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A Comprehensive Review: Biomarkers in the field of Osteoarthritis & Potential of herbal medicinal Plants used in the treatment

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Abstract **Review Article**

This review paper focuses on the biomarkers available for the early diagnosis and investigation in the field of Osteoarthritis. The main aim is to bring out the potential approach in using the herbal medicinal plants in the treatment of osteoarthritis. Considering the adverse effects of synthetic drugs, the western world is looking for natural remedies which are safe and effective. It is also documented that, about 80% of the world's population has a belief in traditional medicine, particularly plant drugs for their primary treatment. Medicinal plants have been known for a golden age and are highly esteemed all over the world as a rich source of therapeutic agents for the prevention of diseases and ailments. Nature has met our nation with a tremendous abundance of restorative plants. OA is a long haul unending sickness described by the degeneration of the cartilage in joints which results in bones scouring together and making solidness, torment, and weakened development. The ailment most generally influences the joints in the knees, hands, feet, and spine and is moderately regular in the shoulder and hip joints. In this way, the portrayal of potential biomarkers is imperative to guarantee their proper and ideal use. The portrayal strategy used to survey biochemical markers in OA is BIPEDS; which represents the Burden of ailment, Investigative, Prognostic, Efficacy of intercession, Diagnostic, and Safety.

Keywords: Osteoarthritis, Biomarkers, Pathogenesis, Herbal medicinal plants,Clinical studies.

INTRODUCTION

Recently, appreciable attention has been paid towards the utilization of herbal products for the prevention and cure of different diseases. Considering the adverse effects of synthetic drugs, the western world is looking for natural remedies which are less harmful and effective. Globally about 80% of the population has faith in traditional medicine, particularly plant drugs for their primary treatment[1]. There has been a move in the all-inclusive state of mind from engineered to herbal prescription, which should be 'Back to Nature'. Medicinal plants have been known for brilliant age and are very regarded everywhere throughout the world as a rich wellspring of restorative specialists for the counteractive action of ailments and afflictions. Nature has favours our nation with a gigantic abundance of medicinal plants. In this regard, India has anupper hand in the world, since a number of recognized traditional systems of medicine viz., Ayurveda, Siddha, Unani, Homeopathy, Yoga and Naturopathy have beenin practice for ensuring good health of people. Herbal drugs are more common among the rural than the urban population of India. Even though a large proportion of the human population is dependant on herbal remedies, only a limited number of plants have been investigated pharmacologically. It iscritical to evaluate the safety, efficacy and quality due to the biological complexities in plants. The World Health Organization (WHO) believe that 4 billion people currently use herbal medicine for primary health care [2].

Osteoarthritis

Osteoarthritis (OA) is a long haul ceaseless malady portrayed by the weakening of the ligament in joints bringing about scouring of bones together and making firmness, torment, and impeded development. The illness, for the most part, influences the joints in the knees, hands, feet, and spine and is generally regular in the shoulder and hip joints. While OA is identified with maturing, it is additionally connected with an assortment of both modifiable and non-modifiable hazard factors, which incorporates heftiness, absence of activity, word related damage, hereditary inclination, bone thickness, injury, and gender[3]. OA, the most prevalent chronic joint disease, increases in prevalence

with age and individuals over the age of 65 are majorly affected [3, 4].OA is one of the most common causes of disability in geriatric population[4]. The 2010 Global Burden of Disease Study reports that the weight of the musculoskeletal issue is a lot bigger than evaluated in past appraisals and records for 6.8% around the world [5]. An expected 10% to 15% of all grown-ups matured more than 60 have some level of OA, with higher commonness among ladies than men [6].OA has ordinarily been arranged into essential (idiopathic) and auxiliary OA dependent on the illness etiology [7,8]. Primary osteoarthritis (POA) is a natural phenomenon due to degenerative changes in the joint. It can be classified into localized and generalized OA. Localized OA impacts one joint while generalized OA shows impacts three or more joints. Secondary OA is typically associated with causes or risk factors leading to OA in the joint. These include congenital diseases, trauma, and other metabolism diseases or disorders in the bone [8,9].

Prevalence of Osteoarthritis

Osteoarthritis stands5thrank among all forms of disability globally [9]. Osteoarthritis is thought to be the most prevalent of all musculoskeletal pathologies, affecting an estimated 10 per cent of the world's population over the age of 60 [10]. The prevalence of OA increases with age and identified risk factors such as obesity, up to 80% in people over age 65 in high-income countries [11].As indicated by the United Nations, individuals matured more than 60 will record for over 20% of the total populace by 2050 [12]. Out of which 20%, a traditionalist gauge of 15% will have symptomatic OA, and 33% of these individuals will be seriously incapacitated. This implies by 2050, 130 million individuals will experience the ill effects of OA everywhere throughout the world, of which 40 million will be seriously impaired by the disease [12].Associated costs with OA incorporate expenses for versatile guides and gadgets, medical procedure, medicines, and downtime at work.

