International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 613-629 www.ijprajournal.com ISSN: 2456-4494

A Breif Review on Phytomedicine in Joint Disorders

Sachin Rathore[1], Arbaj Khan[2], Mr. Abhijit Sahana[3], Prof. Dr. Biswajit Das[4]
1, 2 Scholar, One Beat College of Medical Sciences, Bhira Kheri 262901
3 Assistant Professor, One Beat College of Medical Sciences, Bhira Kheri 262901
4 Principal, One Beat College of Medical Sciences, Bhira Kheri 262901

Date of Submission: 20-01-2025 Date of Acceptance: 30-01-2025

ABSTRACT
A frequent feature of chronic joint inflammatory diseases like rheumatoid arthritis and osteoarthritis is an increase in oxidative stress and inflammation, which leads to increasing histological changes and incapacitating symptoms. The powerful conventional medications that are now in use, which range from biological agents to painkillers, are often linked to severe, even fatal, side effects. Because of their reduced risk of side effects and often equivalent effectiveness to traditional medications, medicinal plants—which have been used for millennia in traditional herbalism—are a possible substitute.

Keywords: Osteoarthritis, Rheumatoid Arthritis, Medicinal plants, Herbs.

I. INTRODUCTION: --

Increased inflammation and oxidative stress are prominent features of chronic joint inflammatory diseases like osteoarthritis and rheumatoid arthritis, which lead to progressive histological changes and incapacitating symptoms.

About 15% of people have osteoarthritis, one of the most prevalent musculoskeletal conditions [1]. It is characterized by bone erosion and irreversible articular cartilage destruction brought on by pro-inflammatory cytokines such as tumour necrosis factor α (TNF-α), interleukin 1 (IL-1), and interleukin 6 (IL-6). These mediators reduced the synthesis of collagenase inhibitors, collagen, and proteoglycans while increasing the synthesis of collagenase or matrix metalloproteinase (MMP) and the breakdown of collagen type II [2]. Collagenase-1 and collagenase-3 (also known as MMP-13) break down collagen type II, which is one of the biochemical indicators of osteoarthritis [3].Many times, the mechanism of action is unclear and/or elusive. There is a dearth of clinical evidence in humans, despite the fact that many of them have been shown to be successful in in vitro or animal model research. The following joint-friendly medicinal plants have been tested in human studies: Arnica montana, Boswellia spp., Curcuma spp., Equisetum arvense, Harpagophytum procumbens, Salix spp., Sesamum indium, Symphytum officinalis, Zingiber officinalis, Panax notoginseng, and Whitania somniferous. The goal of this review is to provide an overview of the scientific data that is currently available on these plants.

Advanced age, sex, obesity, elevated body mass index (BMI), genetics, ethnicity, food, trauma, and certain physical or occupational activities that imply biomechanical stress (e.g., pressure, load-bearing) across the joints are all factors that raise the risk of osteoarthritis (OA) [4,5,6]. Joint imaging for longer studies (one year or more) and pain and physical function evaluation for shorter studies are used to track the progression of OA and its treatment. Visual analog scales (VAS) are used to measure pain, and the Western Ontario and McMaster Universities OA Index (WOMAC) is used to measure functional impairment [7]. The Karnofski Performance Scale Index [9] and the Liquesce Functional Severity Index [8] are further helpful instruments for evaluating functional impairment.One percent of people have rheumatoid arthritis (RA), a chronic progressive systemic autoimmune disease that causes disability and raises the risk of cardiovascular disease, cancer, and death [10]. It is usually linked to elevated levels of oxidative stress and inflammatory mediators. Today, a wide range of medications are used to treat RA, from powerful biological agents that target particular immune and inflammatory pathways, like TNF-alpha (TNF-α) inhibitors and interleukin-1 receptor antagonists, to steroidal/nonsteroidal anti-inflammatory drugs (NSAIDs and painkillers) [11].Acetaminophen is the most commonly used nonsteroidal anti-inflammatory medicine at extremely high dosages (4000 mg/day). In terms of painkillers, tramadol is strongly advised, along with other opioids (such as morphine) [12]. Among the TNF-α inhibitors used to treat severe RA are etanercept, infliximab, and rituximab. [13, 14]. Other treatment options for RA

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 613-629 www.ijprajournal.com ISSN: 2456-4494

include methotrexate [16] and an IL-1 receptor antagonist called anakinra [15].The majority of RA cases, including the more severe ones, have shown great success and efficacy with biologic therapy. Unfortunately, there are many and often serious side effects associated with using standard medications for arthropathies [17]: NSAID-induced gastrointestinal ulcerations, haemorrhagic events, and nephrotoxicity [18]; TNFα inhibitor-induced infusion hypersensitivity reactions and auto-immune responses (e.g., lupus-like syndrome) [19]; biological drugs (Ankinra, rituximab, or abatacept) [20]; methotrexate-induced fatal cytopenia [21]; etc.Numerous herbal extracts discussed in this research shown advantages for pain management and physical mobility in arthritic individuals with minimal risk of adverse effects. Thus, there is a rising interest in botanical medications, which have been used for millennia and have no serious side effects [22]. It's possible that these treatments are improving the disease's progression in addition to its symptoms [23].This review's objective is to provide an overview of the scientific evidence on medicinal plants that have been shown to have anti-arthritic properties in vitro, in animal models, and in human clinical trials. The data was gathered from medical databases and literature. The terms "medicinal plants or herb and osteoarthritis or arthritis or rheumatoid arthritis," "specific herb Latin name or specific herb English name and osteoarthritis or arthritis or rheumatoid arthritis" (e.g., Curcuma longa or turmeric and osteoarthritis or arthritis or rheumatoid arthritis) were used in a literature search in the PubMed database.Only medicinal plants that had been the subject of human clinical trials were chosen, and they were listed according to their Latin names. Using herbal extracts and potentially active phytochemicals, we have examined in vitro, animal, and human clinical investigations for each of the plants in the study. The related publications were located and assessed for their applicability to the current paper's subject. A manual search of numerous literatures, including traditional medicine books, yielded additional material.

II. ANTI-ARTHRITIC MEDICINAL PLANTS: -

2.1 Traditional herbal medicine has utilized Arnica Montana, a member of the Asteraceae family, for centuries to treat conditions involving the locomotor system that are caused by trauma, strain, and/or inflammation [24]. It is also one of the most frequently used natural remedies for rheumatologic conditions [25].Research on animals. In the collagen-induced arthritis rat model, an oral Arnica extract was demonstrated to reduce the radiological and histological alterations in the afflicted joints. This was accompanied by a reduction in the levels of anti-type II collagen antibodies, NO, TNF-α, IL-1β, IL-6, and IL-12, as well as an improvement in the oxidative status (higher antioxidant levels and less peroxidative injury) [24]. Clinical research on humans. A gel made from fresh Arnica montana plants was examined in an open multicentre trial for knee OA and shown to be well tolerated, effective, and symptom-relieving. Adverse effects were noted infrequently. As befits a real Asteraceae herb, allergy may be an issue [26]. Another study [28] confirmed the findings of a double-blind study that compared the effectiveness of Arnica montana and ibuprofen in topical treatments for hand OA in 204 individuals. The study also indicated that Arnica had fewer negative effects than ibuprofen. A Cochrane review also recognized the effectiveness of Arnica in treating hand OA locally when combined with NSAIDs [29].

Phytochemicals that are active. Some authors credit the anti-arthritic effectiveness to the synergism of the primary active principles, flavonoids and phenolic compounds, discovered in a methanol extract that was effective on a rat model of collagen-induced arthritis (CIA) [24].

2.2 Boswellia spp., fam. Burseraceae

Customary wisdom. Boswellia serrata (BS) produces frankincense, a gum resin that has been used for ages in Ayurvedic medicine (where it is referred to as sallaki) to treat inflammatory conditions [30], especially arthritis. These days, BS is present in a lot of anti-arthritic combos.

studies conducted in vitro. A BS preparation rich in active principles was able to prevent the inflammatory response by blocking Intercellular Adhesion Molecule 1 (ICAM-1) and preventing cartilage degradation by metalloproteinase-3 (MMP-3) [31]. Another study found that a B. frère Ana formulation prevented the breakdown of collagen and cartilage by reducing the synthesis and activation of a number of mediators and enzymes linked to inflammation, including MMP-9 and MMP-13, cycloxygenase-2, nitric oxide, and prostaglandin E2 [32].

It has been demonstrated that a polyherbal formulation comprising Zingiber officinal root, TINOSPORA Cord folia stem, PHYLLANTHUS embolic fruit, and oleoresin of BS can prevent cartilage degradation in the knee (reduced release

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 613-629 www.ijprajournal.com ISSN: 2456-4494

of glycosaminoglycans and aggrecan) and has anti-inflammatory properties (measured by decreased nitric oxide levels) [33].

Another combination that has been demonstrated to reduce inflammation and preserve articular cartilage consists of three herbs (Uncaria tomentosa, Boswellia spp., and Lepidium meyenii) and an amino acid (L-leucine). Tested on OA chondrocytes, it inhibited the activation of NF-κB by IL-1β, which in turn stopped the activity of inflammation-related enzymes (ion's, MMP-9, and MMP-13). This resulted in a greater production of structural proteins (such as aggrecan and type II collagen) and a lower rate of NO production and cartilage matrix deterioration (less glycosaminoglycans-GAGs released).

Research on animals. Lactoperoxidase, myeloperoxidase, catalase, superoxide dismutase (SOD), glutathione (GSH), and nitric oxide (NO) all showed improved antioxidant status and pro-inflammatory mediator suppression when an extract of BS was used in a rat model of collagen-induced arthritis [22]. In a rat model of adjuvant-induced arthritis, a combination of Withania somniferous, BS, Zingiber officinale, and Curcuma longa was shown to reduce inflammation and arthritis while also lowering TNF-α and NO production [34].

