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Vanshika Bhardwaj

UG Scholar, KIET School of Pharmacy,
KIET Group of Institutions, Delhi-NCR,
Ghaziabad, 201206, UP, India

Neha Gupta

UG Scholar, KIET School of Pharmacy,
KIET Group of Institutions, Delhi-NCR,
Ghaziabad, 201206, UP, India

Anju

UG Scholar, KIET School of Pharmacy,
KIET Group of Institutions, Delhi-NCR,
Ghaziabad, 201206, UP, India

Khusboo Arora

UG Scholar, KIET School of Pharmacy,
KIET Group of Institutions, Delhi-NCR,
Ghaziabad, 201206, UP, India

Avishek Kumar Jha

UG Scholar, KIET School of Pharmacy,
KIET Group of Institutions, Delhi-NCR,
Ghaziabad, 201206, UP, India

Abhishek Kumar

Division of Pharmacology, KIET School
of Pharmacy, KIET Group of Institutions,
Delhi-NCR, Ghaziabad, 201206, UP,
India

Priya Bansal

Division of Pharmacology, KIET School
of Pharmacy, KIET Group of Institutions,
Delhi-NCR, Ghaziabad, 201206, UP,
India

Correspondence:

Priya Bansal

Division of Pharmacology, KIET School
of Pharmacy, KIET Group of Institutions,
Delhi-NCR, Ghaziabad, 201206, UP,
India

Email: bansalpriya23@gmail.com

Traditional Medicaments Combating Against Fibromyalgia- A Review

Vanshika Bhardwaj, Neha Gupta, Anju, Khusboo Arora, Avishek Kumar Jha, Abhishek Kumar, Priya Bansal*

ABSTRACT

Fibromyalgia syndrome is a persistent condition characterized by frequent body pain at different tender points, sleep disturbance, fatigue, anxiety, impaired condition, joint stiffness. 5% of the world population mainly middle and old aged people suffer from it. Women are more prone towards this disease. The underlying pathophysiology of this syndrome is still unknown. Common symptoms of this syndrome mainly include chronic pain, fatigue, sleep disturbance, depression, joints stiffness, central sensitization, allodynia & hyperalgesia. There is no confirmatory blood test or imaging for diagnosis of fibromyalgia. The diagnosis criteria were set by The American College of Rheumatology (ACR) in 1990 and then modified further in 2010. The main drugs used for treatment mainly include Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants, anticonvulsants, analgesics, Nonsteroidal anti-inflammatory drug, nerve pain medications and muscle relaxants. Therapies are also used for pain relieve such as acupuncture, graded exercise, stretching, massage, chiropractic treatment techniques, cognitive behavioural therapy, hydrotherapy, biofeedback and group support to overcome depression but they have low efficacy. Self-care is another major factor for treatment like stress management, healthy diet, relaxation techniques and physical exercise. Due to various side effects of drugs, nowadays scientist and researchers having an eye on medicinal plants and their secondary constituents for treatment of fibromyalgia. In this review, authors tried to compile various medicinal plants and their secondary metabolites having potential to treat fibromyalgia.

Keywords: Hyperalgesia, Depression, Anticonvulsant, Allodynia, Antidepressants.