Pathogenesis

OA includes degeneration of cartilage, osteophyte formation, abnormal bone remodelling, and joint inflammation [13]. The pathology involves the participation of four components of the synovial joint which are the meniscus (the majority of synovial joints), articular cartilage, subchondral bone and synovial membrane. These components provide support to the joint in a healthy joint. The functions of the meniscus include load bearing and shock absorption in the knee joint. Fibrocartilage is composed mainly of water, type I collagen, and proteoglycans in its extracellular matrix [14,15]. Other components include type II, III, V, and VI collagen. The articular cartilage provides a surface for the synovial joint movement.Articular cartilage is hyaline cartilage composed of proteoglycans and type II collagen in the matrix.Calcified cartilage provides an interface between the bone and articular cartilage. The subchondral bone is composed of mineralized type I collagen andprovides support to the joint. The synovial membrane produces the synovial fluid which is composed of lubricin and hyaluronic acid and lubricates the joint and nourishes the articular cartilage [16,17]. The synovium consists of two types of synoviocytes: fibroblasts and macrophages [18,19]. Synovial fluid components are produced by synovial fibroblasts. The synovial macrophages are dormant usually but are activated during inflammation. Several abnormalitiesin the normal function of these components have resulted in the promotion of OA in the joint. The mechanical abrasion caused in the knee leads to the gradual degenerative changes in the meniscus with loss of both type I and, more extremely, type II collagen [20, 21]. Recent studies depict an inflammatory mechanism for the early stage of the disease which occurs mainly in response to injury caused by mechanical incitement of the joint. Cytokines, such as interleukin-1 (IL-1), IL-4, IL-9, IL-13, and TNF-α, degradative enzymes such as a disintegrin and metalloproteinase thrombospondin-like motifs (ADAMTS), and collagenases or matrix metalloproteinases (MMPs) by chondrocytes, osteoblasts, and synoviocytes are released which triggers the process [20-23]. The innate immune system contributesto OA progression by activating both the compliment and alternative pathways [24]. The released MMPs cause collagen matrix degradation which leads to degradation of the articular cartilage[25].The chondrocytes undergo hypertrophy under this condition, losing the ability to form new cartilage matrix [23]. The release of vascular endothelial growth factor (VEGF) by chondrocytes may additionally lead to the vascularization of the synovium and vascular invasion of the joint [23]. Due to the prolonged mechanical loading on the articular cartilage VEGF is released[26, 27]. The remodelling of the subchondral bone due to its rich innervations may cause painwhich may also be due to the initial inflammation of the synovial membrane (synovitis), which progressively becomes fibrotic over time [22, 23]. AGEs(Advanced glycation end products)deposit in the articular cartilage in geriatrics, bind to receptors on chondrocytes and release pro-inflammatory cytokines and VEGF, which leads to cartilage degeneration [28-30]. This pathway shows that age is an important factor in the development of OA and boosta sequence of natural disease occurrence.

Biomarkers for Osteoarthritis

Biochemical markers which could aid in the monitoring of OAhas been a major topic of research among the researchers.Research has overwhelmingly taken a gander at two fundamental competitors. The first are results of bone and ligament debasement, for example, C-terminal telopeptide of type II collagen, ligament oligomeric matrix protein, a collagen type II-specific neoepitope, an aggrecan neoepitope, various framework metalloproteinases, and procollagen type I amino-terminal propeptide [31].The second gathering of potential hopefuls has become exposed with the

expanded understanding that irritation assumes a key job in OA, which is a move from the notable sentiment that it was exclusively a "mileage" ailment. Ace and mitigating specialists, especially cytokines, have been examined for their relationship with the improvement and movement of OA in both human and animal models. As well as pro- and anti-inflammatory roles (for instance, Interleukin (IL)- 6, IL-1*β*, Tumor Necrosis Factor (TNF- *α*, IL-10, IL-13 and IL-4), cytokines likewise add to the pathophysiology of OA through angiogenesis and chemotaxis [32].Various mixes may indicate distinctive biochemical marker properties at various phases of the illness, mirroring the pathophysiological changes happening inside the joint tissue. In this way, the portrayal of potential biomarkers is essential to guarantee their fitting and ideal use. The portrayal strategy used to survey biochemical markers in OA is BIPEDS: which represents the Burden of malady, Investigative, Prognostic, Efficacy of intercession, Diagnostic and Safety [33,34].

Pro-inflammatory cytokines

Inflammation is being viewed as a significant piece of OA. Irritation can happen locally, inside the synovium, and fundamentally, with fiery specialists coursing in the blood. In the pathophysiology of OA, proinflammatory cytokines have been appeared to assume significant jobs in the demolition of ligament, synovitis, and torment [35]. The seriousness and type of irritation seem to change with malady movement, with various cytokine markers being available in ahead of schedule and propelled phases of the infection.