Clinical research on humans. Two high-quality and two moderate-quality studies showing superiority compared to placebo in reducing pain and increasing functionality, as well as a moderate-quality study indicating a favourable adverse events profile, were cited in a Cochrane systematic review that concluded that preparations from BS "show trends of benefits" (when used for the treatment of OA) coupled with a low burden of side effects [35]. Indeed, a handful of double-blind, randomized, placebo-controlled studies done on patients with knee OA indicated that Phyto preparations from BS gum resin are able to relieve pain and boost functionality after only a few days (a week or two at most) with no major adverse effects [31,36].

When added to the standard management of knee OA, a phytosomal Boswellia preparation has been demonstrated to be helpful in reducing symptoms (lower WOMAC (Western Ontario and McMaster Universities questionnaire) Score) and improving functional status (higher Karnofski Scale Index) [37]. In those with hand arthritis brought on by excessive strain at work, it also speeds up functional recovery and reduces pain and objective physical and humoral indicators of inflammation [38]. In patients with osteoarthritis, a combination of BS and Curcuma longa was found to be safe and effective, reducing objective signs and symptoms even more effectively than celecoxib, a specific COX-2 inhibitor, and having almost no adverse effects [39]. Nevertheless, additional research did not validate the effectiveness of BS in the treatment of active RA [40].

phytochemicals that are active. Initially, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid were the leading candidates among the boswellic acids [41,42], a family of pentacyclic triterpenes, which demonstrate the involvement of bioactive principles. In a bovine serum albumin-induced arthritis model, oral or local boswellic acid therapy improved the synovial fluid proteins' electrophoretic pattern and reduced leucocyte infiltration into the knee joint [43]. Until recently, these substances were thought to reduce lipoxygenase-5 (LOX-5) in vitro and in animal models, hence inhibiting the formation of leukotrienes [30,44]. Additional mechanisms were also cited, including decreased cleavage of C3 into the active components C3a and C3b, inhibition of NF-κB activation, and decreased production of pro-inflammatory cytokines (TNF-α, IL-1, IL-2, IL-4, IL-6, and IFN-γ). These were demonstrated in a number of in vivo studies using different models of inflammation, either arthritic or non-arthritic (e.g., hypersensitive reaction in mice) [46]. The action intensity of 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, as well as their bioavailability—the latter being too low to supply quantities high enough for bioactivity—have been questioned more recently [47]. However, β-boswellic acid, another member of the family, was suggested as the active principle. It can effectively inhibit microsomal prostaglandin E synthase-1 and the serine protease cathepsin G, which may be the substrate of the BS preparations' ability to suppress inflammation, and it can reach much higher levels in plasma [17].

2.3. Curcuma spp., fam. Zingiberaceae

Customary wisdom. Turmeric, or Curcuma longa (CL), is the most significant member of the Curcuma genus that is utilized in traditional medicine. Its rhizome has been used for ages as a spice in food and as an Ayurvedic herb valued for its anti-inflammatory qualities, which explains why it is useful for arthritic disorders like RA. [48].

research on animals. A CL preparation devoid of essential oil significantly reduced periarticular damage and joint inflammation in an animal arthritis model. This was correlated with a

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 613-629 www.ijprajournal.com ISSN: 2456-4494

decrease in NF-κB activation and the subsequent chain of events (involving mediators of inflammation and injury such as chemokines, cyclooxygenase 2, and receptor activator of nuclear factor kappa-B ligand (RANKL)). [49]. It appears that the capacity to stop the damaging alterations in joints and periarticular bone is equivalent to betamethasone [50,51]. The low water-solubility issue that results in poor bioavailability may be resolved with the aid of liposomal encapsulation [52]. While slowing the advancement of OA, the balance between osteoclasts and osteoblasts is skewed in favour of bone formation [52]. In a rat model of experimentally induced arthritis, a combination of ginger and turmeric rhizomes outperformed the powerful NSAID indomethacin in terms of reducing joint histopathological changes as well as extra-articular manifestations such as iron deficiency anaemia, malnutrition (decreased body weight gain, and hypoalbuminemia), and systemic inflammation (leucocytosis, thrombocytosis, and hyperglobulinemia) without compromising kidney function or lowering the risk of cardiovascular disease (favourable lipid and oxidative profile) [53]. Clinical research on humans. In treating osteoarthritis, a combination of Curcuma longa and Boswellia serrata has been demonstrated to be more effective than a standard dosage of celecoxib, a selective COX-2 inhibitor, improving patients' conditions both objectively and subjectively. Laboratory tests (liver, kidney, and hemogram) and clinical examinations have not revealed any toxicity [39]. Extracts from Curcuma domestica have been demonstrated to be effective in treating osteoarthritis in the knee, lowering pain and maintaining function at a rate comparable to that of ibuprofen while having less adverse effects on the gastrointestinal system [54]. Although a recent meta-analysis discovered pertinent scientific data supporting turmeric's effectiveness as a treatment option for arthritis, it came to the conclusion that additional research is required to fully identify it [55].

Phytochemicals that are active. Due to its capacity to positively impact a wide range of signalling pathways and mediators, the active ingredient, diferuloylmethane, a yellow phenolic pigment also referred to as curcumin, has a multifaceted beneficial action in various fields of pathology (diabetes, cancer, inflammation, and oxidative stress) [56]. It has been demonstrated to reduce joint inflammation (as measured by neutrophil infiltrate density) in a rat model of arthritis, with zymosan infiltration being even more efficacious than a low dosage of prednisone in the first six hours following the arthritis-inducing event [57].

The mechanism of action was thought to include lowering systemic oxidative stress, as evidenced by increased GSH, decreased malondialdehyde, and enhanced serum SOD activity [58]. Blocking glial activation reduced the synthesis and secretion of inflammatory mediators in the spinal cord, which was supported by similar findings in studies on astrocyte and microglia cultures [59].

Another phytochemical that may be active in arthropathies is B-element, which is present in Curcuma Wenyujin, a herb used in Traditional Chinese Medicine to treat rheumatoid arthritis. The inhibitory effect on the buildup of fibroblast-like synoviocytes may be explained by this compound's proliferative activity, which is helpful in neoplastic disorders. According to one in vitro investigation, the induction of apoptosis through elevated reactive oxygen species generation and p38 mitogen-activated protein kinase (MAPK) activation may be the underlying mechanism [60].

2.4. Equisetum arvense, fam. Equisetaceae

Equisetum arvense, commonly referred to as horsetail, has been used for centuries in European ethnomedicine as an anti-inflammatory treatment [61]. Research on animals has demonstrated that Equisetum giganteum has a downregulating effect on lymphocyte proliferation in an animal model of arthritis induced by an antigen challenge. The immunomodulatory action of this plant, which is free of cytotoxicity, affects both B and T lymphocytes [62].The salutary effect of horsetail in RA was substantiated by a study that refocused out the drop in TNF- α as one of the contributing mechanisms (63).

Active phytochemicals. Kynurenic acid was proposed as a apparent middleman of theanti-inflammatory and antalgic effect of several sauces salutary in RA, horsetail among them (64). Theanti-inflammatory eventuality of kynurenic acid was showed until now only innon-arthritic beast models (e.g., acute experimental colitis in rat) (65). Kynurenic acid is also an endogenous oxidative metabolite of tryptophan, with glutamate-receptor antagonist exertion, which may explain incompletely its analgesic parcels. One in vitro study showed that kynurenic acid is suitable to inhibit the proliferation of synoviocytes (66).Compared to human participants with OA, its level was significantly lower in RA

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 613-629 www.ijprajournal.com ISSN: 2456-4494

subjects [67], indicating the potential benefits of kynurenic acid supplementation for RA patients.

2.5. Harpagophytum procumbens, fam. Pedaliaceae

Customary wisdom. A "celebrity" among natural therapies for osteoarthritis, Harpagophytum procumbens (HP), often called devil's claw, is an African medicinal plant that has been approved by the German Commission E for the treatment of degenerative illnesses of the musculoskeletal system [68]. In vitro research. HP extracts demonstrated chondroprotective effect, which may be due to a number of mechanisms, including inhibition of matrix metalloproteinases and elastase and decreased generation of inflammatory mediators (such as TNF-α and interleukin-1β) [69].

Research on animals. At 5 and 10 mg/kg, a dried aqueous extract of HP has demonstrated a notable dose-dependent analgesic and anti-inflammatory effect in rats. However, the isolated harpagoside ingredient had no effect on paw oedema caused by carrageenan. This suggests that, at least at the dosage employed in this investigation, harpagoside may not have an anti-inflammatory effect [70,71]. This implies that the anti-inflammatory action might be caused by other HP components.

Clinical research on humans. The clinical picture of individuals with knee and hip osteoarthritis was considerably improved in terms of pain, movement limitation, and joint crepitus by a variety of HP tuber extracts (equivalent to 50–60 mg harpagoside daily, administered for a variable period between 8 and 16 weeks, depending on the study) according to several human clinical studies [72,73,74]. The WOMAC questionnaire, VAS, Lequesne Index, doctor's examination, and/or the dosage of painkillers were used to gauge the intensity of pain and other symptoms.

phytochemicals that are active. The iridoid glycosides (harpagoside, harpagide, and procumbide), which are more abundant in tubers and roots, are the main phytochemicals that have an anti-osteoarthritis action. However, it is important to note that extracts from the entire plant appear to have a more effective medicinal impact than those made from isolated portions [75]. Through the suppression of iNOS and COX-2 expression through the inhibition of NF-κB activation, harpagoside decreased the synthesis of several pro-inflammatory mediators in vitro [76]. However, in one animal model of inflammation (carrageenan-induced paw oedema) [70], it exhibited no anti-inflammatory efficacy. The experimenters hypothecated that HP'santi-inflammatory parcels might be attributed to phytochemicals other than harpagoside(70,77).

2.6. Panax notoginseng, fam. Araliaceae

Customary wisdom. For many years, Panax notoginseng (PN), sometimes referred to as sanqi in Chinese, has been used in medicine to heal severe injuries, aches, and swellings [78].

