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Herbal Drugs in the Management of Osteoarthritis

Aakriti Saini[1,2]*, Saini Hitesh[1], Vir Vikram[2], Geeta Deswal[1], Rohit Kumar[3]

[1.] Guru Gobind Singh College of Pharmacy, Yamunangar
[2.] CT University, Ludhiana
[3.] CT Group Of Colleges, Jalandhar.

Corresponding Author's email address: sainiakki16041991@gmail.com

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Abstract:

Low back discomfort, rheumatoid arthritis (RA), and osteoarthritis (OA) are common rheumatic illnesses. The medications used to treat these conditions have serious adverse effects and are essentially ineffective. To treat these illnesses, a variety of methods are employed in place of traditional medications. Using herbal remedies is one of these strategies. The effects of medicinal plants and herbal remedies used to treat certain illnesses are examined in this study. The increased knowledge of the underlying processes, diagnosis, and treatment of OA has led to numerous possible therapeutic advancements in recent years. In the OA joint cavity, embryonic stem cells and induced pluripotent stem cells can be utilized as a source of injectable therapeutics. These cells can develop into chondrocytes or mesenchymal stem cells (MSCs). Because of their capacity to develop into chondrocytes and their immunomodulatory qualities, MSCs are recognized as the most researched cell therapy products in cell-based OA therapy. They might speed up the healing of cartilage and eventually help joints get back to normal. However, there are still unmet medical needs for the treatment of OA despite the availability of current medicines and research advancements.

Keywords: Osteoarthritis, herbal drugs, treatment, chondrocytes.

Introduction:

Around the world, osteoarthritis (OA) is prevalent. Around 300 million people worldwide and 30.8 million adults in the US are thought to have OA. It causes discomfort, loss of function, and a decline in quality of life (QOL) and is the primary cause of impairment in older persons. Osteoarthritis (OA), a chronic joint disease, is characterized by the progressive deterioration of cartilage, the protective material that cushions the ends of bones [1]. The most common kind of arthritis mostly affects weight-bearing joints, such as the hands, knees, hips, and spine. The disease develops as the cartilage degrades over time, causing pain, stiffness, edema, and reduced joint motion. As the disease progresses, bones may rub against one another, resulting in joint deterioration, inflammation, and bone spurs [2]

Osteoarthritis risk factors include age, obesity, joint injuries, repetitive joint strain, inheritance, and certain metabolic diseases. Often, symptoms start off slowly and worsen with time, impacting daily activities and quality of life. The diagnosis is often made by a physical examination, medical history, imaging testing, and occasionally joint fluid study [3]

Although osteoarthritis cannot be cured, it can be controlled with assistive technology, pain medication, physical therapy, lifestyle modifications, and appropriate weight control. In severe cases, surgery, such as joint replacement, may be necessary. Regular exercise, joint protection practices, and a balanced diet can improve overall joint health and slow the advancement of condition [4].

PATHOLOGY:

In the past, OA was assumed to be only a condition caused by "wear and tear." It was believed that the articular cartilage in the joint would deteriorate due to chronic loading and compromised biomechanics, resulting in inflammation. This resulted in loss of movement, stiffness, and edema. It is now understood that OA is a somewhat more intricate process made up of metabolic and inflammatory elements [5].

In the past, OA was assumed to be only a condition caused by "wear and tear." It was believed that the articular cartilage in the joint would deteriorate due to chronic loading and compromised biomechanics, resulting in inflammation. This resulted in loss of movement, stiffness, and edema. It is now understood that OA is a somewhat more intricate process made up of metabolic and inflammatory elements[6]

The synovium, joint ligaments, and subchondral bone are all impacted, even though the cartilage exhibits the most noticeable alterations. The pathophysiology of OA is significantly influenced by inflammation, including systemic inflammation and active synovitis. One theory is that the synovial cells experience a foreign body reaction as a result of the destroyed cartilage [7]. Additional cartilage degradation may result from the generation of metalloproteases, synovial angiogenesis, and inflammatory cytokines. According to some views, the innate immune system and activated synovial macrophages play a key part in the development of OA. The pathophysiology of OA may potentially involve systemic inflammation [8]

RISK ELEMENTS:

OA is a complicated illness with numerous factors that could influence how it manifests and develops.

OA can be broadly divided into two categories:

Primary OA—no known cause

Secondary OA—caused by other conditions such as trauma, obesity, or disease [9].