IL-6

IL-6 is a 184 amino acid corrosive buildup protein which has been appeared in various examinations to assume an ace incendiary job in the pathophysiology of OA [5,36]. Healthy chondrocytes produce a low amount of IL-6 without the nearness of an animating operator however when presented to specific cytokines, including IL-1*β*, a key player in the inflammation of ligament joints, chondrocytes increase production [37]. In like manner, TNF-α and interferon-*γ* have likewise been appeared to incite IL-6 generation. IL-6 has been appeared to repress the production of type II collagen in animal models. In animal models, more elevated amounts of IL-6 have been found in osteoarthritic groups compared with controls [38]. Higher IL-6 levels were likewise connected with an expanded predominance of osteophytes contrasted and lower IL-6 levels. The investigation proposed that IL-6 may assume a job in ligament misfortune in beginning time OA, due to this beginning time job, IL-6 could be classed as an analytic and prognostic biomarker.

IL-1*β*

A standout amongst the most significant star fiery cytokines to assume a job in the pathophysiology of OA is IL-1*β*. This 17.5 kDa protein [39] is a silencer of type II collagen and aggrecan amalgamation which are key constituents of cartilage [35]. With a diminished creation of these parts, cartilage debasement is intensified. Moreover, IL-1*β* prompts the generation of various cytokines and chemokines which add to the condition of aggravation, these incorporate IL-6 and IL-8 [37]. Because of its enormous association, IL-1*β* has been explored in various investigations as a potential application as a biochemical marker. All around as of late, mouse models have demonstrated that IL-1*β* assumes significant jobs in torment affectability [40]. IL-1*β* has been utilized as a marker of the adequacy of the mediation in an investigation surveying the impacts of intraarticular hyaluronic acid treatment in patients with knee OA.

TNF-*α*

TNF-α is a 17 kDa protein delivered predominately by enacted macrophages which impact the generation of cytokines including IL-6 and IL-8 among others [41]. Soluble TNF receptors in serum tests from OA patients demonstrated a positive connection with torment, joint solidness and higher radiographic seriousness of disease [42]. TNF-*α* has appeared as a marker of treatment viability, and blended outcomes as a burden of disease marker.

IL-15

IL-15 adds to aggravation in OA as a professional incendiary cytokine. There have been moderately few investigations inspecting its potential use as a biochemical marker. Be that as it may, a couple of articles have proposed it could be a prognostic and burden of disease marker. It has likewise been demonstrated that the expanded IL-15 level in the serum corresponds with both the impression of agony and the seriousness of injuries in the X-beam picture [43]. It has been identified that its quality can replicate the secretion of specific types of metalloproteinases from the MMPs group [44]. It tends to be proposed from this that IL-15 is a conceivable burden of disease biomarker for evaluating the torment related with OA yet not, be that as it may, for the appraisal of the movement of ligament devastation and seriousness. IL-15 additionally has potential as a demonstrative biochemical marker.

IL-17

The interleukins-17 (IL-17) is a gathering of cytokines with inflammatory impact, which draws increasingly more consideration of scientists for its support in the pathogenesis of OA. It comprises of six individuals (IL-17A-F) that can be connected through five types of receptors (IL-17RA-E) [45,46]. The IL-17 has fundamentally invigorated CD4+ T cells and mast cells that penetrate the synovial membrane and the whole joint through blood vessels [47]. The fundamental cells in the joint that are influenced by IL-17 are chondrocytes and FLS displaying the declaration of IL-17R on their surface. The dimension of IL-17 estimated in the serum and the synovial liquid of patients is raised and demonstrates a positive relationship with the radiographic picture of injuries in

OA. IL-17 has been appeared to suppress the blend of proteoglycans by chondrocytes and advances the production of enzymes of the MMPs group [48]. Moreover, IL-17 impacts the discharge of different cytokines and mixes adversely influencing the ligament, for example, IL-1β, TNF-α, IL-6, NO, and PGE_2. The impact of IL-17 on the discharge of VEGF by both chondrocytes and FLS is likewise trademark; it supports the inordinate improvement of blood vessels inside the synovial membrane, prompting its hypertrophy [49].

IL-18

Synovial fluid IL-18 levels have been appeared to have no connection with OA grade (KL), BMI or age, IL-18 levels in plasma, synovial fluid and articular ligament tests from knee OA patients have been demonstrated to be altogether higher than in healthy controls. Patients with higher illness seriousness had fundamentally higher IL-18 in each of the three example media [50]. This propose IL-18 can possibly recognize healthy and OA sufferers and to survey the seriousness of the ailment in OA patients. The production of IL-18 in the joint is shown by chondrocytes, osteoblasts, FLS, and macrophages [51]. Its expanded fixation is obvious in the synovial fluid, synovium, ligament, and blood serum and demonstrates a positive relationship with the level of seriousness of the disease seen in radiographic images [52]. IL-18 influences chondrocytes by prompting the upregulation of IL-18Rα on the surface and incitement abundance blend of metalloproteinases MMP-1, MMP-3, and MMP-13 [53]. Notwithstanding expanding the centralization of ligament corrupting proteins, there is a hindrance of a generation of proteoglycans, aggrecan, and type II collagen, also, chondrocytes show morphological changes of cells entering apoptosis [54]. IL-18 influences chondrocytes and synovial cells, increase the production of cytokines and enzymes, for example, the IL-18 of every an autocrine way, IL-6, iNOS, PGE_2, COX-2, and VEGF [55].

