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Review Article

A NOVEL TARGETED FORMULATION FOR OSTEOARTHRITIS: EXPLORING SYNERGISTIC BENEFITS OF *CISSUS QUADRANGULARIS*, *BOSWELLIA SERRATA*, *PROPOLIS* AND *PALMITOYLETHANOLAMIDE*

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Received: 26.04.2025 / Reviised: 14.07.2025 / Accepted: 19.08.2025 / Published online: 01.10.2025

ABSTRACT

Osteoarthritis (OA) is known as a debilitating form of arthritis that is marked by progressive degradation of cartilage, synovial inflammation, chronic pain and subchondral bone remodelling. OA causes progressive stiffness and decreased mobility, significantly affecting the overall quality of life of the person affected. In spite of vast research in this area, the present pharmacological interventions are purely symptomatic. Consequently, there is an expanding interest in exploring multi-dimensional targeting of pathophysiological pathways using natural treatment options, while improving patient compliance by enhancing the safety profile. The current review focusses on a novel, innovative and conceptual formulation that is designed by the authors with the scientific-evidence packed natural compounds for management of OA. This review targets to evaluate the rationale behind formulating a conceptual novel tablet consisting of *Cissus quadrangularis*, *Boswellia serrata*, *Propolis* and *Palmitoylethanolamide (PEA)* for definitive management of OA. To our knowledge, this is the first article to explore this combination. It is designed in such a way that it targets oxidative stress, inflammation, cartilage destruction and pain in OA simultaneously in a synergistic manner. In contrast to conventional treatment options which primarily provide symptom relief, this novel conceptual formulation could offer analgesic, chondroprotective and regenerative effects with reasonable safety profile making it suitable for long-term use. This formulation has a potential to emerge as an effective and safer alternatives for treatment of OA, by helping to bridge the gap between integrative and conventional medicine.

KEYWORDS: *Boswellia, Cissus*, Drug Formulation, Osteoarthritis, *Palmitoylethanolamide, Propolis*

1. Introduction

Osteoarthritis (OA) is a debilitating condition that is said to affect around 303 million people all over the world [1]. It consists of gradual cartilage degradation, matrix degeneration, inflammation of synovium, subchondral remodelling of bone and chronic intolerable pain. It leads to stiffness of joint involved associated with reduced joint mobility, that causes reduction in patient's quality of life [2]. Because of rise in aging population, obesity and sedentary lifestyle, the prevalence of OA is predicted to increase. The current available treatment options include drugs like Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), corticosteroids and major surgical procedures like total joint replacement. However, these treatment options are purely symptomatic, offering temporary pain relief rather than providing a definitive cure [3,4]. Additionally, they present with risk of long-term complications. Recently, various researches are being conducted on Disease-Modifying Osteoarthritis Drugs (DMOADs) that have a potential to provide a curative treatment [5-7]. Consequently, there is an expanding interest in exploring multi-dimensional targeting of pathophysiological pathways using natural treatment options, while improving patient compliance by enhancing the safety profile. In recent days, numerous bioactive compounds of natural sources have shown significant therapeutic potential for OA [8]. Notably, *Cissus quadrangularis*, *Boswellia serrata*, *Propolis* and *Palmitoylethanolamide* (*PEA*) have emerged as

promising treatment options for OA because of their potential antioxidant, anti-inflammatory, analgesic and chondro-protective properties. *C. quadrangularis* is a traditionally used ancient treatment for joint and bone health that has been extensively researched for its positive role in decreasing joint inflammation and improving collagen synthesis [9,10]. *B. serrata* is another notable herbal extract that has rich anti-inflammatory activity, basically through 5-Lipoxygenase (5-LOX) inhibition which is an important enzyme in leukotriene synthesis [11]. *Propolis* is a bee product that is rich in polyphenol, possessing strong immunomodulatory and antioxidant properties [12]. *PEA* is an endogenous fatty acid amide that exerts potential anti-inflammatory and analgesic effects by activation of Peroxisome Proliferator-Activated Receptor- α (PPAR- α) and regulation of mast cell [13,14]. Due to the intricate and multifaceted nature of OA, a combination strategy harnessing these bioactive compounds could offer better treatment outcome compared to individual therapy. The current review focusses on a novel, innovative and conceptual formulation that is designed by the authors with the scientific-evidence packed natural compounds *C. quadrangularis*, *B. serrata*, *Propolis* and *PEA* for management of OA. To our knowledge, this is the first article to explore this combination. This review targets to evaluate the rationale behind formulating a novel conceptual tablet consisting of *C. quadrangularis*, *B. serrata*, *Propolis* and *PEA* for definitive management of OA, that might have a strong clinical translational potential. By assessing their pharmacological activities, possible synergistic effects and mechanisms of action, we try to provide an evidence-based foundation for this novel formulation for OA management.