INTRODUCTION

Fibromyalgia Syndrome is a persistent condition, characterized by frequent body pain at different tender points, sleep disturbance, fatigue, anxiety, impaired condition, joint stiffness^[1]. Fibrositis term was used in 1904 given by Gowers^[2] then Fibromyalgia as “pain syndrome” concept was introduced by Graham in 1950^[3]. Later the “fibromyalgia” was coined by Smythe and Moldofsky in mid 1970s and tender points were also identified by them^[4,5]. In US estimated prevalence rate was 6% to 15% that is five times more in women than men^[6]. Etiology and pathogenesis of fibromyalgia are still unknown. Familial genetic predisposition responsible for pain sensation due to certain genetic compounds like dopamine and serotonin. Sleep abnormalities is due to restorative delta wave sleep loss^[7,8]. Central sensitization and pain inhibitory pathways are considered mechanism involved in pain sensation. Neurotransmitters alteration leads to sensory signals processing in CNS^[6]. Pain centralization occurs due to nociceptors (peripheral pain receptors) activation^[9,10]. Another involved mechanism in fibromyalgia is activation of glial cells which modulate pain transfer in spinal cord which is activated by several sore stimuli. They release some pro inflammatory nitric acid, cytokines, reactive oxygen species and prostaglandins that excite and delay hyperexcitability of spinal cord^[11,12,13]. Other factor that influence pain are cognitive and affective psychological factors. Cognitive factor is responsible for headache and dependent on 2 cognitions self-efficacy (SE), and locus of control (LOC). Affective factor is dependent on emotional state and negative affect: anger, depression and anxiety^[14]. Other affected area are respiratory mechanics, second rib, anterior cervical, suboccipital region and upper trapezius muscle. Women affected with fibromyalgia syndrome have lower thoracic mobility, respiratory muscle toleration and pulmonary muscle strength. Lower pulmonary strength was related with low axillary mobility also increased fatigue and extremely large number of functioning tender points^[15]. There is no confirmatory diagnosis process, blood tests, imaging or any other method for evaluation and analysis of fibromyalgia syndrome. Early diagnosis system is based on symptoms and history of condition. On the basis of pain and tender points count pre-ACR diagnosis system was made^[16-19]. The American College of Rheumatology (ACR) 1990 set the criteria of diagnosis on the basis of chronic widespread pain for regular 3 months or more on 11 tender points out of 18^[17,18] [ar270]. 2011 ACR concept was based on “ABC indicators” that is (A) analgesic, (B) bilateral, axial symmetric pain (C) chronic disease^[20-23]. In 2016 ACR modified the diagnosis criteria on the basis of symptoms^[24]. Fibromyalgia is most probably related with depression^[25].

Treatment of fibromyalgia is done by Antidepressant drugs, most probably duloxetine and milnacipran is used as the inhibitor reuptake of serotonin and balance norepinephrine [26-29]. Pregabalin anticonvulsant drug is also used as it affects influx of calcium and release neuropeptides and excitatory amino acids [30]. Other drugs used are (TCA) tricyclic antidepressant (amitriptyline), SSRI's Tramadol, cyclobenzaprine, strong opioids, Nonsteroidal anti-inflammatory drug (NSAID) [31-33]. Armodafinil and Modafinil are used to treat fatigue occurring due to fibromyalgia [34]. Therapies used in treatment of fibromyalgia other than drugs are acupuncture (electro or manual) [35, 36]. Other method used by physiotherapists are massage, heat/manual therapy, hydro therapy, exercise, pain management, electrotherapy [37-39]. Cupping therapy is also given to patients for improvement in condition [40]. It was observed that drugs used for treatment of fibromyalgia produces side effects like dizziness, nausea and many more. Other treatment given like physiotherapy and acupuncture doesn't show high efficacy. According to current scenario medicinal plants and secondary metabolites are considered for treatment of fibromyalgia syndrome because of their good efficacy and no or less side effects [41]. The main objective of this review article was to summarize the medicinal plants and secondary metabolites that may be used for treatment of fibromyalgia on the basis of their activity to ameliorate pain.

MEDICINAL PLANTS COMBATING FIBROMYALGIA

Zingiber officinale (Zingiberaceae)

Zingiber officinale also known as Ginger is a perennial herbaceous Indian plant. It has diverse medicinal properties, hence used for dietary purpose for many decades. The rhizome is a store house of many volatile and non-volatile compounds such as sesquiterpenoids, monoterpeneoids, 6- gingerols, 6-shogaols, paradols, and zingerones. An experiment was carried out to explore the effect of methanolic extract of powdered Ginger rhizome in an ICS – induced FMS model. The study was done on 48 female mice having 18–22 g weight. The mice were divided into six groups consisting of 8 animals in each group. Various nociception (paw pressure test, hot plate test, tail immersion test) and behavioural parameters (anxiety-related test, traction test, invasion test) were assayed at dose of 0.5% & 1% and it was revealed that ICH-induced FMS model showed a remarkable depletion in the alleviated neuropathic and chronic pain. The dried Ginger rhizome exerts its anti-inflammatory action by lowering the inflammatory response of proinflammatory mediators such as NO, PGE₂, TXB₂, IL-1 β in LPS-stimulated macrophages. Zingerone reduces the level of NF- κ B, hence showing anti-inflammatory activity [42].