Age

Aging is the single biggest risk factor for the development of OA, even if prevalence rates vary, especially because several definitions of the disease exist. As people age, the prevalence of both radiographic and symptomatic OA rises. Age-related increases in knee, hip, and hand rates have been seen. Worldwide estimates are that 9.6% of men and 18% of women older than 60 years have symptomatic According to global estimates, symptomatic OA affects 9.6% of males and 18% of women over 60 [10]. Twelve According to the Framingham Osteoarthritis study, radiographic evidence of knee OA was present in 27% of people aged 63 to 70 and 44% of people aged 80 and older [11].

Predisposition, both genetic and epigenetic

Over 80 genes have been linked to the pathophysiology of OA, making susceptibility to the disease thought to be polygenetic. These genes include those for insulin-like growth factor and vitamin D receptors [12]. A single nucleotide variation in the growth and differentiation factor 5 gene, which is important in the formation of healthy bone and cartilage, has also been linked to OA. The function of epigenetic mechanisms, such as DNA methylation, histone modification, and microRNAs, in the development of OA is presently being studied [13].

Metabolic Syndrome and Obesity

Metabolic syndrome and obesity are also significant risk factors for the onset of OA. According to a meta-analysis, obese or overweight people had a 2.96 odds ratio (OR) for having OA when compared to people of normal weight. There is mounting evidence that type 2 diabetes and dyslipidemia, apart from obesity, are risk factors for OA [14].

Endocrine

Patients with low levels of vitamin C or D have a threefold increased chance of developing knee OA. Although it has been hypothesized, there is no evidence linking increased bone density to a higher risk of OA [15].

Gender

The majority of research indicates that women are more likely than males to experience symptomatic knee issues (analysis shows a pooled OR of 1.84). The relative risk of osteoarthritis (OA) in the hands, knee, and hip was 1.52 times higher in women than in males, according to comprehensive research of Spanish patients conducted by Prieto-Alhambra and colleagues18 (2013) [16]. Compared to the knee (RR 1.19), this difference was more noticeable in the hip/hand (RR 2.50). For the knee and hip, these disparities peaked between the ages of 70 and 75. It's interesting to note that the sex gap for hand OA peaked between the ages of 50 and 55. Men are more likely than women under 50 to have OA, despite this general tendency. After the age of fifty, this prevalence shifts, with women having a larger risk of OA than males [17].

Previous Injury

Any inciting event that results in joint damage, such as fractures, cartilage damage, ligamentous injury, or meniscal injuries, can develop posttraumatic OA. According to a 2006 study by Brown and colleagues19, posttraumatic OA accounts for 12% of all cases. Each joint has a different prevalence of prior injury; posttraumatic OA is responsible for 20% to 78% of ankle OA cases, 10% of knee OA cases, and 2% of hip OA cases [18].

Occupation

There is some evidence that excessive kneeling, squatting, jumping, bending, and lifting can lead to knee OA. Construction workers, forestry workers, and farmers are at particularly high risk. Military populations also have been found to have much higher rates of OA than the general population. An association between the increasing use of technology, computers, and smartphones and hand OA has yet to be proved but is a common concern that requires further investigation, as these technologies have become increasingly prevalent in our lives [19].

Sports

Athletes and younger people may also experience joint degeneration as a result of articular cartilage injury from repeated impact and loading. The majority of impact injuries resulting from direct blunt trauma occur in sports like football and soccer. It has been demonstrated that 10 to 30 years after playing football, over 80% of American football players with a history of knee injuries showed signs of osteoarthritis [20].

Ethnicity

There is some evidence that the prevalence of OA varies by race and ethnicity in various communities. Europeans are more likely than Asians, Africans, and Jamaicans to have OA. Additionally, OA is more common in the US and Europe than it is elsewhere in the world [21]. There might also be variations among joints; for instance, there is evidence that Chinese people may be at a lower risk for hip and hand OA while yet being at a higher risk for knee OA. Ethnic differences may also exist in OA severity, gender prediction, and particular traits [22]

Joint Shape and Dysplasia

The onset and progression of OA are probably influenced by congenital abnormalities of the joints, including acetabular dysplasia, slipping capital femoral epiphysis, hallux valgus, and valgus/valgus joint alignment [23].