In vitro research. In vitro production of pro-inflammatory mediators (TNF-alpha, IL-1, inducible NOS, and MMP-13) was reduced by an n-butanol extract of PN [79]. Research on animals. By inhibiting the synthesis of TNF-alpha, IL-1, iNOS, and MMP-13, PN, when combined with two additional herbs (Rehmanniaglutinosa and Eleutherococcussenticosus), exhibited a suppressive impact on collagen-induced arthritis in mice [80].

clinical research on humans. In 57 patients with knee OA, the same combination of PN with Rehmanniaglutinosa and Eleutherococcussenticosus, given as 400 mg capsules every day for six weeks, improved physical function and pain as measured by the Korean version of the WOMAC questionnaire. Phytochemicals that are active. The primary osteo-active phytochemicals set up in PN are allowed to be saponins. In patients with RA, PN saponins increased the healing of autograft tendon in bone tunnel [81] and enhanced the effects of standard treatment (diclofenac sodium, leflunomide, and prednisone) on joint swelling, tenderness, and pain index, as well as morning stiffness, VAS, and immunological parameters [82].

2.7. Salix spp., fam. Salicaceae

Customary wisdom. Since they were first described in the Ebers papyrus (c. 1550 BC) [85] and later by all of the great medical masters of antiquity, the Middle Ages, and the contemporary day [86], several species of the genus Salix, or willow, were already widely used for pain treatment in antiquity [83,84]. In vitro research. The ability of willow bark extract (WBE) to counteract activated monocytes by inhibiting the activity of pro-inflammatory cytokines (TNFα), enzymes (COX-2), and mediators (NF-κB) is at least largely responsible for its ability to reduce inflammation [87]. Research on animals. Two beast models of arthritis, one acute and one habitual, were used to study the medium of WBE'santi-inflammatory exertion.

WBE was superior to acetylsalicylic acid(ASA) in loweringleukotriene situations and inhibiting COX-

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 613-629 www.ijprajournal.com ISSN: 2456-4494

2, and it was just as effective as ASA in lowering prostaglandin situations. It also reduced inflammatory infiltration and exudate and stopped the cytokine surge with a potency at least equal to ASA. More effectively than ASA or celecoxib (a specific COX-2 inhibitor), WBE had a positive impact on oxidative stress by raising GSH and lowering malondialdehyde levels. Even though WBE is more effective than ASA, its salicin content is significantly lower on a molar basis than ASA's salicylate content. This suggests that active principles other than salicin may contribute to WBE's anti-inflammatory and antioxidative action, with polyphenols being one potential candidate, at least in terms of protection against free radicals [88]. Another investigation on the collagen-induced arthritis animal model confirmed the capacity to reduce oxidative stress and pro-inflammatory cytokines [89]. Clinical research on humans. The English Reverend Edward Stone carried out the first clinical trial of aspirin in the 18th century, though it was uncontrolled and non-randomized. The good fellow was able to cure fever in 50 patients after being struck by the bitterness of aspirin, which was similar to quinine [86]. He also suspected that aspirin had antifebrile properties. Willow dinghy excerpt, at a cure of 240 mg salicin/ day, was shown in a two- week, double-eyeless, randomized, placebo-controlled study to be effective in controlling the symptoms of OA cases,, particularly in reducing pain, albeit with a somewhat muted effect [90]. In two additional six-week randomized, controlled, double-blind trials, patients with OA and RA, respectively, received the same dosage of willow bark extract. The herbal preparation was compared with a strong NSAID (diclofenac) and a placebo. In both trials, willow bark extract did not substantially outperform a placebo in terms of pain alleviation, which is a sobering finding [91]. Physicians and patients alike rated WBE as superior to conventional therapy in terms of both therapeutic efficacy and adverse effects when used for hip and knee degenerative disease in a six-week, open, multicentric observational research with reference treatment [92]. Higher doses should be investigated, according to a comprehensive analysis that found that WBE is effective in treating low back pain with intermediate evidence but insufficient data for OA and RA [84].

WBE was well tolerated and significantly reduced pain in 436 people with OA and back pain in lengthier (six-month) observational research [93]. Phytochemicals that are active. While salicin has historically been thought of as the active principle, some believe that other phytochemicals, such as polyphenols and flavonoids, which have demonstrated inhibitory activity on COX-2 and reduced the synthesis of pro-inflammatory mediators in vitro in human monocytes and differentiated macrophages, may be responsible for the full spectrum of effects of WBE [87,88,94,95,96].

2.8. Sesamum indicum, fam. Pedaliaceae

Customary wisdom. In several Asian traditional remedies, sesame oil (SO), which is derived from Sesamum indicum (SI), is used to relieve pain in inflammatory disorders of the skin, teeth, joints, etc. [97].

Research on animals. The physiological effects of oxidative stress, such as decreased plasmatic levels of thiobarbituric acid reactive compounds and decreased gamma-glutamyl transferase activity in the joints and spleen, were mitigated by SO in a rat model of adjuvant-induced arthritis (Freund's adjuvant) [98]. SO significantly reduced the inflammatory response in a rat model of acute gout-like arthritis by thinning the inflammatory infiltrate, lowering the levels of inflammatory mediators (TNF-α, IL-1β, and IL-6), blocking nuclear factor-κB (NF-κB) activity (at least in the mast cells), and activating the complement system [97]. By preventing oxidative aggression (a decrease in lipid peroxidation, superoxide anion and peroxynitrite production, and an increase in glutathione and glutathione peroxidase levels) in the muscles linked to nuclear factor erythroid-2-related factor, SO reduced joint pain in another rat model of OA [1]. Through its minor constituents (without these minor constituents, SO is inactive), SO is active in experimentally induced arthritis, reducing bone loss as well as clinically visible joint inflammation, serum markers (inflammatory eicosanoids, RA markers, oxidative stress related molecules, and cytokines), and the activity of hydrolytic enzymes [99]. Clinical research on humans. Oral administration of sesame combined with standard therapy yielded superior results in terms of objective and subjective signs than standard therapy alone in a study of individuals with knee OA [100]. After two months of treatment, the administration of sesame seeds was linked to a statistically significant decrease in the levels of high-sensitivity C-reactive protein (hs-CRP) and malondialdehyde in the serum of patients with knee OA in a placebo-controlled experiment. and, following therapy, markedly decreased IL-6 levels [101]. Phytochemicals that are active. The lignans

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 613-629 www.ijprajournal.com ISSN: 2456-4494

appear to be responsible for SI's capacity to defend against the harmful effects of oxidative stress and inflammation, including aging, cancer, and cardiovascular disease, to mention a few. Sesamin and sesamolin, its hydroxylated form, are present. Sesamol (3,4-methylene-dioxy-phenol), a phenolic molecule that is produced when sesamolin breaks down, shows comparable biological activity [102]. In an animal model of adjuvant-induced arthritis, sesamol has been shown to reduce periarticular bone resorption, cartilage deterioration, and joint inflammation. Pro-inflammatory cytokine levels and tissue-destructive enzyme activity decreased in tandem with this effect [103]. Furthermore, oxidant equilibrium was restored, as evidenced by a rise in protective enzyme activity and a drop in oxidative stress indicators [103]. Sesamol's ability to scavenge hydroperoxides allows it to stop iron's oxidation state and, as a result, the transformation of dormant LOX (Fe2+) into active LOX (Fe3+), which inhibits this enzyme that promotes inflammation [102].Sesamin has been shown to prevent cytokine-induced cartilage degeneration by slowing down the breakdown of constitutive glycosaminoglycans and collagen in a study on porcine cartilage explants exposed to the pro-inflammatory action of TNF-α and oncostatin M (as an animal RA model) [104].

2.9. Symphytum officinalis, fam. Boraginaceae

Customary wisdom. Comfrey, or Symphytum officinalis, is a medicinal plant that has long been used in Europe to treat inflammatory conditions [105,106]. In vitro research. Polymorphonuclear leukocytes' respiratory burst was markedly suppressed by a comfrey extract, indicating that it may have anti-inflammatory properties [107]. Research on animals. By preventing rat paw oedema caused by carrageenan, comfrey extracts demonstrated anti-inflammatory properties [108,109].

Clinical research on humans. According to a study on individuals with OA of the knee who were between the ages of 50 and 80, topically applied comfrey preparation reduced pain, but it was unable to slow down the rate of cartilage degradation or the burden of inflammatory molecules; the only obvious side effect was local rash [110].

Another study on a comparable sample of people who had been suffering from OA of the knee for years found that a comfrey-containing ointment enhanced their quality of life by reducing pain and boosting knee mobility [111]. Phytochemicals that are active. In a variety of in vitro models, phenolic acids (such as rosmarinic acid), glycopeptides, and amino acids are thought to be at least partially responsible for the anti-inflammatory properties of comfrey root extracts [108,112]. Rosmarinic acid prevented the production of prostaglandins and the aggregation of erythrocytes caused by gelatine and carrageenan [113].

2.10. Zingiber officinalis, fam. Zingiberaceae

Customary wisdom. Ginger, or Zingiber officinalis (ZO), is a prominent spice in Asian cooking and is utilized in ethnomedicine as a traditional treatment for joint ailments [48].