2. Methodology

This review was carried out to create and evaluate the science behind a conceptual evidence-based formulation targeting the pathophysiology of OA, consisting of *C. quadrangularis*, *B. serrata, Propolis and PEA*. A complete search of literature was done using the relevant keywords and all related studies published during the period 2000-2024 exploring the mechanisms of action, pharmacological effects, safety profile and synergistic interactions of these components were included, which was conducted using scientific repositories like SCOPUS, Google scholar, PubMed and Web of Science. Those articles published in other languages other than English, not focusing on OA and duplicates were excluded. A summary of data was synthesized to derive the potential of these components in specifically targeting different pathophysiological pathways of OA like oxidative stress, inflammation, cartilage degradation and pain. Based on the cumulative evidence, the current novel formulation was conceptualized to offer multifaceted therapeutic benefits comprising of anti-inflammatory, antioxidant, analgesic and chondroprotective effects with a better safety profile in context of long-term use. Eventhough this review was not written using software for systematic review, we have put efforts to reduce selection bias through structured inclusion strategy and search. In further studies, software tools like Rayyan might be utilized to improve methodological rigor.

3. Pathophysiology of OA

Osteoarthritis is defined as a chronic form of degenerative disease of joint that specifically affects the synovium, articular cartilage and subchondral bone eventually causing stiffness, pain and impaired mobility of joint. It was previously considered as a disease of mechanical wear and tear. However, evolving evidence indicates that it is primarily caused by an intricate biochemical and molecular pathway encompassing oxidative stress, inflammation, synovial destruction, cartilage degradation and maladaptive pain signalling [15-17]. Interpretation of this complex pathological processes is crucial in identifying the potential therapeutic targets, in order to provide a definitive treatment for the disease.

3.1. Inflammatory cascades

Inflammation has a critical role in the pathophysiology of OA. Inflammatory mediators like chemokines and cytokines destabilize the balance between catabolic (cartilage-degrading) and anabolic (cartilage-building) processes. This leads to formation of catabolic enzymes that are involved in destruction of the joint [18,19]. The key cytokines that mediate the pathophysiology of OA are Tumor Necrosis Factor-α (TNF- α) and Interleukin-1ß (IL-1 ß) that causes formation of proteases such as Matrix Metalloproteinases and aggrecanases [20-23]. Consequently, this leads to degradation of Extracellular Matrix (ECM) responsible for degradation of cartilage. Additionally, the key enzymes were found to mediate formation of Cyclooxygenase (COX-2) and prostaglandins (PGE2) which further heightens the inflammation and pain [24,25]. Hence, these cytokines are known as pro-inflammatory cytokines that causes the pathological changes in the joint [26]. Also, another critical mediator of inflammation was found to be NLRP3 inflammasome which links this process of inflammation with mechanical stress [27].

3.2. Oxidative stress

In a joint affected by OA, there exists an imbalance between antioxidant defense and oxidative stress [28,29]. Because of inflammation, excess production of Reactive Oxygen Species (ROS) happens in joint [30]. This activates Nuclear Factor-kappa B (NF-κB) which is an essential transcription factor that increases pro-inflammatory cytokines, further intensifying the joint inflammation. Also, this induces MMPs that further degrade Extracellular Matrix (ECM). Overall, the prevailing oxidative damage to synovial cells and chondrocytes causes apoptosis and mitochondrial dysfunction which further increases cartilage breakdown [31].

3.3. Cartilage degradation

The existing imbalance between catabolic and anabolic mechanism causes cartilage degradation, which is known as the hallmark of OA [32,33]. Chondrocytes are the crucial cells in regulating the ECM homeostasis [34]. Increased catabolic processes is marked by excess production catabolic enzymes like MMP-1, MMP-3 and MMP-13 and A Disintegrin and Metalloproteinase with Thrombospondin motifs-4 & -5(ADAMTS-4 & -5), which degrades essential components of ECM like aggrecan and type II collagen [35]. The loss of proteoglycans secondary to

destruction of cartilage matrix reduces cartilage hydration and disrupts the shock-absorbing property, making the joint vulnerable to further mechanical degradation [36,37].

3.4. Synovial Inflammation

The inflammation of synovium known as synovitis, occurs in OA due to inflammation mediated infiltration of immune cells like T cells and macrophages and elevated synovial fluid cytokines. Dur to this condition, the inflamed synovial tissue produces inflammatory mediators like IL-6, TNF-α and PGE2, that leads to synovial vascularization and hyperplasia [38-40]. This leads to excess joint effusion, joint stiffness and further accelerated cartilage degradation.