Pathophysiology of Osteoarthritis

The degenerative joint condition known as osteoarthritis is typified by the deterioration of cartilage, which is the substance that cushions the ends of bones in a joint [24] Pain, stiffness, and decreased movement are the results of this breakdown. Osteoarthritis develops and progresses due to several factors:

- **Cartilage:** Degradation Proteoglycans and collagen make up the majority of cartilage. The synthesis and breakdown of these components are out of balance in osteoarthritis. Cartilage gradually disappears as a result of enzymes like matrix metalloproteinases and aggrecanases breaking it down faster than it can be restored. There are currently no therapies for injured cartilage [25].

- **Inflammation:** Previously thought to be a non-inflammatory condition, osteoarthritis is now understood to be greatly impacted by inflammation, especially when it is advanced. The significance of synovitis, or inflammation of the synovial membrane, and how various joint components contribute to the inflammatory process are highlighted by (Inflammation in Osteoarthritis, n.d.) [26]. Tumor necrosis factor-α and interleukin-1β (IL-1β) are examples of inflammatory cytokines that are secreted within the joint and cause cartilage deterioration and discomfort. Inflammatory cytokines, which are generated in reaction to oxidative stress, are the cause of chronic inflammation [27].

- **Oxidative Stress:** An imbalance between the body's capacity to neutralize reactive oxygen species and their creation leads to oxidative stress. By harming cartilage cells called chondrocytes and other joint tissues, ROS can hasten the development of osteoarthritis. The inflammatory stress linked to osteoarthritis may be mediated by NOX4, a ROS generator [28]

Herbal Drugs as an Alternative or Adjunct Therapy in Osteoarthritis Management

Osteoarthritis is a prevalent chronic joint disease that affects more than 500 million people globally. It is one of the primary causes of disability in older adults (Osteoarthritis: Practice Essentials, Background, Anatomy, 2024) and has a substantial cost impact. Alternative and supplemental therapies, such as herbal medicines, are necessary because orthodox osteoarthritis treatments have limitations [29].

Limitations of Conventional Treatment:

Even if they relieve symptoms, current treatments can be dangerous and often do not address the underlying disease process.

- **NSAIDs:** NSAIDs are useful for treating pain, but they can have negative effects on the heart, liver, and gastrointestinal tract. Because they frequently have comorbidities, older persons should be especially concerned about these risks [30].
- **Corticosteroids:** Long-term usage of intra-articular corticosteroid injections can harm cartilage and raise the risk of infection, even if they can momentarily reduce pain [31].
- **Surgery:** Although it works well for end-stage osteoarthritis, joint replacement surgery is intrusive, risky, and necessitates a lengthy recovery period. Not every patient is a good fit for it [32].

Key Molecular Targets in Osteoarthritis Treatment

In order to treat osteoarthritis, several molecular targets are being researched with the goals of reducing pain, improving joint function, and slowing the disease's progression:

- **Cytokines:** Targeting pro-inflammatory cytokines like IL-1β and TNF-α is a promising approach. (Cytokine, 2024) mentions that cytokines are a possible treatment for pathological pain from inflammation [33].
- **Enzymes:** Another strategy is inhibiting enzymes involved in cartilage degradation, such as MMPs and aggrecanases [34].
- **COX-2:** One enzyme implicated with inflammation and pain is cyclooxygenase-2. Celecoxib and other COX-2 inhibitors are frequently used to treat Osteoarthritis pain, but they don't deal with the fundamental cause of the condition. Growth factors, oxidative stress-related molecules, and signaling pathways involved in cartilage healing are other possible targets [35]. According to Current Concepts in the Pathogenesis of Osteoarthritis (n.d.), no proven treatments exist to repair cartilage or halt the progression of the disease, underscoring the need for more study in this field [36].

Mechanisms of Action and Pharmacological Basis of Osteoarthritis Treatment

Osteoarthritis is a degenerative joint disease characterized by the breakdown of cartilage, the tissue that cushions the ends of bones in a joint. This breakdown leads to pain, stiffness, and reduced mobility [37]. While there is no cure for Osteoarthritis, various treatments aim to manage symptoms and slow disease progression. The pharmacological basis of these treatments lies in targeting the underlying mechanisms involved in Osteoarthritis pathogenesis [38].