Panax ginseng (Araliaceae)

Panax ginseng, an Asian folk medicine, well known for its ability to improve immunity mainly used as an herbal supplement. It can also be used to treat fatigue, weakness, and chronic pain. The present investigation was carried out to check the efficacy of *P. ginseng* extract on patients suffering from fibromyalgia. A randomized, double-blind, controlled clinical trial was conducted for about 12 weeks in 38 patients suffering from fibromyalgia. In this study a comparison between *P. ginseng* (100 mg/d), amitriptyline (25 mg/d) and placebo was done based on various parameters like Visual Analog Scale, Fibromyalgia Impact Questionnaire for analysing pain, fatigue, sleep, anxiety, and quality of life of patient. It was found that *Panax ginseng* root extract showed a significant depletion in the mean score for pain, fatigue, sleep, anxiety and FIQ. Tender point count method was also used to examine pain in fibromyalgia patient and it was found that *P. ginseng* also

attenuate the number of tender points. Hence the authors have suggested that *P. ginseng* can be a possible choice of treatment for fibromyalgia. However further research is required to understand the exact MOA behind its activity [43].

Curcuma Longa (Zingiberaceae)

Curcuma longa also known as Haridra in Ayurveda is widely used in treatment of inflammatory bowel disease, rheumatoid arthritis etc. A study was performed by Ismael San Mauro Martin *et al.* on anti-inflammatory and antioxidant effect of *Curcuma longa* in fibromyalgia patient. A randomized, controlled, prospective study was performed in which 13 women participated aged between 30-60 years. The groups were divided into two parts, group 1 (G1) comprises 6 women and group 2 (G2) consist of 7 women. The study was conducted for one month where following specifications were observed such as diet, pain, anthropometric study, sleep, fatigue and additional symptoms and were evaluated on the basis of questionnaire. At the end of study, it was observed that G1 with turmeric diet has reduced intensity of pain as compared with G2. Hence the authors have suggested that *Curcuma longa* can be used to treat fibromyalgia pain because of its anti-inflammatory & antioxidant characteristics [44].

Tamarix indica (Tamaricaceae)

Tamarix indica is the rich source of tannin, tamarixin, flavones, ellagic acid etc. These compounds have beneficial effect in dysentery, thrombosis, chronic diarrhea and allergy. An experiment was performed to analyze the antinociceptive, anti-inflammatory and antibacterial activities of methanolic extract of root of *Tamarix indica* in Young Swiss albino mice. Antinociceptive and anti-inflammatory activities were determined by acetic-acid induced writhing method and carrageenan induced paw edema test respectively and it was revealed that the polar compound in extract inhibit writhing ($p < 0.001$) at a dose of 500 mg/kg body weight. It also decreases paw volume. Anti-bacterial activity and minimum Inhibitory Concentration of *Tamarix indica* were evaluated by disc diffusion method and micro dilution method respectively and it was revealed that the drug shows promising results as anti-bacterial agent. Hence, according to study of Rahman *et al.* *Tamarix indica* shows/exhibit anti-inflammatory and antinociceptive activity [45].

Piper nigrum (Piperaceae)

Piper nigrum commonly known as Black Pepper has been used for culinary purposes for decades. Piperine, an alkaloid is responsible for its pungency. It is an Ayurvedic and Unani medicine used in the treatment of fever, pain and inflammation. The investigation was carried out to study the analgesic and anti-inflammatory effect of fruit of *Piper nigrum* in Swiss Albino mice and rats at a dose of 5, 10 and 15 mg/kg body wt. The animals were distributed into five groups. The analgesic effect was determined by various parameters such as tail immersion method, analgesy-meter, hot plate method, acetic acid induced writhing method. It was found that *Piper nigrum* exert its therapeutic effect by opioid receptors, neurotransmitter modulation and inhibition of PG synthesis and release. Anti-inflammatory property of *Piper nigrum* was also observed through carrageenan induced paw edema test. The study demonstrated that rats show better safety profile of *Piper nigrum* than mice [46].