3.5. Pain mechanisms

The pain in OA involves multiple patho-mechanisms, which include peripheral sensitization, central sensitization, neuropeptides and subchondral bone remodelling. In OA, the inflammatory mediators like prostaglandins, bradykinin and cytokines sensitize the pain receptors in the joint leading to reduced pain threshold which is called as peripheral sensitization [41,42]. Apart from these, chronic pain causes specific neuroplastic changes that result in exacerbated pain stimuli [43].Additionally, certain neuropeptides such as Calcitonin Gene-Related Peptide (CGRP) and Substance P that are released from nerve endings causes increased response to pain and neurogenic inflammation [44]. As a result of chronic inflammation, remodelling of subchondral bone happens leading to appearance of osteophytes which further aggravates the nociceptive signalling process [45-47].

4. Proposed drug combination

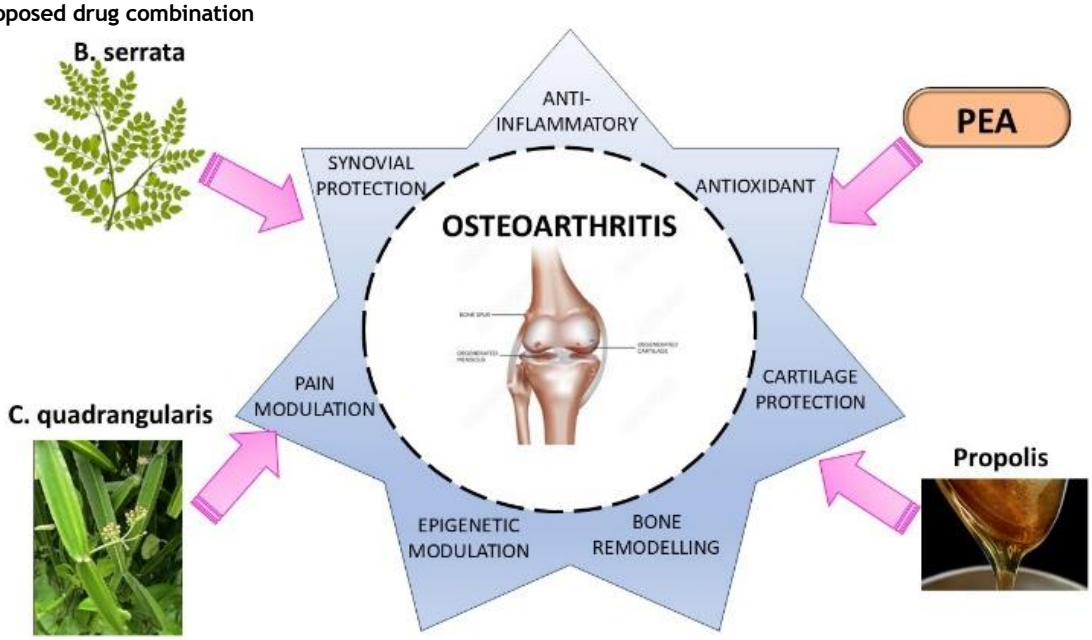

Fig 1. Proposed drug combination.

In the current review, the proposed combination (Figure 1) of drugs for the rationally-designed tablet comprises of *C. quadrangularis*, *B. serrata*, *Propolis* and *PEA*. It is formulated in such a way that it could target various pathways of OA pathophysiology like inflammation, oxidative stress, degradation of cartilage and chronic pain in a synergistic way. This can offer a safer and effective option for treatment of OA, by guiding to bridge the treatment gap that exists between conventional medicine and integrative medicine. Table 1 shows the evidence-based critical analysis of the mechanism of formulation.

Table 1. Evidence-based critical analysis of mechanism of formulation

Mechanism of action	Combination of components	Individual components effects	References
Anti-inflammatory action	*B. serrata, PEA, Propolis*	*B. serrata*: blocks 5-LOX and decreases LT production	[67-71]
		PEA: Induces PPAR-α and decreases pro-inflammatory cytokines	[72-76]
		Propolis: Alleviates NF-κB pathway and reduces IL-6, IL- 11-1β, TNF-α	[77-81]
ECM and Cartilage preservation	*B. serrata, C. quadrangularis*	*B. serrata:* Inhibit MMP and protects cartilage from degradation	[82-86]
		C. quadrangularis: Enhances synthesis of glycosaminoglycans and collagen, increases chondrocyte proliferation	[87-90]
Decrease	*Propolis, B. serrata, PEA*	*Propolis*: Improves SOD, catalase and glutathione peroxidase activities	[91-95]

