[15]. In vitro antimicrobial activity of *Smilax china* was reported by Shu Xiao-Shun *et al*[16].The scavenging activity of plants was may be due to the presence of some important chemical compounds like polyphenol, alkaloids, glycosides, flavonoids, and steroids[17]. These phytochemical compounds were commonly found in plants have been reported to have multiple biological effects[18], including antioxidant activity. The Smilax china extracts have scavenging activity against DPPH radicals. The isolation and characterization of active molecules (compounds) responsible for antioxidant activity work is in progress[19].

Zingiber officinale

The anti-oxidative properties of ginger and its components have been explored in various *in vitro* and *in vivo* tests. Strengthening the body's deafness by improving the antioxidant status will undoubtedly protect human against many chronic diseases[20]. 6-Shogaol has exhibited the most potent antioxidant and anti-inflammatory properties in ginger, which can be attributed to the presence of alpha, beta-unsaturated ketone moiety[21].Gingerol, shogaol, and other structurally-related substances in ginger inhibit prostaglandin and leukotriene biosynthesis through suppression of 5-lipoxygenase or prostaglandin synthetase. It also inhibit synthesis of pro-inflammatory cytokines such as IL-1, TNF-α, and IL-8[22, 23]. In another investigation, Pan et al. showed that in macrophages[24], shogaol can down-regulate inflammatory iNOS and COX-2 gene expression[25]. Jung et al. indicated that rhizome hexane fraction extract of *Zingier officinale* inhibited the excessive production of NO, PGE (2), TNF-alpha, and IL-1beta.[26]. The Anti-inflammatory effect of ginger can reduce muscle pain after intense physical activity. It can treat a wide range of diseases via immunonutrition and anti-inflammatory responses[27]. The various phytochemical constituents of ginger have potential therapeutic roles in amelioration of RA symptoms and the conditions like inflammation and pain but also may make it possible to stop further progress or even reverse the damage caused by RA[28].

Piper nigrum

Singh and Duggal have reported the anti-inflammatory action of piperine.

The pro-inflammatory cytokine GM-CSF, IL-6, TNF-α and IL-1β was decreased by administration of piperine[29]. Black pepper possess anti-inflammatory activity. B caryophyllene from black pepper exhibits anaesthetic activity[30]. *Piper nigrum* has anti pyretic activity[31].Aqueous decotion of black pepper showed antibacterial activity against periodontal bacteria[32]. The piperine is significantly inhibited the production of two important proinflammatory mediators, IL6 and PGE2, in IL1β-stimulated human FLS that piperine has antirheumatic effects in animal models and anti-inflammatory effects on IL1β-stimulated FLSs. Anti-inflammatory and antiarthritic effects of piperine was reported by Jun Soo Bang*et al*[33]. The immunomodulatory effects of macrophages with regards to production of pro-inflammatory cytokines IL-6 and TNF-α in response to aqueous extracts of black pepper and cardamom have been widely investigated by Majdalawieh and Carr in 2010[34]. They showed that at concentrations of 1, 10, 50 and 100µg/ml, aqueous extracts of black pepper enhanced the release of IL-6 and TNF-α from the BALB/c splenocytes. These results were consistent with their findings using *in vitro* proliferation assay using [3H] thymidine incorporation that these four doses of aqueous extracts of black pepper also stimulated the splenocytes to proliferate. Black pepper contains several antioxidants and is one of the most powerful antioxidants for preventing as well as curtailing oxidative stress. Its principle phytochemical, piperine is known to inhibit pro-inflammatory cytokines that are produced by tumour cells. Besides, black pepper also exhibits immunomodulatory properties[35].

Piper longum

Piper longum showed potent antibacterial activity against Bacillus subtilis. Piperine was found to be more effective against Staphylococcus aureus[36]. The anti- tubercular activity of *piper longum* was also reported[37,38]. Ethanol hexane, n-butanol extract of *piper longum* was effective against *Entamoeba histolytica*. Piperine and the ethanol extract of long pepper cures ceacal amoebiasis in rats[39]. In carrageenan induced rat oedema model decotion of *Piper longum* showed marked anti- inflammatory activity[40].the fruits of the plant *Piper longum* was studied for their Anti rheumatoid activity in Freunds Adjuvant Induced Arthritis Rats with the dose of 200 and 400 mg/kg p. o. this was reported by Subhash R. Yende *et al*[41].

