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A REVIEW ON CLINICAL EFFICACY OF TRADITIONAL PLANTS ON OSTEOARTHRITIS

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ABSTRACT: Osteoarthritis is accepted as the most growing, frequent, debilitating and heterogeneous condition that worsens the quality of life globally in the elderly, affecting an estimated 10% of men and 18% of women over 60 years of age with a rise in both prevalence and incidence. At present, there is no definite cure for osteoarthritis and no effective treatments which arrest or slow its progression; however multiple numbers of treatments ranging from newly approved oral medications, topical agents, intra-articular injections to surgery exist, but these treatments are sometimes disappointing and may have a detrimental effect on health. Hence, traditional plants appear to be efficacious and safe with the anti-osteoarthritic effect that aid for greater relief of symptoms and/or disability along with highlighting various phytochemical with scientifically proven, and validated. In this present review study, an effort is made to treat OA by focusing on the clinical, scientific and mechanistic rationale for targeting inflammatory signaling pathways in OA by use of traditional plants.

INTRODUCTION: Osteoarthritis (OA) is a long-term, chronic, progressive, musculoskeletal, degenerative, a rheumatic disorder characterized by deterioration of articular cartilage [1], hypertrophy of bone at the margins [2, 3] leading to Arthralgia, Edema and Ankylosis [4]. It is the most common and destined to become 3 more prominent [5] multifactorial diseases causing disability in the elderly age group all over the world. For the last decades, OA was considered as wear and tear disease [4] (sometimes the condition is called as arthrosis or osteoarthrosis) [7] accompanied by subchondral bone sclerosis; other intrinsic changes such as increased pressure or overload on weight-bearing joints (hips), joint effusion, crepitus, and deformities [6].

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OA is viewed as the second most common rheumatological condition 2 among elderly individuals affecting more than half of the over 65 population with a greater percentage which ranks fourth health impact in women after menopause than in men which ranks eighth in the western world according to World Health Organization (WHO) [4, 9]. With the passage of time, it reduces the quality of life as well as inflicts a lifelong burden on patients and health care resources [2, 6, 8]. According to various surveys, studies, the occurrence of OA across the countries is: In Indian 22-39% [2]. In Chinese population with age ≥ 60 years to be 22% in men and 43% in women, 30% women and 11% men in the Japanese population, in north Pakistan 3.6% in rural and 3.1-4.6% in urban regions; 10 and according to the WHO in the USA, it is estimated that 10% of the world population over 60 years of age has symptomatic knee OA and 12% of adults aged 65 years and older have symptomatic knee OA [6].

Etiology: Although a number of advanced discoveries, theories have explored the different

etiologies, it eventually ends with a common phenotype that involves and disrupts all of the tissue within, and surrounding involved joint [11]. So far the exact etiology of OA remains unclear [6]. Broadly OA is categorized into two different forms:

Primary or Idiopathic OA: This is a gene-dependent or related to aging; due to its polygenic nature, primary OA has a strong hereditary component [2, 4, 6].

Secondary or Post-traumatic OA: This occurs after a traumatic event; it usually associated with repetitive micro-traumas, previous knee surgery, other multiple factors interact such as Endocrinology (Diabetes Mellitus, hypothyroidism, hyperthyroidism, hyperparathyroidism), Metabolic (hemochromatosis, ochronosis, Marfan syndrome, Ehler-Danlos syndrome), hereditary, obesity, *etc*.

In this present era; lifestyle, diet, obesity and lack of exercise are important contributing factors that influence the appearance of OA [4]. In addition, there is clear evidence for multiple risk factors for the cause of OA most notably are as follows: [12, 13]

1. **Age:** According to the modern point of view, OA shows a strong correlation with aging and radiographic evidence shows various degrees of OA roughly in 80% of the human population by age 65 or over [4, 14, 15]. Age-related morphological changes in articular cartilage are probably due to a decrease in chondrocytes' ability to maintain and repair the tissue; in which they undergo age-related decreases in mitotic and synthetic activity and exhibit decreased responsiveness to anabolic growth factors, and synthesize smaller and less uniform large aggregating proteoglycans and fewer functional link proteins [16].

2. **Obesity:** Obesity is a strong risk factor for incident OA, It was observed that 5.1% were due to previous OA and 24.6% were due to excess weight or obesity [4], possibly because of the accumulation of mechanical stress on the knee joint [17]. In a cohort study, older adults were found that almost half of the association between BMI and knee osteoarthritis was explained by leptin levels, which illustrate evidence for a metabolic/ inflammatory pathway between obesity and OA [12, 18, 19].

3. **Gender:** Several epidemiologic studies suggest the relevant difference between pathological pathways occurring during the onset of OA in males and females [4].

4. **Genetics:** A recent study describes that there is an occurrence of OA due to a genetic defect in collagen type-II (Col-II) assemblage; widespread speculation regarding genetic mutation in other collagen-type codifying genes are being done. A study shows over 80 gene mutation is involved in the pathogenesis of OA, among which the most relevant one is the single nucleotide polymorphism; is responsible for the development and maintenance of synovial joints [4].