Key Mechanisms in Osteoarthritis Pathogenesis:

- **Inflammation:** While Osteoarthritis is not primarily an inflammatory disease like rheumatoid arthritis, low-grade inflammation plays a significant role in pain and cartilage degradation. Inflammatory mediators, such as cytokines and chemokines, are released in the joint, contributing to the disease process. (Osteoarthritis Joint Pain: The Cytokine Connection, n.d.) [39].
- **Cartilage Degradation:** The breakdown of cartilage is a hallmark of Osteoarthritis. This involves the degradation of the extracellular matrix components, such as collagen and proteoglycans, by enzymes like matrix metalloproteinases [40].
- **Bone Remodeling:** Changes in bone structure, including subchondral bone sclerosis and osteophyte formation, occur in Osteoarthritis and contribute to joint pain and dysfunction [41].
- **Pain Signaling:** Pain from osteoarthritis can originate from the bone, surrounding tissues, and synovium, among other places. Peripheral nerves become more sensitive to inflammatory mediators and other signaling molecules, which heightens the experience of pain [42].

Table 1: Herbal Drugs in the Management of Osteoarthritis: [43, 44, 45, 46, 47, 48, 49, 50, 51, 52]

S. No.	Name of plants	Family	Plant parts used
1.	*Abrus precatorius* L.	Fabaceae	Root
2.	*Acacia catechu* (L.f.) Willd.	Mimosaceae	Fruits
3.	*Acacia senegal* Britton (Gum from acasia plant)	Mimosaceae	Gum
4.	*Aconitum heterophyllum* Wall.	Ranunculaceae	Root
5.	*Acorus calamus* L.	Arecaceae	Rhizome
6.	*Adhatoda beddomei* Clarke	Acanthaceae	Green leaf
7.	*Aegle marmelos* (L.) Correa	Rutaceae	Root, leaf and fruit
8.	*Ailanthus triphysa* (Dennst.) Alston	Simaroubaceae	Stem bark
9.	*Allium sativum* L.	Liliaceae	Bulb
10.	*Alpinia calcarata* Rosc.	Zingiberaceae	Root
11.	*Andrographis paniculata* (Burm. f.) Wall. *ex* Nees	Acanthaceae	Whole plant
12.	*Anethum graveolens* L.	Apiaceae	Seed
13.	*Asparagus racemosus* Willd.	Liliaceae	Tuber
14.	*Atylosia goensis* (Dalz.) Dalz.	Fabaceae	Whole plant
15.	*Azadirachta indica* A. Juss.	Meliaceae	Root, whole plant
16.	*Bacopa monnieri* (L.) Pennell	Scrophulariaceae	Whole plant

17.	*Boerhavia diffusa* L.	Nyctaginaceae	Root
18.	*Caesalpinia bonduc* (L.) Roxb.	Caesalpiniaceae	Seed, root
19.	*Calophyllum apetalum* Willd.	Clusiaceae	Seed
20.	*Carum carvi* L.	Apiaceae	Seed
21.	*Cassia fistula* L.	Caesalpiniaceae	Stem bark, root
22.	*Cedrus deodara* (Roxb.) G. Don	Pinaceae	Wood
23.	*Chonemorpha macrophylla* (Roxb.) G.Don	Apocynaceae	Root
24.	*Cinnamomum tamala* Th. Nees & Eberm.	Lauraceae	Leaves
25.	*Cinnamomum zeylanicum* Blume	Lauraceae	Flower, stem bark
26.	*Citrullus colocynthis* (L.) Schrad.	Cucurbitacae	Whole plant
27.	*Clerodendrum serratum* (L.) Moon.	Verbenaceae	Root
28.	*Coleus vetiveroides* Jacob.	Lamiaceae	Stem, root
29.	*Commiphora mukul* (Stocks) Hook.	Burseraceae	Exudate
30.	*Coriandrum sativum* L.	Apiaceae	Seed
31.	*Coscinium fenestratum* (Gaertn.) Colebr.	Minispermaceae	Stem bark
32.	*Crataeva nurvala* Buch.- Ham.	Capparidaceae	Root
33.	*Cuminum cyminum* L.	Apiaceae	Seed
34.	*Curculigo orchioides* Gaertn.	Liliaceae	Tuber
35.	*Curcuma longa* L.	Zingiberaceae	Rhizome
36.	*Cyclea peltata* Miers	Minispermaceae	Tuber
37.	*Cyperus rotundus* L.	Cyperaceae	Rhizome
38.	*Desmodium gangeticum* (L.) DC.	Fabaceae	Root
39.	*Dolichos biflorus* L.	Fabaceae	Seed
40.	*Eclipta alba* L.	Asteraceae	Whole plant
41.	*Elettaria cardamomum* (L.) Maton	Zingiberaceae	Seed
42.	*Embelia ribes* Burm.f.	Myrsinaceae	Seed
43.	*Emblica officinalis* Gaertn.	Euphorbiaceae	Fruit pulp