oxidative stress		*B. serrata*: Supresses lipid peroxidation and scavenges free radicals	[96-99]
		PEA: Improves antioxidant defense mechanisms	[100-103]
Modification of pain signalling pathways	*PEA, B. serrata, Propolis*	*PEA*: Decreases mast cell degranulation and prevents TRPV1 receptor activation	[104-108]
		B. serrata: prevents PKA, AKAP and PDE4 signalling to decrease nociception	[109-113]
		Propolis: Modifies cannabinoid receptors and decreases substance P expression	[114-117]
Remodelling and regeneration of bone	*C. quadrangularis, B. serrata*	*C. quadrangularis*: Improves differentiation and mineralization of osteoblast, enhances expression of RUNX2 and Osteopontin	[118-122]
		B. serrata: Decreases activity of osteoclast through inhibition of RANKL pathway	[123,124]
Protection of synovial membrane	*PEA, Propolis, B. serrata*	*PEA*: Supresses inflammation and hyperplasia of synovium	[125-128]
		Propolis: Supresses activation and invasion of synovial fibroblast	[129-132]
		B. serrata: Prevents synovial angiogenesis and inhibits synovial cellular infiltration	[133-136]
Modulation of Gut-joint axis	*Propolis, PEA*	*Propolis*: Improves integrity of gut barrier and decreases microbial dysbiosis	[137-140]
		PEA: Modifies composition of gut microbiota and supresses systemic inflammation	[141-144]
Epigenetic regulation	*B. serrata, C. quadrangularis*	*B. serrata*: controls histone deacetylases and patterns of DNA methylation in chondrocytes	[145-147]
		C. quadrangularis: modifies miRNA expression involved in maintaining cartilage homeostasis	[148-151]

4.1. *C.quadrangularis*

It is a commonly used Ayurveda medicine for management of fractures, osteoporosis and joint disorders. It is also called as "Bone Setter's" plant that was found to have anti-inflammatory, antioxidant, regenerative and chondroprotective actions, through regulation of pro-inflammatory cytokines, supressing NF-κB pathway and activating alkaline phosphatase [48-50]. Previous studies have shown that it can significantly reduce joint pain [51]. Additionally, it activates synthesis of matrix and proliferation of chondrocyte thereby causing chondroprotective effects [52]. Further, it was found to decrease release of pro-inflammatory cytokines and improve genes controlling differentiation of osteoblast [53]. These findings support the fact that it has a potential to protect cartilage and supress inflammation in management of OA.

4.2. *B. serrata*

B. serrata is a medicinal plant, which is otherwise known as frankincense and was used for treating many inflammatory and musculoskeletal conditions. It has boswellic acids as bioactive compounds and AKBA is the most efficient compound in preventing degradation of cartilage and inhibiting inflammatory pathways [54]. It demonstrated inhibition of 5-Lipoxygenase (5-LOX) and supresses further production of leukotrienes [55]. Also, it modifies the NF-κB signalling, thereby decreasing the pro-inflammatory cytokines expression. It was found to inhibit cathepsin G and prostaglandin E synthase – 1 [56]. It was found to prominently reduce pain and improve physical function [57]. It was shown to have disease-modifying effects which was found by decreased levels of MMP-3, a marker of cartilage destruction [58]. Studies have found that it prevents apoptosis of chondrocytes and improves cartilage integrity [59].

4.3. *Propolis*

It is a natural resin derived from bee that is rich in polyphenol with anti-inflammatory and antioxidant effects [60]. It was found to decrease pro-inflammatory cytokines by inhibiting activation of NF-κB and reduce joint inflammation by decreasing

prostaglandins derived from COX-2 [61,62]. It can reduce MMP-13 and production of nitric oxide (NO), thereby supressing oxidative damage [63]. Thereby, it protects cartilage against wear and tear.

4.4. *PEA*

PEA is known as an endogenous fatty acid amide that has important roles like anti-inflammatory, neuroprotective and analgesia [64]. It acts by inducing PPAR-α, thereby reducing pro-inflammatory genes and consequently supresses cytokine release. It also modulates mast cell, thereby preventing its degranulation and histamine mediated in inflammation in synovial tissues [65]. Also, it helps to decrease glial cell activation and controls neurogenic inflammation, thereby decreasing chronic pain. It was reported to interact with TRPV1 channels and cannabinoid receptors, further contributing to analgesia [66].

In this novel formulation, each ingredient targets multiple interconnected pathways in pathophysiology of OA. The consolidated mechanisms provide anti-inflammatory, anti-oxidant, cartilage protection and pain modulation effects. Table 2 shows the comparison of the existing OA treatment with the current formulation. Hence, this formulation holds a potential to offer long-term benefit in OA.

Table 2. Comparison of the existing OA treatment with new formulation.