Acanthus ilicifolius (Acanthaceae)

Acanthus ilicifolius, a perennial herb, popularly known for its wound

healing properties. Various studies suggested that the methanolic extract of *Acanthus ilicifolius* leaves possess hepatoprotective, anti-tumour, leishmanicidal activities. The present study was conducted to explore the anti-inflammatory activity of leaves of *Acanthus ilicifolius*. Anti-inflammatory activity was evaluated by carrageenan induced paw edema test and the results suggested that leaf extract inhibit rat paw edema when given prior as well as after administration of carrageenan. The extract inhibits protein exudation, movement of leukocyte in peritoneal fluid, COX1 and COX2 enzymes, IL-6, TNF α , 5-LOX enzyme and the release of pro-inflammatory cytokines. It was also found that the extract has a potent role in enhancing ferric reducing ability of plasma (FRAP) and attenuating superoxide and hydroxyl radicals. Thus, the authors have concluded that *Acanthus ilicifolius* can be used in fibromyalgia as it possesses anti-inflammatory property [47].

Caesalpinia mimosoides (Leguminosae)

Caesalpinia mimosoides is an Ayurvedic shrub which is a potent carminative and has the ability to treat dizziness. It also shows anti-oxidant activity due to the presence of gallic acid. Both In-vitro and in vivo screening were done to understand the anti-inflammatory effect of ethanolic extract of Caesalpinia mimosoides. In-vitro test was done on the basis of Protein denaturation and Proteinase inhibition. In vivo test was done on adult Wistar albino rats at a dose of 200-400 mg/kg body wt. It was found that Caesalpinia mimosoides treated model showed decreased carrageenan induced edema. It also inhibits the synthesis of prostaglandin, kinin, bradykinin and lysozyme. It was also observed that Caesalpinia mimosoides choked the inflammatory mediators release through the inhibition of proteinase enzyme. In the view of the above results, the authors concluded that Caesalpinia mimosoides exhibits anti-inflammatory property with the safety profile up to 2000 mg/kg body weight [48].

Pongamia pinnata (Leguminosae)

Pongamia pinnata is widely used for the treatment of gout, fever, abdominal colic and inflammation. In the present experiment, extracts of *Pongamia pinnata* seeds were examined for anti-inflammatory

activity in albino rats. Paw oedema was induced by the administration of carrageenan, histamine, 5-HT, bradykinin and PGE subplantarily. And it was found that the polar compound (majority glycoside) present in seed of *Pongamia pinnata* inhibit eicosanoid and sustained late phase mechanism, hence showing anti-inflammatory effect. The flavonoids and sterols were observed to restrict the synthesis of prostaglandin [49, 50].

Derris scandens (Fabaceae)

Derris scandens is a medicinal shrub of Southeast Asia. Its stem possesses diverse medicinal properties such as expectorant, antitussive, antimicrobial, diuretic and immunostimulatory. This shrub is a store house of coumarins, isoflavones and glycosides. The investigation was carried out to explore the actions of chloroform extract of leaf and root of Derris scandens in Albino rats. Extract was administered orally at a dose of 200 mg/kg and 400 mg/kg body weight. Anti-inflammatory activity was evaluated by carrageenan induced paw edema test and it was concluded that Derris scandens show anti-inflammatory property at a dose of 400 mg/kg body weight due to the presence of flavonoid [51, 52].

Aegicerus Corniculatum (Aegicerataceae)

Aegicerus corniculatum has been used for many years for its anti-asthmatic, anti-diabetic, anti-inflammatory and anti-rheumatoid activity, Various studies suggested that flavonoids, polyphenols, β -sitosterol, saponin & triterpenes are present in this plant. A study was performed to explore the theraprutic action of extract of A. corniculatum aerial part in albino mice. The extract was analysed on the basis of various parameters such as paw edema test, carrageenan-induced peritonitis, 5- & 12- lipoxygenase assay and COX-1 assay. It was found that A. corniculatum treated model showed reduced paw edema; inhibited eicosanoid & prostanoid production, COX expression; lowered LTB $_4$, 5-HETE, 12-HHT levels. Thus, based on above findings, the authors have concluded that it can be used in Fibromyalgia due to its anti-inflammatory actions [53, 54].