Cuminum cyminum

Cuminum cyminum having the anti-oxidant property. The spice principle cuminaldehyde from cumin showed scavenging of superoxide anions as measured by inhibition of reduction of nitro-blue-tetrazolium (NBT) in xanthine-xanthine oxidase system to a maximum of 77 percent[42].Souri*et al*(2008) evaluated the antioxidant activity against linoleic acid peroxidation using 1,3-diethyl-2-thiobartiuric acid as reagent. Antioxidant activity (IC_{50}) against peroxidation of linoleic acid (2mg/ml) was 5.76 and phenolic content was 241.41 mg/100g dry weight. The results of this study showed that there was no significant correlation between antioxidant activity and phenolic content of the studied plant materials and phenolic content could not be a good indicator of antioxidant capacity[43].

Elettaria cardamomum

The *Elettaria cardamomum* seed possess anti-inflammatory, analgesic and anti-spasmodic activity. The oil from *Elettaria cardamomum* seeds (175µl/kg and 280µl/kg) were found to show anti-inflammatory activity in carrageenan induced rat paw oedema[44]. The essential oil of cardamom showed antimicrobial acticity[45,46]. K.R.Aneja and Radhika Joshi in their research study have concluded that the ethanol and acetone extract of *Elettaria cardamomum* can be used as a novel anti-microbial agent against periodontal micro organisms[47]. It is found from the study of Hero F. Salah Akyari that methanol, ethanol and aqueous extract of *Elettaria cardamomum* shows strong inhibitory activity against *Staphylococcus aureus* and *Proteus mirabilis*[48]. Ethanol extract *of Elettaria cardamomum* (512 mg/ml) exhibits anti-bacterial activity[49].

Azima tetracantha

The plant is claimed to have anti-inflammatory, antiperiodic, analgesic and wound healing properties. *A. tetracantha* leaves extracts showed both the radical scavenging activity and reducing capability to fight against free radicals. The hydroxyl groups of the phenolic compounds confer the scavenging ability of the plant (Yildrim et al, 2000). The decrease in absorbance of DPPH radical is due to its reduction by different antioxidants, which in turn indicates the free radical scavenging property of the leaves of *A. tetracantha*. In *Vitro* anti-oxidant activity of *Azima tetracantha* was reported by. Gayathri G *et al*[50].

Plumbago zeylanica

The acetone extract of *Pulmbago zeylanica* exhibited significant anti-inflammatory activity. The acetone and petroleum ether extracts of the plant significantly ($p < 0.01$) decreased the pain stimulus[51]. Research studies suggest that *Pulmbago zeylanica* has a potential to be developed into an anti-inflammatory agent[52]. Ethanolic extract *Pulmbago zeylanica* root was active against Methicillin –resistant *Staphylococcus aureus* (MRSA).The anti-inflammatory activities of *P. zeylanica* extracts, administered orally, have been reported in animal models of acute inflammation[53,54]. The root of the plant and its constituents are credited with potential therapeutic properties including anti-atherogenic, cardiotonic, hepatoprotective and neuroprotective properties. The extracts of *P. zeylanica* and its active ingredient plumbagin have significant antioxidant abilities that may possibly explain some of the reported therapeutic effects[55].

Discussion

Modern therapeutic approaches with non-steroidal anti-inflammatory drugs (NSAIDs- eg. Indomethacin, phenyl butazone and ibuprofen), steroidal (cortisone and prednisolone), immuno-suppressive drugs (methotrexate, azathioprine, cyclophosphamide and cyclosporine) and disease modifying anti-rheumatic drugs (gold salts, pencillamine and sulfasalazine) are used to alleviate the agonizing symptoms due to arthritis. None of the existing above treatments can be considered to be curative or definitive therapies for RA and they offer only temporary relief accompanying with various side effects[56, 57,58]. In *Mudakkuvatha Legium* ingredients are of herbal origin, easy availability, cost of effectiveness, high value, prolonged use and least side effects give an opportunity for explore and expect for complete cure in Rheumatoid arthritis from the evident of text "*Aathma Ratchamirtham*[59]".

Conclusion

Rheumatoid arthritis is a systemic autoimmune disease characterized by chronic inflammation of the synovial joints, ultimately leading to joint destruction and permanent disability. Although the pathogenesis of RA remains incompletely understood, the treatment for various forms of arthritis like NSAIDS, diseases modifying anti-rheumatic drugs are available in the market, but they suffer from various drawbacks, such as lack of efficacy, excessive side effects and high cost. Nowadays, with increasing awareness on traditional medicines, many patients look for complementary and alternative medicine for RA. In *Mudakkuvatha Legium*, the drugs are herbal, easily available, low cost and pharmacological activities like anti-inflammatory, anti-oxidant, anti-rheumatism, anti-arthritis and immunomodulator which are responsible for therapeutic activity claimed in literatures.

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