5. **Joint Trauma:** [11, 12, 19] Traumatic joint injuries is a major risk factor for OA, particularly in the knee (*i.e.* meniscal damage, anterior cruciate ligament rupture, or direct articular cartilage injury). The Framingham Study found that men with a history of knee injury were at a 5–6-fold increased risk of developing OA.

Besides the above mentioned risk factors, the development of OA consistently associated with biochemical events which alter the structure and function of the synovial membrane in joint cartilage. A cascade of biochemical events is mediated by major inflammatory mediators which causes upregulation of various catabolic factors such as proteolytic enzymes, pro-inflammatory cytokines (IL1-β and TNF-α), chemokines, proteolytic enzymes and downregulation of anabolic factors such as growth factors and anti-inflammatory cytokines [20]. The major inflammatory cytokines and chemokines linked to OA include IL-8, IL-17, IL-18, and IL-21 and leukemia inhibitory factor and both IL1-β and TNF-α diffuse into a synovial fluid that acts on chondrocytes and suppress matrix synthesis [10, 21].

Goals of Treatment: Progress in the development of medical therapies has eventually modified [5] by using advance innovative diagnostic tools such as

OCT (Optical Coherence Tomography), MRI (Magnetic Resonance Imaging) [13] NIR (Near-infrared) fluorescent probes [10], X-rays, Arthroscopy, ultrasound, *etc*. These advanced techniques are designed with high magnification and resolution that helps to detect and identify the cause. In addition, adherence to the above mentioned techniques the diagnosis of OA can be treated with a combination of non-pharmacologic and pharmacologic modalities [10, 22]. Few of these treatments have alleviated the pain, improved range of movements and stability of affected joints [2].

Non-Pharmacologic Treatments: These therapies have been used for a long time due to its effectiveness in reducing pain and improving joint movement [2, 12]. These are considered as first interventions or together with first-line drug therapies [6, 23]. They include Exercise, Education Weight loss, Acupuncture.

Exercise: This is the most promising and effective intervention which plays a critical role in the management of OA [18, 24]. American College of Rheumatology (ACR) has approved regular exercise as a therapeutic approach for the management of knee OA that improves flexibility and strengthens joint muscles [12]. Evidence suggests that three categories of exercise therapy are used for osteoarthritis: the range of motion and flexibility exercise, muscle conditioning and aerobic cardiovascular exercise which decreases pain and improves muscular strength, functional ability, and psychological well-being [9, 25-27, 30, 31].

Two recent meta-analyses also demonstrate that muscle strengthening and aerobic exercise is important in the management of OA. Muscle strengthening exercises are superior for specific impairment-related outcomes, such as pain, but aerobic exercise contributes to better long-term functional outcomes [28, 30]. Neuromuscular exercise therapy, like aerobic exercise and strength training, also provides effective pain relief in individuals with established OA. The first neuromuscular exercise program developed for use in patients with OA was published in 2010 [29]. A recent Cochrane review identified [32] trials investigating a variety of land-based therapeutic exercise programs. Results of a meta-analysis showed mean treatment benefits for both knee pain and physical function.

Although there is less robust research into the effects of aquatic exercise, a small to moderate effect on the function and a small to moderate effect on the quality of life have been reported in another relatively recent Cochrane review. Typical physiological changes as a result of an effective exercise regime may include improvements in muscle strength, neuromuscular control, and range of motion, joint stability and fitness [12].

Patient Education: Patient education is an ongoing, integral part and a cornerstone of the treatment of osteoarthritis, which is often delivered in groups to enable interaction between participants, individuals *via* the different sources, for instance, paper/social/online media, pamphlets, and seminar [10, 12, 24, 29]. Several RCTs and a meta-analysis have demonstrated the benefits of different educational techniques in reducing pain and increasing coping skills, but with little impact on function in patients with knee OA. In a study of 211 patients with knee OA, 80% of the costs of delivering effective self-care education were offset within a year by the reduced frequency and costs of primary care visits. Education techniques are shown to be effective include individualized education packages with the quality score (QS 12), regular telephone calls (QS 17), group education (QS 20), patient coping skills (QS 13), and spouse assisted coping skills training (QS 15) [9].

Weight Loss: Weight is undoubtedly one of the major risk factors leading to an increasing prevalence of knee OA. Mostly the patients of osteoarthritis are overweight. The weight-bearing joints, in obese persons, becomes an extra burden and leads to the development of OA [10]. A meta-analysis of weight reduction and knee osteoarthritis concluded that weight loss of 5% from baseline was sufficient to reduce disability. Additionally, pain and disability were reduced if patients lost more than 6 kg (13.2 lb) [30]. This is still significant and clinicians should encourage overweight patients with knee OA to lose weight regardless of many other health benefits such as cardiovascular disease, diabetes, *etc*. Atukorala *et al*., also demonstrated dose-dependence between weight loss and a reduction in knee pain and symptoms during an 18-week program, indicating this is an important and valid lifestyle intervention to treat knee pain [32].