Table 1: summarizes and explains various medicinal plants which are studied extensively to be used against Fibromyalgia.

S. No.	Name of the Plant (Family)	Part used	Extract used	Mechanism of Action	References
1	<i>Zingiber officinale</i> (Zingiberaceae)	Rhizome	Methanolic extract	It attenuates the inflammatory response of NO, PGE $_2$, TXB $_2$, IL-1 β & reduce the level of NF-KB.	42
2	<i>Panax ginseng</i> (Araliaceae)	Root	Methanolic extract	Lowers the tender points & deplete score for pain, anxiety, sleep and fatigue.	43
3	<i>Curcuma longa</i> (Zingiberaceae)	Root	Ethanolic extract	Anti-oxidant effect	44
4	<i>Tamarix indica</i> (Tamaricaceae)	Root	Methanolic extract	It shows the inhibition of writhing.	45
5	<i>Piper nigrum</i> (Piperaceae)	Fruit	Hexane extract Ethanolic extract	Modulation of neurotransmitter & inhibition of prostaglandin.	46
6	<i>Acanthus ilicifolius</i> (Acanthaceae)	Leaves	Methanolic extract	It inhibits COX1, COX2 enzyme release & proinflammatory cytokines.	47
7	<i>Caesalpinia mimosoides</i> (Leguminosae)	Aerial part	Ethanolic extract	Decreased the inflammatory mediators release through the inhibition of enzyme.	48
8	<i>Pongamia pinnata</i> (Fabaceae)	Seed	Ethanolic extract	It inhibits late phase inflammation.	49,50
9	<i>Derris scandens</i> (Fabaceae)	Root & leaves	Aqueous extract	It shows the inhibition of oedema.	51,52
10	<i>Aegicerus corniculatum</i> (Myrsinaceae)	Stem	Methanolic extract	It decreases neutrophil infiltration & reduce inflammation.	53,54

Phytoconstituents Role in treatment of Fibromyalgia:

α -Spinasterol

α -Spinasterol, a stigmastane type phytosterol present in many plant varieties such as spinach. The current study was done to evaluate the efficacy of α -Spinasterol on various symptoms of fibromyalgia like nociception, depression in fibromyalgia mouse model. Subcutaneous injection of reserpine (1mg/kg) was given to mice to induce mechanical allodynia. Various parameters like von frey test, thigmotaxis behaviour test, grip test, forced swimming test were studied and it was found that α -Spinasterol (0.3mg/kg), antagonist of TRPV1 channel reduced mechanical allodynia, immobility time, depression in fibromyalgia mice model. Previous studies confirmed that TRPV1 is involve in inflammatory and neuropathic pain, chronic hyperalgesia, and depression. The results suggested that α -Spinasterol, a COX inhibitor is a potent antioxidant and having anti-inflammatory and antidepressant activities. It was also noticed that α -Spinasterol did not cause severe side effects, hence can be a possible safe approach for the treatment of fibromyalgia [55].

Capsaicin

Capsaicin also known as capsicine, capscicin, CPS procure from chilli peppers belonging to genus capsicum. It is widely used as an active component of various pain relief agent. It binds with vanilloid receptor which is also known as Transient Receptor Potential Variet (TRPV) 1 primarily expressed by sensory neurons. Capsaicin releases and reduces substance P from afferent nociceptive specific neurons. A study was carried out to assess the effects of topical capsaicin therapy in fibromyalgia severe patient. In this study 130 people were randomly divided into 2 groups. 1st was a control group comprises 56 women and 4 men who are given medical treatment and 2nd was the capsaicin group comprises 70 women continuing with medical treatment along with topical capsaicin 0.075%, 3 times daily for 6 weeks. At the starting of treatment, no significant changes were found but later on improvement in myalgic score, pressure pain, threshold, FSS, FIQ, VAS of depression etc. The study concluded that capsaicin shows good anti-inflammatory effect and can be used as possible alternative treatment for pain in fibromyalgia [56, 57].