Anti-inflammatory cytokines

Countering the pro-inflammatory cytokines, anti-inflammatory cytokines additionally assume a job in the pathophysiology of OA. Specifically, IL-4 and IL-10, IL-13 add to the suppression of inflammation of the synovial membrane [56]. By lessening inflammation, these mediators can bolster cartilage generation, going about as anabolic effectors which can moderate the progression of OA. In infection free conditions, the balance among anabolic and catabolic cytokines empowers stable dimensions of cartilage. In OA, an imbalance in this harmony adds to the pathophysiology of the ailment. For the most part, nonetheless, anti-inflammatory cytokines have been less all around concentrated in the quest for biochemical markers of OA.

***IL*-4**

Interleukin-4 (IL-4) is a protein of 129 amino acids, which appears to be four interconnected α-helices also balanced out by three disulfide bonds. IL-4 is a ligand whose natural action is intervened through a receptor framework devoted to both IL-4 and IL-13 [57]. The production of IL-4 is principal shown by T cells (Th2) penetrating the synovium of the joint by blood vessels [58]. It was additionally discovered that the dimension of soluble IL-4Rα is elevated in the serum of patients experiencing OA when compared with healthy control groups. The expanded convergence of IL-4 is additionally seen in the synovial fluid and synovial cells [59]. IL-4 is related toa chondroprotective impact. In various investigations, it was discovered that IL-4 has a suppressing impact on the degradation of proteoglycans in the articular ligament, by hindering the secretion of MMPs metalloproteinases, just as lessening the variety in the production of proteoglycans that are unmistakable throughout OA. Strangely, over the span of OA, chondrocytes indicated diminished helplessness with the impacts of IL-4 which might be in charge of the fast degeneration of the articular ligament [60]. Also, IL-4 alone or in the mix with IL-10 shows properties restraining the apoptosis of both the chondrocytes and FLS. Considering the impact of IL-4 on cell culture of chondrocytes and FLS treated with it, there is an abatement of a combination of provocative cytokines, for example, IL-1β, TNF-α, and IL-6 [61]. At the same time, IL-4 can incite upregulation of the statement of TNFα receptors, for example, TNF-R1, and TNF-R2. Notwithstanding an immediate decline in the secretion of incendiary cytokines, there is additionally a decrease in the secretion of other inflammatory mediators, for example, PGE_2, COX-2, PLA2, and iNOS [62].

***IL*-10**

Interleukin-10 (IL-10) is a cytokine fundamentally identified with interferons, which is as a homodimer wherein each monomer is a polypeptide chain comprising of 160 amino acid, taking the structure of 6 interconnected α-helices. IL-10 is another cytokine that demonstrates a chondroprotective impact over the span of OA. Chondrocytes express both the cytokine IL-10 and the receptor IL-10R. It has been demonstrated that IL-10 is associated with stimulating the synthesis of type II collagen and aggrecan. It has been demonstrated that IL-10 is in charge of restraining the creation of MMPs group of metalloproteinases [63]. It confirmed that IL-10 (like IL-4) hinders the apoptosis of chondrocytes. These properties of IL-10 are likely the aftereffect of incitement of the synthesis of IL-1βantagonist, which is IL-1Ra and the tissue inhibitor of metalloproteinases-1 (TIMP-1) just as growth factors [64].

IL-13

Interleukin-13 (IL-13) is cytokine that takes the structure of four interconnected α-helices, which is fundamentally the same as in its impact to IL-4. Like IL-4, the activity of IL-13 as a ligand is mediated through a receptor framework that joins the two cytokines [57,65]. The anti-inflammatory and

chondroprotective impacts of IL-13 on the cells of the resistant reaction, articular ligament, and synovium in OA have been fairly very much documented [66]. The anti-inflammatory impact of IL-13 with regards to OA appears to be most significant as for fibroblasts incorporated into the synovium. It has been appeared, contrasted with the control samples, IL-13 indicated inhibitory impacts on the synthesis of proinflammatory IL-1*β*, TNF-*α*, and MMP-3 with simultaneous increment in the dimension of IL-1Ra.

Chemokines and Angiogenic growth factors

Chemotactic cytokines or chemokines have been appeared to impact inflammation in OA through their ability to impact the number of immune cells in the vicinity of the joint. They additionally animate IL-6 generation and proteoglycan depletion. Angiogenic growth factors add to synovitis and agony just as cartilage destruction[67].

VEGF

Vascular endothelial development factor (VEGF) is a 46-48 kDa glycosylated polypeptide [17] and an intense angiogenic cytokine that has been able to play a role in OA [68]. It is delivered by hypotrophic chondrocytes, macrophages and synovial fibroblasts. VEGF in the synovial fluid has appeared associated with OA severity, and no relationship with BMI, with a 2-overlay increment between evaluation 0 and grade 3-4 patients.

IL-7

IL-7 is a hemopoietic growth factor associated with the improvement of B and T cells. It has been found to increase with age in tests of synovial fluid from OA patients, with the middle concentration in patients more than 60 years of age twofold that of those under 60 years of age.