Acupuncture: The Acupuncture acts as an adjunctive therapy [33] that were used for millennia in traditional Chinese medicine. For the past two decades, intense research has been carried out and is now a popular therapy across the globe [34]. Basic science research suggests that acupuncture relieves pain through activation of the gate-control system, in which large nerve fibers are stimulated and suppress small fibers that transmit signals in the dorsal horn of the spinal cord. Several clinical trials have been conducted in the US and Europe on the effectiveness of acupuncture for osteoarthritis [24]. According to some studies, adding acupuncture to exercise therapy was much more effective in the treatment of knee OA symptoms [25].

In a 2010 systematic review RCTs investigates the acupunctures impact with placebo in pain control and function was found to be improved in function and reduced pain, but the difference in 6-month follow-up was not significant. We found that exercise therapy in combination with acupuncture can boost the positive effects [25, 35].

Few studies often prescribed as an effective non-pharmaco-logical intervention for OA. The research to date on the efficacy of acupuncture in osteoarthritis is inconclusive but has a promising result [24].

Pharmacologic Treatments: The pharmacological treatment generally used for the treatment of the osteoarthritis includes non-steroidal inflammatory drugs, opioids, and acetaminophen.

Non-Steroidal Inflammatory Drugs: NSAIDs are considered as more effective and second-line treatment [36] than other topical NSAIDs for pain relief [18]. The function of NSAIDS is to inhibit the function of COX-1 and COX-2 (synthesis of prostaglandin). This is classified into two types; non-selective NSAIDs and selective COX inhibitors [10]. The choice between a non-selective NSAIDS and a COX-2–specific inhibitor should be made after evaluation of risk factors, particularly for upper gastrointestinal and renal toxicity [28].

Data from epidemiologic studies have shown that among persons 65 years of age or older, 20% to 30% of all hospitalizations and deaths due to peptic ulcer disease were attributable to therapy with NSAIDs [24].

Acetaminophen: Acetaminophen is also known as paracetamol that is approved by WHO and initial analgesic of choice to lessen different types of pains such as headache and fever. For its low cost, effectiveness, and safety, it is recommended by most of the guidelines for the treatment of mild-moderate OA pain. Although it is one of the safest analgesics, acetaminophen can be associated with clinically important adverse events, such as prolongation of the half-life of warfarin. FDA (Food and Drug Administration) has recommended its quantity not to be exceeded from 4325 mg per dosage unit in any prescription. Following FDA, AAOS (American Academy of Orthopaedic Surgeons) guidelines also have decreased the recommendation from 4000 to 3000 mg/day [10, 31, 37].

Opioids: Opioids are another choice of drug to treat pain, moderate to severe and are prescribed when NSAIDs or paracetamol are not proving effective or showing AE [10, 30]. Greater effectiveness is found in using stronger opioids such as oxymorphone, oxycodone, oxytrex, fentanyl, morphine sulfate as compare to weaker such as tramadol. They bind to MOP receptor present in the midbrain, which results in the activation of descending inhibitory neurons, finally reducing the transmission of nociceptive from periphery to thalamus. They are prescribed at a low dose at the initial stage [28] and risks include constipation, vomiting, dizziness, and headache, *etc*. [10] Moreover, the use of opioids is also a controversial issue because of its misuse or addiction. In a 2008 research, 74% of the drug addictions were due to the opioids. In addition, their long-term use may develop tolerance and hyperalgesia, decreasing its efficacy [14].

Intra-Articular Injections: Intraarticular (IA corticosteroid injections have been used for decades in clinical practice for pain relief and control of local inflammation and recommended by the ACR (American College of Rheumatology) for a treatment paradigm for moderate-severe pain in OA. However, long term use of these injections reacts to nuclear steroid receptors, which interfere with different inflammatory and immune system that may promote joint destruction and tissue atrophy. Through this, they cause inhibition of inflammatory agents such as prostaglandins,

phagocytosis, metalloprotease and its activator. These injections are suitable for only short-term treatment for ~4-8 months) [9, 10, 31].

Role of Traditional Medicines: Traditional medicines are one of the ancient therapy known to mankind [38] that has been practiced by all cultures for centuries before the beginning of modern medicine [39] and being the mainstay of about 80% of the population in many rural areas of developing countries [40, 41, 42]. According to the WHO report, 65% of the world's population has incorporated the value of plants as a methodology of medicinal agents into their primary modality of health care [41]. It continued to exist as the most affordable remedy and easily accessible source of treatment [43]. In the present scenario, a vast continuum of disorders including cardiovascular dysfunction, metabolic syndrome, musculoskeletal condition, *etc* are leading to the enormous burden with substantial financial consequences [44]. Hence, traditional medicines are now being used by an increasing number of people to treat various chronic and acute ailments than modern medicines [41, 42].

Likewise, for OA that is claimed as a rheumatological disorder [2, 14] accompanied with pain, disability, and loss of movement resulting in tremendous expenditure on health [45]. Currently available FDA approved drugs are employed for the treatment of OA [5] but prolong consumption of those drugs leads to very serious complications such as GI bleeding, renal dysfunction, *etc*.; moreover those drugs are not always effective [14]. Hence, there is a growing interest in clinical research in various traditional botanical compounds that will likely alleviate the symptoms of OA.