Hecogenin Acetate

Hecogenin acetate (acetylated steroidal sapogenin) is obtained from the plants belonging to genus Agave. It acts as the precursor of steroidal, sexual & protein anabolic hormones. In the present experiment, Hecogenin acetate was administered intraplantarly in Male Swiss mice to assess its antihyperalgesic and analgesic effect associated with c-fos expression on spinal cord and cytokines. Hecogenin acetate exhibits antinociception as tested in tail-flick test. Real Time PCR analysis result revealed the anti-inflammatory property of Hecogenin acetate was due to inhibition of inflammatory cascade as well as cytokine pathway. Hecogenin acetate was proven for its analgesic effect by lowering the expression of Fos and thereby inhibiting the neuronal hyperactivity in the dorsal horn of spinal cord. It also elevates K⁺ATP channel regulation [58].

Umbellatine

Umbellatine, extracted from Psychotria umbellata is a glycoside indole monoterpene alkaloid. A study was performed to explore the analgesic actions of ethanolic extract of Psychotria umbellate on male Albino mice. Various behavioural tests like Tail-flick, Hot-plate, Formalin test Capsaicin-induced pain and Rota rod test were performed and it was found that Umbellatine possess analgesic effect through the opioid receptors. Various studies suggested that capsaicin and formalin enhance the glutamate and aspartate release and capsaicin also activate NMDA glutamate receptors in the dorsal horn of spinal cord and thereby induce acute and chronic pain. Umbellatine was revealed as an antagonist of NMDA receptor, hence exhibits analgesic activity. Other alkaloids of genus Psychotria which possess analgesic effect are hodgkinsine and psychotridine [59].

Resveratrol

Resveratrol, a type of polyphenol present in grapes, blueberries and has the potential to treat cancer & cardiovascular diseases. The current study investigates the efficacy of Resveratrol in the attenuation of neuropathic pain. Various doses of Resveratrol were administered intraperitoneally into female Balb-C mice. The investigation was done based on various parameter like behavior test, ELISA, Western blot, LDH, MTT and RT-PCR assays. The study suggests that it enhances the expression of cytokine & IL-10 which further reduces the pro-inflammatory cytokines production which is the main reason of neuropathic pain. It also showed immunomodulation on microglial cell. Resveratrol also alleviates the expression of IL-6, IL-1 β , IL-8, TNF- α at mRNA and protein level. From the above findings, the authors suggested that it can be used in the treatment of Fibromyalgia [60].

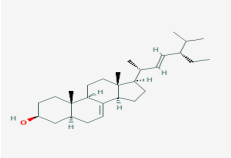
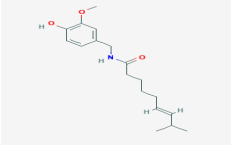
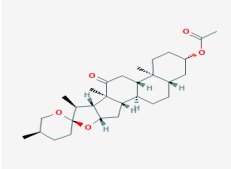
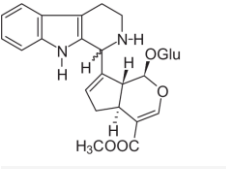
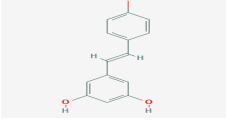
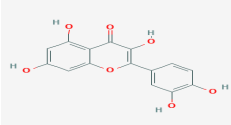

Quercetin

Quercetin (Pentahydroxyflavone) is a type of flavonol present in many plant varieties such as grapes, berries. In the present study, anti-inflammatory property of Quercetin was analysed orally and intracutaneously in female Lewis rats induced by adjuvant arthritis. The result revealed that Quercetin has the ability to choke the production of TNF- α , NO, IL-1 β , MCP-1. It also attenuates the activation of NF- κ B and AP-1. It was observed that Quercetin did not seen to cause toxicity. Thus, the authors concluded that Quercetin possess anti-inflammatory property so it can be used in fibromyalgia [61].

Lycopene

Lycopene, a red-coloured carotenoid is a potent anti-oxidant, commonly present in fruits and vegetables. A study was carried out to explore the anti-inflammatory actions of Lycopene in SW480 human CRC cell through the analysis of cell viability, western blotting, RT-PCR, Prostaglandin E₂ and NO. The study suggests that Lycopene has the ability to inactivate I kappa B kinase alpha (IKK α) and I kappa B alpha (IKB α) phosphorylation which leads to the inhibition of NF- κ B and thereby lowering the production of pro-inflammatory cytokines like TNF- α , IL-1 β , IL-6. It also attenuates COX-2 pathway, iNOS mRNA expression and production of PGE₂ and NO. Thus, on the basis of present findings, the authors confirmed anti-inflammatory potential of lycopene [62].

Table 2 Anti-fibromyalgia phytoconstituent with their mechanism of action

S. No.	Phyto constituents Name	IUPAC Name	Structure	Molecular Formula	MOA	References
1	α -spinasterol	(3S,5S,9R,10S,13R,14R,17R)-17-[(E,2R,5S)-5-ethyl-6-methylhept-3-en-2-yl]-10,13-dimethyl-2,3,4,5,6,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol		C29H48O	It inhibits COX pathway and anti-oxidant.	63
2	Capsaicin	(E)-N-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methylnon-6-enamide		C18H27NO3	Activate TRPV1 induce heat sensation	64
3	Hecogenin acetate	[(1R,2S,4S,5'R,6R,7S,8R,9S,12S,13S,16S,18S)-5',7,9,13-tetramethyl-10-oxospiro[5-oxapentacyclo[10.8.0.02.9.04,8.013,18]jicosane-6,2'-oxane]-16-yl] acetate		C29H44O5	Elevates K+ATP channel regulation, inhibits the neuronal hyperactivity	65
4	Umbellatine	5,6-Dihydro-9,10-dimethoxybenzo[g]-1,3-benzodioxolo[5,6-a]quinolizinium		C21H24O4N2	Acts as antagonist of NMDA receptor	66
5	Resveratrol	5-[(E)-2-(4-hydroxyphenyl)ethenyl]benzene-1,3-diol		C14H12O3	It enhances the expression of cytokine IL-10 and hence reduces the production of pro-inflammatory cytokines.	67
6	Quercetin	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one		C15H10O7	It inhibits the production of pro-inflammatory cytokines.	68
7	Lycopene	(6E,8E,10E,12E,14E,16E,18E,20E,22E,24E,26E)-2,6,10,14,19,23,27,31-octamethyldotriacont-2,6,8,10,12,14,16,18,20,22,24,26,30-tridecaene		C40H56	It inhibits the production of pro-inflammatory cytokines, iNOS mRNA expression and COX-2 pathway.	69

CONCLUSION

Fibromyalgia also known as fibrositis is a disorder characterised by the musculoskeletal pain, fatigue, and tenderness. The pathophysiology of fibromyalgia still remains a mystery for researchers and clinicians. Modern treatment covers both pharmacological (amitriptyline, pregabalin) and non-pharmacological (yoga, exercise) approaches although the management of fibromyalgia still remains a challenge. The current era moves towards the herbal treatment due to lesser side effects as compare to allopathic medicines. This review emphasizes on the significance of herbal plants and phytoconstituents that have been pharmacologically tested and shown to be of effective value in treatment of fibromyalgia. Various medicinal plants (*Phyllanthus amarus*, *Zingiber officinale*, *Tamarix indica*, *Piper nigrum*, etc.) and secondary metabolites (Alkaloids, α -spinasterol, Triterpenoid saponin, Resveratrol, etc.) were investigated for their therapeutic potential to treat fibromyalgia and it was found that various plants exert analgesic, anti-inflammatory, anti-nociceptive effect through various pathways like opioid pathway, NO & K_{ATP} channel pathway; inhibition of COX-1 & COX-2, PG, IL-6, TNF α synthesis. Poor pharmacokinetic profile is the major drawback of plants which limits its therapeutic usage in

fibromyalgia. For example, the absorption of Hecogenin acetate is low but when it is complexed with β -cyclodextrin, its bioavailability improves. It can be concluded that herbal plants provide a promising approach for the management of fibromyalgia. However more research has been required to investigate the exact mechanism of action behind various pharmacological activity that are useful for the treatment of Fibromyalgia.

Abbreviations

PGE₂: Prostaglandin E₂, TXB₂: Thromboxane B₂, IL-1 β : Interleukin-1 β , LPS: Lipopolysaccharide, NF- κ B: Nuclear factor kappa-light-chain-enhancer of activated B cells.

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