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General

Clinically Relevant Toxic Effects of Over-the-Counter Nutraceuticals and Herbal Pain Products

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Purpose of Review

The herbal supplement and nutraceutical industry has grown immensely over the past two decades, with large increases being driven by patients seeking alternative methods for pain management. Unlike pharmaceuticals, supplements face a low barrier to market entry with lax regulations allowing these products to be sold without pre-market testing.

Recent Findings

While products like glucosamine and turmeric are commonly used and have demonstrated moderate efficacy for pain conditions such as osteoarthritis, there is a lack of long-term randomized control trials to support widespread use. Additionally, product use is associated with safety concerns stemming from known toxicities, manufacturing contaminants, and herbal-drug product interactions.

Summary

These limitations have prompted calls for better regulatory oversight of herbal supplements to improve manufacturing standards, recognize safety concerns from product use, and establish long-term data for effective use. Clinicians are also encouraged to recognize known benefits and risks of nutraceutical use to better inform patients using these products and to reduce potential morbidity and mortality.

1.0 INTRODUCTION

The use of plants for healing is among the oldest human practices. Archaeological evidence from a Neanderthal burial site in Shanidar Cave, Iraq, suggests that medicinal plants may have been used therapeutically for over 60,000 years.[1,2] Long before the use of modern analgesics, humans have turned to plants for pain relief, in China (3000 BC) the historic Pen Tsao catalogs the use of poppy, turmeric and ginger to treat arthritis and inflammatory conditions.[3,4] Ayurvedic Physicians documented hundreds of additional remedies, notably the resin of Boswellia serrata for use in joint pain and inflammation.[5]

The search for new nutraceuticals continued in ancient Egypt as the Ebers Papyrus (1550 BC) recorded hundreds of herbal remedies, including the earliest known reference to willow bark for pain.[1,6] This accumulation of botanical knowledge continued into the Greco Roman period where Dioscorides authored the De Materia Medica. A work compiling hundreds of plant based remedies for digestion, fevers, wound care and pain.[1,7] Many of these same botanical, including turmeric, Boswellia, willow bark, ginger, feverfew, comfrey, devil's claw and kratom are now sold as over the counter supplements marketed for pain relief. This makes the evaluation of safety and toxicity profiles an important and timely concern.

One of the most monumental developments in the history of medicine is the transition from traditional remedies to modern pharmaceuticals. In the early 19th century, advances in synthetic chemistry enabled the isolation of active compounds from well-known medicinal plants, morphine from the opium poppy and salicylic acid from willow bark.[8,9] These breakthroughs established the paradigm of single-compound pharmacology that defines modern drug development.[10] Over one-third of modern medicines come from natural products and their derivatives and 25% of commercially available drugs were originally discovered through traditional plant-based medicine.[11,12] According to data compiled by the World Health Organization, an estimated 75% of the world's population still depends on

herbal medicine for basic healthcare needs.[13] These figures imply that herbal medicine is not merely of historical interest but remains foundational to contemporary drug discovery and global health.

The herbal supplement business has seen huge growth over the past two decades. This boom in demand for botanical products started after Congress enacted the Dietary Supplement Health and Education Act (DSHEA) in 1994. In this act, supplements are classified as a category of food rather than drugs.[14,15] Under DSHEA, there is no obligation for manufacturers to demonstrate effectiveness. Manufacturers only need to attest to a product's safety based on its historical use, therefore, supplements can reach the market without premarket clinical trials or FDA approval.[16,17]

Although conventional drugs are firmly regulated, the FDA must show that a supplement poses a real safety risk before it can be pulled from the market.[16] This fueled the market and by 2019, American consumers were spending over $9.6 billion annually on herbal products alone, and the broader supplement industry had grown into a $35 billion enterprise.[16-18] Pain management and joint health supplements have been among the primary beneficiaries of this market growth.[19]

The pain management and joint health segment represents one of the fastest-growing areas of the supplement market. Consumer interest in botanical alternatives has been driven by the limitations of conventional analgesics in terms of long-term safety. The interest in supplements marketed for pain relief such as glucosamine, curcumin, Boswellia serrata extract, ginger extract, and willow bark has been substantial.[20,21] However, a systematic review and meta-analysis of 69 randomized controlled trials evaluating 20 dietary supplements for osteoarthritis (OA) found that while some products demonstrated large short-term effect sizes for pain reduction, widely used supplements such as glucosamine and chondroitin showed small and arguably clinically unimportant effects, and no supplements demonstrated clinically important long-term benefits.[21] The American Academy of Orthopedic Surgeons reached a similar conclusion that the evidence for oral supplements in knee OAis limited.[22] Consumer demand continues to grow even though the evidence base is weak.

A big driver of this market growth in the over-the-counter nutraceutical and herbal pain product market is the common belief that "natural" products carry little risk.[23] Since these supplements are stocked alongside everyday grocery foods instead of behind the pharmacy counter. Consumers often view them as low-risk products they can try without much research. As a result, roughly three out of four users start taking supplements without ever speaking with a healthcare professional first.[18] Another reason for growth of herbal pain supplements is driven by marketing that often crosses into misleading territory.[24] An analysis was done of over 6,000 supplement advertisements and it was found that the structure-function claims used language that strongly implied disease treatment or cure, the very kind of claims the FDA prohibits without solid evidence to support.[25] This rise in consumer demand is driven by aggressive marketing, easy access, and the idea that "natural" remedies are a better alternative to prescription medications.

Related to regulatory asymmetry by DSHEA, safety profiles of most commercially available supplements are largely unknown at the time they reach consumers and fewer than 1% of adverse events tied to dietary supplements are reported to the FDA.[26,27] Several factors contribute to the problem. Many consumers assume supplements to be safe and begin taking them without professional supervision. On the provider side only 38-40% of clinicians know how or where to report a supplement-related adverse event.[27,28] In a landmark study, researchers showed that in the United States there are 23,000 annual visits to the emergency department attributable to adverse effects of dietary supplements. These visits result in over 2,100 hospitalizations each year, and herbal or complementary nutritional products account for nearly two-thirds (65.9%) of single supplement adverse events seen in adults.[29] Perhaps most concerning is the growing recognition of supplement induced hepatotoxicity. The Drug-Induced Liver Injury Network Registry shows that dietary and herbal supplements are now responsible for 20% of all hepatotoxicity cases in the United States. This proportion nearly tripled from 7-9% in 2004-2007 to 19-20% in 2010-2014.[30,31]

This introduction has shown that plant-based remedies have been part of human healthcare for thousands of years. Many of these same botanicals are now packaged and sold as over-the-counter supplements to millions of consumers looking for alternatives for pain management and joint health.[32] As the regulatory framework of nutraceuticals and herbal pain products has not kept pace with their popularity; the limited premarket testing combined with a systematic underreporting of adverse events and an increasing incidence of organ toxicity warrants attention.[33] This review evaluates the toxicities of several widely marketed herbal and nutraceutical pain products, such as glucosamine, kratom, turmeric, comfrey, Boswellia, devil's claw, white willow bark, ginger, and feverfew. Its goal is to help clinicians and consumers better understand the potential risks that come with these widely available products.

2.0 METHODOLOGY

This was a narrative review that was conducted using the PubMed data base. The literature search identified studies that examined the therapeutic applications, efficacy, safety, adverse effects, and regulatory considerations of herbal medicine. The articles were also identified using the relevant key words, and Boolean combinations, which included "herbal medicine", Botanical medicine", "dietary supplements", "nutraceuticals", and then specific terms such as "turmeric", "Boswellia", "Devils Claw", and "ginger" for example. There were also additional targeted searches, and manual review of references from the selected papers. No strict dates were used in this inclusion criteria, and priority was given to peer-reviewed studies, systematic reviews, and guidelines when available.

3.0 CURRENT CONCEPTS IN NUTRACEUTICAL AND HERBAL MEDICINE USE

3.1. DEFINITION OF NUTRACEUTICALS

1. DISTINCTION BETWEEN NUTRACEUTICALS, DIETARY SUPPLEMENTS, AND PHARMACEUTICALS

Nutraceuticals are considered as food, nutrient or herbal products that consumers use for treatment and disease prevention.[33] The term was introduced in 1989 by Stephan DeFelice who coined the term and defined it as "a food or part of a food that provide medical or health benefits, including the prevention and/or treatment of a disease".[34]

Despite the term's widespread adoption, nutraceuticals are not formally defined by US law and other regulatory bodies, and its terminology has varied among other terms like functional foods or fortified foods.[35] Similarly, regulation of nutraceuticals varies globally, with products being subject to different standards for claims, safety, and labeling in different countries.[36]

Dietary supplements are distinct in that they contain dietary ingredients to supplement regular diet and are formally recognized and regulated by the DSHEA of 1994.[37] In addition, dietary supplements can make claims about structure/function support, but cannot claim to treat or prevent a disease without FDA authorization and significant scientific support.[38] Likewise, medicinal compounds are highly regulated products with active ingredients that have proven pharmacological and therapeutical effects.[35]

A medicinal product has a specific formulation that the drug is prepared in (i.e. tablet, capsule, cream), and is approved by a federal agency for treatment or prevention of a specific disease.[35] Unlike nutraceuticals and dietary supplements, medicinal compounds must demonstrate safety and efficacy through randomized controlled trials, strict manufacturing practices, and be approved for specific medical indications by a federal agency.[35] In summary, nutraceutical products lack legal definition and pre-market testing standards, which makes these products distinct from dietary supplements and medicinal products.

*2. **COMMON CATEGORIES OF PAIN-RELATED SUPPLEMENTS***

Nutraceutical use for chronic pain is widespread with 32% of patients admitting to self-use of one or more herbal related compounds.[39] Pain related nutraceuticals and similar products are classified based on mechanistic classes: anti-inflammatory, joint supplements, polyunsaturated fatty acids, polyphenols, and essential oils. Anti-inflammatory botanicals, like Boswellia and Curcumin, reduce pain by inhibiting cyclooxygenase (COX) and Lipoxygenase (LOX) and downstream inflammatory mediators.[40]

Joint specific supplements, like Chondroitin and glucosamine are used for pain relief and stiffness improvement in knee and hip OA.[41] Transient receptor potential (TRP) channel modulators affect peripheral nociception, with Capsaicin being used for chronic low back pain, and menthol being used for topical analgesia.[41,42]

Polyunsaturated fatty acids like fish oil and omega-3 fatty acids modulate inflammation by reducing prostaglandin production.[43,44] Essential oils are also used topically and in aromatherapy for management of neuropathic pain, but limited studies have established their safety and efficacy.[41,45] Polyphenols, like Resveratrol and Epigallocatechin, exert analgesic effects through antioxidant, anti-apoptotic and neuroprotective mechanisms, and have been studied for use in neuropathic pain.[46] Vitamins, minerals, and amino acids manage pain related to specific deficiencies or neuromodulator pathways.[19,47,48]

Across these categories, herbal supplements promote analgesic effects through shared anti-inflammatory, antioxidant, anti-apoptotic, neuroprotective, and calcium inhibitory mechanisms.[40] Evidence quality varies across these existing supplement categories, with strong evidence for alpha-lipoic acid in diabetic nephropathy, omega-3 fatty acids in rheumatoid arthritis (RA) and topical capsaicin for neuropathic pain.[44,49,50] Other supplements, like minerals, have high-quality preclinical evidence but have limited existing clinical studies to support use.[51] Existing nutraceutical studies are also highly susceptible to placebo effects, which affects interpreted efficacy among subjects.

3.2. EPIDEMIOLOGY OF USE

Nutraceutical and dietary supplement use is highly prevalent with 60% of US adults reporting use in 2023, a 51% increase from 1999.[51] Age is one of the major predictors for supplement use, with 78% of adults age 65 and older reporting consumption.[18] Other groups that report higher supplement use include female, non-Hispanic white, college graduate, and high socioeconomic status populations.[18]

Among patients who report nutraceutical use, 70% of them do not report this information during routine anesthetic assessments.[39] Chronic pain is one of the leading indications for nutraceutical use among 49.2% US adults who used complementary therapies in 2022.[52] Supplement use for chronic pain is most robust for conditions such as osteoarthritis, lower back pain, chronic musculoskeletal pain, migraine, and neuropathic pain.[21,42,48,53,54]

The nutraceutical market has grown significantly over the last two decades, with it representing a global value of approximately $200 billion and it composing 44% of US spending for complementary and alternative medical practices.[18,52,55] The most commonly reported reason for supplement consumption is to maintain or improve overall health, with women more likely to use calcium products for bone health and men more likely to use products for heart health.[56] The greatest increase in supplement use has been for products marketed as anti-inflammatory such as curcumin, vitamin D, ashwagandha and collagen.[18] Declines in goldenseal, ginkgo, and ginseng have been reported, which may reflect concerns with known drug-nutraceutical interactions.[18]

3.3. SAFETY CHALLENGES

MANUFACTURING VARIABILITY

Because there is no standardized definition for nutraceuticals, manufacturing practices for nutraceuticals vary significantly. The FDA considers nutraceuticals as a "food product" or "supplement", meaning do not require approval or review before being manufacturing and marketed.[57]

Although manufacturers are required to comply with good manufacturing practices (cGMP) to ensure product quality and safety, enforcement of these practices by federal agencies is limited to post-market surveillance.[57] These lack of regulations have raised concerns about product quality issues, as nutraceutical compounds are regulated under lax standards, increasing the risk of safety issues for consumers.

Variation in manufacturing standards has resulted in many nutraceuticals products on the market being adulterated with herbal or animal extracts that weren't ingredients in the original product.[36] Product contaminants that have been previously found include heavy metals, mycotoxins, pesticides, fertilizers, and drugs of abuse.[58] Furthermore, independent sampling of commercial herbal products sold globally has found that a large proportion of products have incorrect ingredient amounts, substituted plant species, and absent active ingredients, raising concerns for the reliability of nutraceutical manufacturing practices.[59]

Safety challenges also arise from clinically significant drug interactions associated with popular nutraceuticals.

The most well-established interactions are with metabolizing enzymes that affect drug pharmacokinetics like cytochrome P450, organic anion transport proteins, and P-glycoprotein transporters (P-gp).[60] The adverse effects from these drug interactions can be significant, with preoperative herbal use being associated with bleeding, cardiovascular effects, bronchospasm, diuresis, and hepatic dysfunction.[61] It is critical for providers to ask patients about supplements and stop consumption one to two weeks before surgery, as recommended by professional society guidelines.[61] But even with existing evidence on nutraceutical and herbal side effects, limited long-term safety data is limited.[60] Together, these challenges highlight the need for better regulatory oversight for nutraceutical manufacturing, safety event monitoring, as well as guidelines for clinicians regarding supplement use in patients.

4. GLUCOSAMINE AND POTENTIAL NEURODEGENERATIVE RISKS

4.1. CLINICAL USES

1. TREATMENT OF OSTEOARTHRITIS AND JOINT PAIN

OAis one of the most common forms of arthritis, affecting more than 500 million individuals worldwide in 2019.[62] With obesity and overall lifespans increasing, there have been projections that this number will rise to 78 million individuals in the U.S. alone who will suffer chronically from this disease process by 2040.[63] To combat this rising incidence of OA, many therapeutics have been studied, with glucosamine rising to the top.

Chondroitin has also become a popular supplement, having been studied across 18 of 69 RCTs analyzing its effects on OA.[21] Glucosamine has been believed to decrease proinflammatory cytokines such as IL-1, IL-6, and TNF-α, as well as pathways such as the NF-κB cellular pathway.[62] However, many studies were conducted over a short period of time, and those conducted over a longer duration of time demonstrated minimal or no effect compared to placebos.[63] Furthermore, clinical studies have not shown long-term benefits when used in tandem with other supplements, suggesting that sustained use may prove ineffective when managing chronic conditions.[21] Additionally, the Osteoarthritis Research Society International (OARSI) rejected the use of supplements like glucosamine and chondroitin in their most recent guidelines for managing OA, due to their lack of efficacy and quality research.[64]

2. COMMON FORMULATIONS AND DOSING STRATEGIES

Most studies on glucosamine prioritize oral intake, as topical formulations are believed to be less effective.[62] However, many studies often fail to maintain consistent glucosamine dosing across trials.[21] However, the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) recommends supplementing with full doses of glucosamine and chondroitin alongside a low-does acetaminophen regimen, demonstrating a disagreement with OARSI recommendations.[64]

3. POPULARITY AMONG AGING POPULATIONS

Glucosamine and chondroitin account for approximately one-third of the $25 billion supplement market.[21] As the population ages, the prevalence of OA across the globe increases,[65] with as many as 69 percent of patients with OA consuming some form of dietary supplement.[21] Glucosamine use has become increasingly more widely used among aging populations, as OAtends to affect older adults, with more than 70% of patients being 55 years or older.[62] Glucosamine has also been shown to have fewer acute adverse effects when studied over the short term, with GI complications being the most commonly observed, which could aid in its rising popularity among older adult populations.[63] However, older adults tend to be on common anticoagulants for other diseases such as cardiovascular disease, and caution is advised when combining warfarin with glucosamine as adverse effects have been shown to arise from this interaction.[63]

4.2. PROPOSED MECHANISMS OF TOXICITY

1. EFFECTS ON GLUCOSE METABOLISM

Glucosamine is molecularly similar in structure to the molecule glucose, allowing it to compete for the same cellular transporters: GLUT1, GLUT2, and GLUT4, with GLUT2 hav-

ing an overall greater affinity for glucosamine compared to glucose.[66] In the cell, glucosamine undergoes phosphorylation to form glucosamine 6-phosphate, which can inhibit hexokinase, an enzyme critical in glucose metabolism.[66] In addition, phosphate depletion reduces ATP production, thereby downregulating the Akt and mTORC1 signaling pathways, both of which have been shown to contribute to insulin resistance in animal models.[66]