Medicinal Herbal Plants used in the treatment of Osteoarthritis

Medicinal plants have been traditionally used to control pain and improve dysfunction in osteoarthritis. In developing countries, most of the people rely on herbal medicine[68-70]. Herbal medicines are prescribed worldwide for the management of osteoarthritis since ancient times [71]. Herbs and plants always have been prescribed in the management of different diseases including gouty arthritis and other associated musculoskeletal disorders.

***Achyranthes japonica* (Amaranthaceae)**

The leaves and stems and roots contain a few chemical constituents. The seed contains insect shedding hormones including rubrosterone, ecdysterone, and inokosterone. The root contains triterpenoids and saponins. Likewise, it contains protocatechuic acid.The anti-inflammatory and anti-arthritic effects of the fermented *Achyranthes japonica* (Miq.) Nakai extract (FAJE) was evaluated in this study. Our experiments showed that the FAJE was effective in vitro (LPS-treated RAW264.7 cells) and in vivo (OA-induced SD rats) study. FAJE clearly decreased the NO levels in vitro study, and the inflammation markers (TNF-*α*, IL-1*β*, MMP-2 and MMP-9) *in vivo* study. Moreover, the damages on the cartilage were recovered and the proteoglycans were increased by FAJE. These overall results strongly suggest that the FAJE has anti-inflammatory effects and contributes to improving osteoarthritis conditions by suppressing the expression of inflammatory cytokines TNF-α, IL-1*β*, MMP-2 and MMP-9 which are a major cause of proteoglycan decomposition in osteoarthritis[72].

***Arnica montana*, (Asteraceae)**

The antiarthritic action of the plant is credited to the phenolic and flavonoid intensifies, the general most active constituent, present in a methanolic extract. An orally administered *Arnica* extract appeared to (on the collagen-induced arthritis rodent model) to mitigate both the histological and radiological changes in the influenced joints, in parallel with a reduction in NO, TNF-*α*, IL-1*β*, IL-6, and IL-12 fixations, against type II collagen level, and an improvement of the oxidative status (higher cell reinforcement levels and milder peroxidative damage) [73-75]. In a Human clinical trial, a gel prepared from *Arnica montana* new plant was tried in OA knee and demonstrated to reduce indications, improve mobility. A two-fold visually impaired examination on 204 patients contrasting *Arnica montana* and ibuprofen in topical applications [76].

***Artemisia herba-alba* Asso (Asteraceae)**

The whole plant is prescribed for the management of numerous disorders [75]. It contains piperitone, carvone, cis-thujone, chrsanthenone and camphor, trans-pinocarveol, camphor, borneol, alpha-thujone, beta-thujone, trans-sabinyl acetate, 1-8 cineole, chrysanthenone, cirsilineol and hispidulin [76,77]. It is used in diabetes mellitus, osteoarthritis, nervous disorders, pyrexia, syphilis, scabies, neuralgia, diarrhoea, bronchitis, cough, a cold and fungal infection. It is anti-inflammatory, antioxidant, hypoglycemic, antileishmania and smooth muscle relaxant [78]. Arshad *et al*. reported the ethnomedicinal use of this plant in arthritis [79].

***Boswellia serrata* (Burseraceae)**

Chemical constituents are pentacyclic triterpene acids and beta-boswellic acid [80]. It is used in asthma, inflammation, cancer and osteoarthritis [81]. Pharmacological activities are anticancer, antioxidant, anti-asthmatic and anti-inflammatory [82]. *Boswellia serrata* is prescribed in the treatment of osteoarthritis [83]. Kimmatkar *et al*. depicted the efficiency of *Boswellia serrata* extract in the management of knee osteoarthritis. In clinical trials, 56 patients were randomized into two groups.*Boswellia serrata* 500 mg capsule was administered to the first group in three divided doses. Capsules were administered with

lukewarm water. Total patients were 29 in the 1st group. 23 patients were in the 2nd group and capsule was administered with Luke water. In the 2nd group, *Boswellia serrata* ointment was applied on joints. This treatment was given for 2-month duration. There was symptomatic development in both groups. Improvement in the first group was with promising results [84].

Commiphora mukul **(Burseraceae)**

It is used in haemorrhoids [85]. It is a laxative, antiseptic, expectorant, carminative, astringent, antimicrobial, anti-inflammatory, demulcent, hepatoprotective and anti-diabetic [86]. Singh *et al*. reported the efficiency of *Commiphora mukul* for osteoarthritis of the knee. *Commiphora mukul* has been investigated for its efficacy to treat osteoarthritis. Preclinical and clinical trials show that *Commiphora mukul* is effective in osteoarthritis. In a clinical trial, thirty male and female patients were selected for the study. *Commiphora mukul* was administered to patients at a dose of 500 mg in the form of a capsule. There was a significant improvement in mobility and functions of joints when taken for 1 month continuously. *Commiphora mukul* was effective in participants during the trial. During the trial, no significant adverse effects were reported. This study showed that *Commiphora mukul* is a safe and effective alternative to treat osteoarthritis [87].