Parameters	Existing OA treatment	New evidence-based formulation	References
Examples/ Composition	NSAIDs like Diclofenac, Ibuprofen, Corticosteroids like Prednisolone, Intra-articular Hyaluronic Acid injection, Tramadol	*Cissus quadrangularis, Boswellia serrata, Propolis, Palmitoylethanolamide (PEA)*	[152-154]
Mechanism of action	Symptomatic treatment and supressing inflammation	Multi-dimensional: Anti-inflammatory, antioxidant, matrix regeneration, cartilage protection and pain reduction	[152-154]
Inflammatory marker reduction	Moderate	Significant, as it targets multiple pathways	[155,156]
Cartilage protection	Mild to potentially destructive	Potential regenerative and protective effects	[157-159]
Safety profile	High risk of adverse effects	Minimal side effects	[160-162]
Long-term use	Not suitable, because of risk of organ toxicity	Promising tissue preservation that makes convenient long-term use and can be formulated in newer drug delivery designs.	[163-165]

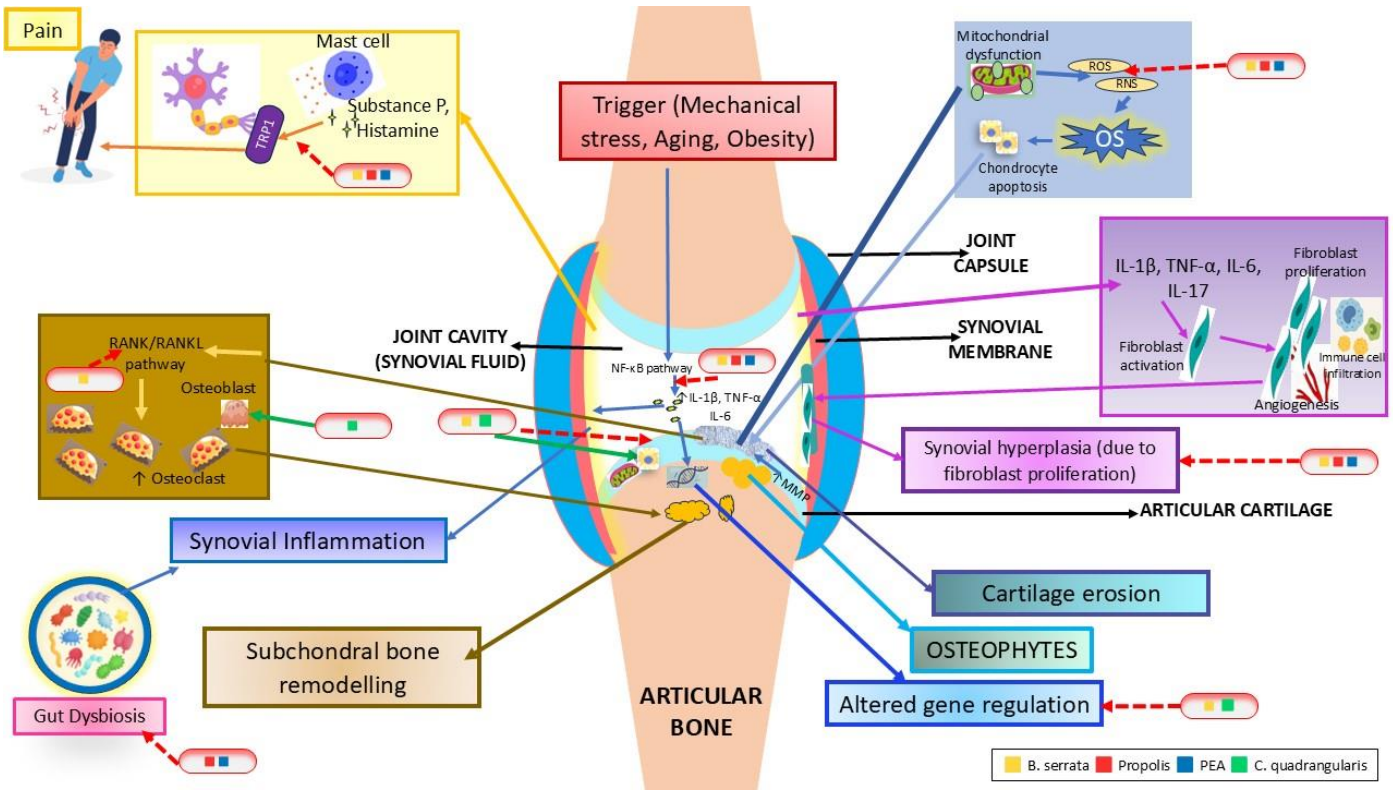

Fig 2. Combined mechanistic action of components of the drug

Figure Legend: Obesity, aging and mechanical stress activate mitochondrial dysfunction and consequently oxidative stress, causing apoptosis of chondrocyte and initiation of NF-κB signalling pathway. This leads to production of pro-inflammatory cytokines like TNF-α, IL-17, IL-6 and IL-1β, fibroblast proliferation, synovial inflammation and angiogenesis, ending in cartilage erosion and synovial hyperplasia. RANK/ RANKL pathway increases subchondral bone remodelling and osteoclastogenesis. Mast cell activation through TRPV1 causes release of histamine and substance P, leading to pain perception. This combination of drugs acts synergistically at different targets: *B. serrata* supresses NF-κB pathway causing inhibition of MMP expression and cytokine release; *C. quadrangularis* increases the osteoblast function and bone repair process; *PEA* supresses TRPV1 signalling, controls mast cells and decreases neurogenic inflammation and pain; *Propolis* decreases immune activation and oxidative stress. Together, this evidence-based conceptual formulation decreases cartilage destruction, synovial inflammation, osteophyte development and pain in OA.