In vitro research. By blocking COX-1, COX-2, and LOX, ZO is believed to have anti-inflammatory properties [114,115,116]. However, the synthesis of pro-inflammatory cytokines (TNF-α, IL-6, and monocyte chemotactic protein-1) in RAW 264 cell culture was strangely boosted by the squeezed ginger extract [117]. Research on animals. Squeezed ginger extract administered orally had two effects on mice's peritoneal cells' production of TNF-α: ZO extract increased it at first, but after several administrations, it lowered it [117]. Furthermore, it raised the level of corticosterone in the blood, which could help explain why ZO has anti-inflammatory properties According to a number of other studies, ZO extract improved the clinical condition of OA patients as measured by their VAS pain score, decreased the need for rescue medication, had mainly mild gastrointestinal side effects, and had efficacy and satisfaction scores that were comparable to or better than those of the standard treatment recommended by the orthopedic specialist [119,120,121].clinical research on humans. According to a recent study, patients with knee OA who take ZO powder (1 g/day) for three months see a decrease in their serum levels of nitric oxide and high-sensitivity reactive protein (hs-CRP). After three weeks of treatment, the inflammatory markers began to decline [118]. According to a number of other studies, ZO extract improved the clinical condition of OA patients as measured by their VAS pain score, decreased the need for rescue medication, had mainly mild gastrointestinal side effects, and had efficacy and satisfaction scores that were comparable to or better than those of the standard treatment recommended by the orthopedic specialist [119,120,121]. According to a different study, 21 patients with confirmed knee and hip OA experienced significantly less arthritic pain when standing and moving after receiving 1000 mg of glucosamine and 340 mg of one ZO preparation

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 613-629 www.ijprajournal.com ISSN: 2456-4494

(EV.EXT 35 Zingiber officinalis extract) orally every day for four weeks. Furthermore, because this medication increased the levels of gastroprotective prostaglandins (PGE1, PGE2, and PGF2α) in the stomach mucosa and decreased gastrointestinal pain, it was more safe than diclofenac (100 mg/day) plus glucosamine (1000 mg/day) [122]. But in one cross-over research, which involved a one-week wash-out phase followed by three treatment periods of three weeks each, there was no discernible difference between ginger extract and a placebo in OA patients [123].

phytochemicals that are active. It was believed that pungent components of ZO contributed to this medicinal plant's anti-inflammatory properties. For example, 1-dehydro-[10]-gingerdione decreased NF-κB-regulated expression of inflammatory genes in lipopolysaccharide S-activated macrophages and inhibited κB kinase β activity necessary for NF-κB activation [124]. 6-Dehydrogingerdione reduced the expression of the genes for iNOS, COX-2, IL-1β, IL-6, and TNF-α in RAW 264.7 macrophages in vitro. [114]. In vitro, other ZO drugs (10-gingerol, 8-shogaol, and 10-shogaol) demonstrated the ability to reduce COX-2 activity [115].

2.11. Whitaniasomnifera, fam. Solanaceae

Ashwagandha, or Withaniasomnifera (WS), is a powerful anti-inflammatory and anti-osteoarthritic herb used in Ayurveda [125].In vitro. The WS extract was found to have no effect on the synthesis of IL-6, but it suppressed the production of pro-inflammatory cytokines (TNF-alpha, IL-1beta, and IL-12) in peripheral and synovial fluid mononuclear cells from rheumatoid arthritis sufferers when liposaccharyde S was present in vitro [126]. Additionally, the WS extract had inhibitory effects on collagenase activity against the breakdown of type I collagen in the bovine Achilles tendon, which could be helpful in the treatment of joint diseases [127].

research on animals. In rats with experimentally induced arthritis, WS root powder protected bone collagen [128].Clinical research on humans. The aqueous extract of WS significantly reduced pain, stiffness, and disability scores in human patients with knee joint discomfort, according to a randomized, double blind, placebo-controlled trial [129]. Phytochemicals that are active. One of the substances believed to contribute to the positive benefits of WS in OA individuals is withaferin A, a member of the steroid class of phytochemicals [126]. Mice with monosodium urate crystal-induced arthritis showed increases in paw volume, lysosomal enzymes, lipid peroxidation, and TNFα, but whitaferin A returned to almost normal levels [130]. According to molecular docking and molecular dynamics simulation studies, withaferin A suppresses NF-κB activation by inhibiting the formation of the NF-κB Essential Modulator/IκB kinase β association complex and by targeting a critical cysteine 179 in IκB kinase β [131,132].

III. CONCLUDING REMARKS

In patients with arthritis, a number of medicinal plant extracts demonstrated patterns of clinical and biochemical advantages with minimal risk of adverse effects, which call for additional research, including imaging and histological analysis. Due to variations in study design and technique, the pursuit of efficacious herbal supplements as a supplemental treatment for degenerative arthropathies is a complicated matter and entails a protracted process from which conclusions are challenging to draw [133]. The trials that are now available did not assess how plant extracts affect the course of the disease or whether they prevent arthropathies from getting worse. Longer-term studies ought to be conducted for this reason.

The biological mechanisms of herbal extracts found in vitro or in animal research have hardly been validated in humans, with most of the existing studies concentrating solely on assessing the clinical alleviation brought about by the herbal treatment.Despite their benefits, herbal remedies present a number of issues, including the potential for adulteration due to drug–herbal interactions, inadequate bioavailability, lack of standardization, and a lack of national and international regulatory requirements [134,135,136,137].

Before herbal treatments may be included in OA and RA therapy guidelines, more proof of the safety, effectiveness, and mechanisms of action of medicinal plants is required.

Author Contributions

As primary authors, Dorin Dragos and Marilena Gilca made equal contributions to this work. The following procedures were all completed by the authors: (1) the study's idea, literature search, and data collection; (2) the analysis and interpretation of the data gleaned from the literature; and (3) the creation of the manuscript draft and article revision. The final manuscript has been read and approved by all writers.

Conflicts of Interest

The authors declare no conflict of interest

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 613-629 www.ijprajournal.com ISSN: 2456-4494

REFERENCES

[1]. Hsu, D.-Z.; Chu, P.-Y.; Jou, I.-M. Daily sesame oil supplement attenuates joint pain by inhibiting muscular oxidative stress in osteoarthritis rat model. J. Nutr. Biochem. 2016, 29, 36–40. [Google Scholar] [CrossRef] [PubMed]

[2]. Park, S.-H.; Kim, S.-K.; Shin, I.-H.; Kim, H.-G.; Choe, J.-Y. Effects of AIF on Knee Osteoarthritis Patients: Double-blind, Randomized Placebo-controlled Study. Korean J. Physiol. Pharmacol. 2009, 13, 33–37. [Google Scholar] [CrossRef] [PubMed]

[3]. Peat, G.; McCarney, R.; Croft, P. Knee pain and osteoarthritis in older adults: A review of community burden and current use of primary health care. Ann. Rheum. Dis. 2001, 60, 91–97. [Google Scholar] [CrossRef] [PubMed]

[4]. McWilliams, D.F.; Leeb, B.F.; Muthuri, S.G.; Doherty, M.; Zhang, W. Occupational risk factors for osteoarthritis of the knee: A meta-analysis. Osteoarthr. Cartil. 2011, 19, 829–839. [Google Scholar] [CrossRef]

[5]. Smith, R.L.; Carter, D.R.; Schurman, D.J. Pressure and shear differentially alter human articular chondrocyte metabolism: A review. Clin. Orthop. Relat. Res. 2004, 427, S89–S95. [Google Scholar]

[6]. Murphy, N.J.; Eyles, J.P.; Hunter, D.J. Hip Osteoarthritis: Etiopathogenesis and Implications for Management. Adv. There. 2016, 33, 1921–1946. [Google Scholar] [CrossRef]

[7]. Dougados, M. Monitoring osteoarthritis progression and therapy. Osteoarthr. Cartil. 2004, 12 (Suppl. A), S55–S60. [Google Scholar] [CrossRef] [PubMed]

[8]. Lequesne, M.G.; Mery, C.; Samson, M.; Gerard, P. Indexes of severity for osteoarthritis of the hip and knee. Validation—Value in comparison with other assessment tests. Scand. J. Rheumatol. Suppl. 1987, 65, 85–89. [Google Scholar] [CrossRef] [PubMed]

[9]. Johnson, M.J.; Bland, J.M.; Davidson, P.M.; Newton, P.J.; Oxberry, S.G.; Abernethy, A.P.; Currow, D.C. The relationship between two performance scales: New York Heart Association Classification and Karnofsky Performance Status Scale. J. Pain Symptom Manag. 2014, 47, 652–658. [Google Scholar] [CrossRef] [PubMed]

[10]. Yang, C.L.H.; Or, T.C.T.; Ho, M.H.K.; Lau, A.S.Y. Scientific Basis of Botanical Medicine as Alternative Remedies for Rheumatoid Arthritis. Clin. Rev. Allergy Immunol. 2013, 44, 284–300. [Google Scholar] [CrossRef] [PubMed]

[11]. Smolen, J.S.; Landewe, R.; Breedveld, F.C.; Buch, M.; Burmester, G.; Dougados, M.; Emery, P.; Gaujoux-Viala, C.; Gossec, L.; Nam, J.; et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann. Rheum. Dis. 2014, 73, 492–509. [Google Scholar] [CrossRef] [PubMed] [Green Version]

[12]. Hochberg, M.C.; Altman, R.D.; April, K.T.; Benkhalti, M.; Guyatt, G.; McGowan, J.; Towheed, T.; Welch, V.; Wells, G.; Tugwell, P. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res. 2012, 64, 465–474. [Google Scholar] [CrossRef]

[13]. Hyrich, K.L.; Watson, K.D.; Silman, A.J.; Symmons, D.P.M. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register. Rheumatology 2006, 45, 1558–1565. [Google Scholar] [CrossRef] [PubMed]

[14]. Soliman, M.M.; Hyrich, K.L.; Lunt, M.; Watson, K.D.; Symmons, D.P.M.; Ashcroft, D.M. Effectiveness of rituximab in patients with rheumatoid arthritis: Observational study from the British Society for Rheumatology Biologics Register. J. Rheumatol. 2012, 39, 240–246. [Google Scholar] [CrossRef] [PubMed]

[15]. Cavalli, G.; Dinarello, C.A. Treating rheumatological diseases and co-morbidities with interleukin-1 blocking therapies. Rheumatology 2015, 54, 2134–2144. [Google Scholar] [CrossRef] [PubMed]

[16]. Nishina, N.; Kaneko, Y.; Kameda, H.; Kuwana, M.; Takeuchi, T. Reduction of

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 613-629 www.ijprajournal.com ISSN: 2456-4494

plasma IL-6 but not TNF-alpha by methotrexate in patients with early rheumatoid arthritis: A potential biomarker for radiographic progression. Clin. Rheumatol. 2013, 32, 1661–1666. [Google Scholar] [CrossRef] [PubMed]