44.	*Erythrina variegata* L.	Fabaceae	Leaf, stem bark
45.	*Foeniculum vulgare* Mill.	Apiaceae	Seed
46.	*Fritillaria roylei* Hook.	Liliaceae	Tuber
47.	*Glycyrrhiza glabra* L.	Fabaceae	Root
48.	*Gmelina arborea* Roxb.	Verbenaceae	Root
49.	*Hemidesmus indicus* (L.) Br.	Perilocaceae	Root
50.	*Holarrhena pubescens* (Buch.-Ham.) Wall. *ex* G. Don	Apocynaceae	Seed, stem bark
51.	*Holoptelea integrifolia* (Roxb.) Planch.	Ulmaceae	Stem bark
52.	*Hordeum vulgare* L.	Poaceae	Seed
53.	*Hygrophila auriculata* (K. Schum.) Heine	Acanthaceae	Whole plant, seed
54.	*Ipomoea paniculata* R. Br.	Convolvulaceae	Tuber
55.	*Kaempferia galanga* L.	Zingiberaceae	Rhizome
56.	*Lepidium sativum* L.	Brassicaceae	Seed
57.	*Lilium polyphyllum* D.Don *ex* Royle	Liliaceae	Tuber
58.	*Malaxis acuminata* non D. Don	Orchidaceae	Rhizome
59.	*Malaxis muscifera* (Lindl.) Kuntze	Orchidaceae	Rhizome
60.	*Moringa oleifera* Bedd	Moringaceae	Leaf, seed, root, stem bark
61.	*Oldenlandia corymbosa* L.	Rubiaceae	Whole plant
62.	*Operculina turpethum* (L.) Manso	Convolvulaceae	Root
63.	*Oroxylum indicum* (L.) Benth. *ex* Kurz	Bignoniaceae	Root
64.	*Paederia foetida* L.	Rubiaceae	Whole plant
65.	*Phaseolus mungo* L.	Fabaceae	Seed
66.	*Phaseolus roxburghii* W. & A.	Fabaceae	Seed
67.	*Phaseolus trilobus* Baker	Fabaceae	Whole plant
68.	*Picorhiza kurroa* Royle *ex* Benth.	Plantaginaceae	Root
69.	*Piper chaba* Hunter	Piperaceae	Root

70.	*Piper longum* L.	Piperaceae	Fruit, root
71.	*Piper nigrum* L.	Piperaceae	Seed, leaf
72.	*Plantago ovata* Forssk.	Plantaginaceae	Seed
73.	*Pluchea lanceolata* (DC.) C. B. Clarke	Asteraceae	Tuber
74.	*Plumbago rosea* L.	Plumbaginaceae	Root
75.	*Polygonatum multiflorum* (L.) All.	Liliacae	Medha
76.	*Polygonatum vertcillatum* (L.) All.	Liliacae	Root
77.	*Pongamia pinnata* (L.) Pierre	Fabaceae	Stem bark, Leaf
78.	*Premna serratifolia* L.	Verbenaceae	Root
79.	*Pseudarthria viscida* (L.) Wight & Arn.	Fabaceae	Root
80.	*Psoralea corylifolia* L.	Fabaceae	Seeds
81.	*Pterocarpus marsupium* Roxb.	Fabaceae	Heart wood
82.	*Pterocarpus santalinus* L.f.	Fabaceae	Heart wood
83.	*Ptychotis ajowan* DC.	Apiaceae	Seeds
84.	*Ricinus communis* L.	Euphorbiaceae	Root, oil, leaf
85.	*Rubia cordifolia* L.	Rubiaceae	Root
86.	*Santalum album* L.	Santalaceae	Heartwood
87.	*Saussurea lappa* Clarke	Asteraceae	Root
88.	*Scindapsus officinalis* (Roxb.) Schott	Araceae	Dried mature inflorescence
89.	*Semecarpus anacardium* L.f.	Anacardiaceae	Seed
90.	*Sida rhombifolia* L.	Malvaceae	Root
91.	*Solanum indicum* L.	Solanaceae	Root
92.	*Solanum melongena* L.	Solanaceae	Root
93.	*Solanum melongena* L. - Wild	Solanaceae	Root
94.	*Solanum xanthocarpum* Schrad. & Wendl.	Solanaceae	Root
95.	*Stereospermum suaveolens* (G. Don) DC.	Bignoniaceaae	Root