Abbreviations: OA-Osteoarthritis; *PEA-palmitoylethanolamide*; IL-1β – Interleukin 1β, NF-κB-Nuclear Factor kappa-light-chain-enhancer of activated B cells; IL-6- Interleukin 6; IL-17- Interleukin-17; MMPs-Matrix Metalloproteinases; RANK-Receptor Activator of Nuclear factor κB; RANKL-RANK Ligand; RNS-Reactive Nitrogen Species; ROS-Reactive Oxygen Species; TNF-α-Tumor Necrosis Factor-alpha; TRPV1- Transient Receptor Potential Vanilloid 1.

5. Discussion

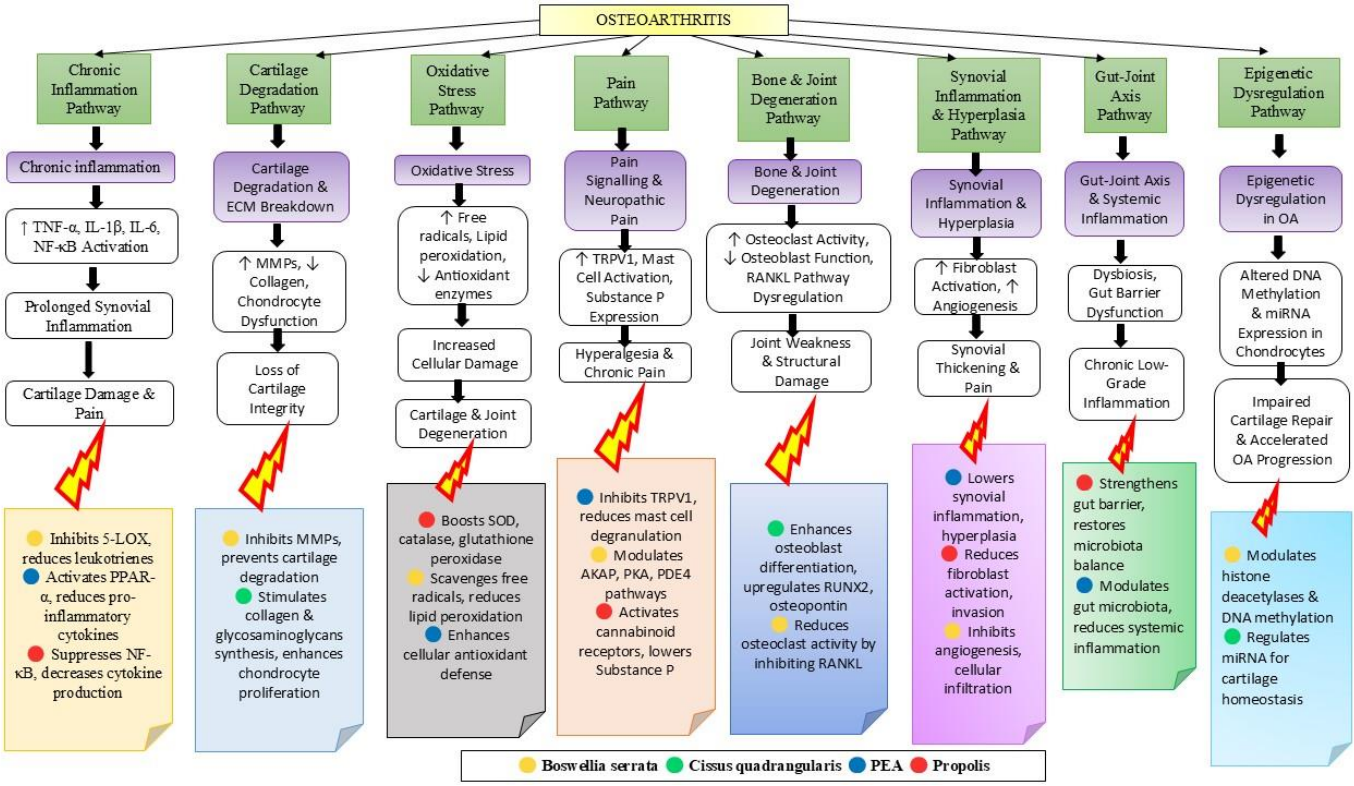

Fig 3. Combined mechanistic action of components of the drug

Figure legend: This infographic depicts the interrelated pathways that contribute to pathophysiology of OA and the specific actions of *B. serrata*, *C. quadrangularis*, *PEA* and *Propolis* in targeting these pathways to execute therapeutic effects in OA. The pathways involved in pathophysiology are chronic inflammation, oxidative stress, cartilage degradation, bone and joint degradation, pain signalling, gut-joint axis dysfunction, synovial inflammation and epigenetic dysregulation. *B. serrata* (Yellow code) supresses inflammatory mediators. *C. quadrangularis* (Green code) prevents degradation of cartilage, improves chondrocyte proliferation and supports collagen synthesis. *PEA* (Blue code) modulates pain signalling and reduces neurogenic inflammation. *Propolis* (Red code) controls gut microbiota and alleviates systemic inflammation in OA. Together, these

compounds are hypothesized to provide a multi-dimensional strategy to treat OA by its anti-inflammatory, antioxidant, improving cartilage integrity, matrix regeneration and pain reduction properties based on exiting scientific evidences.