Oral glucosamine is thought to have lower bioavailability, leading to plasma concentrations of 3-8 μmol/L, which are much lower than those observed in many animal models.[67] The clinical effect of glucosamine on glucose metabolism varies. A systematic review of 11 human studies found that only 4 showed adverse effects of glucosamine on glucose metabolism.[68] A small number of participants already had preexisting glucose resistance or insulin resistance and were more likely to show an adverse effect. However, diabetic participants did not show a significant change in glucose metabolism outcomes, although these studies lacked adequate sample size and study duration.[68]

2. INFLUENCE ON PROTEIN GLYCOSYLATION PATHWAYS

Glucosamine might influence the hexosamine biosynthesis pathway (HBP). After uptake into cells, it is phosphorylated by hexokinase into glucosamine 6-phosphate through the HBP salvage pathway. Glucosamine 6-phosphate is then used to produce UDP-N-acetylglucosamine (UDP-GlcNAc), which is critical in N-linked glycosylation of secretory and membrane proteins as well as of intracellular proteins through O-linked GlcNAcylation.[66]

O- GlcNAcylation is a reversible post-translational modification of proteins that specifically alters amino acid residues serine and threonine by adding O-GlcNAc using O-GlcNAc transferase (OGT) or removing O-GlcNAc by O-GlcNAcase (OGA). UDP-GlcNAc from the hexosamine biosynthesis pathway is the substrate for OGT.[69] Additionally, O-linked GlcNAcylation occurs in the brain and modifies the tau and amyloid precursor protein (APP), both of which are involved in Alzheimer's disease.[69] Experimental evidence in mouse models has shown that inhibition of OGA can reduce insoluble pathological tau protein and tau measured in the CSF.[70] However, recent evidence has shown increased N-linked glycosylation in postmortem brain tissue samples from patients with Alzheimer's disease and in Alzheimer's disease mouse models, while O-linked glycosylation was reduced.[71]

3. POTENTIAL INTERACTIONS WITH NEURONAL CELLULAR PROCESSES

In the brain, the hexosamine pathway and the product O-GlcNAc have been shown to be more metabolically active when compared to peripheral tissue, specifically when observing OGT. OGT has demonstrated nearly ten times as much activity in the brain compared to the peripheral neuronal tissues.[69] In addition, OGT and OGA are critical for neuronal cell survival; when OGT or OGA is genetically deleted in mice, embryonic death occurs due to OGT knockout and perinatal death occurs as a result of OGA knockout.[72] Additionally, abnormal hyperphosphorylation of tau is observed when OGT is knocked out alone.[69]

Acutely raising levels of O-GlcNAc can reduce neuronal excitability in hippocampal tissues by increasing voltage-gated potassium channel activity and decreasing sodium channel activity.[72] Furthermore, levels of hippocampal OGT and O-GlcNAc decrease in aging mice, which may suggest a more protective role of O-GlcNAc.[72] Dysregulation of glycosylation has been indicated in Alzheimer's disease pathology. In Alzheimer's disease brains, the UDP-GlcNAc generated from the hexosamine biosynthesis is used by three main pathways: N-linked, O-linked, and hyaluronic acid synthesis.[71] However, this appears not to occur in healthy brains that can maintain glycosylation homeostasis, as opposed to brains already under neurodegenerative processes.[71]

4.3. EVIDENCE REGARDING NEURODEGENERATIVE DISEASE

1. EXPERIMENTAL FINDINGS INVOLVING TAU PHOSPHORYLATION AND AMYLOID PATHWAYS

In experimental findings involving tau phosphorylation and amyloid pathways, Tau protein has been shown to be O-GlcNAcylated, which affects the way it is phosphorylated.[73] Additionally, cultured cells and mice that both had restricted glucose intake exhibited lower O-GlcNAcylation, which led to higher tau phosphorylation. However, pharmacologically increasing O-GlcNAc was able to reverse this process.[73] Human brain tissue in AD brains had 22% less O-GlcNAc, and neurofibrillary tangles of tau contained no O-GlcNAc.[73]

In mouse models engineered to develop Alzheimer's disease through amyloid plaques, the use of Thiamet-G and an inhibitor of OGA resulted in a decrease in tau in CSF and insoluble tau.[70] The use of another OG inhibitor, NButGT, resulted in increased O-GlcNAc of nicastrin, which is a protein that helps produce amyloid-β. This resulted in reduced amyloid production and decreased brain inflammation, but NButGT demonstrated no effect in healthy mouse models.[74]

2. ANIMAL AND CELLULAR STUDIES EVALUATING COGNITIVE EFFECTS

Despite earlier research suggesting positive benefits to glycosylation through O-GlcNAc, the separate pathway of N-linked glycosylation revealed that when decreased through both genetic and pharmacological approaches, it resulted in increased social memory despite no changes in tau or amyloid buildup in Alzheimer's mice.[71] Additionally, when Alzheimer's disease mice received glucosamine, there was worsening of social memory through increased N-linked glycosylation, but there was no change in memory for healthy wildtype mice.[71] This same pattern was also observed in humans.[71]

3. HUMAN EVIDENCE AND CURRENT CONTROVERSIES

When observing medical records of over 24,000 patients with either Alzheimer's or dementia, as well as almost 42,000 patients with cognitive decline, there was a 25% increased risk of death among those taking glucosamine who were between Alzheimer's and mild cognitive decline.[71] However, this effect was not observed in those taking glucosamine who were between mild cognitive decline and being considered healthy patients.[71] Furthermore, in a prospective cohort study of UK Biobank data from over 288,000 participants who initially had no dementia or Parkinson's, no association was found with either disease when consuming glucosamine, despite factoring in other lifestyle factors and demographics.[75]

4.4. CLINICAL SAFETY CONSIDERATIONS

1. RISK-BENEFIT ASSESSMENT

The evidence for the risk of glucosamine use has risen recently, particularly in animal models and studies surrounding cognitive decline and supplementation with glucosamine.[71] Additionally, long-term trials have not demonstrated a significant difference between glucosamine and the placebo, with organizations such as OARSI not recommending it as therapeutic.[63,64]

2. LIMITATIONS OF EXISTING EVIDENCE

Many of the studies have failed to consistently keep a standardized dosing of glucosamine, and the supplement is often not isolated from supplementation with chondroitin.[21] Furthermore, early studies lacked long-term analysis of the effects of glucosamine on human metabolism.[68]

3. NEED FOR LONG-TERM NEUROCOGNITIVE STUDIES

To date, there is a lack of long-term prospective studies of glucosamine use in humans, with much evidence of glucosamine effects on neurocognitive disorder being demonstrated in 5xFAD-manipulated mice with Alzheimer's.[71] There is also conflicting evidence for glucosamine use in humans. A retrospective study in individuals with Alzheimer's disease and mild cognitive decline showed increased risk of mortality,[71] while a prospective cohort study of over 288,000 UK Biobank participants found no association of glucosamine use and risk of Parkinson's or dementia in healthy individuals.[75] Such discrepancies demonstrate that there is a need for more long term prospective human studies of the neurocognitive effects of glucosamine rather than solely relying on retrospective studies or animal models before any broad conclusions can be made of glucosamine safety in aging or high-risk populations.

5.0 KRATOM AND SYSTEMIC TOXICITY

5.1. BACKGROUND AND CLINICAL USE

Kratom, also known as *Mitragyna speciosa*, is derived from a tropical tree indigenous to Southeast Asia. Traditionally, populations in Thailand, Malaysia, Indonesia, and surrounding regions have chewed, brewed as tea, or incorporated kratom into beverages. These preparations were used to improve energy and endurance during physically demanding work, relieve musculoskeletal discomfort, and reduce fatigue, typically using relatively low-concentration whole-leaf preparations rather than the highly concentrated extracts and purified alkaloid products found in modern Western markets.[76,77] The clinical effects of kratom have been shown to vary greatly with dose and preparation, producing stimulant-like effects at lower doses and opioid-like analgesic and sedative effects at higher doses.[76,78]

Kratom use has continued to expand outside Southeast Asia, particularly in the United States and Europe. The expansion of kratom use has been facilitated by greater availability of kratom through internet vendors, specialty stores, and commercial retail outlets. Consumer surveys identify avoidance of prescription opioids, pain management, and relief of opioid withdrawal symptoms as common reasons for use.[78,79] Although these applications suggest kratom as a potential therapeutic agent, evidence supporting its efficacy and long-term safety remains substantially less developed than evidence for conventional analgesics or medications for opioid use disorder.[78,80]

The principal psychoactive effects of kratom are attributed to the alkaloids mitragynine and 7-hydroxymitragynine (7-HMG) found in its leaves. Mitragynine is found in higher concentrations in most natural kratom products, whereas 7-HMG is typically present but at much lower concentrations. Notably, 7-HMG demonstrates a substantially greater potency at the μ-opioid receptor than mitragynine.[76,79,80] While less prominent, more than 40 other alkaloids have been identified in natural kratom products, with widely varied relative concentrations when compared across plant genetics, geographic origin, harvesting conditions, processing, and commercial preparations.[80,81] Because kratom composition can vary substantially between preparations, the labeled dose alone may not reliably predict its pharmacologic effects.

5.2. KRATOM MECHANISMS OF ACTION

Kratom produces its pharmacologic effects through activity across multiple neurotransmitter systems. The two primary alkaloids, mitragynine and 7-HMG, both demonstrate activity at the μ-opioid receptor. Both occur naturally in kratom leaves; however, mitragynine can be converted to 7-HMG through CYP3A-dependent metabolism.

Mitragynine functions as a relatively low-efficacy partial μ-opioid receptor agonist, whereas 7-HMG has greater μ-opioid receptor potency and efficacy and therefore produces stronger opioid-like effects.[80,82,83] Mitragynine also

interacts with adrenergic and serotonergic systems in experimental receptor binding studies, contributing to the complex clinical presentation of kratom exposure.[81,84] Additionally, mitragynine interacts with cytochrome P450 enzymes, particularly CYP3A, suggesting the potential for pharmacokinetic interactions with concurrently administered medications.[85,86] These interactions are particularly dangerous for kratom users taking opioids, benzodiazepines, antidepressants, anticoagulants, or other medications with narrow therapeutic windows.

Kratom's clinical presentation also varies according to dose. Lower doses are generally associated with stimulant-like effects, with symptoms including increased alertness, energy, and sociability while higher doses typically produce analgesia, sedation, dizziness, and opioid-like effects.[76,78] Of note, this dose-dependent symptomatic profile is not necessarily predictable because commercially available kratom preparations vary in mitragynine and 7-HMG concentrations. When administered orally, both mitragynine and 7-HMG demonstrate systemic uptake and exposure with plasma concentrations of these two psychoactive alkaloids typically peaking at 1-2 hours post-ingestion.[87]

5.3. TOXIC EFFECTS

Despite its marketing as a natural alternative to conventional opioids, kratom has been shown to produce tolerance, physical dependence, craving, and clinically significant withdrawal syndrome. Surveys of regular kratom users have demonstrated both physical and psychological dependence, with the likelihood and severity of withdrawal increasing with frequency and duration of use.[88] Some of the common withdrawal symptoms include irritability, anxiety, restlessness, insomnia, rhinorrhea, lacrimation, gastrointestinal symptoms, myalgias, tremor, sweating, and generalized discomfort.

A systematic review of kratom withdrawal similarly identified a syndrome characterized by both opioid-like physical symptoms and prominent affective symptoms in this patient population.[88,89] Additionally, research suggests that frequency of dosing may be more strongly associated with withdrawal and kratom-use-disorder symptoms than the amount consumed on an individual occasion.[90] While many individuals may initiate kratom to manage opioid withdrawal, they are at risk of subsequently developing dependence on kratom itself. Additionally, this kratom withdrawal may require pharmacologic intervention with case reports of patients requiring α2-adrenergic agonists and, in selected cases, buprenorphine-naloxone or other opioid-based strategies to manage the withdrawal symptoms.[89,91]

A second major risk surrounding kratom use is respiratory toxicity. As previously noted, studies suggest mitragynine demonstrates substantially lower respiratory-depressant effect than morphine and other opioids, consistent with its partial μ-opioid receptor activity. Likewise in rodent models, high doses of mitragynine produced less respiratory depression than oxycodone, once again suggesting isolated mitragynine demonstrates safer respiratory effects than conventional opioids.[92] However, 7-HMG is substantially more potent at the μ-opioid receptor than mitragynine and has demonstrated respiratory-depressant effects in animal models.[83,93] Additionally, poison centers have also documented reported cases of respiratory depression, coma, and cardiopulmonary arrest in humans secondary to kratom exposure.[94] The limitation is that these cases often involve polysubstance exposure, making it difficult to determine the independent contribution of kratom alone.[95] Though human evidence is limited, respiratory depression can be considered a potential complication, particularly with concentrated kratom products high in 7-HMG or concomitant polysubstance exposure.

Another potential risk of kratom use is neurologic adverse effects including dizziness, confusion, agitation, hallucinations, altered mental status, and seizures. Of these various neurologic effects, seizures have been well described in case reports involving individuals with confirmed or reported kratom exposure. A Malaysian case series identified recurrent seizures among young adults consuming kratom beverages. Additional case reports describe tonic-clonic seizures associated with kratom consumption. This research, however, is limited by polysubstance exposure in these individuals making it difficult to establish a direct causal relationship.[94,96,97] The association between kratom and seizures should be interpreted cautiously, available evidence supports seizures as a potential adverse event associated with kratom use but does not establish a definitive dose-response relationship or prove that kratom alone is responsible for most reported cases.[98,99]

Cardiovascular effects represent another important component of kratom toxicity. Tachycardia and hypertension are among the most frequently reported acute cardiovascular effects in poison-center datasets.[94] Experimental and observational evidence has also raised concern regarding QT-interval effects, arrhythmias, cardiomyopathy, and, in severe cases, cardiopulmonary arrest with kratom use. In vitro research suggests mitragynine can interfere with cardiac ion channels and may prolong ventricular repolarization; however, these findings have not been consistently demonstrated in human observational studies. In one study of regular kratom users, overall ECG abnormality rates were not higher than those of controls, although sinus tachycardia and borderline QTc findings were more frequent.[100,101] Case reports have also described ventricular arrhythmias, cardiomyopathy, myocardial injury, and cardiac arrest in patients exposed to kratom; however, many of these reports involve polypharmacy or comorbidities that may independently contribute to cardiovascular risk. Consequently, kratom-associated cardiovascular toxicity is best regarded as a plausible risk rather than an inevitable consequence of exposure. Patients with underlying cardiovascular disease or those taking other QT-prolonging or sympathomimetic medications may warrant caution.

Other systemic toxicities include kratom-associated liver injury, described as a predominantly cholestatic or mixed hepatocellular-cholestatic syndrome, typically developing after repeated exposure and resolving after discontinuation in reported cases.[102] Additionally, renal injury, rhabdomyolysis, gastrointestinal toxicity, and

infectious complications have also been reported, although the frequency and causal relationship of these events remain uncertain.[95,103]

5.4. REGULATORY CONCERNS

Kratom regulation is difficult because it is marketed as a botanical or herbal product while possessing pharmacologically active compounds with opioid-receptor activity. Regulatory policies also vary considerably between jurisdictions, creating an inconsistent legal environment. The U.S. Food and Drug Administration has not approved kratom for the treatment of pain, opioid withdrawal, or any other medical indication, and the product has not undergone standardized efficacy and safety evaluation required for approved pharmaceuticals. The Drug Enforcement Administration has historically identified kratom as a substance of concern and, in 2016, considered emergency federal scheduling, a proposal that was subsequently withdrawn.[78,79]

A second major regulatory challenge is quality control. Commercial kratom products can vary substantially in alkaloid concentration, and product labeling does not reliably predict the amount of mitragynine or 7-HMG present in the product. Studies comparing the composition of commercially available kratom products have identified variation in mitragynine concentration as well as contamination with microorganisms and toxic metals, including lead, nickel, and chromium.[81,104]

Published product-testing data also suggest that the risk of exceeding permissible exposure limits for certain elemental contaminants increases substantially at high daily kratom consumption.[105] Highly concentrated extracts and 7-HMG-enriched products further complicate the regulatory landscape, as some commercial products intentionally concentrating opioid-active constituents.[82,106]

Such products may therefore produce pharmacologic exposures substantially different from those historically associated with traditional Southeast Asian kratom use. From a public health perspective, the increasing availability of potent extracts, inconsistent labeling, polysubstance use, and limited clinician awareness create a combination of factors that may increase the risk of dependence, drug interactions, and acute toxicity. Future research should therefore prioritize standardized preparations, quantitative pharmacokinetic and toxicologic measurements, controlled clinical trials, systematic evaluation of drug interactions, and improved manufacturing standards.

6.0 TURMERIC (CURCUMIN) AND SUPPLEMENT-ASSOCIATED HEPATOTOXICITY

6.1. THERAPEUTIC APPLICATIONS

USE IN ARTHRITIS AND CHRONIC INFLAMMATORY CONDITIONS

Turmeric is a yellow spice obtained from the rhizome of *Curcuma longa* and has been an essential component of Ayurvedic medicine. The biological activity of turmeric is due to curcuminoids, which comprise 3-6% of its dry weight.[107] The three major curcuminoids are curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC), with curcumin being the most abundant and active.[108] Due to their hydrophobic chemical structures, it possesses strong antioxidant and anti-inflammatory properties.[109] Thus, it has been widely used as an over-the-counter herbal supplement in various inflammatory diseases.

Curcumin has also demonstrated improved pain and joint function comparable to that of nonsteroidal anti-inflammatory drugs (NSAIDs), conventional articular cartilage nutritional supplements, and disease-modifying antirheumatic drugs (DMARDs).[110,111] A systematic review and meta-analysis by Zeng et al. included 29 randomized controlled trials involving 2396 patients and found that patients who supplemented with curcumin reported less joint pain, better physical function and mobility, and reduced joint stiffness, with no significant difference in side effects.[111]

Beyond mediating symptoms, curcumin may also exhibit immunomodulatory capability. In ankylosing spondylitis (AS) patients, four months of nanocurcumin administration increased the number of regulatory T cells (Tregs) and FoxP3 expression.[111] Treatment also increased the anti-inflammatory cytokines transforming growth factor-β (TGF-β) and interleukin-10 (IL-10) while reducing the pro-inflammatory cytokine interleukin-6 (IL-6).[111] These findings suggest that adjunct curcumin for inflammatory arthritic diseases is safe and effective due to its ability to reduce antigen presentation and limit tissue damage in patients. However, the available evidence remains heterogeneous because of the variability in study populations, curcumin formulations, dosing regimens, and treatment durations.