Curcuma longa **(Zingiberaceae)**

The plant is used in rheumatism. It contains curcumin, bisdemethoxycurcumin, demethoxycurcumin, zingiberone, tumerone, atlantone, resins, protein and sugars [88]. It is used in acute coronary syndrome, psoriasis, vitiligo, arthritis,cardiovascular disorders, tumor, gastric ulcer, peptic ulcer, diabetes mellitus, ulcerative proctitis, gastric inflammation, Crohn's disease, diabetic nephropathy, ulcerative colitis, lupus nephritis, irritable bowel disease, acquired immune deficiency syndrome, tropical pancreatitis, atherosclerosis, idiopathic orbital inflammatorypseudotumor, diabetic microangiopathy, oral lichen planus, β-thalassemia, chronic bacterial prostatitis, biliary dyskinesia and cholecystitis [89]. It is efficient in anti-inflammatory, antioxidant and anticancer activity[90]. Curcumin containing formulation exhibited anti-inflammatory activity in patients with osteoarthritis [91].

Dalbergia sissoo **Roxb (Fabaceae)**

Plant parts used are roots and wood. Active constituents are isoflavones, flavonols and lignan glucoside [92]. It is used in arthritis, boils, the eruption of the skin, leprosy, vomiting and inflammation [93]. It is astringent, anti-inflammatory, anti-arthritic and gastroprotective [94]. Ethanol extract of this plant contains various constituents that have osteogenic effect in primary calvarial osteoblast cultures. Some compounds of this plant increased alkaline phosphatase activity. Osteogenic activity is evident from mineralization [95].

Harpagophytum procumbens **(Pedaliaceae)**

The plant contains iridoids that show anti-inflammatory effect. Chantre *et al*. reported the potential of *Harpagophytum procumbens* in comparison with diacerein in the management of osteoarthritis in a randomized clinical study. It was a comparative study, in which the efficacy of the herbal product (Harpadol) was investigated against diacerein. Six capsules of herbal medicine were given to the patient daily. Each of the capsules contained 435 mg of powdered material. Diacerein was given at a dose of 100 mg/day. The total duration of treatment was four months. Total no. of patients with osteoarthritis were 122. The pain was significantly reduced in both management clusters. Effectiveness of both drugs was comparable. After completion of the trial duration, Harpadol treated patients were taking significantly fewer NSAIDs and analgesic drugs. Fewer side effects occurred in a harpadol group than the control group. 8.1% of patients suffered from diarrhoea and 26.7% were in the control group. This research indicated that test drug is equally effective and better in safety to control group [96].

Phyllanthus emblica **(Euphorbiaceae)**

Fruit of this plant is used in osteoarthritis [97]. Chemical constituents include minerals, amino acids, emblicol, curcuminoids, phyllembelic acid, tannins and phenolic compounds [98]. It is used in inflammation, jaundice, diarrhoea and cancer [99]. Pharmacological activities include antioxidant, gastroprotective, hepatoprotective, antiulcerogenic, antibacterial, hypolipidemic and anticancer [100]. Sumantran *et al*. reported the chondroprotective activity of *Phyllanthusemblica* in patients with osteoarthritis. Aqueous extract of *Phyllanthus emblica* was investigated for its chondroprotective activity. *In vitro*study, hyaluronidase and collagenase type 2 activities were inhibited by the use of the aqueous extract of *Phyllanthus emblica*. The data shows that *Phyllanthus emblica* extract can be used as a chondroprotective agent in the treatment of osteoarthritis [101].

Punica granatum **(Lythraceae)**

Chemical constituents include punicalagin, tannins and anthocyanins [102]. It is used in pain, inflammation, arthritis, obesity, Alzheimer's disease, male infertility, infant brain ischemia, bacterial infections, erectile dysfunction, dental cavities, diabetes mellitus, cardiovascular disorders and cancer [103]. Pharmacological activities are anticancer, diuretic, anti-angiogenesis, antimutagenic, astringent, antioxidant and anti-inflammatory [104]. Pomegranate juice reduced proteoglycan loss and cartilage damage in the mouse model with osteoarthritis [105].

Salix spp. **(Salicaceae)**

Although traditionally salicin was considered as the active principle, there are opinions that this substance can't explain the entire scope of WBE