6. Challenges and limitations

From the current review, it is proposed that this novel formulation might have a promising synergistic potential but with several limitations which needs proper consideration. Firstly, this formulation is purely a conceptual based on existing preclinical and clinical data for the individual components of the combination without any direct scientific evidence for the combination as a whole. Secondly, the natural extracts of these individual components has potential variability in terms of bioavailability, quality and standardization that could signficantly affect formulation and thereby posing a regulatory challenge. Also, other aspects of this combination formulation on long-term safety and drug interactions are yet to be explored. These limitations emphasizes the need for large-scale clinical trial on this formulation for a robust clinical validation and clinical adoption.

7. Future directions

In future, large scale clinical trials must be conducted to properly validate its clinical efficacy, safety profile and long-term benefits. Effective pharmaceutical formulation is crucial to ensure its efficient therapeutic outcomes. Table 3 represents the key aspects of pharmaceutical formulation. Additionally, its potential role in other phenotypes of OA must be investigated properly to validate its clinical utility. A proper regulatory standardization is mandatory for its successful translation into a rationale-based, commercially possible OA treatment. Based on the promising mechanistic synergy and scientific support for the individual components, further studies are needed to explore its development, efficacy, stability and safety. The authors are open to further translational research partnerships or academic collaboration to further explore and validate its potential as a novel treatment option for OA.

Table 3. Key aspects of pharmaceutical formulation.

Key aspects	Analysis
Bioavailability challenges and solutions	• *B. serrata*: Phospholipid complexation could improve the bioavailability of boswellic acid by 7-fold. • *Propolis*: Liposomal encapsulation might improve flavonoid bioavailability • *PEA*: Micronization might increase bioavailability and efficacy of PEA
Standardization	• Standardization is mandatory to ensure consistent level of active bioactive compounds like AKBA (>30%) in B. serrata, flavonoid/ phenolic content in *propolis* and ketosteroid in *C. quadrangularis*. Modern analytical methods like Spectroscopy, HPLC and LC-MS/MS can ensure its effective concentration.
Stability	• To develop a tablet with good shelf-life, stability and consistent release profiles of active compounds, it is essential to do suitable excipient selection, compression properties and stability analysis. • Hydroxypropyl Methylcellulose (HPMC) might improve controlled release of polyphenolic compounds A thorough stability analysis must be done to assess any possible interactions among active compounds and to assess oxidative degradation of phenolic compounds through standard stability testing.
Drug interactions	• *Propolis* components have been suggested to influence immunomodulatory pathways by few studies, that caution might be warranted in patients on immunosuppressive therapies. • *B. serrata* may enhance anticoagulants and hence use in caution with aspirin or warfarin • *PEA* has low drug interaction risk but has theoretical interaction with some CNS depressants • Intra-formulation interactions: Presence of antioxidant polyphenols in *propolis* could theoretically compete with PEA for metabolism and the added anti-inflammatory effects may improve efficacy but could also intensify immune modulation or mild GI side effects.
Possible formulation type	• Possibly given as once-a-day oral tablet

	• Possible oral delivery formats are capsule, tablet or softgel • The choice depends upon target release kinetics, stability and bioavailability
Dosing strategy	• *B. serrata*: 100-250mg/ day of standardized Boswellia extract • *C. quadrangularis*: 500-1000mg/day of standardized ketosteroid containing cissus extract • *PEA*: 300-600mg/day of micronized PEA • *Propolis*: 250-500mg/day of standardized propolis extract
Target patient group	• The potential target patient group include inflammatory OA phenotype, adjuvant OA therapy, patients contraindicated to NSAIDS • It has a strong conceptual potential to be used as a treatment of OA, as a part of early intervention

8. Purpose of this review

The current review was proposed in context of an academic initiative to appraise thoroughly the possible synergistic potential of *C. quadrangularis*, *B. Serrata*, *Propolis and PEA* in specifically targeting the multifaceted pathophysiology of OA. Eventhough the proposed formulation was not yet evaluated clinically, it is entirely built upon existing robust preclinical and clinical stuides on mechanistic evidence. The prinicipal goal of this eview article is not to recommend the proposed formulation for immediate clinical application, rather it is aimed to offer a scientifically sound rational basis for the purpose of further translational research and robust evidence-based drug development. Through presenting a evidence-based novel formulation strategy, the authors aim for future clinical translation of this conceptual formulation by further research collaboration and clinical validation.