[17]. Abdel-Tawab, M.; Werz, O.; Schubert-Zsilavecz, M. Boswellia serrata: An overall assessment of in vitro, preclinical, pharmacokinetic and clinical data. Clin. Pharmacokinet. 2011, 50, 349–369. [Google Scholar] [CrossRef] [PubMed]

[18]. McAlindon, T.E.; Bannuru, R.R.; Sullivan, M.C.; Arden, N.K.; Berenbaum, F.; Bierma-Zeinstra, S.M.; Hawker, G.A.; Henrotin, Y.; Hunter, D.J.; Kawaguchi, H.; et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthr. Cartil. 2014, 22, 363–388. [Google Scholar] [CrossRef] [PubMed]

[19]. Matucci, A.; Cammelli, D.; Cantini, F.; Goletti, D.; Marino, V.; Milano, G.M.; Scarpa, R.; Tocci, G.; Maggi, E.; Vultaggio, A. Influence of anti-TNF immunogenicity on safety in rheumatic disease: A narrative review. Expert Opin. Drug Saf. 2016, 15, 3–10. [Google Scholar] [CrossRef] [PubMed]

[20]. Cabral, V.P.; Andrade, C.A.; Passos, S.R.; Martins, M.F.; Hökerberg, Y.H. Severe infection in patients with rheumatoid arthritis taking anakinra, rituximab, or abatacept: A systematic review of observational studies. Rev. Bras. Reumatol. 2016, 56, 543–550. [Google Scholar] [CrossRef] [PubMed]

[21]. Mameli, A.; Barcellona, D.; Marongiu, F. Fatal Cytopenia Induced by Low-Dose Methotrexate in Elderly With Rheumatoid Arthritis. Identification of Risk Factors. Am. J. Ther. 2017, 24, e106–e107. [Google Scholar] [CrossRef]

[22]. Umar, S.; Umar, K.; Sarwar, A.H.M.G.; Khan, A.; Ahmad, N.; Ahmad, S.; Katiyar, C.K.; Husain, S.A.; Khan, H.A. Boswellia serrata extract attenuates inflammatory mediators and oxidative stress in collagen induced arthritis. Phytomedicine 2014, 21, 847–856. [Google Scholar] [CrossRef]

[23]. Akhtar, N.; Miller, M.J.; Haqqi, T.M. Effect of a Herbal-Leucine mix on the IL-1β-induced cartilage degradation and inflammatory gene expression in human chondrocytes. BMC Complement. Altern. Med. 2011, 11, 66. [Google Scholar] [CrossRef] [PubMed]

[24]. Sharma, S.; Arif, M.; Nirala, R.K.; Gupta, R.; Thakur, S.C. Cumulative therapeutic effects of phytochemicals in Arnica montana flower extract alleviated collagen-induced arthritis: Inhibition of both pro-inflammatory mediators and oxidative stress. J. Sci. Food Agric. 2016, 96, 1500–1510. [Google Scholar] [CrossRef] [PubMed]

[25]. Álvarez-Hernández, E.; César Casasola-Vargas, J.; Lino-Pérez, L.; Burgos-Vargas, R.; Vázquez-Mellado, J. Frecuencia de uso de medicinascomplementarias y alternativasensujetos que acudenporprimeravez al servicio de reumatología. Análisis de 800 casos. Reumatol. Clín. 2006, 2, 183–189. [Google Scholar] [CrossRef]

[26]. Knuesel, O.; Weber, M.; Suter, A. Arnica montana gel in osteoarthritis of the knee: An open, multicenter clinical trial. Adv. Ther. 2002, 19, 209–218. [Google Scholar] [CrossRef] [PubMed]

[27]. Widrig, R.; Suter, A.; Saller, R.; Melzer, J. Choosing between NSAID and Arnica for topical treatment of hand osteoarthritis in a randomised, double-blind study. Rheumatol. Int. 2007, 27, 585–591. [Google Scholar] [CrossRef]

[28]. Ross, S.M. Osteoarthritis. Holist. Nurs. Pract. 2008, 22, 237–239. [Google Scholar] [CrossRef] [PubMed]

[29]. Cameron, M.; Chrubasik, S. Topical herbal therapies for treating osteoarthritis. CDSR 2013, 2013, CD010538. [Google Scholar] [CrossRef]

[30]. Ammon, H.P.T. Boswellic acids (components of frankincense) as the active principle in treatment of chronic inflammatory diseases. Wien. Med. Wochenschr. 2002, 152, 373–378. (In German) [Google Scholar] [CrossRef] [PubMed]

[31]. Sengupta, K.; Krishnaraju, A.V.; Vishal, A.A.; Mishra, A.; Trimurtulu, G.; Sarma, K.V.S.; Raychaudhuri, S.K.; Raychaudhuri, S.P. Comparative efficacy and tolerability of 5-Loxin and AflapinAgainst osteoarthritis of the knee: A double blind, randomized, placebo controlled clinical study. Int. J. Med. Sci. 2010, 7, 366–377. [Google Scholar] [CrossRef] [PubMed]

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 613-629 www.ijprajournal.com ISSN: 2456-4494

[32]. Blain, E.J.; Ali, A.Y.; Duance, V.C. Boswellia frereana (frankincense) suppresses cytokine-induced matrix metalloproteinase expression and production of pro-inflammatory molecules in articular cartilage. Phyther. Res. 2009, 24, 905–912. [Google Scholar] [CrossRef] [PubMed]

[33]. Sumantran, V.N.; Joshi, A.K.; Boddul, S.; Koppikar, S.J.; Warude, D.; Patwardhan, B.; Chopra, A.; Chandwaskar, R.; Wagh, U.V. Antiarthritic Activity of a Standardized, Multiherbal, Ayurvedic Formulation containing Boswellia serrata: In Vitro Studies on Knee Cartilage from Osteoarthritis Patients. Phyther. Res. 2011, 25, 1375–1380. [Google Scholar] [CrossRef] [PubMed]

[34]. Dey, D.; Chaskar, S.; Athavale, N.; Chitre, D. Inhibition of LPS-Induced TNF-α and NO Production in Mouse Macrophage and Inflammatory Response in Rat Animal Models by a Novel Ayurvedic Formulation, BV-9238. Phyther. Res. 2014, 28, 1479–1485. [Google Scholar] [CrossRef]

[35]. Cameron, M.; Chrubasik, S. Oral herbal therapies for treating osteoarthritis. CDSR 2014, 2014, CD002947. [Google Scholar] [CrossRef]

[36]. Vishal, A.A.; Mishra, A.; Raychaudhuri, S.P. A double blind, randomized, placebo controlled clinical study evaluates the early efficacy of aflapin in subjects with osteoarthritis of knee. Int. J. Med. Sci. 2011, 8, 615–622. [Google Scholar] [CrossRef] [PubMed]

[37]. Belcaro, G.; Dugall, M.; Luzzi, R.; Ledda, A.; Pellegrini, L.; Cesarone, M.R.; Hosoi, M.; Errichi, M.; Francis, S.; Cornelli, U. FlexiQule (Boswellia extract) in the supplementary management of osteoarthritis: A supplement registry. Minerva Med. 2014, 105, 9–16. [Google Scholar]

[38]. Belcaro, G.; Feragalli, B.; Cornelli, U.; Dugall, M. Hand "stress" arthritis in young subjects: Effects of Flexiqule (pharma-standard Boswellia extract). A preliminary case report. Minerva Gastroenterol. Dietol. 2015, in press. [Google Scholar]

[39]. Kizhakkedath, R. Clinical evaluation of a formulation containing Curcuma longa and Boswellia serrata extracts in the management of knee osteoarthritis. Mol. Med. Rep. 2013, 8, 1542–1548. [Google Scholar] [CrossRef] [PubMed]

[40]. Sander, O.; Herborn, G.; Rau, R. Is H15 (resin extract of Boswellia serrata, "incense") a useful supplement to established drug therapy of chronic polyarthritis? Results of a double-blind pilot study. Z. Rheumatol. 1998, 57, 11–16. [Google Scholar] [CrossRef] [PubMed]

[41]. Wang, H.; Zhang, C.; Wu, Y.; Ai, Y.; Lee, D.Y.-W.; Dai, R. Comparative pharmacokinetic study of two boswellic acids in normal and arthritic rat plasma after oral administration of Boswellia serrata extract or Huo Luo Xiao Ling Dan by LC-MS. Biomed. Chromatogr. 2014, 28, 1402–1408. [Google Scholar] [CrossRef] [PubMed]

[42]. Hamidpour, R.; Hamidpour, S.; Hamidpour, M.; Shahlari, M. Frankincense (RǔXiāng; Boswellia Species): From the Selection of Traditional Applications to the Novel Phytotherapy for the Prevention and Treatment of Serious Diseases. J. Tradit. Complement. Med. 2013, 3, 221–226. [Google Scholar] [CrossRef] [PubMed]

[43]. Sharma, M.L.; Bani, S.; Singh, G.B. Anti-arthritic activity of boswellic acids in bovine serum albumin (BSA)-induced arthritis. Int. J. Immunopharmacol. 1989, 11, 647–652. [Google Scholar] [CrossRef]

[44]. Singh, S.; Khajuria, A.; Taneja, S.C.; Johri, R.K.; Singh, J.; Qazi, G.N. Boswellic acids: A leukotriene inhibitor also effective through topical application in inflammatory disorders. Phytomedicine 2008, 15, 400–407. [Google Scholar] [CrossRef] [PubMed]

[45]. Ammon, H.P.T. Modulation of the immune system by Boswellia serrata extracts and boswellic acids. Phytomedicine 2010, 17, 862–867. [Google Scholar] [CrossRef] [PubMed]

[46]. Khajuria, A.; Gupta, A.; Suden, P.; Singh, S.; Malik, F.; Singh, J.; Gupta, B.D.; Suri, K.A.; Srinivas, V.K.; Ella, K.; et al. Immunomodulatory activity of biopolymeric fraction BOS 2000 from Boswellia serrata. Phyther. Res. 2008, 22, 340–348. [Google Scholar] [CrossRef] [PubMed]