Clinically Proven Ingredients for the Management of OA: For the past few decades, countless number of researches are carried on new strategies to treat OA. Despite many conventional pharmacologic agents that being used till now, as mentioned before can cause various life-threatening side effects; [14] hence the perception of traditional medicines being "natural" and "safe" can be one of the most compelling reasons for the treatment of OA 46. In addition, there are clinically studied effective botanical ingredients with various photochemical that not only relieve pain but also heal, build the strength of joints and are easily obtainable and inexpensive [47]. An abundant number of traditional or herbal plants with a wide range of therapeutic properties are available for the treatment of OA [33, 41, 48].

This current review discusses briefly the traditional plants with both clinical and laboratory evidence of effectiveness. This paper emphasizes the information about the plant secondary metabolites.

***Curcuma longa* (Turmeric):** Turmeric, derived from the rhizomes of *Curcuma longa* belonging to the family *Zingiberaceae* is the most promising, ancient, traditionally used medicinal herb known for centuries throughout the Asian countries with well-established biological activities including anti-oxidant, anti-inflammation and various other properties; [49, 50] its usage is associated with a plethora of beneficial effects on human health [51]. Curcumin [1, 7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] also called diferuloylmethane [52], is the main natural bioactive polyphenol [50] which regulates various biochemical and molecular pathways by modulating several molecular targets, including transcription factors, cytokines enzymes and genes regulating cell proliferation or apoptosis because of its anti-inflammatory property [36]. Turmeric has captured the attention of western medicine mainly for its anti-inflammatory effects [53].

Role of Curcumin in OA: As previously mentioned, different cytokines may play different roles during OA onset and progression along with several IL-1 and TNF-α, that are considered as strong inflammatory cytokines pivotal to the process of OA induced tissue destruction [10, 21, 54]. Kraus et al proposed that the altered inflammatory state is the underlying cause of OA [36]. Various studies reveal that curcumin acts as a powerful master switch of inflammation by acting on different levels of pro-inflammatory enzymes and inflammatory transcription factors [55]. Curcumin suppresses the activation of IKB (inhibitor of nuclear factor kappa-light chain-enhancer of activated B cells [NF-κB]) kinase (IKK) and the phosphorylation of AKT and the association between the two signaling molecules induced by IL-1β which results in the inhibition of phosphorylation and degradation of nuclear factor of kappa light polypeptide gene enhancer in B-cells

inhibitor, alpha (IKBα), the endogenous blocker of NF-κB. Therefore, curcumin is able to inhibit translocation of NF-κB into the nucleus, thus preventing the inflammation response of the cells [36].

Clinical Studies: A total of 75 clinical trials with curcumin have retrieved in ClinicalTrials.gov; various clinical efficacy of curcumin in OA has been evaluated in many clinical trials [36, 46, 56].

An RCT study by Y. Nakagawa *et al*., compared the effect of highly-bioavailable curcumin that is Theracurmin® (180 mg/day of curcumin) with Placebo (6 placebo capsules per day). JKOM score was higher in the Theracurmin® group than in the placebo group. Significant reduction in pain assessment, oxidative stress was shown in the treatment group compared to the placebo group [57]. A retrospective observational study conducted in 820 patients with various forms of painful osteoarthritis was treated with a new Curcuma extract (Flexofytol®, 4-6 capsules per day), for more than 6 months showed a reduction in pain and also helped in regeneration of cartilage [58].

A previous 3 month pilot registry study conducted in 50 OA patients suffering from mild-to-moderate KOA received Meriva, which shows significant improvement in joint stiffness, physical function and decreased joint pain assessed by WOMAC score along with improvement of mobility assessed on the treadmill and another recent 8 month study which included 100 OA patients which showed significant improvements in WOMAC score, Karnofsky Performance score and treadmill walking performance. Positive results were obtained from the endpoints include a series of biochemical markers of inflammation were observed and evaluated for Mervia compared to the control group that suggests an excellent, effective and safe agent [36, 55].

A multicenter study was carried out in Thailand to evaluate turmeric on pain reduction and functional improvement in 367 patients with KOA. Patients' pain score was 5 or more on a 10-point scale using ACR criteria. Patients received either 1,200 mg per day of ibuprofen or 1,500 mg per day of turmeric extract in divided doses for 4 weeks. Outcome measures were WOMAC scores; with pain, stiffness, and function subscales ranging from 0 to 10. Outcomes in each group significantly improved compared with their baseline values. The WOMAC stiffness score showed greater improvement than ibuprofen [59]. A systematic review and meta-analysis study was conducted in 606 patients to provide the highest level of evidence on the efficacy of curcuminoids in patients with painful conditions the primary efficacy was to measure pain intensity. Curcuminoids were found to be significant in reducing pain [52].