96.	*Strobilanthes heyneanus* Nees	Acantaceae	Leaf, root
97.	*Strychnis potatorum* L. f.	Loganiaceae	Seed
98.	*Terminalia bellirica* (Gaertn.) Roxb.	Combretaceae	Seed pulp
99.	*Terminalia chebula* Retz.	Combretaceae	Fruit, fruit pulp
100.	*Tinospora cordifolia* (Willd.) Hook.f. & Thoms.	Minispermaceae	Stem
101.	*Tragia involucrata* L.	Euphorbiaceae	Root
102.	*Tribulus terrestris* L.	Zygophyllaceae	Fruit
103.	*Trichosanthes cucumerina* L.	Cucurbitaceae	Root, whole plant
104.	*Trigonella foenum graecum* L.	Fabaceae	Seed
105.	*Valeriana wallichii* DC.	Valerianaceae	Root
106.	*Abutilon indicum* (L.) Sweet	Malvaceae	Root
107.	*Vetiveria zizanioides* (L.)	Poaceae	Root
108.	*Vitex negundo* L.	Verbenaceae	Root, leaf
109.	*Withania somnifera* (L.) Dunal	Solanaceae	Root
110.	*Zingiber officinale* Rosc.	Zingiberaceae	Rhizome
111.	*Zizyphus mauritiana* Lam.	Rhemnaceae	Seed

Pharmacological Basis of Osteoarthritis Treatments:

The main goal of the pharmacological treatments for osteoarthritis currently available is to manage symptoms, especially pain. There are presently no treatments that can reverse or considerably halt cartilage loss, and disease-modifying osteoarthritis medications are still being developed [53].

Here's a summary of common drug classes used in Osteoarthritis management and their mechanisms of action:

- **Analgesics:**

  - **Acetaminophen:** Its precise mode of action is unclear, but it reduces pain through central pathways [54].

- **Opioids:** reduce the perception of pain by binding to opioid receptors in the central nervous system. They do, however, have the potential to cause dependence and other negative effects [55].

- **Nonsteroidal Anti-inflammatory Drugs:**

- Reduce the synthesis of prostaglandins, which are implicated in pain and inflammation, by inhibiting the cyclooxygenase enzymes. Both COX-2 selective inhibitors (like celecoxib) and conventional NSAIDs (like ibuprofen and naproxen) are used [56].

- **Intra-articular Injections:**

  - **Corticosteroids:** Potent anti-inflammatory agents that can provide temporary pain relief [57].

- **Hyaluronic Acid:** Viscosupplementation with hyaluronic acid aims to improve joint lubrication and reduce pain, although its efficacy is debated [58].

- **Other Treatments:**

  - **Topical Agents:** One topical analgesic that can relieve localized pain is capsaicin cream [59].

  - **Disease-Modifying Agents:** Growth factors, cytokines, and Wnt signaling are among the pathways implicated in the pathophysiology of osteoarthritis that are being targeted by several putative DMOADs. (The Assessment of Joint Mechanics and Their Contribution to the Development and Advancement of Osteoarthritis, n.d.) [60].

  - **Safety, Toxicity, and Drug Interactions of Osteoarthritis Treatments**

Osteoarthritis treatments encompass various medications, each with potential safety concerns, toxicity risks, and drug interactions. [61] Here's a breakdown:

Acetaminophen

- **Safety:** When taken as prescribed, it is generally safe. Serious liver damage can result from overdosing. When using acetaminophen, stay away from alcohol [62]

- **Toxicity:** The main issue is liver damage, particularly with large dosages or extended use [63].

- **Drug Interactions:** Interacts with warfarin (a blood thinner), increasing bleeding risk.

NSAIDs

- **Safety**: Increased risk of ulcers, heart issues such heart attacks and strokes, and gastrointestinal bleeding, particularly with prolonged use. (NSAIDs, 2024) [64].

- **Toxicity:** High blood pressure, fluid retention, and kidney injury are all possible outcomes [64].

- **Drug Interactions:** may increase the risk of bleeding when taken with blood thinners; lithium can raise levels of lithium; and methotrexate can increase the toxicity of methotrexate. (NSAIDs, 2024) [65].