ANTI-INFLAMMATORY MECHANISMS

Curcumin hinders the activation of Toll-like receptors (TLRs), preventing downstream signaling via TRAF6 and TAK1.[109] This diminishes the initiation of the Mitogen-Activated Protein Kinase (MAPK) pathway, decreasing activation of Activator Protein-1 (AP-1), p38, JNK, and ERK. Additionally, curcumin suppresses the IKKα/IκB/NF-κB pathway and subsequently VEGF, MMP-2, MMP-9, and COX-2. Because NF-κB is required for priming the NLRP3 inflammasome, curcumin indirectly suppresses NLRP3 activation and the subsequent secretion of cytokines IL-1β and IL-18.[109]. JAK/STAT signaling is also inhibited by preventing phosphorylation of STAT proteins.[109]. Persistent activation of these signaling molecules has been implicated in chronic inflammation, autoimmune disorders, and cancer progression.[109]. With reduced activation of these immune-mediated pathways, curcumin limits the expression of pro-inflammatory, pro-angiogenetic, and extracellular matrix-degrading enzymes found in common inflammatory diseases.

Studies using peripheral blood mononuclear cells from patients with RA demonstrated that curcumin suppresses macrophage colony-stimulating factor (M-CSF) and

RANKL-induced osteoclast formation by inhibiting the ERK1/2, p38, and JNK MAPK signaling pathways.[112]

6.2. INCREASING REPORTS OF LIVER INJURY

DRUG-INDUCED LIVER INJURY ASSOCIATED WITH SUPPLEMENTS

Though antibiotics remain the leading cause of DILI in the Western hemisphere, herbal and dietary supplement-related liver injury (HDS) has steadily risen. For example, an Australian retrospective analysis demonstrated a 32% increase in HDS-related DILI when comparing cases reported between 2009–2011 and 2018–2020.[113]

CASE REPORTS AND PHARMACOVIGILANCE FINDINGS

Evidence is primarily based on case reports and observational studies rather than randomized clinical trials. The lack of standardized dosing and the use of supplements containing multiple ingredients make it challenging to attribute liver injury to turmeric alone. Thus, larger prospective studies using standardized variables would be useful in clarifying curcumin's hepatic safety. The hepatotoxic effects of turmeric have been documented in Table 1.

6.3. MECHANISMS OF TOXICITY

IDIOSYNCRATIC HEPATIC INJURY

Turmeric-associated liver injury is not dose-dependent but rather an idiosyncratic immune-mediated reaction.[107,114] Although the exact mechanism remains unknown, hepatotoxicity has been hypothesized to result from a combination of genetic susceptibility, underlying comorbidities, and enhanced curcumin exposure.[107] It has been theorized that curcumin or one of its metabolites may interact with HLA-B*35:01, activating T cells that attack hepatocytes.[113] Furthermore, patient-specific risk factors, including polypharmacy, underlying liver disease, excessive alcohol consumption, and metabolic syndrome, may further increase susceptibility to turmeric-induced hepatotoxicity by impairing hepatic reserve or altering hepatic metabolism.

BIOAVAILABILITY ENHANCERS AND TOXICITY CONCERNS

The therapeutic efficacy of turmeric is limited by poor absorption, rapid metabolism, and minimal tissue distribution.[115] For example, rats receiving 1 g/kg of curcumin showed plasma concentrations below 5 μg/mL, while 75% of the administered dose was excreted in the feces.[116] Turmeric alone is unlikely to cause hepatotoxicity. However, when turmeric is combined with piperine, the primary alkaloid in black pepper (Piper nigrum), the substantial increase in bioavailability may permit hepatotoxicity.[113] Piperine can increase curcumin bioavailability by 2000% by inhibiting UDP-glucuronosyltransferase (UGT) and CYP3A4 enzymes involved in xenobiotic metabolism.[117,118] Current evidence does not prove that piperine itself is hepatotoxic. Rather, it likely increases hepatic exposure to curcumin.[113]

Multiple clinical studies have supported that standardized turmeric extracts and curcumin are well-tolerated. In the randomized controlled trial by Na et al., 100 patients with diabetes and obesity receiving 300 mg/day of curcuminoids for 3 months reported no serious adverse events.[119] Furthermore, a randomized, double-blind, placebo-controlled clinical trial also found no significant difference in gastrointestinal tolerance between 60 individuals consuming 1000 mg of a highly bioavailable turmeric extract formulation (TF) and placebo over five weeks.[120]

While there is an increasing number of cases of turmeric-induced hepatotoxicity, this discrepancy may be explained by several factors. The participants in Laval et al.'s trial received a standardized dose and schedule, whereas many case reports involve longer durations, higher cumulative exposure, or products with variable formulations.[120] The case reports often involve commercial supplements containing bioavailability enhancers, like piperine, or other ingredients that may increase systemic exposure. These differences in dosage, duration, participant characteristics, and supplement composition may explain why the clinical trial found no significant difference in gastrointestinal tolerance between turmeric and placebo groups, whereas isolated case reports have documented serious adverse events.

POTENTIAL INTERACTIONS WITH MEDICATIONS

Curcumin has also been used alongside chemotherapy to enhance different cancer treatments. An immunohistochemical analysis demonstrated that, by suppressing NF-κB, COX-2, and VEGF signaling, curcumin sensitizes pancreatic cancer cells to the cytotoxic effects of gemcitabine, further limiting inflammation, angiogenesis, and metastasis.[121] It has also been shown to overcome tamoxifen resistance in patients with estrogen receptor-positive (ER-positive) breast cancer by diminishing oxidative stress and suppressing pro-inflammatory signaling.[122]

However, curcumin has also been shown to negatively interact with numerous prescription medications by inhibiting several enzymes within the cytochrome P450 (CYP450) system.[123] Consequently, inhibition of these enzymes can slow drug metabolism, causing medications to remain in the bloodstream longer than intended. Curcumin may alter the peak serum drug concentration of several classes of medications, including cardiovascular drugs, antidepressants, anticoagulants, antibiotics, chemotherapeutic agents, and antihistamines.[124] Both curcumin and BDMC significantly prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) at concentrations of 5 μM or greater.[125] Individuals taking multiple medications, particularly those with chronic medical conditions, may therefore be at greater risk of clinically significant drug interactions when using curcumin supplements.

6.4. CLINICAL IMPLICATIONS

RECOGNITION AND DIAGNOSIS

Diagnosing DILI is difficult because there is no single diagnostic test that confirms the condition. Instead, it relies on linking supplement use to the onset of liver injury while excluding other potential causes.[113] Patients commonly exhibit delayed-onset hepatocellular injury with recovery following withdrawal, validating that turmeric-associated DILI is a rare but adverse reaction.[126] As summarized in Table 1, hepatotoxicity occurred after 2 weeks-1 year of use and improved after discontinuation (e.g., positive dechallenge).[107,127] It was also possible for liver injury to recur upon rechallenge.[107]

MONITORING RECOMMENDATIONS

Using turmeric as a spice in cuisine is generally considered safe. While supplements may have higher doses or contain absorption enhancers, they may also increase systemic exposure and raise the risk of adverse effects.[124] Thus, turmeric supplement bottles should have warning labels indicating these risks.

PATIENT COUNSELING CONSIDERATIONS

At-risk patients should consult with their healthcare providers about supplement use, and providers should assess liver disease severity and monitor liver enzymes if use continues. Because certain herbs and spices are culturally meaningful, practitioners should be open to discussing various supplements with their patients while being cautious of possible toxicities.

7.0 COMFREY AND PYRROLIZIDINE ALKALOID TOXICITY

Another over the counter nutraceutical that is used for pain management is the plant comfrey, formally known as Symphytum officinale.[129] Comfrey has been used for over 2000 years for inflammatory muscle and joint pain.[130] It is particularly effective for conditions like osteoarthritis, tendonitis, and for healing sprains and fractures.[130] While comfrey has traditionally been used as a cream or ointment for external application to sprains and joint pain, it has also been ingested orally through tea or capsules with the intent to heal gastric ulcers and general musculoskeletal complications.[131] Notably, oral ingestion of comfrey has fallen out of use due to it having a much higher concentration of pyrrolizidine alkaloids, the compound responsible for the herb's toxicity.[132]

Specifically, comfrey includes multiple pyrrolizidine alkaloids, such as symphytine, echimidine, and lycopsamine, and their concentration depends on which part of the comfrey plant is used and when it is harvested.[133] Comfrey root usually contains higher concentrations of pyrrolizidine alkaloids compared to comfrey leaf, making it important to distinguish which preparation is used.[133] Pyrrolizidine alkaloids are recognized as hepatotoxic and potentially carcinogenic, which is why oral comfrey products are widely avoided today.[134] When comfrey is ingested, these pyrrolizidine alkaloids are metabolized by the liver into reactive dehydropyrrolizidine alkaloid (DHPA) intermediates, which are responsible for the acute toxic effect.[135] These intermediates bind to cellular proteins and specifically damage hepatic sinusoidal endothelial cells via glutathione depletion and direct extracellular matrix destruction.[136] This endothelial damage widens intercellular gaps, allowing blood to obstruct hepatic sinusoidal flow.[137] This process is formally recognized as hepatic sinusoidal obstruction syndrome, also known as hepatic veno-occlusive disease.[137]

Clinically, comfrey-induced hepatic sinusoidal obstruction syndrome presents as hepatomegaly, ascites, and jaundice due to destruction of hepatic veins.[138] Furthermore, there is an increased risk of sinusoidal obstruction syndrome when comfrey is ingested orally, with one case biopsy showing sublobular vein occlusion along with hemorrhagic hepatocyte necrosis.[138] Untreated sinusoidal obstruction syndrome can lead to complete obliteration of hepatic sinusoidal veins, which results in cirrhosis and ultimately liver failure.[139] One notable case documents a 49-year-old woman who ingested oral comfrey daily for six months, and developed acute ascites and edema requiring a portocaval shunt.[140] While liver failure is a known end result of untreated comfrey toxicity, there may also be carcinogenic potential. The metabolites of the pyrrolizidine alkaloids have been shown to be genotoxic and even induce p53 and K-ras gene mutations, raising concerns that comfrey-induced toxicity could have a carcinogenic effect in humans.[141]

Given the documented liver toxicity, there have been regulations created across multiple countries to restrict or remove orally ingested comfrey from the market. Most notably, in 2001 the U.S. Food and Drug Administration advised manufacturers to remove oral comfrey products from the market and to cease marketing comfrey for internal use.[132] Additionally, other countries like the United Kingdom, Australia, and Canada have similarly restricted or banned oral comfrey use.[141] It should be noted that topical formulations like creams and ointments remain relatively unrestricted.[134] Furthermore, current recommendations state that the use of topical comfrey products should only be used for short term use on intact skin, while oral ingestion is entirely discouraged due to its hepatotoxicity.[142] However, some may argue that the advised short term use of topical comfrey is too conservative with recent studies showing that the absorption of pyrrolizidine alkaloids through intact human skin is minimal, supporting the use of well-formulated topical comfrey products for musculoskeletal pain and inflammation.[143]

8.0 BOSWELLIA (*BOSWELLIA SERRATA*)

Boswellia serrata, or Indian frankincense, is an herbal supplement that has been used in Ayurvedic medicine for centuries to help treat inflammatory conditions and joint pain.[144] Its active compounds, known as boswellic acids,

Table 1. Case Studies of Turmeric-Induced Acute Hepatitis Disorders

Study	Intervention	Results	Conclusion
Case report[128]	67 y/o male patient developed acute toxic hepatitis while receiving intravenous paclitaxel chemotherapy and concurrently taking turmeric, milk thistle, and chlorella supplements. Exact supplement doses not reported.	Liver function tests showed AST 2784, ALT 4188, TB 9.0, DB 6.8. Patient's liver tests recovered with no permanent injury 5 days after hospitalization and cessation of all drugs and supplements.	Liver injury was likely multifactorial and resulted from turmeric's inhibition of CYP enzymes, amplifying serum paclitaxel concentration.
Systematic review[127]	Analyzed 23 patients aged 48-63 y/o that developed acute hepatitis after consuming turmeric supplements produced by various manufacturers. 7 cases were based in Tuscany, Italy (2018–2019). Many formulations contained piperine. Exact doses not reported.	Liver injury and inflammation was confirmed by marked elevations in ALT and AST in all patients. Out of the 23 patients, 17 experienced positive dechallenge, 1 was hospitalized, 2 died, and 3 had unknown clinical outcomes.	Elevated liver enzyme values and positive rechallenge support turmeric-induced acute hepatitis.
Comprehensive review of multiple published cases[107]	Analyzed 4 females and 1 male aged 50-78 y/o for recovery of liver injury after cessation of turmeric supplementation. Latency period 1-10 months. Exact doses not reported.	Liver injury improved across all patients following discontinuation of turmeric. 1 patient experienced recurrence of liver injury upon rechallenge, with resolution after discontinuation.	Positive dechallenge and consistent improvement after discontinuation strengthen evidence for turmeric-induced liver injury.
Case report[114]	61-year-old man with metabolic syndrome and a history of high-risk alcohol consumption who consumed an oral dietary supplement containing turmeric and black pepper (piperine). Exact dose not reported.	Patient developed acute hepatocellular liver injury. At initial examination, AST 1250, ALT 2534, DB 172, TB 247. All lab values returned to baseline 43 days after discontinuation of turmeric supplementation. RUCAM = 8.	Liver injury was likely multifactorial, involving turmeric supplementation, piperine-enhanced curcumin bioavailability, metabolic syndrome, and alcohol use. Liver function showed positive dechallenge after discontinuation of turmeric supplementation.
Case report[113]	40 y/o female consumed an oral daily "wellness shot" containing turmeric and black pepper (piperine) for approximately 5 months. Exact turmeric and piperine doses were unknown.	Liver function tests showed TB 99, ALT 2519, AST 1296, gamma-glutamyl transferase 68. Liver biopsy revealed Zone 3 necrosis and bridging with apoptotic cells, macrophages, and rosettes.	Liver function tests and biopsy confirm acute hepatocellular injury. The chronological association between supplement use and symptom onset support turmeric-associated DILI.
Case report[126]	49 y/o female patient developed severe hepatocellular injury after consuming a daily oral turmeric supplement containing curcumin for 1.5 months. Exact dose not reported.	Liver function tests showed TB 7.1, ALP 138, ALT 3289, AST 1894. AST and ALT values improved >45% 3 days after hospitalization and discontinuation. R = 42. RUCAM = 7.	The chronological association between supplement use and symptom onset support turmeric-associated DILI. Improvement of AST and ALT after discontinuation also support DILI.

especially AKBA and KBA, are responsible for most of its anti-inflammatory effects and work differently than traditional NSAIDs.[145]

CLINICAL USES

Historically, Boswellia resin was used to treat inflammatory conditions including joint pain, respiratory illness, and digestive disorders.[144] Today, Boswellia serrata extract (BSE) is most commonly used as a complementary treatment for OA and chronic joint pain. Standardized oral extracts are widely available, and most clinical trials have used doses of 150–300 mg twice daily.[146] The European Pharmacopoeia recognizes KBA and AKBA as quality markers for Boswellia products.[5]

OA remains the main condition for which Boswellia is used, but researchers have also explored its use in RA, inflammatory bowel disease, asthma, and peritumoral brain edema. Studies in animal models suggest Boswellia may reduce joint inflammation and may even improve the effects of methotrexate while limiting liver toxicity, although this has not yet been confirmed in people.[147,148] Boswellia has also shown promise in inflammatory bowel disease and

other chronic inflammatory conditions, although additional clinical research is needed.[5,149]

MECHANISMS OF ACTION

Researchers believe Boswellia works through several different anti-inflammatory pathways. Much of the research has focused on inhibition of 5-lipoxygenase (5-LOX), which decreases leukotriene production and helps limit joint inflammation.[150] More recent work suggests AKBA may also encourage the production of molecules involved in resolving inflammation.[151] However, because AKBA is poorly absorbed after oral administration, these effects are likely explained by several boswellic acids acting together rather than AKBA alone.[5,150] Boswellia also suppresses NF-κB signaling, reducing the production of inflammatory cytokines including TNF-α, IL-1β, and IL-6.[152] Clinical studies have reported corresponding decreases in inflammatory markers such as TNF-α, hs-CRP, and IL-6 in patients with OA following supplementation.[146,153] Boswellia may also help slow cartilage damage. Both animal and human studies have found lower levels of cartilage breakdown markers along with increased collagen production after treatment.[148,154] β-boswellic acid has also been shown to inhibit inflammatory signaling through TLR4 and IL-1R pathways in joint cells.[155] Unlike NSAIDs, which primarily inhibit COX enzymes, Boswellia acts on multiple inflammatory pathways, including leukotrienes, NF-κB signaling, and cartilage-degrading enzymes. This broader mechanism may contribute to its benefit in inflammatory joint diseases.[5]

EVIDENCE FOR THERAPEUTIC EFFECTIVENESS

Most clinical studies evaluating Boswellia have focused on patients with osteoarthritis. Although many of these studies are relatively small, the overall findings have been promising. A 2020 systematic review and meta-analysis of seven randomized controlled trials found that Boswellia significantly reduced pain, stiffness, and improved physical function compared with control groups, with benefits typically seen after at least four weeks of treatment.[156] Another systematic review reported similar findings but noted that many studies were small and that direct comparisons with NSAIDs are lacking.[157] More recent randomized trials have reported similar findings. In a placebo-controlled trial, patients taking Boswellia serrata extract experienced significant improvements in pain, function, and inflammatory markers, with no serious adverse events reported.[146] Similar improvements in pain, stiffness, and function were observed with the standardized extract BOSMAX®, which was also well tolerated.[153] Another randomized trial suggested that Boswellia, combined with celery seed extract, may also support cartilage health by reducing markers of cartilage breakdown and increasing collagen synthesis.[154]

Evidence for RA is more limited and comes primarily from animal studies. Boswellia has reduced joint inflammation in preclinical models and has shown potential to enhance methotrexate therapy while reducing liver toxicity, but additional human studies are needed.[147,148] Overall, Boswellia extracts have been estimated to improve symptoms in 60–70% of patients with chronic inflammatory conditions.[145] The Department of Veterans Affairs clinical practice guideline recognizes the positive findings from systematic reviews and randomized trials but notes that larger, high-quality studies are still needed before strong clinical recommendations can be made.[158] Taken together, current evidence suggests Boswellia may be a useful addition to OA treatment, but larger studies are still needed before it can be recommended routinely.