***Boswellia serrata* (Indian Frankincense):** *Boswellia serrata* is Indian frankincense, one of the most ancient, medicinal and valued herbs among all the traditional plants in Ayurveda, belonging to the family *Burseraceae* [60, 61]. It has been used since antiquity in religious rituals and cultural ceremonies [62, 63]. Indian Frankincense has been native to tropical parts of Africa, China, India and Middle East countries. Its medicinal properties have been recognized and prized for millennia. Large varieties of compounds are found in *Boswellia* and its each and every part of it is useful to mankind [61, 64]. An oleo gum resin is extracted from the incision made in the trunk of the tree that is composed of pentacyclic triterpenes in which boswellic acid is the active functional group, particularly 3-O-Acetyl-11-Keto-β-Boswellic Acid (AKBA), 11-Keto-beta-Boswellic Acid (KBA), and the various β-boswellicacids (βBAs), and α-boswellic acids (αBAs) [60, 64-66]. Gum portion is consisting of pentose and hexose sugar with some oxidizing and digestive enzymes. The volatile oils, composed of monoterpenes and sesquiterpenes diterpenes including incensole, incensole acetate and cembrenol (serratol) lipophilic pentacyclic triterpene acids of the oleanane-(α-boswellic acids), ursane-(β-boswellic acids) and lupane-type (lupeolic acids), as well as an ether-insoluble fraction containing polysaccharides (arabinose, galactose, xylose) [64, 66]. Due to its immense Phyto-constituents, it gained considerable attention [67] as a potent antiseptic, antifungal antimicrobial, anti-inflammatory, arthritis, anti-obesity asthma, cardiotonic, and anticonvulsant [60, 61, 65, 67].

Role of *Boswellia* in OA: The Ayurvedic medicine and modern research have implicated a beneficial role for the gum- resin in the treatment OA, soft tissue rheumatism, low back pain, Gout and rheumatoid arthritis for years. In vitro studies and

animal models show that boswellic acids were found to inhibit the synthesis of a pro-inflammatory enzyme, 5-lipoxygenase (5- LO) including 5-hydroxyeicosatetraenoic acid (5- HETE) and leukotriene B4 (LTB-4) [61, 62].

Clinical Studies: Extensive research in the past 30 years has been identified the active component of this resin as BA (a pentacyclic triterpenic acid) and its derivatives (acetyl-b-boswellic acid, 11-keto-b-boswellic acid, and acetyl-11-keto-b-boswellic acid) [68]. Several numbers of clinical trials of gum-resin of *Boswellia* alone have shown to improve symptoms in patients with osteoarthritis [62]. Kimmatkar *et al.* conducted a randomized double-blind placebo-controlled crossover study to assess the efficacy, safety, and tolerability of *B. serrata* extract in 30 patients with knee OA.

During this study, 15 patients each received active drug or placebo for 8 weeks. All patients who received drug treatment reported a decrease in knee pain, improvement in knee flexion, and walking distance. Furthermore, the frequency of swelling in the knee joint was decreased. The observed differences between drug- and placebo-treated patients were statistically significant and clinically relevant [69]. A clinical trial conducted by Ray Chaudhuri and co-workers in India has shown that the extract of the plant, *B. serrata*, can reduce pain and considerably improve knee-joint functions, in some cases providing relief even within seven days [62].

A 90-day double-blind, randomized, placebo-controlled study of 5-Loxin®, a novel *Boswellia serreta* extract enriched with 30% AKBA conducted by Senagupta.K *et al.*, found that the extract significantly reduced pain and improved physical function by inhibiting 5-LOX. 75 OA patients received either 100 mg or 250 mg of 5-Loxin® or a placebo for 90 days, patients were evaluated for pain and physical function using the VAS, Lequesne's Functional Index (LFI), and WOMAC Index at baseline and at days 7, 30, 60, and 90; moreover the cartilage-degrading enzyme matrix metalloproteinase-3 was also evaluated in synovial fluid from OA patients. At the end of the study, both doses of *boswellia* extract conferred clinically and statistically significant improvements in pain scores and physical function scores.

Additionally, there was a significant reduction in synovial fluid MMP-3 in the treatment groups. Compared with the placebo group, the low-dose (100 mg) and high-dose (250 mg) 5-Loxin® groups showed 31.37% (P=0.002) and 46.4% (P<0.001) reductions in MMP-3 concentration, respectively [70].

A 30-day, double-blind, randomized, placebo-controlled study was conducted to validate the efficacy of Aflapin® novel synergistic composition containing *B. serrata* extract enriched to 20% AKBA and *B. serrata* non-volatile oil, which is considered as more efficacious as an anti-inflammatory agent compared to the existing *Boswellia* products, 5-Loxin® and traditional 65% *Boswellia* extract. A total of 60 subjects received either 100 mg (n=30) of Aflapin® or placebo (n=30) daily, Pain, stiffness and physical function were assessed using WOMAC, LFI and VAS scores. For the safety of Aflapin®, laboratory parameters were evaluated in serum, urine and whole blood of all subjects at each visit of the study duration.