9. Conclusions

This novel conceptual formulation, consisting of *B. serrata*, *C. quadrangularis*, *PEA* and *propolis* provides a multi-targeted treatment strategy for OA, as it addresses various pathophysiological pathways in OA like oxidative stress, chronic inflammation, cartilage degradation and pain signalling. In contrast to conventional treatment options which primarily provide symptom relief, this novel formulation could offer analgesic, chondroprotective and regenerative effects with reasonable safety profile making it suitable for long-term use. The overall effects of this formulation could make it a potential drug to treat OA, especially in patients with inflammatory OA and those contraindicated to conventional NSAIDs. Based on existing evidences about treating OA by individual components from various studies on their rationale and safety profile, this current review suggest that this formulation has a strong translational potential.

Author Contributions: Conceptualization, Dr.B.Dharani and Dr.Suba.A; methodology, Dr.B.Dharani.; validation, Dr.B.Dharani and Dr.Suba.A; investigation, Dr.B.Dharani; resources, Dr.Suba.A.; data curation, Dr.B.Dharani; writing—original draft preparation, Dr.B.Dharani; writing—review and editing, Dr.Suba.A.; visualization, Dr.B.Dharani; supervision, Dr.Suba.A; project administration, Dr.B.Dharani. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Informed Consent Statement: Not applicable

Acknowledgments: We express our sincere thanks to all the scientists and researchers whose invaluable contribution has serves as the major pillar for this research. The authors conceptualized this novel formulation as a part of an academic initiative to develop evidence-based combination formulation for management of OA. To our knowledge, this is the first review article to explore this combination. This formulation is presented for academic discussion and exploration for future translation and the authors welcome further research collaboration and development inquiries.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators Global, Regional, and National Incidence, Prevalence, and Years Lived with Disability for 354 Diseases and Injuries for 195 Countries and Territories, 1990-2017: A Systematic Analysis for the Global Burden of Disease Study 2017. *Lancet* 2018, *392*, 1789–1858, doi:10.1016/S0140-6736(18)32279-7.

2. Clynes, M.A.; Jameson, K.A.; Edwards, M.H.; Cooper, C.; Dennison, E.M. Impact of Osteoarthritis on Activities of Daily Living: Does Joint Site Matter? *Aging Clin. Exp. Res.* 2019, *31*, 1049–1056, doi:10.1007/s40520-019-01163-0.

3. Ranjithkumar, N.; Paul, J.; Alagesan, J.; Viswanathan, R. Comparative Effectiveness of Extracorporeal Short Wave Therapy, Low-Level Laser Therapy, and Ultrasound in the Treatment of Rotator Cuff Tendinopathy. *Biomed. Pharmacol. J.* 2025, *18*, 849–866, doi:10.13005/bpj/3134.

4. Oleshchuk, O.; Pinyazhko, O.; Klantsa, M.; Posokhova, K.; Lukanyuk, M.; Mahanova, T.; Shanaida, M. Critical

Assessment of Effectiveness and Safety of Tramadol and Evaluation of Its Market in Ukraine. *Biomed. Pharmacol. J.* 2024, *17*, 2087–2109, doi:10.13005/bpj/3010.

5. Fu, K.; Si, S.; Jin, X.; Zhang, Y.; Duong, V.; Cai, Q.; Li, G.; Oo, W.M.; Zheng, X.; Boer, C.G.; et al. Exploring Antidiabetic Drug Targets as Potential Disease-Modifying Agents in Osteoarthritis. *EBioMedicine* 2024, *107*, 105285, doi:10.1016/j.ebiom.2024.105285.

6. Li, S.; Cao, P.; Chen, T.; Ding, C. Latest Insights in Disease-Modifying Osteoarthritis Drugs Development. *Ther. Adv. Musculoskelet. Dis.* 2023, *15*, 1759720X231169839, doi:10.1177/1759720X231169839.

7. Kim, H.; Seo, J.; Lee, Y.; Park, K.; Perry, T.A.; Arden, N.K.; Mobasheri, A.; Choi, H. The Current State of the Osteoarthritis Drug Development Pipeline: A Comprehensive Narrative Review of the Present Challenges and Future Opportunities. *Ther. Adv. Musculoskelet. Dis.* 2022, *14*, 1759720X221085952, doi:10.1177/1759720X221085952.

8. Maouche, A.; Boumediene, K.; Baugé, C. Bioactive Compounds in Osteoarthritis: Molecular Mechanisms and Therapeutic Roles. *Int. J. Mol. Sci.* 2024, *25*, 11656, doi:10.3390/ijms252111656.

9. Azam, Z.; Sapra, L.; Baghel, K.; Sinha, N.; Gupta, R.K.; