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USE OF MEDICINAL PLANTS IN TREATMENT OF FIBROMYALGIA

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ABSTRACT

Fibromyalgia (FM) or Fibromyalgia Syndrome (FMS) is a chronic disorder causing musculoskeletal pain in body. It mostly affects people of old ages but reported in middle aged groups also. Though there are various medicines and drugs for the treatment of this disorder, natural efficacies are still preferred. This review summarizes some of the most common plants that are used for treatment of Fibromyalgia. The potential mechanism of action of the compounds obtained from such plants is also evaluated. Natural compounds are preferred for the treatment of fibromyalgia because of less side effects. This review mainly focusses on the use of indigenous plants which are found in India. Hence, effects and mechanism of natural remedies for treatment of Fibromyalgia are summarized.

Keywords: TRPV1, Cyclodextrins, Cyclooxygenase, Flexofytol

INTRODUCTION

Fibromyalgia is a disorder of musculoskeletal pain in which sleep and memory are also affected along with fatigue(1). Fibromyalgia is considered as rheumatologic disease(2). One of the characteristics of fibromyalgia is elevated levels of Substance P in the cerebrospinal fluid (CSF) of the patients. Substance P is a peptide which is composed of 11 amino acids. It acts as a neurotransmitter and believed to play a major role in pain stimulations from peripheral nervous system to central nervous system(1). FM patients have about 3 fold increase in the levels of substance P in CSF(3). Elevated levels of substance P are believed to activate neurokinin (NK) receptors that induce pain(4). Besides NK receptors, excitation of amino acid receptors such as NMDA or N-methylD-aspartate receptors also lead to hyperalgesia in fibromyalgia(3). There is hyper excitability of somatosensory system(5).

Dopamine deficiency is also seen in Fibromyalgia patients. It is a neurotransmitter of Central nervous system (CNS) and regulates the pain processing of CNS. Dopamine is released into basal ganglia in response to painful stimulus but in fibromyalgia patients, it is absent(6). Many plants have been used in clinical trials to see the effect of natural products on the pain induced in fibromyalgia. There is no successful medication yet that has been proven to treat fibromyalgia completely. Herbs are believed to be more effective than the drugs and other synthetic compounds in treating fibromyalgia. The plants or herbs are not used as such, instead compounds such as alkaloids are extracted from them and used topically or orally depending upon the type of compound used. The effects of some common medicinal plants are discussed one by one in this review(7).

MEDICINAL PLANTS OR HERBS USED IN TREATMENT OF FIBROMYALGIA

- ***Capsicum***

Capsicum is known through various names such as bell pepper, pepper, chilly etc. Chillies have been used for various purposes in home, be it food and spices, or for treating conditions like stomach-ache, high cholesterol or high blood pressure(8). Capsicum genus belongs to family Solanaceae and include various species such as *Capsicum annuum, Capsicum frutescent, Capsicum longum* etc. It originated in America and from Sanctuaries, it has been used as a folk medicine(9).

The principle behind the use of Capsicum in treatment of fibromyalgia is the active compound 'Capsaicin' produced by Capsicum species i.e. chilli peppers. Capsaicin and other related compounds form a group called Capsaicinoids which are secondary metabolites derived from dried fruits of Capsicum(10). However, a study suggests that capsaicin is not produced by the bell pepper i.e. Capsicum annum(11).

Capsaicin is the main pungent smelling compound of capsicum that makes the taste of chillies hot. Other capsaicinoids differ from Capsaicin in double bond or the length of long aliphatic chain(9).