In comparison with the placebo, at the end of the study, the Aflapin® supplemented group showed statistically significant improvements in all pain scores, including VAS, LFI, WOMAC pain, WOMAC stiffness, and WOMAC function scores. Aflapin® provided significant reductions in pain scores of VAS and LFI in as early as 5 days when compared with the previous study Aflapin® demonstrated significant relief from joint pain and physical discomfort in OA subjects after 7 days of treatment. These findings clearly suggested that Aflapin® confers quick and significant pain relief, improvement in physical ability and quality of life in OA subjects [67].

A comparative, randomized, double-blind, placebo-controlled phase-2 study was conducted to assess the efficacy and safety of curcuminoid complex extract from turmeric rhizome with turmeric volatile oil CuraMed® and its combination with boswellic acid extract from Indian frankincense root Curamin® vs placebo for the treatment of 40- to 70-yr-old patients with OA. A total of 201 patients was investigated and received CuraMed® 500-mg capsules (333 mg curcuminoids) and Curamin® 500-mg capsules (350 mg curcuminoids

and 150 mg boswellic acid) orally three times a day for 12 weeks. Joint pains, morning stiffness, limitations of physical function were assessed by physical function performance-based tests and WOMAC score. The results of this study showed that 12-week use of curcumin complex or its combination with boswellic acids reduces pain-related symptoms. Curcumin in combination with boswellic acid is more effective. Combining *Curcuma longa* and *Boswellia serrata* extracts in Curamin® increases the efficacy of treatment of OA presumably due to the synergistic effects of curcumin and boswellic acid [71].

Reji K. conducted a two-arm clinical study containing a formulation of *Curcuma longa* and *Boswellia serrata* extracts (CB formulation) for safety and efficacy in OA patients and compared with the selective COX-2 inhibitor, celecoxib. The CB formulation consisted of 350 mg Curcuma longa extract (BCM 95®) containing 70% curcumin, 17% demethoxycurcumin, 3.5% bisdemethoxycurcumin and 7.5% turmeric essential oils and 150 mg *Boswellia serrata* extract (BosPure®) containing 75% boswellic acids and 10% AKBA in 500-mg hard gelatin capsules. 30 patients were enrolled in the study and received treatment for 12 weeks.

The two groups received oral administration of CB formulation 500 mg capsule (twice daily) and, oral administration of celecoxib 100 mg capsule (twice daily). The efficacy of the CB formulation was evaluated by symptom scoring and clinical examination. The CB formulation 500 mg demonstrated a greater improvement in the treatment of OA than celecoxib 100 mg in the scores for pain, walking distance, and joint line tenderness. The CB formulation was equally as effective as celecoxib in alleviating crepitus and increasing the range of joint movements [72].

Capsicum (Chili Fruit): Chili fruit is one of the traditional plants used as a spice ingredient and consumed by humans for a long year belonging to the member of a vanilloid family of compounds such as vanillin, eugenol, *etc.* This chili pepper contains capsaicin (8-methyl-N-vanillyl-6-nonenamide), a phenolic compound, an alkaloid (capsaicinoids) responsible for their characteristic taste, burning, irritant effect, and pungency. Capsaicinoids include dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin, and homocapsaicin. All these molecules share structural and activity similarities with capsaicin. Its concentration is higher in the placental tissue that protects the seed and acts as a deterrent against rodents and other mammals. Capsaicin binds to Transient Receptor Potential receptor Variant (TRPV1) receptors expressed by nociceptors that produce burning and itching sensations [73, 74].

Role of Capsaicin in OA: Capsaicin has been used for a number of diverse clinical conditions for many years, having pleiotropic pharmacological activities such as an analgesic, anti-obesity, anti-pruritic, anti-inflammatory, anti-apoptotic, anti-cancer, anti-oxidant, and neuroprotective functions. Various studies have shown the use of capsaicin in the treatment of joint pains due to its analgesic characteristics. In chronic musculoskeletal pain, the relative benefit achieved with capsaicin compared with other medicinal products [73, 74, 75].

Clinical Studies: Several studies have been conducted to check the efficacy of capsaicin in treating OA. A 2003 single-blind, randomized controlled clinical study, which evaluated effect of a topical herbal cream on OA of the hand and knee in which subjects were randomized to an active (17) or a placebo (19) group, subjects applied the herbal ointment to the affected joint(s) for 42 consecutive days and level of the pain and stiffness was recorded daily on VAS. This showed significant improvement in pain and stiffness for patients with hand and knee osteoarthritis who applied the ointment to the affected joint(s). A meta-analysis study conducted by Cameron *et al*. reported that capsaicin alleviates OA pain and another systematic review of recent trials indicated that capsaicin is effective in reducing pain intensity in older adults with painful OA[75, 76].

***Zingiber officinale* (Ginger):** Ginger is a creeping herbaceous rhizomatous of the plant Zingiber *officinale* belonging to one of the largest family Zingiberaceae. It is the globally one of the most versatile, ancient, significant, medicinal, nutritional herb with several ethnomedical values. This plant is recognized due to its immense phytotherapeutic properties including antibiotic, antimicrobial, anti-emetic, antioxidant effects, an ability to inhibit the

formation of inflammatory compounds, and direct anti-inflammatory effects, anti-spasmodic, anticancer, a stimulating effect on the immune system. *Z. officinale* is a complex substance consisting of more than 60 compounds along with good source of essential macronutrients and micronutrients such as essential oils, phenolic compounds, flavonoids, carbohydrates, proteins, alkaloids, glycosides, saponins, steroids, terpenoids and tannin and has rich source of volatile oil and has important constituents such as zingiberol, zingiberene, phellandrene and linalool [77-80].