(Willow bark extract), and that different phytochemical may be involved, for example, polyphenols and flavonoids, which demonstrated inhibitory movement on COX-2 and diminished blend of professional inflammatory arbiters *in vitro*, in human monocytes and separated macrophages [106,107,108,109]. *In vitro* examinations, demonstrated the inflammation-suppressing impact of willow bark extract (WBE) depends, at any rate somewhat, on its capacity to threaten the initiated monocytes, by blocking the action of inflammatory cytokines (TNFα), enzymes (COX-2), and mediators (NF-κB) [108]. In concluded in animal studies the mechanism of the anti-inflammatory action of WBE was examined on two animal models of arthritis, an acute and a chronic one. WBE diminished the inflammatory infiltrate and exudate and obstructed the cytokine with power in any event identical to that of acetylsalicylic acid (ASA), was superior to ASA in reducing leukotrienes levels and in inhibiting COX-2, and in the same class as ASA in decreasing prostaglandins levels. WBE influenced positively the oxidative pressure increasing GSH and decreasing malondialdehyde levels more effectively than ASA or celecoxib (a particular COX-2 inhibitor). In spite of being more strong than ASA, on a molar basis, the salicin in WBE is considerably less than the salicylate substance of ASA, suggesting that active principles other than salicin may play a role in the anti-inflammatory and antioxidative activity of WBE, the polyphenols being among the hopefuls, at any rate regarding the security against free radicals. The capacity to moderate genius inflammatory cytokines and oxidative pressure were examined on the collagen-induced arthritis animal model [110]. The primary clinical trials of aspirin, yet uncontrolled and non-randomized, was led in the eighteenth century by the English Reverend Edward Stone—the great individual, struck by the quinine-like harshness of aspirin, derived an antifebrile movement and, indeed, had the option to fix fever in 50 patients [111]. A fourteen day, twofold blind, randomized, placebotreatment controlled trials showed the capacity of willow bark extract (in a portion proportionate to 240 mg salicin/day) to control the side effects of patients with OA, particularly to diminish pain, in spite of the fact that with rather quelled effectiveness [112]. A similar portion of willow bark concentrate was utilized in two other six-week, randomized, controlled, twofold blind trials in patients with OA and Rheumatoid arthritis, individually, the natural arrangement being contrasted and an intense NSAID (diclofenac) and with placebo treatment. The two trials yielded results, as in nor was willow bark extract essentially superior to placebo treatment in pain alleviation [113]. In a six-week, open, multicentric observational examination with reference treatment, WBE was assessed as better as a regular treatment by doctors and patients alike, regarding both helpful productivity and reactions, when utilized for hip and knee degenerative illness [114]. In a more drawn out (a half year) observational investigation on 436 patients with OA and back pain, WBE altogether diminished pain and was very much endured [115].

***Symphytum Officinalis* (Boraginaceae)**

Phenolic acids (rosmarinic acid), glycopeptides and amino acids are viewed as, in any event, in charge of the anti-inflammatory capability of comfrey root separate, in different *in-vitro* models [116,117]. Rosmarinic acid inhibited prostaglandin combination, and carrageenan and gelatine-induced erythrocyte aggregation [118]. *In vitro* studies concentrate on comfrey essentially inhibited the respiratory burst of polymorphonuclear leukocytes, recommending an anti-inflammatory potential of the plant [119]. Animal studies on Comfrey concentrates indicated anti-inflammatory action, by hindering carrageenan-induced rodent paw oedema [116,120]. In Human clinical studies, an investigation on individuals matured 50–80 with OA of the knee demonstrated that topically applied comfrey diminished torment, despite the fact that was unable to diminish the burden of inflammatory molecules or the rate of ligament breakdown, the main detectable unfavourable impact being neighbourhood rashes [121]. Comparative outcomes yielded in another examination on a comparable population of years-long sufferers from OA of the knee: a comfrey-containing treatment improved the personal satisfaction by diminishing torment and increasing knee-versatility [122].

***Withania somnifera* (Solanaceae)**

Withania somnifera, also called asAshwagandha, is a potent anti-osteoarthritic and anti-inflammatory plant utilized in Ayurveda [123]. *In vitro* study in which extract inhibited liposaccharide induced synthesis of pro-inflammatory cytokines (TNF-α, IL-1β and IL-12) in peripheral and synovial fluid mononuclear cells from rheumatoid joint pain subjects *in vitro*, yet had no impact on IL-6 synthesis [124]. The extract additionally indicated inhibitory consequences for collagenase activity against the degradation of the bovine Achilles tendon type I collagen, that might be valuable in joint disease treatment [125]. In animal studies,root powder protectively affected bone collagen-induced arthritis model in rodents [126]. In clinical trials, a randomized, twofold, placebo-controlled study demonstrated that the aqueous extract produced a huge decrease of scores for torment, solidness and incapacity in human subjects with knee joint agony [127]. Withaferin A, having a place with the steroid class of phytochemicals, is believed to be one of the benefits to the OA subjects [124]. Withaferin A returned to close normal levels the increase in paw volume, lysosomal enzymes, lipid peroxidation, and TNFα in a monosodium urate crystal-induced arthritis in mice [128].

***Zingiber officinale* (Zingiberaceae)**

It contains hexacosanoic acid 2,3-dihydroxypropyl ester, adenine, diterpenes, glycol monopalmitate, 6-shogaol, isovanillin, p-

hydroxybenzaldehyde, *β*-sitosterol palmitate, 1-(omegaferulyloxyceratyl) glycerols, steroids, gingerol analogue, maleimide-5-oxime and diarylheptanoids. It is anti-inflammatory, digestive, xanthine oxidase inhibitor, cyclooxygenase-2 inhibitor and antiarthritic [129]. It is used in indigestion, inflammation, gouty arthritis and rheumatoid arthritis [130]. The anti-inflammatory activity shows its efficacy in osteoarthritis as well[131]. The improvement in symptoms, defined as a reduction in the mean change, was superior in the *Zingiber officinale* extract and ibuprofen groups than the placebo group. *Zingiber officinale* extract and ibuprofen showed better results than placebo in the symptomatic treatment of osteoarthritis, while there was no significant distinction between the *Zingiber officinale* extract and ibuprofen group in a test for numerous correlations [132].