SAFETY AND CLINICAL CONSIDERATIONS

Across published clinical trials, Boswellia has generally been well tolerated with few adverse effects. The most common side effects are mild gastrointestinal symptoms, including nausea, acid reflux, and diarrhea, while allergic reactions are rare.[145] Recent clinical trials also reported no serious adverse events, supporting its favorable safety profile.[146,153] Although significant drug interactions have not been confirmed, Boswellia may interact with anticoagulants, antiplatelet medications, NSAIDs, and other highly protein-bound drugs, so caution is advised.[147,150] AKBA also has poor oral bioavailability, although absorption improves when taken with food, and newer formulations may improve absorption.[5,145,159]

One practical concern is product quality. Because Boswellia is sold as a dietary supplement, products can vary in their boswellic acid content and degree of standardization.[5] While current evidence suggests Boswellia is a safe option for managing OA symptoms, it should not replace disease-modifying therapy for conditions such as RA. Based on the available evidence, Boswellia appears to have a favorable risk-benefit profile, particularly when compared with long-term NSAID therapy. However, more research is needed to clarify its long-term safety and establish stronger clinical recommendations.[5,157,160]

9.0 DEVIL'S CLAW (*HARPAGOPHYTUM PROCUMBENS*)

The genus *Harpagophytum*, commonly referred to as devil's claw, is composed of two distinct species: *Harpagophytum procumbens*(Hp) and *Harpagophytum zeyheri* (Hz).[161] Hp is a southern African plant with an ethnobotanical history spanning centuries and many documented traditional preparations, uses, and rituals associated with it.[161] Various commercial extracts and preparations of Hp intended for human consumption are now widely available, mostly marketed as herbal medicinal products (HMP), food supplements (FS), and dietary supplements DS.[162] This section aims to review the main clinical uses of Hp, the complex biochemical interactions that might lead to its effects, the clinical evidence available on its use, and toxicological and safety data.

9.1. CLINICAL USES

Devil's claw has no well-established therapeutic indications[163] though many different possible uses have been investigated, including musculoskeletal and rheumatologic conditions (OA, low-back pain (LBP), RA), inflammatory and immune-related conditions (familial Mediterranean fever, chemosis, endometriosis), and others (dyspepsia, follicular lymphoma, prevention of sore throat after tracheal intubation).[42,164-167] Despite this long list of applications, most clinical research on Hp centers on muscoloskeletal disorders, in particular OA and LBP, and evidence regarding use in acute inflammatory conditions, severe disease states, or central pain syndromes remains scarce or weak.[167] The European Medicines Agency (EMA) in its monograph on devil's claw, recognizes two traditional uses based on long-standing use: (a) relief of minor articular pain and (b) relief of mild digestive disorders.[163]

9.2. MECHANISMS OF ACTION

The mechanism(s) of action of Hp remains clinically uncertain,[167] though *in vitro* and animal studies show inhibition of multiple components and pathways of the inflammatory cascade.[168-170] Different Hp extracts have been found to decrease the production of IL-1β, IL-6, and TNF-α,[168,169] and an *ex vivo* experiment found reduction of COX-2 expression while testing a laboratory extract.[171] Fiebich et al. (2012) found that Hp inhibited AP-1-mediated transcription of pro-inflammatory genes, e.g., IL-1β, IL-6, TNF-α, and COX-2.[168] Another study, focused on CB2 receptor-mediated anti-inflammatory activity, a molecular mechanism possibly involved with OA.[170] The authors found a statistically significant down-regulation of *c-Fos* mRNA expression, a component of the AP-1 transcription factor complex involved in expression of MMP-13.[170] They also reported that the whole Hp extract increased CB2 mRNA expression and decreased cAMP levels and MMP-13 mRNA expression.[170] An *in vivo* study using a rat model of RA showed that Hp's anti-inflammatory effect was more pronounced at the chronic stage, as indicated by reduced paw swelling on days 14 and 19, but did not investigate whether this delay of action was attributable to transcriptional modulation, cumulative exposure to Hp, or disease progression.[169]

Mariano et al. (2022) also separately tested harpagoside and the three volatile compounds most represented in the extract, β-caryophyllene, α-humulene, and eugenol, to investigate their individual contribution.[170] Harpagoside is often described as one of the major active iridoid glycosides in Hp,[169,170] and it has been shown *in vitro* to inhibit IL-1β, IL-6, and TNF-α production.[169] The whole extract increased CB2 mRNA expression and reduced cAMP production and MMP-13 expression more than any of the components tested separately or a mixture of all four.[170] These findings suggest that the anti-inflammatory and potential anticatabolic activities of Hp depend on multiple phytochemicals, limiting the generalizability of single-compound research and the standardization efforts based on harpagoside content only.[168-171]

9.3. EVIDENCE FOR THERAPEUTIC EFFECTIVENESS

Evidence for the clinical effectiveness of Hp is heterogeneous, involving different preparations, indications, and outcome measures,[167] severely limiting data pooling and the ability to draw a simple efficacy conclusion.[42,165,167] Despite these limitations, available research on Hp use in OA points to modest short term efficacy in terms of improved pain and stiffness outcomes, and a decrease in usage of other anti-inflammatory or analgesic medications.[165] A 2014 Cochrane review of herbal therapies for OA analyzed evidence from four clinical trials using Hp.[165] Two of the trials used an ethanol-based extract and registered no improvement in WOMAC pain scores.[165] One other used a water-based extract, which showed an improvement in pain, measured on a 0-4 categorical rating scale.[165] The remaining study was a 16-week randomized trial of 122 patients with knee or hip OA that compared one commercially available, powdered Hp product with diacerhein 100 mg/day.[165] Hp was found to be noninferior to diacerhein in reducing pain, measured with a 100-mm visual analog scale (VAS).[165] Participants in the Hp group also showed lower NSAIDs and analgesics (paracetamol plus caffeine) use than the diacerhein group at all time points.[165] The same limitations and similar conclusions apply to clinical studies on the use of Hp for LBP.[42] A different 2014 Cochrane review analyzed 3 clinical trials of Hp extract use in acute exacerbations of chronic non-specific LBP (NSLBP), finding low quality evidence for the use of daily Hp extracts, standardized to 50 or 100 mg of harpagoside content, and very low quality evidence for an Hp product's relative equivalence to rofecoxib 12.5 mg/day.[42]

Results from clinical studies that used Hp in patients with mixed indications also share the limitations in generalizability mentioned above.[172,173] The studies analyzed here found significant improvements in pain and function,[172,173] while also reporting improvements in specific outcome measures.[172,173]

An 8-week uncontrolled study enrolled 259 patients with "arthritis and other rheumatic conditions" to observe the effectiveness, tolerability, safety, and quality of life (QoL) changes during treatment with Hp.[173] Two hundred twenty-two patients (intention-to-treat (ITT) population) were included in the effectiveness assessments, of whom 207 patients had complete data.[173] Significant improvements were found in patient-assessed global pain, stiffness, and function, and in the same sample SF-12 questionnaire scores also increased, indicating improved QoL.[173] Furthermore, among patients taking analgesics for general rheumatic disorders (154 patients), 60% either reduced or stopped concomitant pain medication use.[173]

An uncontrolled, 54-week surveillance study, one of the longest clinical study on Hp, monitored 114 patients with NSLBP, knee or hip OA, treated with a proprietary Hp extract.[172] Pain and functional capacity were measured every 4-6 weeks using disease-specific and generic outcome measures.[172] MANOVA showed a significant change over time and most individual measures improved, except for the WOMAC stiffness and Arhus invalidity scores.[172] As this

study did not have a control group, these changes cannot be confidently attributed to Hp.[172]

9.4. SAFETY AND CLINICAL CONSIDERATIONS

The EMA monograph on Hp and Hz outlines the general safety profile of devil's claw products.[163] In the monograph there are listed three categories of undesirable effects, all with unknown frequency: gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal pain), central nervous system effects (headache, vertigo), and hypersensitivity reactions (rash, hives, facial edema).[163]

A safety-focused review analyzed 28 clinical trials using different Hp formulations and found that minor adverse events (mainly gastrointestinal) were described in 20 studies with a rate of adverse events around 3%.[174] In none of the double-blind studies scrutinized was the incidence of adverse events in the Hp group higher than that of placebo.[174] As only two of the included studies were carried out over a year of surveillance, no characterization of long-term safety of Hp products can be made.[174]

EMA lists two contraindications to the use of Hp: (a) hypersensitivity to the plant and (b) active gastric or duodenal ulcers.[163] The latter was also identified by Vlachojannis et al. (2008).[174] Both sources issue a warning for gallstones[163, 174] and another paper suggests a possible mechanistic explanation, mentioning older research that evidenced the choleretic effect of iridoids.[175] Use of *Harpagophytum* during pregnancy, lactation, and in people under 18 is not recommended as no adequate data are available on these patient populations.[163] Fertility, genotoxicity, and carcinogenicity data are severely limited or lacking as well.[163] One preclinical toxicological study on rats used three different laboratory Hp extracts.[176]

10. WHITE WILLOW BARK (*SALIX ALBA*)

White willow bark, derived from *Salix alba* has long been used as a medicinal botanical for treating pain, fever, and inflammatory disorders. Willow bark has salicin that is a phenolic glycoside that is metabolized to salicylic acid after taken orally.[177] It is commonly described as nature's aspirin. This comparison isn't accurate because willow bark does not have acetylsalicylic acid. Unlike aspirin, salicylic acid does not irreversibly acetylate COX enzymes. Along with salicylin, willow bark extracts have flavonoids, polyphenols, tannins, and other phenolic compounds that can contribute to analgesic and anti-inflammatory effects.[177-179]

10.1. CLINICAL USES

The main clinical role of willow bark extract is to manage nonspecific chronic low back pain and other musculoskeletal pain conditions.[180] Traditionally it's used in treatment of rheumatic complaints, arthritis discomfort, and inflammatory disorders. Clinical evidence shows that it is best for short term symptomatic relief of chronic low back pain. Willow bark is considered a complementary therapy, and it is not supposed to replace evidence-based treatments such as physical therapy, and conventional medical therapy.[180]

10.2. MECHANISMS OF ACTION

The therapeutic effects of standardized white willow bark extracts are thought to result from the combined activity of multiple phytochemical constituents rather than salicin alone, including flavonoids, polyphenols, and tannins, which may contribute to their anti-inflammatory and analgesic properties.[178,179] Because the phytochemical composition varies among plant species, growing conditions, and extraction methods, differences in extract composition remain an important limitation when comparing studies and commercial preparations.[180,181] After oral administration, salicin is metabolized to salicylic acid, which inhibits prostaglandin synthesis through reversible COX modulation.[182,183] Unlike aspirin, however, salicylic acid does not irreversibly acetylate COX enzymes, resulting in a distinct pharmacologic profile and less prolonged effects on platelet function.[182,183]

Experimental studies have demonstrated that the pharmacologic effects of white willow bark extend beyond the activity of salicin alone, suggesting that additional phytochemical constituents contribute to its anti-inflammatory properties.[179,180] Flavonoids and polyphenolic compounds have been shown to reduce oxidative stress, regulate the release of inflammatory mediators, and modulate nuclear factor kappa B (NF-κB) signaling pathways involved in cytokine production.[179] In vitro investigations have also demonstrated inhibition of COX and LOX inflammatory pathways, supporting potential mechanisms of analgesic and anti-inflammatory activity.[179,180] However, these findings are derived primarily from experimental and laboratory studies, and corresponding clinical evidence demonstrating improved patient outcomes remains limited.[180]

10.3. EVIDENCE FOR THERAPEUTIC EFFECTIVENESS

Clinical evidence supporting white willow bark is mostly derived from randomized controlled trials about chronic low back pain. in a randomized blind placebo trial with 210 adults, it was demonstrated that standardized willow bark extract with 240mg of salicin daily resulted in reductions of pain compared to the placebo group.[184] 39% of the participants that received the higher dose had complete pain relief during the final treatment week without needing extra analgesic medication, and a smaller 120mg dose of the salicin showed less therapeutic effect. This suggests that there is a possible dose-response relationship.[184]

A randomized controlled trial comparing standardized willow bark extract with the selective cyclooxygenase-2 (COX-2) inhibitor rofecoxib in patients with chronic low back pain demonstrated clinically meaningful pain reduction with willow bark treatment. However, the study was not designed or statistically powered to establish therapeutic equivalence between willow bark and prescription anti-inflammatory therapy.[184] These findings are supported by subsequent systematic reviews, which have concluded that willow bark may provide modest analgesic benefits, partic-

ularly for chronic musculoskeletal and low back pain, while emphasizing that the overall quality of evidence remains limited.[129,185] Interpretation of the available literature is complicated by substantial heterogeneity among studies, including differences in plant species, extract standardization, salicin content, treatment duration, patient populations, and outcome measures, making direct comparisons across trials difficult.[129,185] The Cochrane review of herbal therapies for low back pain identified promising early evidence for willow bark but concluded that additional well-designed randomized controlled trials are necessary before firm clinical recommendations can be made.[129] More recent reviews have similarly suggested potential benefit in OA and other arthritis-related pain conditions while continuing to emphasize the need for larger, higher-quality clinical studies to confirm efficacy and define optimal treatment protocols.[185]

10.4. SAFETY AND CLINICAL CONSIDERATIONS

White willow bark is generally well tolerated when used appropriately for short-term treatment; however, adverse effects including gastrointestinal discomfort, nausea, dyspepsia, dizziness, and hypersensitivity reactions have been reported.[179,180] Because salicin is metabolized to salicylic acid after absorption, individuals with aspirin hypersensitivity should avoid willow bark preparations due to the potential for cross-reactivity 2017.[163,182]; Although salicylic acid differs pharmacologically from aspirin by not irreversibly acetylating COX enzymes, patients with aspirin allergy may still experience hypersensitivity reactions, and caution is therefore recommended. Clinicians should also consider potential interactions with anticoagulants, antiplatelet medications, and other drugs that increase bleeding risk, particularly in older adults and patients with multiple comorbidities.[179,181]

11. GINGER

Ginger (*Zingiber officinale*) has emerged as a widely investigated botanical therapy. Its main constituents, gingerols and shogaols, influence several pathways involved in inflammation, oxidative stress, and pain perception.[186] These compounds suppress the production of inflammatory mediators, reduce oxidative damage, and help alleviate joint pain and stiffness. It shows promise in the complementary treatment for patients with OA.[187,188]

The primary mechanism of ginger's anti-inflammatory and analgesic effects is through the inhibition of the COX pathway.[187] The COX pathway consists of two major isoenzymes, COX-1 and COX-2. While COX-1 supports normal physiological functions such as gastric mucosal protection and platelet function, COX-2 is upregulated during inflammation. It is responsible for the prostaglandins that promote vasodilation, edema, and pain sensitization.[189] This pathway promotes inflammation and is upregulated in OA patients.[190]

Although COX-1 is inhibited, ginger mainly targets the inflammatory COX-2 enzyme.[191] Gingerols and shogaols are the primary active compounds in ginger. Fresh ginger is particularly rich in gingerols, specifically 6-gingerol, whereas shogaols, specifically 6-shogaol, are formed during drying, heating, or processing of ginger.[186] A study with mice by Wu in 2010 found that 6-shogaol is more potent than 6-gingerol in the inhibition of COX-2.[192] Both 6-gingerol and 6-shogaol inhibit COX-2 activity, reducing the production of prostaglandin E_2 (PGE_2), a principal mediator of inflammatory pain.[186] Lower PGE_2 concentrations decrease peripheral nociceptor sensitization, resulting in reduced pain perception and improved joint function.[187]

Ginger has other anti-inflammatory mechanisms as well, such as the inhibition of the 5-LOX pathway. This pathway synthesizes leukotrienes, which promote leukocyte recruitment and increase vascular permeability. By suppressing leukotriene synthesis, ginger limits inflammatory cell infiltration into joints and reduces synovial inflammation.[187] Another mechanism involves suppression of the nuclear factor-kappa B (NF-κB) pathway. NF-κB regulates the expression of numerous pro-inflammatory genes such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). In suppressing NF-κB, it limits other pro-inflammatory biomarkers.[188] All of these contribute to synovial inflammation and pain sensitization in osteoarthritis. Gingerols and shogaols exhibit antioxidant properties by scavenging reactive oxygen species (ROS).[193] Oxidative stress contributes to chondrocyte damage, extracellular matrix degradation, and progression of osteoarthritis. Gingerols and shogaols help stabilize ROS with their phenol hydroxyl group.[193] Through antioxidant activity, these compounds help protect joint tissues from inflammatory and oxidative injury. Conventional NSAIDs inhibit COX enzymes.

In contrast, ginger modulates various inflammatory pathways simultaneously. This multifaceted inhibition allows ginger to target multiple components of the inflammatory response. All of these contribute to synovial inflammation and pain sensitization in osteoarthritis.