Various capsaicinoids occur in different compositions as follows:

- capsaicin 33–59 %
- dihydrocapsaicin 30–51 %
- nordihydrocapsaicin 7–15 %
- and the remainder, less than 5 % are homodihydrocapsaicin, homocapsaicin, nonanoyl-vanillylamide, and decanoyl-vanillylamide(9)

So, Capsaicin is the major capsicinoid. Capsaicin was first isolated in crystalline form by Bucholz in 1816. Later, L.T. Thresh isolated it and named it as 'Capsaicin'. Spath and Darling first synthesised Capsaicin. Pure capsaicin is a colourless, odourless, hydrophobic, and crystalline to waxy compound. Its synthesis occurs in the interlocular septa of chilli peppers by addition of a branched-chain fatty acid to vanillylamine(10). Chemically capsaicin is 8-methyl-N-vanillyl-trans-6-nonenamide (9,12)**.**

Capsaicin is composed of a vanillyl(methyl catechol) headgroup (A-region) and an aliphatic tail (hydrophobic—C-region) linked by a central amide bond (B-region)(12).

Mechanism of action of Capsaicin:

The understanding of action of Capsaicin led to the discovery of its receptor 'Transient receptor potential (TRP) vanilloid subfamily member1(TRPV1)' which is a part of the superfamily of TRP receptors that sense external events(11). Capsaicin binds to nociceptors in skin and this causes initial excitation of the neurones and a period of enhanced sensitivity(13).

Capsaicin,the main active capsaicinoid ingredient of chili peppers (Capsicum spp.), an agonist of the transient receptor potential vanilloid1(TRPV1) receptor is highly expressed on nociceptors(2). Capsaicin binds selectively to vanilloid receptor subtype 1 (VR1). VR1 is ion-channel-type receptor which is related to transient receptor potential vanilloid 1 (TRPV1)(10)**.**

Fibromyalgia patients have elevated levels of substance P in their Cerebrospinal fluid (CSF). The physiological effects of substance P are influenced by serotonin level. Serotonin is a key mediator of sleep and perception of pain. Hence deficiency of serotonin may also occur in FM patients(1).

Initially exposure to capsaicin leads to a painful burning sensation due to release of substance P, but multiple administrations of low concentrations, or a single administration of a high concentration reduces sensitization. This may lead to complete desensitization(14).Though topically applied capsaicin induces the release of substance P but additionally there is a specific blockade of transport and de novo synthesis of substance P. In this way, repeated applications of capsaicin lead to a long-lasting desensitization to pain thus resulting in increase in pain threshold(15).

Capsaicin primarily exerts its major pharmacologic effects on the peripheral part of the sensory nervous system on the primary afferent neurons of C-fiber type(16). Capsaicin binds to a receptor at the site of nerve ending and therefore it interferes with the binding of substance P. It is believed that there are two phases of action, first excitation and then desensitization of the nerve to nociceptive impulses. In the excitation phase there is burning/tingling sensation when capsaicin is applied to the skin. In the desensitization phase, there is depletion of Substance P and results in interference with afferent transmission in a nontetrodotoxin dependent manner. The overall effect of this cascade is pain relief(17).**)** Thus prolonged repeated applications of capsaicin deplete the peripheral sensory C-fiber of substance P, resulting in inhibition of pain sensation(16). Due to desensitizing action of capsaicin it has become popular for use as a peripherally acting analgesic for treating chronic painful syndromes(9).

In a study, patients suffering from chronic soft tissue pain were treated with a cream containing 0.05% capsaicin and they showed significant improvement in pain after 3 weeks of treatment(18).

Patients of Fibromyalgia also show significant improvement in myalgic scores, pain threshold, mood and fatigue when they are treated with 0.075% capsaicin 3 times daily for six weeks(4). Most creams have concentrations of 0.025% to 0.075% capsaicin. Maximum pain relief is generally seen after 14 days when the cream is applied for 3-4 times daily(8).

The enhacement of analgesic effects of capsaicin during inflammation support the fact that the stimulation of vanilloid receptor type 1 perhaps constitute a suitable strategy to avoid inflammatory hyperalgesia(19).

- ***Ocimum***

The leaves of *Ocimum basilicum* are produce LEO (Leaves essential oils) which are rich in monoterpenes(20)**.** Monoterpenes are a group of naturally occurring organic compounds. Their basic structure comprises of two linked isoprene units which are formed by C5 base. Linalool (LIN) which is a monoterpene enantiomer is one of the volatile components of the essential oils of *Ocimum basilicum*. Its analgesic effect is seen in animal models with non-inflammatory chronic muscle pain, that mimics fibromyalgia(21). Many members of the Lamiaceae family (mints) and Lauraceae family (laurels, cinnamon, rosewood) produce linalool which is a plant-derived monoterpene alcohol(22).