COX-2 Inhibitors

- **Safety:** Similar cardiovascular risks as NSAIDs, but potentially lower risk of gastrointestinal bleeding [66]

- **Toxicity:** Kidney problems, fluid retention, and high blood pressure [67].
- **Drug Interactions:** Similar to NSAIDs.

Opioids

- **Safety:** Risk of addiction, tolerance, respiratory depression, constipation, and overdose.
- **Toxicity:** Overdose can be fatal [68].
- **Drug Interactions:** hazardous interactions with benzodiazepines, alcohol, and other drugs that depress the central nervous system [69].

Corticosteroids

- **Safety:** short-term pain alleviation, but frequent injections may harm cartilage.
- **Toxicity:** Skin thinning surrounding the injection site, hemorrhage, and joint infection.
- **Drug Interactions:** Few significant drug interactions [70].

Hyaluronic Acid

- **Safety:** Although injections are generally safe, some patients may have moderate pain and edema.
- **Toxicity:** Low toxicity.
- **Drug Interactions:** No notable medication interactions are known [71].

Other Treatments

- **Safety:** Although their effectiveness is up for debate, chondroitin sulfate and glucosamine are generally regarded as safe. Capsaicin and other topical treatments can irritate skin [72].
- **Toxicity:** Low toxicity for glucosamine, chondroitin, and topical treatments.
- **Drug Interactions:** Warfarin and glucosamine may interact [73].

The Need for Large-Scale Clinical Trials of Osteoarthritis: Future Perspectives and Research Gaps

Millions of people throughout the world suffer from osteoarthritis, a common and crippling joint condition. OA causes pain, stiffness, and functional restrictions due to the gradual deterioration of articular cartilage [74]. Even though it affects many people, the majority of current treatment options concentrate on managing symptoms rather than treating the fundamental cause of the illness. This emphasizes how important it is to conduct extensive clinical trials to research and create disease-modifying treatments [75].

Several factors highlight the importance of large-scale trials in OA research:

- **Heterogeneity of OA:** Each person experiences OA differently, with differences in the joints afflicted, the course of the disease, and the intensity of symptoms. Diverse patient groups can be included in large-scale studies, which improves the findings' generalizability and makes subgroup analysis possible to determine the best courses of action for particular patient profiles [76].

- **Detection of Small Treatment Effects:** Treatments that alter the course of a disease may have subtle but significant clinical impacts. The statistical power required to identify these subtle treatment effects—which smaller studies could overlook—is provided by large sample sizes. MRI's potential for conducting extensive clinical trials and epidemiological research to evaluate how well structure-modifying medications work [77].
- **Evaluation of Long-Term Effects:** As a chronic illness, OA necessitates ongoing care. Extensive studies can evaluate the safety and effectiveness of therapies over the long term, offering important information on their long-term effects on patient outcomes and the course of disease [78].
- **Assessment of Rare Adverse Events:** Only in large-scale trials with prolonged follow-up periods may rare but substantial side events linked to novel medicines become apparent. Accurately assessing the risk-benefit profile of innovative therapies requires this knowledge [79].
- **Cost-Effectiveness Analysis:** Economic analyses can be incorporated into large-scale trials to determine the cost-effectiveness of various treatment approaches, which can help guide decisions about healthcare policy and resource allocation [80].

Future perspectives in OA research should prioritize:

- **Identification of Novel Therapeutic Targets:** Our growing knowledge of the pathophysiology of OA has identified several possible treatment targets, including as subchondral bone alterations, cartilage matrix degradation, and inflammatory pathways. The effectiveness of treatments aimed at these pathways must be assessed through extensive trials [81].
- **Development of Biomarkers:** To speed up medication research and customize treatment plans, accurate biomarkers for OA diagnosis, prognosis, and response to treatment are essential. The usefulness of these biomarkers in a range of patient populations can be confirmed by extensive trials [82].
- **Implementation of Innovative Trial Designs:** There are chances to improve the efficacy and efficiency of OA research through pragmatic trials, platform trials, and adaptive trial designs. These designs enable quicker evaluation of several interventions by providing flexibility in changing trial parameters in response to gathering data [83].
- **Focus on Prevention:** The requirement for top-notch randomized controlled trials to look into OA prevention tactics, especially when it comes to sports and leisure injuries. To assess the long-term effects of prophylactic therapies on OA risk, large-scale trials are necessary [84].

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