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 613-629 www.ijprajournal.com ISSN: 2456-4494

[47]. Sengupta, K.; Kolla, J.N.; Krishnaraju, A.V.; Yalamanchili, N.; Rao, C.V.; Golakoti, T.; Raychaudhuri, S.; Raychaudhuri, S.P. Cellular and molecular mechanisms of anti-inflammatory effect of Aflapin: A novel Boswellia serrata extract. Mol. Cell. Biochem. 2011, 354, 189–197. [Google Scholar] [CrossRef] [PubMed]

[48]. Sharma, R.; Dash, B. Caraka Samhita, 2006th ed.; Chowkhamba Sanskrit Series Office: Varanasi, India, 2006. [Google Scholar]

[49]. Funk, J.L.; Frye, J.B.; Oyarzo, J.N.; Kuscuoglu, N.; Wilson, J.; McCaffrey, G.; Stafford, G.; Chen, G.; Lantz, R.C.; Jolad, S.D.; et al. Efficacy and mechanism of action of turmeric supplements in the treatment of experimental arthritis. Arthritis Rheum. 2006, 54, 3452–3464. [Google Scholar] [CrossRef] [PubMed]

[50]. Taty Anna, K.; Elvy Suhana, M.R.; Das, S.; Faizah, O.; Hamzaini, A.H. Anti-inflammatory effect of Curcuma longa (turmeric) on collagen-induced arthritis: An anatomico-radiological study. Clin. Ter. 2011, 162, 201–207. [Google Scholar] [PubMed]

[51]. Kamarudin, T.A.; Othman, F.; Mohd Ramli, E.S.; Md Isa, N.; Das, S. Protective effect of curcumin on experimentally induced arthritic rats: Detailed histopathological study of the joints and white blood cell count. EXCLI J. 2012, 11, 226–236. [Google Scholar] [PubMed]

[52]. Chang, H.-I.; Su, Y.-H.; Lin, Y.-J.; Chen, P.-J.; Shi, C.-S.; Chen, C.-N.; Yeh, C.-C. Evaluation of the protective effects of curcuminoid (curcumin and bisdemethoxycurcumin)-loaded liposomes against bone turnover in a cell-based model of osteoarthritis. Drug Des. Dev. Ther. 2015, 9, 2285–2300. [Google Scholar] [CrossRef] [PubMed]

[53]. Ramadan, G.; El-Menshawy, O. Protective effects of ginger-turmeric rhizomes mixture on joint inflammation, atherogenesis, kidney dysfunction and other complications in a rat model of human rheumatoid arthritis. Int. J. Rheum. Dis. 2013, 16, 219–229. [Google Scholar] [CrossRef] [PubMed]

[54]. Kuptniratsaikul, V.; Dajpratham, P.; Taechaarpornkul, W.; Buntragulpoontawee, M.;

[55]. Lukkanapichonchut, P.; Chootip, C.; Saengsuwan, J.; Tantayakom, K.; Laongpech, S. Efficacy and safety of Curcuma domestica extracts compared with ibuprofen in patients with knee osteoarthritis: A multicenter study. Clin. Interv. Aging 2014, 9, 451–458. [Google Scholar] [CrossRef] [PubMed]

[56]. Daily, J.W.; Yang, M.; Park, S. Efficacy of Turmeric Extracts and Curcumin for Alleviating the Symptoms of Joint Arthritis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. J. Med. Food 2016, 19, 717–729. [Google Scholar] [CrossRef] [PubMed]

[57]. Ghosh, S.; Banerjee, S.; Sil, P.C. The beneficial role of curcumin on inflammation, diabetes and neurodegenerative disease: A recent update. Food Chem. Toxicol. 2015, 83, 111–124. [Google Scholar] [CrossRef] [PubMed]

[58]. Nonose, N.; Pereira, J.A.; Machado, P.R.M.; Rodrigues, M.R.; Sato, D.T.; Martinez, C.A.R. Oral administration of curcumin (Curcuma longa) can attenuate the neutrophil inflammatory response in zymosan-induced arthritis in rats. Acta Cir. Bras. 2014, 29, 727–734. [Google Scholar] [CrossRef] [PubMed]

[59]. Panahi, Y.; Alishiri, G.H.; Parvin, S.; Sahebkar, A. Mitigation of Systemic Oxidative Stress by Curcuminoids in Osteoarthritis: Results of a Randomized Controlled Trial. J. Diet. Suppl. 2016, 13, 209–220. [Google Scholar] [CrossRef] [PubMed]

[60]. Chen, J.-J.; Dai, L.; Zhao, L.-X.; Zhu, X.; Cao, S.; Gao, Y.-J. Intrathecal curcumin attenuates pain hypersensitivity and decreases spinal neuroinflammation in rat model of monoarthritis. Sci. Rep. 2015, 5, 10278. [Google Scholar] [CrossRef]

[61]. Zou, S.; Wang, C.; Cui, Z.; Guo, P.; Meng, Q.; Shi, X.; Gao, Y.; Yang, G.; Han, Z. β-Elemene induces apoptosis of human rheumatoid arthritis fibroblast-like synoviocytes via reactive oxygen species-dependent activation of p38 mitogen-activated protein kinase. Pharmacol. Rep. 2016, 68, 7–11. [Google Scholar] [CrossRef]

[62]. Gründemann, C.; Lengen, K.; Sauer, B.; Garcia-Käufer, M.; Zehl, M.; Huber, R. Equisetum arvense (common horsetail)

modulates the function of inflammatory immunocompetent cells. BMC Complement. Altern. Med. 2014, 14, 283. [Google Scholar] [CrossRef]

[63]. Farinon, M.; Lora, P.S.; Francescato, L.N.; Bassani, V.L.; Henriques, A.T.; Xavier, R.M.; de Oliveira, P.G. Effect of Aqueous Extract of Giant Horsetail (Equisetum giganteum L.) in Antigen-Induced Arthritis. Open Rheumatol. J. 2013, 7, 129–133. [Google Scholar] [CrossRef] [PubMed]

[64]. Jiang, X.; Qu, Q.; Li, M.; Miao, S.; Li, X.; Cai, W. Horsetail mixture on rheumatoid arthritis and its regulation on TNF-α and IL-10. Pak. J. Pharm. Sci. 2014, 27, 2019–2023. [Google Scholar] [PubMed]

[65]. Zgrajka, W.; Turska, M.; Rajtar, G.; Majdan, M.; Parada-Turska, J. Kynurenic acid content in anti-rheumatic herbs. Ann. Agric. Environ. Med. 2013, 20, 800–802. [Google Scholar] [PubMed]

[66]. Varga, G.; Erces, D.; Fazekas, B.; Fulop, M.; Kovacs, T.; Kaszaki, J.; Fulop, F.; Vecsei, L.; Boros, M. N-Methyl-D-aspartate receptor antagonism decreases motility and inflammatory activation in the early phase of acute experimental colitis in the rat. Neurogastroenterol. Motil. 2010, 22, 217–225. [Google Scholar] [CrossRef] [PubMed]

[67]. Parada-Turska, J.; Rzeski, W.; Zgrajka, W.; Majdan, M.; Kandefer-Szerszen, M.; Turski, W. Kynurenic acid, an endogenous constituent of rheumatoid arthritis synovial fluid, inhibits proliferation of synoviocytes in vitro. Rheumatol. Int. 2006, 26, 422–426. [Google Scholar] [CrossRef]

[68]. Parada-Turska, J.; Zgrajka, W.; Majdan, M. Kynurenic acid in synovial fluid and serum of patients with rheumatoid arthritis, spondyloarthropathy, and osteoarthritis. J. Rheumatol. 2013, 40, 903–909. [Google Scholar] [CrossRef] [PubMed]

[69]. Blumenthal, M.; Busse, W.R. The Complete German Commission E Monographs; American Botanical Council: Austin, TX, USA, 1998. [Google Scholar]

[70]. Fiebich, B.; Heinrich, M.; Hiller, K.; Kammerer, N. Inhibition of TNF-α synthesis in LPS-stimulated primary human monocytes by Harpagophytum extract SteiHap 69. Phytomedicine 2001, 8, 28–30. [Google Scholar] [CrossRef]

[71]. Lanhers, M.; Fleurentin, J.; Mortier, F.; Al, E. Antiinflammatory and analgesic effects of an aqueous extract of Harpagophytum procumbens. Planta Med. 1992, 58, 117–123. [Google Scholar] [CrossRef] [PubMed]

[72]. Akhtar, N.; Haqqi, T.M. Current nutraceuticals in the management of osteoarthritis: A review. Ther. Adv. Musculoskelet. Dis. 2012, 4, 181–207. [Google Scholar] [CrossRef] [PubMed]

[73]. Wegener, T.; Lupke, N. Treatment of patients with arthrosis of hip or knee with an aqueous extract of devil's claw (Harpagophytum procumbens DC.). Phytother. Res. 2003, 17, 1165–1172. [Google Scholar] [CrossRef] [PubMed]

[74]. Chantre, P.; Cappelaere, A.; Leblan, D.; Al, E. Efficacy and tolerance of Harpagophytum procumbens versus diacerhein in treatment of osteoarthritis. Phytomedicine 2000, 7, 177–183. [Google Scholar] [CrossRef]

[75]. Chrubasik, S.; Thanner, J.; Kunzel, O.; Al, E. Comparison of outcome measures during treatment with the proprietary Harpagophytum extract Doloteffin in patients with pain in the lower back, knee, or hip. Phytomedicine 2002, 9, 181–194. [Google Scholar] [CrossRef] [PubMed]

[76]. Harpagophytum procumbens (devil's claw). Monograph. Altern. Med. Rev. 2008, 13, 248–252.