Mechanism of action of *Ocimum*:

In fibromyalgia, Aδ type myelinated afferent nerve fibres obtain similar characteristics like those of C-type non-myelinated fibres which result in secondary pain. Recent studies have showed that linalool which is a major compound of LEO, blocks the excitability and conduction of all types of myelinated fibres of the sciatic nerve with greater pharmacological potency for the fibres with slower conduction speed, in a concentration-dependent and reversible manner. This is turn blocks the generation of action potentials and thus inhibits the voltage-gated Na+ current of dissociated dorsal root ganglion neurons(20). Poor chemical stability, water insolubility and short half-life restrain the medical uses of LEO. However, these limitations can be overcome by using drug delivery systems such as cyclodextrins. LEO is complexed with β-CD to improve the pharmacological activity of isolated LEO(20)**.** In a study **,** the antinociceptive effect of linalool/ β-CD was shown to have more significant improvement as compared to linalool alone(22).

- ***Turmeric***

Turmeric is known from the biological name as *Curcuma longa*. The medicinal power of turmeric is due to the antioxidants present in it. Rhizomes or roots of turmeric are used for medicinal purposes. The phytochemical components of turmeric include diarylheptanoids, which is a class including numerous curcuminoids, such as curcumin, demethoxycurcumin, and bisdemethoxycurcumin(23).

Curcumin is one of the antioxidants of turmeric(7). It is a yellow pigment of Turmeric and chemically known as 'diferuloylmethane'. It was first isolated in 1815 by two German Scientists, Vogel and Pelletier. Curcumin has been shown to exhibit anti-inflammatory activity by suppressing various signalling pathways(24). It is a low molecular weight polyphenol and was first chemically characterised by Milobedzka et al. in 1910. It is also known to lower the markers of oxidative stress(25).

Mechanism of action of curcumin:

Curcumin can inhibit all mediators of the inflammatory response such as cytokines, chemokines, adhesion molecules and growth factors along with some other mediators such as cyclooxygenase-2, inducible nitric oxide, tissue factor and epigenetic alterations . These effects of curcumin are because of its ability to inhibit the NF-kB pathway and other pro-inflammatory signalling pathways which include COX-2, AP-1, Egr-1, STAT (signal transducers and activators of transcription) members and mitogen-activated protein (MAP) kinases(26). Curcumin exerts antinociceptive effects and has been shown to have analgesic effects in neuropathic pain in mice(27). Curcumin inhibits the cyclooxygenase pathway. Cyclooxygenase is an enzyme that catalyzes the conversion of arachidonic acid to prostaglandins (PGs) which are the key mediators in exaggeration of sensation of pain. Thus, curcumin affects the activity of Cyclooxygenase enzyme for regulation of pain(28). Recent studies have also shown that Curcumin can inhibit transient receptor potential cation channel 1 (TRPA1) and transient receptor potential cation channel subfamily V member 1 (TRPV1), which are transient receptor potential ion channels and involved in generation of painful stimuli(29). Recently, a purified curcumin extract, Flexofytol, was administered as a food supplement with the indication of its ability to improve musculoskeletal flexibility. Flexofytol thus appears as an alternative to conventional treatments of Fibromyalgia(30).

DISCUSSION:

There are various other plants that can be used in treatment of fibromyalgia. Capsicum, *Ocimum* and Turmeric are the most common medicinal plants that have been proven to show improvement in the chronic pain of fibromyalgia. Various clinical trials and studies on animal models have experimentally shown how the use of topical medications obtained from these medicinal plants provided relief to pain in fibromyalgia patients. Using natural compounds have also helped to prevent the side effects that could occur by using drugs and steroids for treating fibromyalgia. However, research is going on to find

out more alternative options that can be used for treating various chronic conditions.

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