The therapeutic efficacy of ginger supplementation for OA has been evaluated in numerous randomized controlled trials (RCTs) and systematic reviews, with evidence suggesting modest but clinically meaningful reductions in pain and improvements in physical function.[194,195] Although the magnitude of benefit varies depending on the formulation, dosage, treatment duration, and patient population, the overall body of evidence supports ginger as a safe complementary therapy for managing OA symptoms.[194,195]

An early placebo-controlled trial investigated a standardized ginger extract in patients with symptomatic knee OA.[194,195] This trial found that the extract produced improvements in knee OA compared with placebo over 6 weeks. Among the 247 participants, 63% receiving ginger supplementation showed improvements, compared to 50% in the placebo group (P = 0.048). Additionally, fewer patients in the ginger group required rescue analgesics, suggesting that ginger supplementation may reduce dependence on conventional pain medications.[194,195] A more recent meta-analysis conducted evaluated five randomized placebo-controlled trials with OA patients and found that

oral ginger supplementation produced statistically significant reductions in pain and disability compared with placebo.[194,195] Although the effect sizes were classified as small to moderate (SMD = -0.30, 95% CI: [0.50, 0.09], P = 0.005), they reported a favorable safety profile. The paper also reported a low degree of inconsistency across trials (I^2 = 27%). Most adverse events were mild gastrointestinal symptoms, including heartburn and dyspepsia, with serious adverse effects occurring infrequently.[194,195] These papers show a clear positive effect for treatment. Overall, the clinical evidence shows that ginger supplementation provides modest but meaningful improvements in OA pain, joint stiffness, and physical function, particularly when used alongside conventional interventions such as exercise therapy, weight management, and pharmacologic treatment.

Conducted a trial comparing a standardized ginger extract with ibuprofen and placebo.[196] 120 OA patients received 30 mg of standardized ginger extract twice daily, 400 mg of ibuprofen three times daily, or placebo over 4 weeks. Both the ginger and ibuprofen groups experienced significantly greater reductions in pain than the placebo group. The placebo group showed only a modest decrease in the Visual Analog Scale (VAS) scores, from 64.2 ± 2.8 mm to 56.5 ± 3.6 mm. In contrast, the ginger extract group experienced a substantial reduction, with VAS scores decreasing from 71.7 ± 3.5 mm to 30.0 ± 3.7 mm, while the ibuprofen group showed a similar improvement, with scores declining from 71.2 ± 2.48 mm to 28.0 ± 3.0 mm. The difference among the three groups was highly significant (P < 0.0001), while no statistically significant difference was observed between the ginger and ibuprofen groups. The authors concluded that standardized ginger extract may represent an effective alternative for managing OA symptoms. Both the ginger and the ibuprofen at their doses carried a similar effect.[196]

An early trial directly comparing ginger extract with an NSAID was conducted by Bliddal et al., 2000.[197] In this study, patients with hip or knee OA received ginger extract, ibuprofen, and placebo in randomized three-week treatment periods. They were separated by a one-week washout. Overall, treatment efficacy ranked ibuprofen (-15 mm) above ginger (-6 mm) and placebo (-4 mm), which were equal for both pain intensity measured by VAS. The functional impairment assessed using the Lequesne Index followed the same trends for the 3 groups: -15, -1, and 2, respectively. The crossover analysis did not demonstrate a statistically significant difference between ginger and placebo. However, this wasn't true during the initial treatment. The first treatment period, before crossover occurred, a reviewer commented that both ginger and ibuprofen produced significantly greater pain relief than placebo (P < 0.05). The authors suggested that carryover effects from the crossover design may have reduced the ability to detect treatment differences during later study periods. The washout period may have been too short to notice a difference in subsequent treatments. Importantly, no serious adverse events were reported, indicating that ginger extract was well tolerated throughout the trial. The authors concluded that ginger showed promise, but the carryover effects diminished evidence to establish that ginger's efficacy is comparable with ibuprofen.[197]

A more recent trial by Amorndoljai et al., 2017 compared ginger extract with 1% diclofenac gel.[198] The study used 120 patients with knee OA treated for 12 weeks. Both treatment groups showed significant improvements to the topical medicine. The two treatments produced comparable improvements in OA symptoms. A greater proportion of patients treated with ginger achieved at least a 50% reduction in pain intensity compared with those receiving diclofenac gel (67.7% vs. 45.7%, $p < 0.05$, which indicates significance). Neither treatment group experienced significant adverse events.[198]

Ginger is generally regarded as a safe, tolerated herbal treatment when consumed in the standard clinical doses.[199] Doses are typically 500–2,000 mg/day of standardized extract or up to 3 g/day of dried ginger powder.[199] Clinical trials evaluating ginger for OA and other musculoskeletal disorders typically administer this quantity of ginger. The studies ranged from several weeks to three months, and they showed excellent safety profile within these usage ranges.[195,199]

12. FEVERFEW (*TANACETUM PARTHENIUM*)

Feverfew, or *Tanacetum parthenium*, is a flowering plant belonging to the Asteraceae family. Traditionally, the herb was valued for its antipyretic properties, and its common name is derived from the Latin *febrifugia*, meaning "fever reducer." One of the earliest physicians, Dioscorides, used feverfew to treat inflammatory conditions, reflecting a long history in ancient medicine earning the nickname "medieval aspirin".[200] During its flowering season, July through October, the plant produces clusters of small flowers with yellow centers surrounded by a single row of white florets.[200] Growing in subtropical climates, feverfew is cultivated throughout Europe, Asia, North America, Australia, and North Africa.[201] The plant contains numerous bioactive chemicals, which contribute to its medicinal properties.[202]

12.1. CLINICAL USES

It has been widely used in folk medicine as a herbal remedy for fever, pain, inflammation, asthma, rheumatic and menstrual disorders, insect bites, infertility, and toothache.[203] Interest in feverfew as a potential treatment for migraines increased after a publication in 1972 described substantial reductions in headache frequency in a long term sufferer after beginning eating feverfew leaves.[204] In addition to migraine prevention, feverfew has traditionally been used to relieve toothaches and other mild pain conditions, although modern clinical evidence supporting these indications remains limited.[200]

12.2. MECHANISMS OF ACTION

Feverfew contains several biologically active phytochemicals, including sesquiterpene lactones such as partheno-

lide, 3β-hydroxyparthenolide, canin, and artecanin, flaveenoids, and essential oils.[203] Among these, parthenolide is considered the principal pharmacologically active compound and is found in the highest concentrations within the leaves and flowers.[200] Its antimigraine activity is due to multiple mechanisms, including inhibition of platelet serotonin release, relaxation of vascular smooth muscle, and anti-inflammatory effects.[205] In addition, parthenolide inhibits the IκB kinase complex, thereby suppressing NF-κB activation and reducing the production of pro-inflammatory cytokines.[206]

Another important constituent is the lipophilic flavonoid tanetin, which further contributes to its effects by inhibiting prostaglandin production.[207] Feverfew suppresses serotonin-induced contraction of vascular smooth muscle, inhibits platelet granule release through sulfhydryl group neutralization, and decreases histamine release from mast cells, possibly by modulating calcium influx.[208] The essential oil component chrysanthenyl acetate has demonstrated inhibition of prostaglandin synthetase and appears to possess analgesic properties, as well. In addition, the relatively high melatonin content found in certain feverfew varieties has been proposed as another factor involved in migraine prevention, as migraine attacks have been associated with decreased melatonin excretion.[209]

12.3. EVIDENCE FOR THERAPEUTIC EFFECTIVENESS

Clinical studies evaluating feverfew for migraine prevention have been positive but inconsistent. In one trial, patients who continued feverfew treatment for up to six months experienced fewer headaches, whereas participants switched from feverfew to placebo experienced nearly a threefold increase in headache frequency($P < 0.02$).[210] Although the study included a small sample and participants had previously self-medicated with feverfew, the findings suggest that continued use may help reduce recurrent headaches.[200] A meta-analysis reported that feverfew significantly reduced both the frequency of migraine and migraine compared with placebo.[208] Despite these favorable outcomes, the authors report considerable variability in study design, treatment regimens, and patient populations.[208] One trial using the standardized feverfew extract MIG-99 demonstrated a modest but statistically significant reduction in monthly migraine frequency compared with placebo, the overall evidence was considered insufficient to recommend feverfew as a routine therapy for migraine prevention.[211]

Although clinical investigations have focused primarily on migraine prophylaxis, preclinical studies suggest feverfew may possess broader analgesic properties. In a randomized controlled animal model of neuropathic pain, daily administration of *Tanacetum parthenium* extract for two weeks significantly reduced mechanical allodynia and thermal hyperalgesia following sciatic nerve injury.[212] While these findings indicate potential benefits beyond migraine prevention, additional human studies are needed to determine their clinical applicability.[202] In 2012 and 2024, the Canadian Guidelines rated feverfew as a strong recommendation for migraine prevention and the quality of evidence as moderate.[213] Overall, current evidence suggests that feverfew reduces the frequency and duration of migraine attacks while demonstrating emerging analgesic effects in experimental pain models. However, variability in study quality, dosing regimens, and feverfew formulations continues to emphasize the need for larger, standardized clinical trials.

12.4. SAFETY AND CLINICAL CONSIDERATIONS

Feverfew appears to have a favorable safety profile, although several adverse effects have been reported. The most common reactions include oral ulceration, lip swelling, loss of taste, and dermatitis, with mouth ulceration representing the most frequently reported adverse event.[200] Less frequently, gastrointestinal complaints, including nausea and abdominal discomfort, have also been described.[200] Abrupt discontinuation following prolonged feverfew use may result in a withdrawal phenomenon commonly referred to as "post-feverfew syndrome".[214] Reported symptoms include rebound headaches, insomnia, nervousness, muscle and joint stiffness, fatigue, poor sleep quality, and tension, suggesting that long term users should avoid sudden discontinuation.[214]

Feverfew is contraindicated during pregnancy because of its emmenagogic properties, which may stimulate uterine contractions and increase the risk of pregnancy loss, although more studies are warranted.[215] Individuals with allergies to members of the Asteraceae family, such as sunflowers, should avoid feverfew because of the potential for allergic reactions.[202]Although definitive drug interactions have not been reported, feverfew may increase bleeding risk due to its antiplatelet effects, so it is advised to restrict concomitant use with anticoagulants or antiplatelets.[216]

13.0 CONCLUSION

Despite widespread use of nutraceuticals and herbal supplements for consumers for pain management, these products raise existing concerns due to limited evidence and known safety risks. There is a lack of established guidance for nutraceutical products, with no standardized definition among global regulatory bodies a lack of rigorous safety and manufacturing guidelines associated with pharmaceuticals and dietary supplements.

These relaxed regulatory standards allow nutraceutical products to bypass manufacturing standards and premarket testing, raising safety concerns for products that can be directly sold to consumers.

Nutraceuticals and herbal pain products also contain known toxicity risks that clinicians must recognize in clinical and operative settings. Pain supplement use by patients often goes underreported, increasing the risk of post-operative side effects. As these supplements grow in popularity, it is necessary for clinicians to screen their patients for use, counsel them on associated risks and benefits, and ensure that use does not interfere with traditional medical treatment. Coordinated efforts across research, policy and clinical practice are also necessary to strengthen oversight.

Because herbal products do not go through the rigors of testing that drugs are required, onset, duration, and other critical pharmacological properties can be variable. Therefore, the American Society of Anesthesiologists and the American Association of Nurse Anesthetists (AANA) recommended that all herbal products and nutraceuticals be held at least 1-2 weeks prior to any interventional pain procedures or surgery to minimize risk of potential morbidity or mortality. In this regard, many of the herbals can cause an increased risk of bleeding which would be of significant concern for interventional pain procedures. Further, if multiple products are taken, there can be additive and/or synergistic effects leading to increased sedation, arrythmia, liver toxicity, and even death.[217]

This review demonstrates a disconnect between the popularity of nutraceuticals and limited evidence supporting their efficacy and safety. While some products demonstrate short-term pain relief, limited high-quality long-term studies remain a major barrier to established clinical use for nutraceuticals. Future research through randomized control trials and post-market surveillance are necessary to solidify gaps in nutraceutical safety and efficacy. Since the majority of patients undergoing pain procedures or surgery do not disclose their use of these products, clinicians should carefully review product use for all of their patients.[39]

Regulatory standards for herbals and nutraceuticals are complex, as they sit in a gray area between complementary medicine practices and western medicine. Given the immense popularity of nutraceuticals and advocacy for increased use by patients and manufacturers, concerns for contamination and organ toxicity cannot be ignored. As additional safety data is collected on nutraceutical use by consumers, ongoing regulations will require balanced input incorporating patient needs, existing research evidence, and clinical guidelines.

As pain products grow in popularity for patients looking for an alternative to traditional analgesic use, the medical community must take leadership in establishing appropriate standards for nutraceutical use. Steps to strengthen patient education and increase clinician awareness about supplement toxicities will enable providers to promote transparent conversations to encourage safe product use. Meanwhile, clinicians should also possess knowledge of existing regulatory standards and advocate for meaningful change to enable better safety protections for nutraceuticals and herbal products. Making these changes will help align consumer trends to scientific evidence and, as a result, help patients make safe and informed decisions when consuming nutraceutical and herbal products.

KEY REFERENCES

Kaye AD, Clarke RC, Sabar R, Vig S, Dhawan KP, Hofbauer R, et al. Herbal medicines: current trends in anesthesiology practice—a hospital survey. J Clin Anesth 2000;12:468–71. https://doi.org/10.1016/S0952-8180(00)00195-1

**outstanding study demonstrated that the majority of patients do not disclose taking nutraceutical of herbal products undergoing pain procedures or surgery.

Eastlack SC, Cornett EM, Kaye AD. Kratom—Pharmacology, Clinical Implications, and Outlook: A Comprehensive Review. Pain Ther 2020;9:55–69. https://doi.org/10.1007/s40122-020-00151-x.**Excellent review focused on kratom pharmacology

Elvir Lazo OL, White PF, Lee C, Cruz Eng H, Matin JM, Lin C, Del Cid F, Yumul R. Use of herbal medication in the perioperative period: Potential adverse drug interactions. J Clin Anesth. 2024 Aug;95:111473. doi: 10.1016/j.jclinane.2024.111473. Epub 2024 Apr 12. PMID: 38613937.

*Important summary of recommendations from the American Society of Anesthesiologists and other societies.

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AUTHORS CONTRIBUTIONS

All authors have read and approved the final version to be published and agreed to be accountable for all aspects of the work.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest Dr. Kaye discloses his role as editor-in-chief of the Current Pain and Headache Reports Journal. The other authors have no conflict of interest to declare.

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REFERENCES

1. Langmead L, Rampton DS. Review article: herbal treatment in gastrointestinal and liver disease--benefits and dangers. *Aliment Pharmacol Ther*. 2001;15:1239-1252. doi:10.1046/j.1365-2036.2001.01053.x

2. Hintz T, Matthews KK, Di R. The Use of Plant Antimicrobial Compounds for Food Preservation. *BioMed Res Int*. 2015;2015:246264. doi:10.1155/2015/246264

3. Akaberi M, Sahebkar A, Emami SA. Turmeric and Curcumin: From Traditional to Modern Medicine. *Adv Exp Med Biol*. 2021;1291:15-39. doi:10.1007/978-3-030-56153-6_2

4. Shishodia S, Sethi G, Aggarwal BB. Curcumin: getting back to the roots. *Ann N Y Acad Sci*. 2005;1056:206-217. doi:10.1196/annals.1352.010

5. 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. doi:10.2165/11586800-000000000-00000

6. Vane JR. The fight against rheumatism: from willow bark to COX-1 sparing drugs. *J Physiol Pharmacol Off J Pol Physiol Soc*. 2000;51:573-586.

7. Ashraf MA. Phytochemicals as Potential Anticancer Drugs: Time to Ponder Nature's Bounty. *BioMed Res Int*. 2020;2020:8602879. doi:10.1155/2020/8602879

8. Goldman P. Herbal Medicines Today and the Roots of Modern Pharmacology. *Ann Intern Med*. 2001;135:594-600. doi:10.7326/0003-4819-135-8_Part_1-200110160-00010

9. Rishton GM. Natural Products as a Robust Source of New Drugs and Drug Leads: Past Successes and Present Day Issues. *Am J Cardiol*. 2008;101:S43-9. doi:10.1016/j.amjcard.2008.02.007

10. Li FS, Weng JK. Demystifying traditional herbal medicine with modern approach. *Nat Plants*. 2017;3:17109. doi:10.1038/nplants.2017.109

11. Liperoti R, Vetrano DL, Bernabei R, Onder G. Herbal Medications in Cardiovascular Medicine. *J Am Coll Cardiol*. 2017;69:1188-1199. doi:10.1016/j.jacc.2016.11.078

12. Patridge E, Gareiss P, Kinch MS, Hoyer D. An analysis of FDA-approved drugs: natural products and their derivatives. *Drug Discov Today*. 2016;21:204-207. doi:10.1016/j.drudis.2015.01.009

13. Pan SY, Litscher G, Gao SH, Zhou SF, Yu ZL, Chen HQ, et al. Historical Perspective of Traditional Indigenous Medical Practices: The Current Renaissance and Conservation of Herbal Resources. *Evid Based Complement Alternat Med*. 2014;2014:525340. doi:10.1155/2014/525340

14. Bailey RL. Current regulatory guidelines and resources to support research of dietary supplements in the United States. *Crit Rev Food Sci Nutr*. 2020;60:298-309. doi:10.1080/10408398.2018.1524364

15. Wallace TC. Twenty Years of the Dietary Supplement Health and Education Act--How Should Dietary Supplements Be Regulated? *J Nutr*. 2015;145:1683-1686. doi:10.3945/jn.115.211102

16. Fontana RJ, Liou I, Reuben A, Suzuki A, Fiel MI, Lee W, et al. AASLD practice guidance on drug, herbal, and dietary supplement-induced liver injury. *Hepatology*. 2023;77:1036-1065. doi:10.1002/hep.32689

17. Tucker J, Fischer T, Upjohn L, Mazzera D, Kumar M. Unapproved Pharmaceutical Ingredients Included in Dietary Supplements Associated With US Food and Drug Administration Warnings. *JAMA Netw Open*. 2018;1:e183337. doi:10.1001/jamanetworkopen.2018.3337

18. Lam CS, O'Connell K, Monroy-Iglesias MJ, Wang P, Hou YN, Du M, et al. Emerging Patterns in Dietary Supplement Use Among US Adults, 1999-2023. *JAMA Netw Open*. 2026;9:e2619291. doi:10.1001/jamanetworkopen.2026.19291

19. Mobasheri A, Spring-Charles A, Gamaleri FC, McSwan J, Garg M, Sethi VS. Evidence-Based Opinions from Multidisciplinary Experts on Use of Naturopathic Herbal Remedies in Pain Management. *J Pain Res*. 2024;17:599-608. doi:10.2147/JPR.S432090

20. Henrotin Y, Mobasheri A. Natural Products for Promoting Joint Health and Managing Osteoarthritis. *Curr Rheumatol Rep*. 2018;20:72. doi:10.1007/s11926-018-0782-9

21. Liu X, Machado GC, Eyles JP, Ravi V, Hunter DJ. Dietary supplements for treating osteoarthritis: a systematic review and meta-analysis. *Br J Sports Med*. 2018;52:167-175. doi:10.1136/bjsports-2016-097333

22. Brophy RH, Fillingham YA. AAOS Clinical Practice Guideline Summary: Management of Osteoarthritis of the Knee (Nonarthroplasty), Third Edition. *J Am Acad Orthop Surg*. 2022;30:e721-9. doi:10.5435/JAAOS-D-21-01233

23. Meier BP, Lappas CM. The Influence of Safety, Efficacy, and Medical Condition Severity on Natural versus Synthetic Drug Preference. *Med Decis Mak Int J Soc Med Decis Mak*. 2016;36:1011-1019. doi:10.1177/0272989X15621877

24. Starr RR. Too little, too late: ineffective regulation of dietary supplements in the United States. *Am J Public Health*. 2015;105:478-485. doi:10.2105/AJPH.2014.302348

25. Avery RJ, Eisenberg MD, Cantor JH. An examination of structure-function claims in dietary supplement advertising in the U.S.: 2003-2009. *Prev Med*. 2017;97:86-92. doi:10.1016/j.ypmed.2017.01.008

26. Timbo BB, Chirtel SJ, Ihrie J, Oladipo T, Velez-Suarez L, Brewer V, et al. Dietary Supplement Adverse Event Report Data From the FDA Center for Food Safety and Applied Nutrition Adverse Event Reporting System (CAERS), 2004-2013. *Ann Pharmacother*. 2018;52:431-438. doi:10.1177/1060028017744316

27. Woo JJY. Adverse event monitoring and multivitamin-multimineral dietary supplements. *Am J Clin Nutr*. 2007;85:323S-324S. doi:10.1093/ajcn/85.1.323S

28. Rittenhouse M, Scott J, Deuster P. Dietary Supplements: Knowledge and Adverse Event Reporting Practices of Department of Defense Health Care Providers. *Mil Med*. 2020;185:2076-2081. doi:10.1093/milmed/usaa157

29. Geller AI, Shehab N, Weidle NJ, Lovegrove MC, Wolpert BJ, Timbo BB, et al. Emergency Department Visits for Adverse Events Related to Dietary Supplements. *N Engl J Med*. 2015;373:1531-1540. doi:10.1056/NEJMsa1504267

30. Hoofnagle JH, Björnsson ES. Drug-Induced Liver Injury — Types and Phenotypes. *N Engl J Med*. 2019;381:264-273. doi:10.1056/NEJMra1816149

31. Navarro VJ, Khan I, Björnsson E, Seeff LB, Serrano J, Hoofnagle JH. Liver injury from herbal and dietary supplements. *Hepatology*. 2017;65:363-373. doi:10.1002/hep.28813

32. Gottlieb S, McClellan MB. Reforms Needed to Modernize the US Food and Drug Administration's Oversight of Dietary Supplements, Cosmetics, and Diagnostic Tests. *JAMA Health Forum*. 2022;3:e224449. doi:10.1001/jamahealthforum.2022.4449

33. Chandra S, Saklani S, Kumar P, Kim B, Coutinho HDM. Nutraceuticals: Pharmacologically Active Potent Dietary Supplements. *BioMed Res Int*. 2022;2022:2051017. doi:10.1155/2022/2051017

34. DeFelice SL. The nutraceutical revolution: its impact on food industry R&D. *Trends Food Sci Technol*. 1995;6:59-61. doi:10.1016/S0924-2244(00)88944-X

35. Aronson JK. Defining "nutraceuticals": neither nutritious nor pharmaceutical. *Br J Clin Pharmacol*. 2017;83:8-19. doi:10.1111/bcp.12935

36. Sattigere VD, Ramesh Kumar P, Prakash V. Science-based regulatory approach for safe nutraceuticals. *J Sci Food Agric*. 2020;100:5079-5082. doi:10.1002/jsfa.9381

37. Mueller C. The regulatory status of medical foods and dietary supplements in the United States. *Nutrition*. 1999;15:249-251. doi:10.1016/s0899-9007(98)00186-5

38. Fernandes FA, Carocho M, Prieto MA, Barros L, Ferreira ICFR, Heleno SA. Nutraceuticals and dietary supplements: balancing out the pros and cons. *Food Funct*. 2024;15:6289-6303. doi:10.1039/d4fo01113a

39. Kaye AD, Clarke RC, Sabar R, Vig S, Dhawan KP, Hofbauer R, et al. Herbal medicines: current trends in anesthesiology practice—a hospital survey. *J Clin Anesth*. 2000;12:468-471. doi:10.1016/S0952-8180(00)00195-1

40. Yousofvand N, Moloodi B. An overview of the effect of medicinal herbs on pain. *Phytother Res*. 2023;37:1057-1081. doi:10.1002/ptr.7697

41. Lawson E, Singla P, Adler J, Argoff CE, Bettinger JJ, Bhaskar A, et al. Topical analgesics for neuropathic pain: an evidence-informed guide for the practicing clinician. *Pain Med*. 2026;27:279-316. doi:10.1093/pm/pnaf130

42. Oltean H, Robbins C, van Tulder MW, Berman BM, Bombardier C, Gagnier JJ. Herbal medicine for low-back pain. *Cochrane Database Syst Rev*. 2014;2014:CD004504. doi:10.1002/14651858.CD004504.pub4

43. Prego-Dominguez J, Hadrya F, Takkouche B. Polyunsaturated Fatty Acids and Chronic Pain: A Systematic Review and Meta-analysis. *Pain Physician*. 2016;19:521-535.

44. Xie L, Wang X, Chu J, He X, Bao J, Xi Y, et al. Effects of omega-3 fatty acids on chronic pain: a systematic review and meta-analysis. *Front Med*. 2025;12:1654661. doi:10.3389/fmed.2025.1654661

45. Ridouh I, Hackshaw KV. Essential Oils and Neuropathic Pain. *Plants*. 2022;11:1797. doi:10.3390/plants11141797

46. Boadas-Vaello P, Vela JM, Verdu E. New Pharmacological Approaches Using Polyphenols on the Physiopathology of Neuropathic Pain. *Curr Drug Targets*. 2017;18:160-173. doi:10.2174/1389450117666160527142423

47. Boyd C, Crawford C, Berry K, Deuster P, HERB Working Group. Conditional Recommendations for Specific Dietary Ingredients as an Approach to Chronic Musculoskeletal Pain: Evidence-Based Decision Aid for Health Care Providers, Participants, and Policy Makers. *Pain Med*. 2019;20:1430-1448. doi:10.1093/pm/pnz051

48. Frediani JK, Lal AA, Kim E, Leslie SL, Boorman DW, Singh V. The role of diet and non-pharmacologic supplements in the treatment of chronic neuropathic pain: A systematic review. *Pain Pract Off J World Inst Pain*. 2024;24:186-210. doi:10.1111/papr.13291

49. Cassanego G, Rodrigues P, De Freitas Bauermann L, Trevisan G. Evaluation of the analgesic effect of α-lipoic acid in treating pain disorders: A systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res*. 2022;177:106075. doi:10.1016/j.phrs.2022.106075

50. Casanueva B, Rodero B, Quintial C, Llorca J, González-Gay MA. Short-term efficacy of topical capsaicin therapy in severely affected fibromyalgia patients. *Rheumatol Int*. 2013;33:2665-2670. doi:10.1007/s00296-012-2490-5

51. Kim H, Ko DS. Effects of Iron, Copper, Zinc, and Magnesium on Chronic Widespread Pain: A Two-Sample Mendelian Randomization. *J Clin Med*. 2024;13:5908. doi:10.3390/jcm13195908

52. Nahin RL, Barnes PM, Stussman BJ, Bloom B. Costs of complementary and alternative medicine (CAM) and frequency of visits to CAM practitioners: United States, 2007. *Natl Health Stat Rep*. Published online 2009:1-14.

53. Crawford C, Boyd C, Paat CF, Meissner K, Lentino C, Teo L, et al. Dietary Ingredients as an Alternative Approach for Mitigating Chronic Musculoskeletal Pain: Evidence-Based Recommendations for Practice and Research in the Military. *Pain Med*. 2019;20:1236-1247. doi:10.1093/pm/pnz040

54. Rajapakse T, Pringsheim T. Nutraceuticals in Migraine: A Summary of Existing Guidelines for Use. *Headache J Head Face Pain*. 2016;56:808-816. doi:10.1111/head.12789

55. Anand S, Bharadvaja N. Potential Benefits of Nutraceuticals for Oxidative Stress Management. *Rev Bras Farmacogn*. 2022;32:211-220. doi:10.1007/s43450-022-00246-w

56. Bailey RL, Gahche JJ, Miller PE, Thomas PR, Dwyer JT. Why US Adults Use Dietary Supplements. *JAMA Intern Med*. 2013;173:355-361. doi:10.1001/jamainternmed.2013.2299

57. *Dietary Supplement Health and Education Act of 1994*. Vols 103–417.

58. Gupta RC, Doss RB. Toxicity Potential of Nutraceuticals. *Methods Mol Biol*. 2025;2834:197-230. doi:10.1007/978-1-0716-4003-6_10

59. Ichim MC, Booker A. Chemical Authentication of Botanical Ingredients: A Review of Commercial Herbal Products. *Front Pharmacol*. 2021;12. doi:10.3389/fphar.2021.666850

60. Ronis MJJ, Pedersen KB, Watt J. ADVERSE EFFECTS OF NUTRACEUTICALS AND DIETARY SUPPLEMENTS. *Annu Rev Pharmacol Toxicol*. 2018;58:583-601. doi:10.1146/annurev-pharmtox-010617-052844

61. Elvir Lazo OL, White PF, Lee C, Cruz Eng H, Matin JM, Lin C, et al. Use of herbal medication in the perioperative period: Potential adverse drug interactions. *J Clin Anesth*. 2024;95:111473. doi:10.1016/j.jclinane.2024.111473

62. Baden KER, Hoeksema SL, Gibson N, Gadi DN, Craig E, Draime JA, et al. The Safety and Efficacy of Glucosamine and/or Chondroitin in Humans: A Systematic Review. *Nutrients*. 2025;17:2093. doi:10.3390/nu17132093

63. Vo NX, Le NNH, Chu TDP, Pham HL, Dinh KXA, Che UTT, et al. Effectiveness and Safety of Glucosamine in Osteoarthritis: A Systematic Review. *Pharmacy*. 2023;11:117. doi:10.3390/pharmacy11040117

64. Arden NK, Perry TA, Bannuru RR, Bruyère O, Cooper C, Haugen IK, et al. Non-surgical management of knee osteoarthritis: comparison of ESCEO and OARSI 2019 guidelines. *Nat Rev Rheumatol*. 2021;17:59-66. doi:10.1038/s41584-020-00523-9

65. GBD 2021 Osteoarthritis Collaborators. Global, regional, and national burden of osteoarthritis, 1990-2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Rheumatol*. 2023;5:e508-22. doi:10.1016/S2665-9913(23)00163-7

66. Paneque A, Fortus H, Zheng J, Werlen G, Jacinto E. The Hexosamine Biosynthesis Pathway: Regulation and Function. *Genes*. 2023;14:933. doi:10.3390/genes14040933

67. Simon RR, Marks V, Leeds AR, Anderson JW. A comprehensive review of oral glucosamine use and effects on glucose metabolism in normal and diabetic individuals. *Diabetes Metab Res Rev*. 2011;27:14-27. doi:10.1002/dmrr.1150

68. Dostrovsky NR, Towheed TE, Hudson RW, Anastassiades TP. The effect of glucosamine on glucose metabolism in humans: a systematic review of the literature. *Osteoarthritis Cartilage*. 2011;19:375-380. doi:10.1016/j.joca.2011.01.007

69. Yuzwa SA, Vocadlo DJ. O-GlcNAc and neurodegeneration: biochemical mechanisms and potential roles in Alzheimer's disease and beyond. *Chem Soc Rev*. 2014;43:6839-6858. doi:10.1039/c4cs00038b

70. Hastings NB, Wang X, Song L, Butts BD, Grotz D, Hargreaves R, et al. Inhibition of O-GlcNAcase leads to elevation of O-GlcNAc tau and reduction of tauopathy and cerebrospinal fluid tau in rTg4510 mice. *Mol Neurodegener*. 2017;12:39. doi:10.1186/s13024-017-0181-0

71. Hawkinson TR, Liu Z, Ribas RA, Medina T, Nielsen RS, Clarke HA, et al. Hyperglycosylation is a metabolic driver of Alzheimer's disease. *Nat Metab*. 2026;8:1410-1425. doi:10.1038/s42255-026-01538-4

72. Lee BE, Suh PG, Kim JI. O-GlcNAcylation in health and neurodegenerative diseases. *Exp Mol Med*. 2021;53:1674-1682. doi:10.1038/s12276-021-00709-5

73. Liu F, Iqbal K, Grundke-Iqbal I, Hart GW, Gong CX. O-GlcNAcylation regulates phosphorylation of tau: a mechanism involved in Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2004;101:10804-10809. doi:10.1073/pnas.0400348101

74. Kim C, Nam DW, Park SY, Song H, Hong HS, Boo JH, et al. O-linked β-N-acetylglucosaminidase inhibitor attenuates β-amyloid plaque and rescues memory impairment. *Neurobiol Aging*. 2013;34:275-285. doi:10.1016/j.neurobiolaging.2012.03.001

75. Ai B, Chen L, Cai M, Fu J, Li H, Lin H, et al. No Associations Between Glucosamine Supplementation and Dementia or Parkinson's Disease: Findings From a Large Prospective Cohort Study. *J Gerontol A Biol Sci Med Sci*. 2024;79:glad123. doi:10.1093/gerona/glad123

76. Eastlack SC, Cornett EM, Kaye AD. Kratom—Pharmacology, Clinical Implications, and Outlook: A Comprehensive Review. *Pain Ther*. 2020;9:55-69. doi:10.1007/s40122-020-00151-x

77. Singh D, Narayanan S, Vicknasingam B, Corazza O, Santacroce R, Roman-Urrestarazu A. Changing trends in the use of kratom (Mitragyna speciosa) in Southeast Asia. *Hum Psychopharmacol Clin Exp*. 2017;32:e2582. doi:10.1002/hup.2582

78. McCurdy CR, Sharma A, Smith KE, Veltri CA, Weiss ST, White CM, et al. An update on the clinical pharmacology of kratom: uses, abuse potential, and future considerations. *Expert Rev Clin Pharmacol*. 2024;17:131-142. doi:10.1080/17512433.2024.2305798

79. Grundmann O. Patterns of Kratom use and health impact in the US—Results from an online survey. *Drug Alcohol Depend*. 2017;176:63-70. doi:10.1016/j.drugalcdep.2017.03.007

80. Hemby SE, McIntosh S, Leon F, Cutler SJ, McCurdy CR. Abuse liability and therapeutic potential of the Mitragyna speciosa (kratom) alkaloids mitragynine and 7-hydroxymitragynine. *Addict Biol*. 2019;24:874-885. doi:10.1111/adb.12639

81. Obeng S, Kamble SH, Reeves ME, Restrepo LF, Patel A, Behnke M, et al. Investigation of the Adrenergic and Opioid Binding Affinities, Metabolic Stability, Plasma Protein Binding Properties, and Functional Effects of Selected Indole-Based Kratom Alkaloids. *J Med Chem*. 2020;63:433-439. doi:10.1021/acs.jmedchem.9b01465

82. Todd DA, Kellogg JJ, Wallace ED, Khin M, Flores-Bocanegra L, Tanna RS, et al. Chemical composition and biological effects of kratom (Mitragyna speciosa): In vitro studies with implications for efficacy and drug interactions. *Sci Rep*. 2020;10:19158. doi:10.1038/s41598-020-76119-w

83. Hill R, Kruegel AC, Javitch JA, Lane JR, Canals M. The respiratory depressant effects of mitragynine are limited by its conversion to 7-OH mitragynine. *Br J Pharmacol*. 2022;179:3875-3885. doi:10.1111/bph.15832

84. Kruegel AC, Gassaway MM, Kapoor A, Váradi A, Majumdar S, Filizola M, et al. Synthetic and Receptor Signaling Explorations of the Mitragyna Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators. *J Am Chem Soc*. 2016;138:6754-6764. doi:10.1021/jacs.6b00360

85. Tanna RS, Nguyen JT, Hadi DL, Layton ME, White JR, Cech NB, et al. Clinical Assessment of the Drug Interaction Potential of the Psychotropic Natural Product Kratom. *Clin Pharmacol Ther*. 2023;113:1315-1325. doi:10.1002/cpt.2891

86. Hartley C, Bulloch M, Penzak SR. Clinical Pharmacology of the Dietary Supplement Kratom (Mitragyna speciosa). *J Clin Pharmacol*. 2022;62:577-593. doi:10.1002/jcph.2001

87. Boyer EW, Babu KM, Adkins JE, McCurdy CR, Halpern JH. Self-treatment of opioid withdrawal using kratom (Mitragynia speciosa korth). *Addiction*. 2008;103:1048-1050. doi:10.1111/j.1360-0443.2008.02209.x