[77]. Huang, T.H.-W.; Tran, V.H.; Duke, R.K.; Tan, S.; Chrubasik, S.; Roufogalis, B.D.; Duke, C.C. Harpagoside suppresses lipopolysaccharide-induced iNOS and COX-2 expression through inhibition of NF-κB activation. J. Ethnopharmacol. 2006, 104, 149–155. [Google Scholar] [CrossRef] [PubMed]

[78]. Kaszkin, M.; Beck, K.; Koch, E.; Al, E. Downregulation of iNOS expression in rat mesangial cells by special extracts of Harpagophytum procumbens derives from harpagoside-dependent and independent effects. Phytomedicine 2004, 11, 585–595. [Google Scholar] [CrossRef]

[79]. Liu, Z.; Liu, L. Essentials of Chinese Medicine; Liu, Z., Liu, L., Eds.; Springer: London, UK, 2009. [Google Scholar]

[80]. Chang, S.-H.; Choi, Y.; Park, J.-A.; Jung, D.-S.; Shin, J.; Yang, J.-H.; Ko, S.-Y.;

Kim, S.-W.; Kim, J.-K. Anti-inflammatory effects of BT-201, an n-butanol extract of Panax notoginseng, observed in vitro and in a collagen-induced arthritis model. Clin. Nutr. 2007, 26, 785–791. [Google Scholar] [CrossRef] [PubMed]

[81]. Chang, S.-H.; Sung, H.-C.; Choi, Y.; Ko, S.-Y.; Lee, B.-E.; Baek, D.-H.; Kim, S.-W.; Kim, J.-K. Suppressive effect of AIF, a water extract from three herbs, on collagen-induced arthritis in mice. Int. Immunopharmacol. 2005, 5, 1365–1372. [Google Scholar] [CrossRef] [PubMed]

[82]. Zhang, L.; Li, Z.; Sun, J.; Ma, J.; Zhang, S.; Liu, J.; Zhu, J. Effect of Panax Notoginseng Saponins on autograft tendon healing in bone tunnel: Interface histological characteristics. Zhongguo Gu Shang 2011, 24, 132–136. [Google Scholar] [PubMed]

[83]. Zhang, J.; Wang, J.; Wang, H. Clinical study on effect of total Panax notoginseng saponins on immune related inner environment imbalance in rheumatoid arthritis patients. Zhongguo Zhong Xi Yi Jie He Za Zhi/Chin. J. Integr. Tradit. West. Med. 2007, 27, 589–592. [Google Scholar]

[84]. Appelboom, T. Arthropathy in art and the history of pain management—Through the centuries to cyclooxygenase-2 inhibitors. Rheumatology 2002, 41 (Suppl. 1), 28–34. [Google Scholar] [CrossRef] [PubMed]

[85]. Vlachojannis, J.E.; Cameron, M.; Chrubasik, S. A systematic review on the effectiveness of willow bark for musculoskeletal pain. Phyther. Res. 2009, 23, 897–900. [Google Scholar] [CrossRef] [PubMed]

[86]. Mackowiak, P.A. Brief History of Antipyretic Therapy. Clin. Infect. Dis. 2000, 31, S154–S156. [Google Scholar] [CrossRef]

[87]. Vane, J.R. The fight against rheumatism: From willow bark to COX-1 sparing drugs. J. Physiol. Pharmacol. 2000, 51, 573–586. [Google Scholar] [PubMed]

[88]. Bonaterra, G.A.; Heinrich, E.U.; Kelber, O.; Weiser, D.; Metz, J.; Kinscherf, R. Anti-inflammatory effects of the willow bark extract STW 33-I (Proaktiv®) in LPS-activated human monocytes and differentiated macrophages. Phytomedicine 2010, 17, 1106–1113. [Google Scholar] [CrossRef] [PubMed]

[89]. Khayyal, M.; El-Ghazaly, M.; Abdallah, D.; Okpanyi, S.; Kelber, O.; Weiser, D. Mechanisms Involved in the Anti-inflammatory Effect of a Standardized Willow Bark Extract. Arzneimittelforschung 2011, 55, 677–687. [Google Scholar] [CrossRef] [PubMed]

[90]. Sharma, S.; Sahu, D.; Das, H.R.; Sharma, D. Amelioration of collagen-induced arthritis by Salix nigra bark extract via suppression of pro-inflammatory cytokines and oxidative stress. Food Chem. Toxicol. 2011, 49, 3395–3406. [Google Scholar] [CrossRef] [PubMed]

[91]. Schmid, B.; Lüdtke, R.; Selbmann, H.K.; Kötter, I.; Tschirdewahn, B.; Schaffner, W.; Heide, L. Efficacy and tolerability of a standardized willow bark extract in patients with osteoarthritis: Randomized placebo-controlled, double blind clinical trial. Phytother. Res. 2001, 15, 344–3

[92]. Biegert, C.; Wagner, I.; Lüdtke, R.; Kötter, I.; Lohmüller, C.; Günaydin, I.; Taxis, K.; Heide, L. Efficacy and safety of willow bark extract in the treatment of osteoarthritis and rheumatoid arthritis: Results of 2 randomized double-blind controlled trials. J. Rheumatol. 2004, 31, 2121–2130. [Google Scholar]

[93]. Beer, A.-M.; Wegener, T. Willow bark extract (Salicis cortex) for gonarthrosis and coxarthrosis—Results of a cohort study with a control group. Phytomedicine 2008, 15, 907–913. [Google Scholar] [CrossRef] [PubMed]

[94]. Uehleke, B.; Müller, J.; Stange, R.; Kelber, O.; Melzer, J. Willow bark extract STW 33-I in the long-term treatment of outpatients with rheumatic pain mainly osteoarthritis or back pain. Phytomedicine 2013, 20, 980–984. [Google Scholar] [CrossRef] [PubMed]

[95]. Nahrstedt, A.; Schmidt, M.; Jäggi, R.; Metz, J.; Khayyal, M.T. Willow bark extract: The contribution of polyphenols to the overall effect. Wien. Med. Wochenschr. 2007, 157, 348–351. [Google Scholar] [CrossRef] [PubMed]

[96]. Drummond, E.M.; Harbourne, N.; Marete, E.; Martyn, D.; Jacquier, J.; O'Riordan, D.; Gibney, E.R. Inhibition of Proinflammatory Biomarkers in THP1 Macrophages by Polyphenols Derived From Chamomile, Meadowsweet and Willow bark. Phyther. Res. 2013, 27, 588–

594. [Google Scholar] [CrossRef] [PubMed]
[97]. Shara, M.; Stohs, S.J. Efficacy and Safety of White Willow Bark (Salix alba) Extracts. Phyther. Res. 2015, 29, 1112–1116. [Google Scholar] [CrossRef] [PubMed]
[98]. Hsu, D.-Z.; Chen, S.-J.; Chu, P.-Y.; Liu, M.-Y. Therapeutic effects of sesame oil on monosodium urate crystal-induced acute inflammatory response in rats. Springerplus 2013, 2,659. [Google Scholar] [CrossRef] [PubMed]
[99]. Sotnikova, R.; Ponist, S.; Navarova, J.; Mihalova, D.; Tomekova, V.; Strosova, M.; Bauerova, K. Effects of sesame oil in the model of adjuvant arthritis. Neuro Endocrinol. Lett. 2009, 30 (Suppl. 1), 22–24. [Google Scholar]
[100]. Yadav, N.V.; Sadashivaiah; Ramaiyan, B.; Acharya, P.; Belur, L.; Talahalli, R.R. Sesame Oil and Rice Bran Oil Ameliorates Adjuvant-Induced Arthritis in Rats: Distinguishing the Role of Minor Components and Fatty Acids. Lipids 2016, 51, 1385–1395. [Google Scholar] [CrossRef] [PubMed]
[101]. Eftekhar Sadat, B.; Khadem Haghighian, M.; Alipoor, B.; Malek Mahdavi, A.; Asghari Jafarabadi, M.; Moghaddam, A. Effects of sesame seed supplementation on clinical signs and symptoms in patients with knee osteoarthritis. Int. J. Rheum. Dis. 2013, 16, 578–582. [Google Scholar] [CrossRef] [PubMed]
[102]. Khadem Haghighian, M.; Alipoor, B.; Malek Mahdavi, A.; Eftekhar Sadat, B.; Asghari Jafarabadi, M.; Moghaddam, A. Effects of sesame seed supplementation on inflammatory factors and oxidative stress biomarkers in patients with knee osteoarthritis. Acta Med. Iran. 2015, 53, 207–213. [Google Scholar] [PubMed]
[103]. Yashaswini, P.S.; Rao, A.G.A.; Singh, S.A. Inhibition of lipoxygenase by sesamol corroborates its potential anti-inflammatory activity. Int. J. Biol. Macromol. 2017, 94, 781–787. [Google Scholar] [CrossRef] [PubMed]
[104]. Hemshekhar, M.; Thushara, R.M.; Jnaneshwari, S.; Devaraja, S.; Kemparaju, K.; Girish,K.S. Attenuation of adjuvant-induced arthritis by dietary sesamol via modulation of inflammatory mediators, extracellular matrix degrading enzymes and antioxidant status. Eur. J. Nutr. 2013, 52, 1787–1799. [Google Scholar] [CrossRef] [PubMed]
[105]. Khansai, M.; Boonmaleerat, K.; Pothacharoen, P.; Phitak, T.; Kongtawelert, P. Ex vivo model exhibits protective effects of sesamin against destruction of cartilage induced with a combination of tumor necrosis factor-alpha and oncostatin M. BMC Complement. Altern. Med. 2016, [GooglScholar] [CrossRef] [PubMed]
[106]. Cavero, R.Y.; Calvo, M.I. Medicinal plants used formusculoskeletal disorders in Navarra and theirpharmacological validation. J.Ethnopharmacol. 2015, 168, 255–259. [Google Scholar] [CrossRef] [PubMed]
[107]. Di Lorenzo, C.; Dell'Agli, M.; Badea, M.; Dima, L.;Colombo, E.; Sangiovanni, E.; Restani, P.; Bosisio,E. Plant food supplements with anti-inflammatory properties: A systematic review (II). Crit. Rev. Food Sci. Nutr. 2013, 53, 507–516. [Google Scholar] [CrossRef] [PubMed]
[108]. Gilca, M.; Gaman, L.; Lixandru, D.; Stoian, I. Estimating the yin-yang nature of Western herbs: A potential tool based on antioxidation-oxidation theory. Afr. J. Tradit. Complement. Altern.Med. 2014, 11, 210–216. [Google Scholar] [CrossRef] [PubMed]
[109]. Hiermann, A.; Writzel, M. Antiphlogistic glycopeptide from the roots of Symphytum officinale. Pharm. Pharmacol. Lett. 1998, 8, 154–157. [Google Scholar]
[110]. Mascolo, N.; Autore, G.; Capasso, F.; Menghini, A.; Fasulo, M.P. Biological screening of Italian medicinal plants for anti-inflammatory activity. Phyther.\Res. 1987, 1, 28–31. [Google
[111]. Scholar] [CrossRef]
[112]. Laslett, L.L.; Quinn, S.J.; Darian-Smith, E.; Kwok,M.; Fedorova, T.; Körner, H.; Steels, E.; March, L.; Jones, G. Treatment with 4Jointz reduces knee pain over 12 weeks of treatment patients with clinical knee osteoarthritis: A randomised controlled trial. Osteoarthr. Cartil. 2012, 20, 1209–1216. [Google Scholar] [CrossRef] [PubMed]
[113]. Grube, B.; Grünwald, J.; Krug, L.; Staiger, C. Efficacy of a comfrey root (Symphytioffic. radix) extract ointment in the treatment of patients with painful

osteoarthritis of the knee: Results of a doubleblind, randomised, bicenter, placebo-controlled trial. Phytomedicine 2007, 14, 2–10. [Google Scholar] [CrossRef] [PubMed]

[114]. Gracza, L.; Koch, H.; Loffler, E. Biochemicalpharmacologic studies of medicinal plants. 1.

[115]. Isolation of rosmarinic acid from Symphytum officinale L. and its anti-inflammatory activity in anin vitro model. Arch. Pharm. 1985, 318, 1090–1095. [Google Scholar] [CrossRef]

[116]. Gracza, L. Prüfung der membranabdichtendenWirkungeinesPhyto pharmakons und dessen

[117]. Wirkstoffe. Z. Phytother. 1987, 8, 78–81. [Google Scholar]

[118]. Huang, S.-H.; Lee, C.-H.; Wang, H.-M.; Chang, Y.- W.; Lin, C.-Y.; Chen, C.-Y.; Chen, Y.-H. 6-Dehydrogingerdione restrains lipopolysaccharideinduced inflammatory responses in RAW 264.7macrophages. J. Agric. Food Chem. 2014, 62, 9171–9179. [Google Scholar] [CrossRef] [PubMed]

[119]. Van Breemen, R.B.; Tao, Y.; Li, W.Cyclooxygenase-2 inhibitors in ginger (Zingiber officinale). Fitoterapia 2011, 82, 38–43. [Google Scholar] [CrossRef] [PubMed]

[120]. Grzanna, R.; Lindmark, L.; Frondoza, C.G. Ginger— An herbal medicinal product with broad anti-inflammatory actions. J. Med. Food 2005, 8, 125–132. [Google Scholar] [CrossRef] [PubMed]

[121]. Ueda, H.; Ippoushi, K.; Takeuchi, A. Repeated oral administration of a squeezed ginger (Zingiber officinale) extract augmented the serum corticosterone level and had anti-inflammatory properties. Biosci. Biotechnol. Biochem. 2010, 74,2248–2252. [Google Scholar] [CrossRef]

[122]. [PubMed]

[123]. Naderi, Z.; Mozaffari-Khosravi, H.; Dehghan, A.;Nadjarzadeh, A.; Huseini, H.F. Effect of ginger powder supplementation on nitric oxide and Creactive protein in elderly kneeosteoarthritis patients: A 12-week double-blind randomized placebo controlled clinical trial. J.Tradit. Complement. Med. 2016, 6, 199–203. [Google Scholar] [CrossRef]

[124]. Altman, R.D.; Marcussen, K.C. Effects of a ginger extract on knee pain in patients with

[125]. osteoarthritis. Arthritis Rheum. 2001, 44, 2531–2538.[Google Scholar] [CrossRef]

[126]. Alipour, Z.; Asadizaker, M.; Fayazi, S.; Yegane, N.;Kochak, M.; Haghighi Zadeh, M.H. The Effect of Ginger on Pain and Satisfaction of Patients withKnee Osteoarthritis. Jundishapur J. Chronic Dis. Care 2016, 6, e34798. [Google Scholar] [CrossRef]

[127]. Haghighi, M.; Khalvat, A.; Toliat, T.; Jallaei, S. Comparing the effects of ginger extract and ibuprofen in patients with osteoporosis. Arch. Iran. Med. 2005, 8, 267–271. [Google Scholar]

[128]. Drozdov, V.N.; Kim, V.A.; Tkachenko, E.V.;Varvanina, G.G. Influence of a specific ginger combination on gastropathy conditions in patients with osteoarthritis of the knee or hip. J. Altern.

[129]. Complement. Med. 2012, 18, 583–588. [Google Scholar] [CrossRef] [PubMed]

[130]. Bliddal, H.; Rosetzsky, A.; Schlichting, P.; Weidner, M.S.; Andersen, L.A.; Ibfelt, H.H.; Christensen, K.; Jensen, O.N.; Barslev, J. A randomized, placebo controlled, cross-over study of ginger extracts and ibuprofen in osteoarthritis. Osteoarthr. Cartil. 2000, 8, 9–12. [Google Scholar] [CrossRef] [PubMed]

[131]. Lee, H.Y.; Park, S.H.; Lee, M.; Kim, H.-J.; Ryu, S.Y.; Kim, N.D.; Hwang, B.Y.; Hong, J.T.; Han, S.-B.; Kim, Y. 1-Dehydro-[10]-gingerdione from ginger inhibits IKKβ activity for NF-κB activation and suppresses NF-κB-regulated expression of inflammatory genes. Br. J. Pharmacol. 2012, 167,128–140. [Google Scholar] [CrossRef] [PubMed]

[132]. Singh, N.; Bhalla, M.; de Jager, P.; Gilca, M. An overview on Ashwagandha: A Rasayana

[133]. (Rejuvenator) of Ayurveda. Afr. J. Tradit. Complement. Altern. Med. 2011, 8, 208–213.[Google Scholar] [CrossRef] [PubMed]

[134]. Singh, D.; Aggarwal, A.; Maurya, R.; Naik, S.Withaniasomnifera inhibits NF-κB and AP-1

[135]. transcription factors in human peripheral blood and synovial fluid mononuclear cells. Phytother.

[136]. Res. 2007, 21, 905–913. [Google Scholar] [CrossRef] [PubMed]
[137]. Ganesan, K.; Sehgal, P.K.; Mandal, A.B.; Sayeed, S. Protective effect of Withaniasomnifera and Cardiospermum halicacabum extracts against collagenolytic degradation of collagen. Appl.
[138]. Biochem. Biotechnol. 2011, 165, 1075–1091. [Google Scholar] [CrossRef] [PubMed]
[139]. Rasool, M.; Varalakshmi, P. Protective effect ofWithaniasomnifera root powder in relation to lipid peroxidation, antioxidant status, glycoproteins and bone collagen on adjuvant-induced arthritis in rats. Fundam. Clin. Pharmacol. 2007, 21, 157–164. [Google Scholar] [CrossRef] [PubMed]
[140]. Ramakanth, G.S.H.; Uday Kumar, C.; Kishan, P.V.; Usharani, P. A randomized, double blind placebo controlled study of efficacy and tolerability of Withainasomnifera extracts in knee joint pain. J. Ayurveda Integr. Med. 2016, 7, 151–157. [Google Scholar] [CrossRef] [PubMed]
[141]. Sabina, E.P.; Chandal, S.; Rasool, M.K. Inhibition of monosodium urate crystal-induced inflammation by withaferin A. J. Pharm. Pharm. Sci. 2008, 11, 46–55.[Google Scholar [PubMed]
[142]. Grover, A.; Shandilya, A.; Punetha, A.; Bisaria, V.S.; Sundar, D. Inhibition of the NEMO/IKKβ association complex formation, a novel mechanism associated with the NF-κB activation suppression by Withaniasomnifera's key metabolite withaferin A. BMC
[143]. Genom. 2010, 11 (Suppl. 4), S25. [Google Scholar] [CrossRef] [PubMed]
[144]. Heyninck, K.; Lahtela-Kakkonen, M.; van der Veken, P.; Haegeman, G.; Vanden Berghe, W. Withaferin A inhibits NF-κB activation by targeting cysteine 179 in IKKβ. Biochem. Pharmacol. 2014, 91, 501–509. [Google Scholar] [CrossRef] [PubMed]
[145]. Bee, T.A.; Liew, A.; Hons, P. Dietary Supplements Used in Osteoarthritis. Proc. Singap.
[146]. Healthc. 2010, 19, 237–247. [Google Scholar] [CrossRef]
[147]. Posadzki, P.; Watson, L.; Ernst, E. Contamination and adulteration of herbal medicinal products (HMPs): An overview of systematic reviews. Eur. J.Clin. Pharmacol. 2013, 69, 295–307. [Google Scholar] [CrossRef] [PubMed]
[148]. Ernst, E. Risks of herbal medicinal products. Pharmacoepidemiol. Drug Saf. 2004, 13,
[149]. 767–771. [Google Scholar] [CrossRef] [PubMed]
[150]. Posadzki, P.; Watson, L.; Ernst, E. Herb-drug interactions: An overview of systematic reviews. Br. J. Clin. Pharmacol. 2013, 75, 603–618. [Google Scholar] [CrossRef] [PubMed]
[151]. Bhattaram, V.A.; Greece, U.; Kohlert, C.; Veit, M.;Derendorf, H. Pharmacokinetics and bioavailability of herbal medicinal products. Phytomedicine 2002, 9 (Suppl. 3), 1–33.[Google Scholar] [CrossRef] [PubMed]