Role of Ginger in OA: Ginger is effective to relieve arthritis symptoms for over 1000 years, often in combination with other hot herbs. It is also listed in the FDA as a medicine. Modern scientific research has revealed ginger consists of a complex combination of bio-active constituents like gingerols, shogoals, and paradols for the majority of its anti-inflammatory properties. Various powders, formulations, and extracts have been commercially used and tested, both *in-vitro*, *in-vivo* and in pre-clinical. Pre-clinical research has been shown to act as a dual inhibitor of both cyclooxygenase (COX) and lipooxygenase, to inhibit leukotriene synthesis and to reduce carrageenan-induced rat-paw edema (an animal model of inflammation). Gingerols and Diarylheptanoids were identified as active compounds that would be active against arachionate 5-lipoxygenase, an enzyme of leukotriene (LT) biosynthesis which can be used in decrease the inflammation in OA [77, 78, 80-83].

Clinical Studies: Various clinical studies have shown the effectiveness of treating OA. A randomized, open-label study by Paramdeep. G evaluated the safety and efficacy of ginger in 60 no of patients and divided into 3 groups of 20 each; received Diclofenac 50 mg and Cap. placeborally BD (Grp-1), Ginger 750 mg and Cap. placeborally BD (Grp-2) and Ginger 750 mg and Tab. Diclofenac 50 mg orally BD (Grp-3) for a period of 12 weeks. The assessment of efficacy was done using the WOMAC index and VAS.

This showed statistically significant ($P<0.001$) improvement in WOMAC score and VAS score among three groups from baseline. The study also suggests the probable reason due to the add-on effect of both the ginger and Diclofenac, as both these agents inhibit COX. In addition, ginger also inhibits LOX which may be the probable reason for add-on effect. An RCT study performed by Zakeri *et al.,* evaluated the effects of ginger extract on knee pain, stiffness and difficulty in 320 patients and allocated into 2 groups of 160 patients with KOA. The patients were given 1 capsule of ginger called zintoma or placebo (BD) for 6 weeks, respectively. The zintoma capsules contained 250 mg of powdered ginger and the placebo capsules, being matched with the zintoma capsules, contained starch.

The results showed ginger to be more effective in reducing knee pain on standing and immediately after walking 50 meters, and also more effective in improving WOMAC indexes, compared with placebo ($P<0.05$), shown a significant greater pain reduction in ginger group both on standing and after 50 meters walking according to VAS score.

A meta-analyses study was conducted to assess efficacy and safety of ginger in OA patients that compared oral ginger treatment with placebo. Outcomes were reduction in pain and disability; the statistically significant pain reduction was shown after intake of ginger. Ginger was modestly efficacious and reasonably safe for treatment of OA [81, 84, 85].

***Harapagophytum Procumbens* (Devil's Claw):** *Harpagophytum procumbens* is a ground trailing, weedy perennial [86] and important traditional herbal plant naturally native to the southern part of the African continent [75]. It is an extract obtained from the root of the *H. procumbens* plant belonging to the family Pedaliaceae [87]. The major chemical constituents of *Harpagophytum* are iridoid glycosides (primarily harpagoside, harpagide, and procumbide), sugars (mainly the tetrasaccharide, stachyose), triterpenoids (oleanolic and ursolic acid), phytosterols (primarily beta-sitosterol), aromatic acids (caffeic, cinnamic, and chlorogenic acids), and flavonoids such as luteolin and kaempferol [88]. Harpagoside, harpagide, and procumbide are found in both the primary and secondary roots, but only the latter is used for the herbal drug because they have been found to contain high amounts of therapeutically important constituents [86, 88].

Role of Devils Claw in OA: The medical effects of this plant are from an extract obtained from its roots. A lot of evidence indicates that Devil's Claw may be an effective treatment in OA because of its pain-relieving and purported anti-inflammatory actions [86, 89].

Clinical Studies: Various monographs have found to be published in 1990, 1996, and 2003 that have implicated a role for Devil's Claw in the treatment of rheumatic disorders, including the treatment of painful OA [87].

A review of clinical trials utilizing *H. procumbens* preparations for the treatment of joint and lower back pains with extracts containing 50-60 mg harpagoside daily showed more reliable data and were more effective in alleviating pain and improving mobility than extracts with lower amounts [90].