88. Singh D, Müller CP, Vicknasingam BK. Kratom (Mitragyna speciosa) dependence, withdrawal symptoms and craving in regular users. *Drug Alcohol Depend*. 2014;139:132-137. doi:10.1016/j.drugalcdep.2014.03.017

89. Stanciu CN, Gnanasegaram SA, Ahmed S, Penders T. Kratom Withdrawal: A Systematic Review with Case Series. *J Psychoactive Drugs*. 2019;51:12-18. doi:10.1080/02791072.2018.1562133

90. Rogers JM, Weiss ST, Epstein DH, Grundmann O, Hill K, Smith KE. Kratom addiction per DSM-5 SUD criteria, and kratom physical dependence: Insights from dosing amount versus frequency. *Drug Alcohol Depend*. 2024;260:111329. doi:10.1016/j.drugalcdep.2024.111329

91. Bin Abdullah MFIL. Kratom Dependence and Treatment Options: A Comprehensive Review of the Literature. *Curr Drug Targets*. 2020;21:1566-1579. doi:10.2174/1389450121666200719011653

92. Henningfield JE, Rodricks JV, Magnuson AM, Huestis MA. Respiratory effects of oral mitragynine and oxycodone in a rodent model. *Psychopharmacology (Berl)*. 2022;239:3793-3804. doi:10.1007/s00213-022-06244-z

93. Zuarth Gonzalez JD, Ragsdale AK, Mukhopadhyay S, McCurdy CR, McMahon LR, Obeng S, et al. Mitragynine and 7-hydroxymitragynine: Bidirectional effects on breathing in rats. *J Pharmacol Exp Ther*. 2025;392:103720. doi:10.1016/j.jpet.2025.103720

94. Eggleston W, Stoppacher R, Suen K, Marraffa JM, Nelson LS. Kratom Use and Toxicities in the United States. *Pharmacother J Hum Pharmacol Drug Ther*. 2019;39:775-777. doi:10.1002/phar.2280

95. Smallets S, Litvin S, Abele G, Kirsh S, Paustenbach D. The acute adverse health effects of kratom: an evaluation of case reports. *Front Pharmacol*. 2025;16:1620601. doi:10.3389/fphar.2025.1620601

96. Halim SA, Low JH, Chee YC, Alias MR. Seizures among young adults consuming kratom beverages in Malaysia: A case series. *Epilepsy Behav*. 2021;121:108057. doi:10.1016/j.yebeh.2021.108057

97. Afzal H, Esang M, Rahman S. A Case of Kratom-induced Seizures. *Cureus*. Published online 2020. doi:10.7759/cureus.6588

98. Turla T, Abele G, Hua M, Paustenbach D. Reported associations between kratom and seizures: a systematic review. *Front Pharmacol*. 2025;16:1632835. doi:10.3389/fphar.2025.1632835

99. Suhaimi FW, Khari NHM, Hassan Z, Müller CP. Exploring the cognitive effects of kratom: A review. *Behav Brain Res*. 2025;480:115387. doi:10.1016/j.bbr.2024.115387

100. Leong Abdullah MFI, Tan KL, Narayanan S, Yuvashnee N, Chear NJY, Singh D, et al. Is kratom (Mitragyna speciosa Korth.) use associated with ECG abnormalities? Electrocardiogram comparisons between regular kratom users and controls. *Clin Toxicol*. 2021;59:400-408. doi:10.1080/15563650.2020.1812627

101. Leong Bin Abdullah MFI, Singh D. The Adverse Cardiovascular Effects and Cardiotoxicity of Kratom (Mitragyna speciosa Korth.): A Comprehensive Review. *Front Pharmacol*. 2021;12:726003. doi:10.3389/fphar.2021.726003

102. Schimmel J, Dart RC. Kratom (Mitragyna Speciosa) Liver Injury: A Comprehensive Review. *Drugs*. 2020;80:263-283. doi:10.1007/s40265-019-01242-6

103. Sangani V, Sunnoqrot N, Gargis K, Ranabhotu A, Mubasher A, Pokal M. Unusual Presentation of Kratom Overdose With Rhabdomyolysis, Transient Hearing Loss, and Heart Failure. *J Investig Med High Impact Case Rep*. 2021;9:23247096211005069. doi:10.1177/23247096211005069

104. Prozialeck WC, Edwards JR, Lamar PC, Plotkin BJ, Sigar IM, Grundmann O, et al. Evaluation of the Mitragynine Content, Levels of Toxic Metals and the Presence of Microbes in Kratom Products Purchased in the Western Suburbs of Chicago. *Int J Environ Res Public Health*. 2020;17:5512. doi:10.3390/ijerph17155512

105. Snow Caroti K, Joseph A, Sapowadia A, Michael White C. Elemental impurities (heavy metals) in kratom products: an assessment of published individual product analyses. *Clin Toxicol*. 2024;62:651-660. doi:10.1080/15563650.2024.2395552

106. Alsbrook S, Pro G, Koturbash I. From kratom to 7-hydroxymitragynine: evolution of a natural remedy into a public-health threat. *Pharm Biol*. 2025;63:896-911. doi:10.1080/13880209.2025.2590311

107. Philips CA, Ahamed R, Rajesh S, George T, Mohanan M, Augustine P. Comprehensive review of hepatotoxicity associated with traditional Indian Ayurvedic herbs. *World J Hepatol*. 2020;12:574-595. doi:10.4254/wjh.v12.i9.574

108. Lantz RC, Chen GJ, Solyom AM, Jolad SD, Timmermann BN. The effect of turmeric extracts on inflammatory mediator production. *Phytomedicine*. 2005;12:445-452. doi:10.1016/j.phymed.2003.12.011

109. Sivani BM, Azzeh M, Patnaik R, Pantea Stoian A, Rizzo M, Banerjee Y. Reconnoitering the Therapeutic Role of Curcumin in Disease Prevention and Treatment: Lessons Learnt and Future Directions. *Metabolites*. 2022;12:639. doi:10.3390/metabo12070639

110. Kou H, Huang L, Jin M, He Q, Zhang R, Ma J. Effect of curcumin on rheumatoid arthritis: a systematic review and meta-analysis. *Front Immunol*. 2023;14:1121655. doi:10.3389/fimmu.2023.1121655

111. Zeng L, Yang T, Yang K, Yu G, Li J, Xiang W, et al. Efficacy and Safety of Curcumin and Curcuma longa Extract in the Treatment of Arthritis: A Systematic Review and Meta-Analysis of Randomized Controlled Trial. *Front Immunol*. 2022;13. doi:10.3389/fimmu.2022.891822

112. Chandran B, Goel A. A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. *Phytother Res PTR*. 2012;26:1719-1725. doi:10.1002/ptr.4639

113. Shrestha A, Elliott S, Abasszade JH, Wu K, Worland T, Simpson I, et al. Drug-Induced Liver Injury Associated with Turmeric and Piperine: A Case and Review. *Case Rep Gastroenterol*. 2025;19:96-106. doi:10.1159/000543679

114. Pugnale S, Schilter L, Galofaro L. Drug-Induced Liver Injury Associated With Turmeric and Black Pepper Based Dietary Supplements Consumption: A Case Report. *Clin Case Rep*. 2025;13:e71489. doi:10.1002/ccr3.71489

115. Goswami S, Saxena S, Yadav S, Goswami D, Brahmachari K, Karmakar S, et al. Review of Curcumin and Its Different Formulations: Pharmacokinetics, Pharmacodynamics and Pharmacokinetic-Pharmacodynamic Interactions. *OBM Integr Complement Med*. 2022;7:1-35. doi:10.21926/obm.icm.2204057

116. Holder GM, Plummer JL, Ryan AJ. The metabolism and excretion of curcumin (1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) in the rat. *Xenobiotica Fate Foreign Compd Biol Syst*. 1978;8:761-768. doi:10.3109/00498257809069589

117. Bhardwaj RK, Glaeser H, Becquemont L, Klotz U, Gupta SK, Fromm MF. Piperine, a Major Constituent of Black Pepper, Inhibits Human P-glycoprotein and CYP3A4. *J Pharmacol Exp Ther*. 2002;302:645-650. doi:10.1124/jpet.102.034728

118. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PSSR. Influence of Piperine on the Pharmacokinetics of Curcumin in Animals and Human Volunteers. *Planta Med*. 1998;64:353-356. doi:10.1055/s-2006-957450

119. Na LX, Li Y, Pan HZ, Zhou XL, Sun DJ, Meng M, et al. Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: a double-blind, placebo-controlled trial. *PubMed*. Published online 2012. doi:10.1002/mnfr.201200131

120. Laval J, Phipps KR, Brinet S, Fournier MC, Douillard B, Pham S, et al. Safety assessment and gastrointestinal tolerance of a novel highly bioavailable turmeric extract formulation: A randomised, double-blind, placebo controlled clinical trial. *Toxicol Rep*. 2026;16:102176. doi:10.1016/j.toxrep.2025.102176

121. Kunnumakkara AB, Guha S, Krishnan S, Diagaradjane P, Gelovani J, Aggarwal BB. Curcumin Potentiates Antitumor Activity of Gemcitabine in an Orthotopic Model of Pancreatic Cancer through Suppression of Proliferation, Angiogenesis, and Inhibition of Nuclear Factor-κB–Regulated Gene Products. *Cancer Res*. 2007;67:3853-3861. doi:10.1158/0008-5472.CAN-06-4257

122. Jiang M, Huang O, Zhang X, Xie Z, Shen A, Liu H, et al. Curcumin Induces Cell Death and Restores Tamoxifen Sensitivity in the Antiestrogen-Resistant Breast Cancer Cell Lines MCF-7/LCC2 and MCF-7/LCC9. *Molecules*. 2013;18:701-720. doi:10.3390/molecules18010701

123. Appiah-Opong R, Commandeur JNM, van Vugt-Lussenburg B, Vermeulen NPE. Inhibition of human recombinant cytochrome P450s by curcumin and curcumin decomposition products. *Toxicology*. 2007;235:83-91. doi:10.1016/j.tox.2007.03.007

124. Bahramsoltani R, Rahimi R, Farzaei MH. Pharmacokinetic interactions of curcuminoids with conventional drugs: A review. *J Ethnopharmacol*. 2017;209:1-12. doi:10.1016/j.jep.2017.07.022

125. Kim DC, Ku SK. Anticoagulant activities of curcumin and its derivative. *BMB Rep*. 2012;45:221-226. doi:10.5483/BMBRep.2012.45.4.221

126. Sunagawa SW, Houlihan C, Reynolds B, Kjerengtroen S, Murry DJ, Khoury N. Turmeric-Associated Drug-Induced Liver Injury. *ACG Case Rep J*. 2022;9:e00941. doi:10.14309/crj.0000000000000941

127. Lombardi N, Crescioli G, Maggini V, Ippoliti I, Menniti-Ippolito F, Gallo E, et al. Acute liver injury following turmeric use in Tuscany: An analysis of the Italian Phytovigilance database and systematic review of case reports. *Br J Clin Pharmacol*. 2021;87:741-753. doi:10.1111/bcp.14460

128. Costa ML, Rodrigues JA, Azevedo J, Vasconcelos V, Eiras E, Campos MG. Hepatotoxicity induced by paclitaxel interaction with turmeric in association with a microcystin from a contaminated dietary supplement. *Toxicon*. 2018;150:207-211. doi:10.1016/j.toxicon.2018.05.022

129. Gagnier JJ, Oltean H, van Tulder MW, Berman BM, Bombardier C, Robbins CB. Herbal Medicine for Low Back Pain: A Cochrane Review. *Spine*. 2016;41:116-133. doi:10.1097/BRS.0000000000001310

130. Liu X, Huang X, Song X. Ethnopharmacological insights into *Symphytum officinale* L.: traditional uses, phytochemical composition, therapeutic potential, and clinical-toxicological implications. *Front Pharmacol*. 2026;17. doi:10.3389/fphar.2026.1793084

131. Staiger C. Comfrey root: from tradition to modern clinical trials. *Wien Med Wochenschr 1946*. 2013;163:58-64. doi:10.1007/s10354-012-0162-4

132. Kimel K, Godlewska S, Gleńsk M, Gobis K, Ośko J, Grembecka M, et al. LC-MS/MS Evaluation of Pyrrolizidine Alkaloids Profile in Relation to Safety of Comfrey Roots and Leaves from Polish Sources. *Molecules*. 2023;28:6171. doi:10.3390/molecules28166171

133. Trifan A, Zengin G, Sinan KI, Esslinger N, Grubelnik A, Wolfram E, et al. Influence of the Post-Harvest Storage Time on the Multi-Biological Potential, Phenolic and Pyrrolizidine Alkaloid Content of Comfrey (Symphytum officinale L.) Roots Collected from Different European Regions. *Plants*. 2021;10:1825. doi:10.3390/plants10091825

134. Comfrey. *LiverTox Clin. Res. Inf. Drug-Induc. Liver Inj.* National Institute of Diabetes and Digestive and Kidney Diseases; 2012.

135. Xu J, Wang W, Yang X, Xiong A, Yang L, Wang Z. Pyrrolizidine alkaloids: An update on their metabolism and hepatotoxicity mechanism. *Liver Res*. 2019;3:176-184. doi:10.1016/j.livres.2019.11.004

136. Yang M, Ruan J, Fu PP, Lin G. Cytotoxicity of pyrrolizidine alkaloid in human hepatic parenchymal and sinusoidal endothelial cells: Firm evidence for the reactive metabolites mediated pyrrolizidine alkaloid-induced hepatotoxicity. *Chem Biol Interact*. 2016;243:119-126. doi:10.1016/j.cbi.2015.09.011

137. Teschke R, Vongdala N, Quan NV, Quy TN, Xuan TD. Metabolic Toxification of 1,2-Unsaturated Pyrrolizidine Alkaloids Causes Human Hepatic Sinusoidal Obstruction Syndrome: The Update. *Int J Mol Sci*. 2021;22:10419. doi:10.3390/ijms221910419

138. Yeong ML, Swinburn B, Kennedy M, Nicholson G. Hepatic veno-occlusive disease associated with comfrey ingestion. *J Gastroenterol Hepatol*. 1990;5:211-214. doi:10.1111/j.1440-1746.1990.tb01827.x

139. Stickel F, Seitz HK. The efficacy and safety of comfrey. *Public Health Nutr*. 2000;3:501-508. doi:10.1017/S1368980000000586

140. Ridker PM, Ohkuma S, McDermott WV, Trey C, Huxtable RJ. Hepatic venocclusive disease associated with the consumption of pyrrolizidine-containing dietary supplements. *Gastroenterology*. 1985;88:1050-1054. doi:10.1016/s0016-5085(85)80027-5

141. Rode D. Comfrey toxicity revisited. *Trends Pharmacol Sci*. 2002;23:497-499. doi:10.1016/S0165-6147(02)02106-5

142. Jedlinszki N, Balázs B, Csányi E, Csupor D. Penetration of lycopsamine from a comfrey ointment through human epidermis. *Regul Toxicol Pharmacol*. 2017;83:1-4. doi:10.1016/j.yrtph.2016.11.015

143. Kuchta K, Schmidt M. Safety of medicinal comfrey cream preparations (Symphytum officinale s.l.): The pyrrolizidine alkaloid lycopsamine is poorly absorbed through human skin. *Regul Toxicol Pharmacol*. 2020;118:104784. doi:10.1016/j.yrtph.2020.104784

144. Beghelli D, Isani G, Roncada P, Andreani G, Bistoni O, Bertocchi M, et al. Antioxidant and Ex Vivo Immune System Regulatory Properties of Boswellia serrata Extracts. *Oxid Med Cell Longev*. 2017;2017:7468064. doi:10.1155/2017/7468064

145. Ammon HPT. Boswellic Acids and Their Role in Chronic Inflammatory Diseases. *Adv Exp Med Biol*. 2016;928:291-327. doi:10.1007/978-3-319-41334-1_13

146. Majeed A, Majeed S, Satish G, Manjunatha R, Rabbani SN, Patil NVP, et al. A standardized Boswellia serrata extract shows improvements in knee osteoarthritis within five days-a double-blind, randomized, three-arm, parallel-group, multi-center, placebo-controlled trial. *Front Pharmacol*. 2024;15:1428440. doi:10.3389/fphar.2024.1428440

147. Banji D, Banji OJF, Rashida S, Alshahrani S, Alqahtani SS. Bioavailability, anti-inflammatory and anti-arthritic effect of Acetyl Keto Boswellic acid and its combination with methotrexate in an arthritic animal model. *J Ethnopharmacol*. 2022;292:115200. doi:10.1016/j.jep.2022.115200

148. Majeed M, Nagabhushanam K, Lawrence L, Nallathambi R, Thiyagarajan V, Mundkur L. Boswellia serrata Extract Containing 30% 3-Acetyl-11-Keto-Boswellic Acid Attenuates Inflammatory Mediators and Preserves Extracellular Matrix in Collagen-Induced Arthritis. *Front Physiol*. 2021;12:735247. doi:10.3389/fphys.2021.735247

149. Algieri F, Rodriguez-Nogales A, Rodriguez-Cabezas ME, Risco S, Ocete MA, Galvez J. Botanical Drugs as an Emerging Strategy in Inflammatory Bowel Disease: A Review. *Mediators Inflamm*. 2015;2015:179616. doi:10.1155/2015/179616

150. Siemoneit U, Pergola C, Jazzar B, Northoff H, Skarke C, Jauch J, et al. On the interference of boswellic acids with 5-lipoxygenase: mechanistic studies in vitro and pharmacological relevance. *Eur J Pharmacol*. 2009;606:246-254. doi:10.1016/j.ejphar.2009.01.044

151. Parvez S, Werner M, Perkowski BJ, Schumann A, Werz O, Aparoy P. Combined computational and experimental studies reveal an altered regiospecific switch in 5-lipoxygenase targeted by AKBA. *Biochem Biophys Res Commun*. 2026;821:153885. doi:10.1016/j.bbrc.2026.153885

152. Syrovets T, Büchele B, Krauss C, Laumonnier Y, Simmet T. Acetyl-boswellic acids inhibit lipopolysaccharide-mediated TNF-alpha induction in monocytes by direct interaction with IkappaB kinases. *J Immunol*. 2005;174:498-506. doi:10.4049/jimmunol.174.1.498

153. Jayaram M, Kim J, Baek KS, Jung H, Kim J, M MKP, et al. Clinical Benefits of Boswellia Serrata (BOSMAX®) in Early Knee Osteoarthritis: A Randomized, Placebo-Controlled, Double-Blind Study. *J Med Food*. Published online 2025. doi:10.1177/1096620X251392467

154. Vaidya N, Agarwal R, Dipankar DG, Patkar H, Ganu G, Nagore D, et al. Efficacy and Safety of Boswellia serrata and Apium graveolens L. Extract Against Knee Osteoarthritis and Cartilage Degeneration: A Randomized, Double-blind, Multicenter, Placebo-Controlled Clinical Trial. *Pharm Res*. 2025;42:249-269. doi:10.1007/s11095-025-03818-2

155. Franco-Trepat E, Alonso-Pérez A, Guillán-Fresco M, López-Fagúndez M, Pazos-Pérez A, Crespo-Golmar A, et al. β Boswellic Acid Blocks Articular Innate Immune Responses: An In Silico and In Vitro Approach to Traditional Medicine. *Antioxidants*. 2023;12:371. doi:10.3390/antiox12020371

156. Yu G, Xiang W, Zhang T, Zeng L, Yang K, Li J. Effectiveness of Boswellia and Boswellia extract for osteoarthritis patients: a systematic review and meta-analysis. *BMC Complement Med Ther*. 2020;20:225. doi:10.1186/s12906-020-02985-6

157. Bannuru RR, Osani MC, Al-Eid F, Wang C. Efficacy of curcumin and Boswellia for knee osteoarthritis: Systematic review and meta-analysis. *Semin Arthritis Rheum*. 2018;48:416-429. doi:10.1016/j.semarthrit.2018.03.001

158. Krishnamurthy A, Lang AE, Pangarkar S, Edison J, Cody J, Sall J. Synopsis of the 2020 US Department of Veterans Affairs/US Department of Defense Clinical Practice Guideline: The Non-Surgical Management of Hip and Knee Osteoarthritis. *Mayo Clin Proc*. 2021;96:2435-2447. doi:10.1016/j.mayocp.2021.03.017

159. Joseph A, Abhilash MB, Mulakal JN, Madhavamenon KI. Pharmacokinetics of a Natural Self-emulsifying Reversible Hybrid-Hydrogel (N'SERH) Formulation of Full-Spectrum Boswellia serrata Oleo-Gum Resin Extract: Randomised Double-Blinded Placebo-Controlled Crossover Study. *Biol Pharm Bull*. 2024;47:1583-1593. doi:10.1248/bpb.b24-00306

160. Liu X, Eyles J, McLachlan AJ, Mobasheri A. Which supplements can I recommend to my osteoarthritis patients? *Rheumatology*. 2018;57:iv75-87. doi:10.1093/rheumatology/key005

161. Mncwangi N, Chen W, Vermaak I, Viljoen AM, Gericke N. Devil's Claw—A review of the ethnobotany, phytochemistry and biological activity of Harpagophytum procumbens. *J Ethnopharmacol*. 2012;143:755-771. doi:10.1016/j.jep.2012.08.013

162. Bargsten FE, Seifert R. Devil's claw (Harpagophytum procumbens): is the buzz in Google justified? *Naunyn Schmiedebergs Arch Pharmacol*. 2025;398:10823-10842. doi:10.1007/s00210-025-03974-7

163. European Medicines Agency. *European Union Herbal Monograph on Harpagophytum Procumbens DC. and/or Harpagophytum Zeyheri Decne., Radix*. European Medicines Agency; 2016.

164. Brendler T. From Bush Medicine to Modern Phytopharmaceutical: A Bibliographic Review of Devil's Claw (Harpagophytum spp.). *Pharmaceuticals*. 2021;14:726. doi:10.3390/ph14080726

165. Cameron M, Chrubasik S. Oral herbal therapies for treating osteoarthritis. *Cochrane Database Syst Rev*. 2014;2016. doi:10.1002/14651858.CD002947.pub2

166. Gagnier JJ, Chrubasik S, Manheimer E. Harpgophytum procumbens for osteoarthritis and low back pain: a systematic review. *BMC Complement Altern Med*. 2004;4:13. doi:10.1186/1472-6882-4-13

167. Hong JY, Lee J, Kim H, Kim H, Jeon WJ, Yeo C, et al. Harpagophytum procumbens in musculoskeletal disorders: current evidence and comparison with NSAIDs. *Front Pharmacol*. 2026;17:1839470. doi:10.3389/fphar.2026.1839470

168. Fiebich BL, Muñoz E, Rose T, Weiss G, McGregor GP. Molecular targets of the antiinflammatory Harpagophytum procumbens (devil's claw): inhibition of TNFα and COX-2 gene expression by preventing activation of AP-1. *Phytother Res PTR*. 2012;26:806-811. doi:10.1002/ptr.3636

169. Inaba K, Murata K, Naruto S, Matsuda H. Inhibitory effects of Devil's claw (secondary root of Harpagophytum procumbens) extract and harpagoside on cytokine production in mouse macrophages. *J Nat Med*. 2010;64:219-222. doi:10.1007/s11418-010-0395-8

170. Mariano A, Bigioni I, Mattioli R, Di Sotto A, Leopizzi M, Garzoli S, et al. Harpagophytum procumbens Root Extract Mediates Anti-Inflammatory Effects in Osteoarthritis Synoviocytes through CB2 Activation. *Pharmaceuticals*. 2022;15:457. doi:10.3390/ph15040457

171. Ouitas NA, Heard CM. Estimation of the relative antiinflammatory efficacies of six commercial preparations of Harpagophytum procumbens (Devil's claw). *Phytother Res*. 2010;24:333-338. doi:10.1002/ptr.2930

172. Chrubasik S, Chrubasik C, Künzel O, Black A. Patient-perceived benefit during one year of treatment with Doloteffin®. *Phytomedicine*. 2007;14:371-376. doi:10.1016/j.phymed.2007.04.011

173. Warnock M, McBean D, Suter A, Tan J, Whittaker P. Effectiveness and safety of Devil's Claw tablets in patients with general rheumatic disorders. *Phytother Res PTR*. 2007;21:1228-1233. doi:10.1002/ptr.2288

174. Vlachojannis J, Roufogalis BD, Chrubasik S. Systematic review on the safety of Harpagophytum preparations for osteoarthritic and low back pain. *Phytother Res PTR*. 2008;22:149-152. doi:10.1002/ptr.2314

175. Douros A, Bronder E, Andersohn F, Klimpel A, Thomae M, Ockenga J, et al. Drug-induced acute pancreatitis: results from the hospital-based Berlin case–control surveillance study of 102 cases. *Aliment Pharmacol Ther*. 2013;38:825-834. doi:10.1111/apt.12461

176. Joshi K, Parrish A, Grunz-Borgmann EA, Gerkovich M, Folk WR. Toxicology studies of aqueous-alcohol extracts of Harpagophytum procumbens subsp. procumbens (Burch.) DC.Ex Meisn. (Pedaliaceae) in female and male rats. *BMC Complement Med Ther*. 2020;20:9. doi:10.1186/s12906-019-2789-9

177. Saller R, Brignoli R, Melzer J, Meier R. An updated systematic review with meta-analysis for the clinical evidence of silymarin. *Forsch Komplementarmed*. 2008;15:9-20. doi:10.1159/000113648

178. März RW, Kemper F. [Willow bark extract--effects and effectiveness. Status of current knowledge regarding pharmacology, toxicology and clinical aspects]. *Wien Med Wochenschr*. 2002;152:354-359. doi:10.1046/j.1563-258x.2002.02053.x

179. Shara M, Stohs SJ. Efficacy and Safety of White Willow Bark (Salix alba) Extracts. *Phytother Res PTR*. 2015;29:1112-1116. doi:10.1002/ptr.5377

180. Vlachojannis JE, Cameron M, Chrubasik S. A systematic review on the effectiveness of willow bark for musculoskeletal pain. *Phytother Res PTR*. 2009;23:897-900. doi:10.1002/ptr.2747

181. *European Union Herbal Monograph on Salix [Various Species Including S. Purpurea L., S. Daphnoides Vill., S. Fragilis L.], Cortex*. European Medicines Agency; 2017.

182. Boarzon N, Furst D. Nonsteroidal Anti-Inflammatory Drugs, Disease Modifying Antirheumatic Drugs, Nonopiod Analgesics & Drugs Used in Gout. In: Vanderah TW, ed. *Basic Clin. Pharmacol.* Fifteenth. McGraw-Hill; 2021.

183. Vane JR, Botting RM. The mechanism of action of aspirin. *Thromb Res*. 2003;110:255-258. doi:10.1016/s0049-3848(03)00379-7

184. Chrubasik S, Künzel O, Model A, Conradt C, Black A. Treatment of low back pain with a herbal or synthetic anti-rheumatic: a randomized controlled study. Willow bark extract for low back pain. *Rheumatology*. 2001;40:1388-1393. doi:10.1093/rheumatology/40.12.1388

185. Lin CR, Tsai SHL, Wang C, Lee CL, Hung SW, Ting YT, et al. Willow Bark (Salix spp.) Used for Pain Relief in Arthritis: A Meta-Analysis of Randomized Controlled Trials. *Life*. 2023;13:2058. doi:10.3390/life13102058

186. Attallah KA, El-Dessouki AM, Abd-Elmawla MA, Ghaiad HR, Abo-Elghiet F, Mustafa AM, et al. The therapeutic potential of naturally occurring 6-shogaol: an updated comprehensive review. *Inflammopharmacology*. Published online 2025. doi:10.1007/s10787-025-01812-z

187. Grzanna R, Lindmark L, Frondoza CG. Ginger—An Herbal Medicinal Product with Broad Anti-Inflammatory Actions. *J Med Food*. 2005;8:125-132. doi:10.1089/jmf.2005.8.125

188. Rahmani AH, shabrmi FMA, Aly SM. Active ingredients of ginger as potential candidates in the prevention and treatment of diseases via modulation of biological activities. *Int J Physiol Pathophysiol Pharmacol*. 2014;6:125-136.

189. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *The Lancet*. 2019;393:1745-1759. doi:10.1016/S0140-6736(19)30417-9

190. Srivastava KC, Mustafa T. Ginger (Zingiber officinale) in rheumatism and musculoskeletal disorders. *Med Hypotheses*. 1992;39:342-348. doi:10.1016/0306-9877(92)90059-l

191. Ballester P, Cerdá B, Arcusa R, Marhuenda J, Yamedjeu K, Zafrilla P. Effect of Ginger on Inflammatory Diseases. *Molecules*. 2022;27:7223. doi:10.3390/molecules27217223

192. Wu H, Hsieh MC, Lo CY, Liu CB, Sang S, Ho CT, et al. 6-Shogaol is more effective than 6-gingerol and curcumin in inhibiting 12-O-tetradecanoylphorbol 13-acetate-induced tumor promotion in mice. *Mol Nutr Food Res*. 2010;54:1296-1306. doi:10.1002/mnfr.200900409

193. Dugasani S, Pichika MR, Nadarajah VD, Balijepalli MK, Tandra S, Korlakunta JN. Comparative antioxidant and anti-inflammatory effects of [6]-gingerol, [8]-gingerol, [10]-gingerol and [6]-shogaol. *J Ethnopharmacol*. 2010;127:515-520. doi:10.1016/j.jep.2009.10.004

194. Altman RD, Marcussen KC. Effects of a ginger extract on knee pain in patients with osteoarthritis. *Arthritis Rheum*. 2001;44:2531-2538. doi:10.1002/1529-0131(200111)44:11%3C2531::aid-art433%3E3.0.co;2-j

195. Bartels EM, Folmer VN, Bliddal H, Altman RD, Juhl C, Tarp S, et al. Efficacy and safety of ginger in osteoarthritis patients: a meta-analysis of randomized placebo-controlled trials. *Osteoarthritis Cartilage*. 2015;23:13-21. doi:10.1016/j.joca.2014.09.024

196. Haghighi M, Khalvat A, Toliat T, Jallaei S. COMPARING THE EFFECTS OF GINGER (ZINGIBER OFFICINALE) EXTRACT AND IBUPROFEN ON PATIENTS WITH OSTEOARTHRITIS. *Arch Iran Med*. 2005;8.

197. Bliddal H, Rosetzsky A, Schlichting P, Weidner MS, Andersen LA, Ibfelt HH, et al. A randomized, placebo-controlled, cross-over study of ginger extracts and ibuprofen in osteoarthritis. *Osteoarthritis Cartilage*. 2000;8:9-12. doi:10.1053/joca.1999.0264

198. Amorndoljai P, Taneepanichskul S, Niempoog S, Nimmannit U. A Comparative of Ginger Extract in Nanostructure Lipid Carrier (NLC) and 1% Diclofenac Gel for Treatment of Knee Osteoarthritis (OA). *J Med Assoc Thail Chotmaihet Thangphaet*. 2017;100:447-456.

199. Crichton M, Davidson AR, Innerarity C, Marx W, Lohning A, Isenring E, et al. Orally consumed ginger and human health: an umbrella review. *Am J Clin Nutr*. 2022;115:1511-1527. doi:10.1093/ajcn/nqac035

200. Pareek A, Suthar M, Rathore GS, Bansal V. Feverfew (Tanacetum parthenium L.): A systematic review. *Pharmacogn Rev*. 2011;5:103-110. doi:10.4103/0973-7847.79105

201. Pablos I, Eichhorn S, Briza P, Asam C, Gartner U, Wolf M, et al. Proteomic profiling of the weed feverfew, a neglected pollen allergen source. *Sci Rep*. 2017;7:6049. doi:10.1038/s41598-017-06213-z

202. Kashkooe A, Jalali A, Zarshenas MM, Hamedi A. Exploring the Phytochemistry, Signaling Pathways, and Mechanisms of Action of Tanacetum parthenium (L.) Sch.Bip.: A Comprehensive Literature Review. *Biomedicines*. 2024;12:2297. doi:10.3390/biomedicines12102297

203. Lechkova B, Karcheva-Bahchevanska D, Ivanov K, Todorova V, Benbassat N, Penkova N, et al. A Study of the Chemical Composition, Acute and Subacute Toxicity of Bulgarian Tanacetum parthenium Essential Oil. *Molecules*. 2023;28:4906. doi:10.3390/molecules28134906

204. Saranitzky E, White CM, Baker EL, Baker WL, Coleman CI. Feverfew for Migraine Prophylaxis: A Systematic Review. *J Diet Suppl*. 2009;6:91-103. doi:10.1080/19390210902861809

205. Furhad S, Bokhari AA. Herbal Supplements. In: *StatPearls*. StatPearls Publishing; 2026.

206. Kwok BHB, Koh B, Ndubuisi MI, Elofsson M, Crews CM. The anti-inflammatory natural product parthenolide from the medicinal herb Feverfew directly binds to and inhibits IκB kinase. *Chem Biol*. 2001;8:759-766. doi:10.1016/S1074-5521(01)00049-7

207. Michalak M, Stryjecka M, Żarnowiec P, Zagórska-Dziok M, Kiełtyka-Dadasiewicz A. Chemical Composition of Extracts from Various Parts of Feverfew (Tanacetum parthenium L.) and Their Antioxidant, Protective, and Antimicrobial Activities. *Int J Mol Sci*. 2024;25:12179. doi:10.3390/ijms252212179

208. Nelaturi V, Viswanatha GL, Shenoy RR, Khanna S, Krishnadas N. Systematic review and meta-analysis of Tanacetum parthenium: evaluating its efficacy in migraine relief. *Nat Prod Res*. 2025;0:1-8. doi:10.1080/14786419.2025.2602038

209. Pittler MH, Ernst E. Feverfew for preventing migraine. *Cochrane Database Syst Rev*. Published online 2004. doi:10.1002/14651858.CD002286.pub2

210. Johnson ES, Kadam NP, Hylands DM, Hylands PJ. Efficacy of feverfew as prophylactic treatment of migraine. *Br Med J*. 1985;291:569-573. doi:10.1136/bmj.291.6495.569

211. Tepper SJ, Tepper K. Nutraceuticals and Headache 2024: Riboflavin, Coenzyme Q10, Feverfew, Magnesium, Melatonin, and Butterbur. *Curr Pain Headache Rep*. 2025;29:33. doi:10.1007/s11916-025-01358-3

212. Safakhah HA, Tatar M, Ghanbari A. Tanacetum parthenium relieves chronic constriction injury-induced neuropathic pain in male rats. *Ann Trop Med Public Health*. 2017;10:1500. doi:10.4103/ATMPH.ATMPH_418_17

213. Medrea I, Cooper P, Lagman-Bartolome AM, Sandoe CH, Amoozegar F, Hussain WM, et al. Updated Canadian Headache Society Migraine Prevention Guideline with Systematic Review and Meta-analysis. *Can J Neurol Sci*. 2025;52:450-472. doi:10.1017/cjn.2024.285

214. Wider B, Pittler MH, Ernst E. Feverfew for preventing migraine. *Cochrane Database Syst Rev*. 2015;2015:CD002286. doi:10.1002/14651858.CD002286.pub3

215. Yao M, Ritchie HE, Brown-Woodman PD. A Reproductive screening test of feverfew: Is a full reproductive study warranted? *Reprod Toxicol*. 2006;22:688-693. doi:10.1016/j.reprotox.2006.04.014

216. Rajapakse T, Davenport WJ. Phytomedicines in the Treatment of Migraine. *CNS Drugs*. 2019;33:399-415. doi:10.1007/s40263-018-0597-2

217. Elvir Lazo OL, White PF, Lee C, et al. Use of herbal medication in the perioperative period: Potential adverse drug interactions. *J Clin Anesth*. 2024;95:111473. doi:10.1016/j.jclinane.2024.111473. PMID:38613937