CONCLUSION

This review highlights the importance of natural drugs that have been demonstrated to be powerful in the treatment-related with OA could help to bring down the utilization of NSAIDs, thus decreasing in the side effects and seriousness of their unfavourable impacts. To bring the importance of the herbal medicinal plants used in the treatment of OA with *in-vitro* studies &clinical trial carried on humans. More studies need to be carried out on the herbal medicinal plants to put forth the importance in the OA treatment. As the scientific data available with us is not sufficient therefore more plants need to be explored.Some of them mentioned in the review include *Achyranthes japonica*, *Boswellia serrata*, *Commiphora mukul*, Symphytum Officinalis to name a few.The review also put emphasis on the available biomarkers of Osteoarthritis for early diagnosis and investigation.

Table-1: Herbal Medicinal plants used in the treatment of Osteoarthritis

S.No	Plant name	Chemical constituent	Mechanism	Reference
1.	*Achyranthes japonica*(Amaranthaceae)	Rubrosterone, ecdysterone,inokosterone, triterpenoids,saponins, protocatechuic acid	NO levels in vitro study, and the inflammation markers (TNF-*α*, IL-1*β*, MMP-2 and MMP-9) *in vivo* study.	[72]
2.	*Arnica montana, (Asteraceae)*	Phenolic and Flavonoid compounds	NO, TNF-*α*, IL-1*β*, IL-6, and IL-12	[74]
3.	*Artemisia herba-alba* Asso (Asteraceae)	Piperitone, carvone, cis-thujone, chrsanthenone and camphor, trans-pinocarveol, camphor, borneol, alpha-thujone, beta-thujone, trans-sabinyl acetate, 1-8 cineole, chrysanthenone, cirsilineol and hispidulin	Ethnomedicinal use of this plant in arthritis.	[76-79]
4.	*Boswellia serrata* (Burseraceae)	Pentacyclic triterpene acids and beta-boswellic acid	Anti-inflammatory, osteoarthritis	[82-84]
5.	*Commiphora mukul* (Burseraceae)	Haemorrhoids	Preclinical and clinical data show that *Commiphora mukul* is effective in osteoarthritis.	[85-87]
6.	*Curcuma longa* (Zingiberaceae)	Curcumin, bisdemethoxycurcumin, demethoxycurcumin, zingiberone, tumerone, atlantone, resins, protein and sugars	Curcumin containing formulation exhibited anti-inflammatory activity in patients with osteoarthritis.	[88-91]
7.	*Dalbergia sissoo* Roxb (Fabaceae)	Isoflavones, flavonols and lignan glucoside	Ethanol extract of this plant contains various constituents that have osteogenic effect in primary calvarial osteoblast cultures.	[92-95]
8.	*Harpagophytum procumbens* (Pedaliaceae)	Iridoids	*Harpagophytum procumbens* in comparison with diacerein in the management of osteoarthritis in a randomized clinical study.	[96]
9.	*Phyllanthus emblica* (Euphorbiaceae)	Amino acids, emblicol, curcuminoids, phyllembelic acid, tannins and phenolic compounds	Aqueous extract of *Phyllanthus emblica* was investigated for its chondroprotective activity. *In vitro*study, hyaluronidase and collagenase type II	[97-101]

			activities were inhibited by the use of the aqueous extract of *Phyllanthus emblica*	
10	*Punica granatum* (Lythraceae)	punicalagin, tannins and anthocyanins	Pomegranate juice reduced proteoglycan loss and cartilage damage in the mouse model with osteoarthritis	[102-105]
11.	Salix spp. (Salicaceae)	Salicin	(TN-α), enzymes (COX-2), and mediators (NF-κB)	[106-113]
12.	Symphytum officinalis (Boraginaceae)	Phenolic acids (e.g., rosmarinic acid), glycopeptides and amino acids	Acomfrey-containing ointment improved the quality of life by decreasing pain and increasing knee-mobility	[114-118]
13.	Whitania somnifera (Solanaceae)	Withaferin A	TNF- α, IL-1β and IL-12	[121-126]
14	*Zingiber officinale* (Zingiberaceae)	hexacosanoic acid 2,3-dihydroxypropyl ester, adenine, diterpenes, glycol monopalmitate, 6-shogaol, isovanillin, p-hydroxybenzaldehyde, β-sitosterol palmitate, 1-(omegaferulyloxyceratyl) glycerols, steroids, gingerol analogue, maleimide-5-oxime and diarylheptanoids	The anti-inflammatory activity shows its efficacy in osteoarthritis.	[129-132]

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