TABLE 1: DETAILS OF CLINICALLY PROVED TRADITIONAL PLANTS USED FOR THE TREATMENT OF OA

Name of the plant	Clinical Trials	Results
Pinus pinaster (Pinaceae) [91]	1. In 2007 Belcaro, *et al.*, performed a randomized, double-blind, placebo-controlled study in patients with OA grade I or II in one or both knees, they were treated with 100 mg Pycnogenol® (n = 77) or placebo (n = 79) for 3 months. Several clinical studies report that Pycnogenol® can improve subjective symptoms of osteoarthritis of the knee	1. The global WOMAC score showed a 50% decrease from baseline in OA symptoms in Pycnogenol®-treated patients (baseline score: 79.2, 3-month score: 34.6; $p<0.05$), which was significantly better than placebo treatment. Pycnogenol® treatment resulted in a significant increase in muscular/walking performance compared with placebo
Cichorium intybus (Asteraceae) [92]	2. A Placebo-controlled, dose-escalation, phase-1study was conducted to evaluate the safety and tolerability of a proprietary bioactive extract of chicory root in patients with OA for a period of 1 month; A total of 40 patients were enrolled in 3 cohorts and were treated with escalating chicory doses of 600 mg/day, 1200 mg/day and 1800 mg/day for 1 month	2. Improvement was defined as a positive change of at least 20% in at least 2 of the 3 domains (pain, stiffness and global). Using this definition, in cohort 1, 2 of 4 patients, 1 each on active treatment and placebo, were improved. In cohort 2, 4 of 6 were improved, 2 each on active treatment and placebo. In cohort 3, 13 patients were improved, 4 on placebo and 9 on chicory. In this study, 6 of the 9 chicory responders showed improvement in both the pain and stiffness domains; two had a response in the pain and global domains and one showed response in the stiffness and global domains
Urtica dioica (Urticaceae) [93, 94]	3. One retrospective interview study, which includes 18 self-selected patients. 4. A randomized double-blind parallel-group, the clinical trial compared Phytalgic® to placebo for 3 months, in 81 patients with OA of the knee or hip using NSAIDs and/or analgesics regularly	3. There was the improvement in joint or muscular pain by use of nettle, mostly by rubbing, beating or touching (apparently) fresh nettle leaves to the affected area (*i.e.*, counter-irritation). 4. Phytalgic® was 76% more efficacious than intra-articular corticosteroid therapy for knee OA
Withaina somnifera (Solanaceae) [95,96]	5. A randomized, double-blind, placebo-controlled study was carried out to evaluate efficacy and tolerability of a standardized aqueous extract of roots plus leaves of *W. somnifera* in patients with knee joint pain and discomfort. 60 patients with knee joint pain and discomfort were treated with *W. somnifera* 250 mg, *W. somnifera* 125 mg and placebo, orally BD 6. In a double-blind, placebo-controlled crossover study, a total number of 42 patients with OA were randomized to receive a formula containing Ashwagandha (turmeric, *Boswellia* and zinc complex) or placebo for 3 months	5. At the end of 12 weeks, compared to baseline and placebo, significant reductions were observed in mean WOMAC and KSI in *W. somnifera* 250 mg ($p<0.001$), *W. somnifera* 125 mg ($p<0.05$) groups. VAS scores for pain, stiffness and disability were significantly reduced in *W. somnifera* 250 mg ($p<0.001$), 6. *W. somnifera* 125 mg ($p<0.01$) groups. *W. somnifera* 250 mg group showed the earliest efficacy (at 4 weeks). 7. The herbal formula significantly reduced the severity of pain ($p<0.001$) and disability ($p<0.05$) scores

In a multicenter, uncontrolled trial, a tableted medication, Doloteffin® (2,400 mg aqueous extract of devil's claw tubers equivalent to 50 mg harpagoside daily) was given to 75 OA patients daily for 12 weeks.

The pain was assessed by WOMAC questionnaire, VAS and physician exam at baseline, 6 and 12 weeks. At 12 weeks the WOMAC total pain score was reduced by 22.9% and the VAS pain score decreased by 24.5% compared to baseline. Physician assessment of pain reported a 46% improvement in pain on palpation, 35% improvement in movement limitation and 25.4% improvement in joint crepitus at 12 weeks. A similar study of Doloteffin® with large no of patients (250) with KOA (n=85) or hip (n=61), or nonspecific low-back pain (n=104) over 8 weeks. Doloteffin® dosage was 60 mg harpagoside daily. After 8 weeks, patients in the hip-pain and knee-pain groups' demonstrated 35% and 37% improvement in WOMAC scores compared to baseline, respectively. This study indicates a significant benefit of Doloteffin® for OA [86].

Here, we have systematically arranged some more traditional plants which are very effective in treating OA in **Table 1**. Current evidence is quite limited but shows promising results.

CONCLUSION: Since time immemorial, nature provides a wide variety of clinically helpful traditional plants and people take plant originated products to make life better, healthy and wealthy because of better cultural acceptability, better compatibility with the human body and lesser side effects. The uses of traditional remedies drugs and other dietary supplements derived from plants have accelerated in recent years in the field of research and clinical practices.

Pharmacologist, microbiologist, biochemist, botanist and natural product chemists are currently investigating traditional plants for phytochemicals and lead compounds that could be developed for the treatment of several ailments. The main purpose of traditional medicines is to supplement some of the benefits from existing pharmaceutical treatment modalities. This review justifies pharmacological properties and clinical efficacy showing a positive and effective result in treating OA.

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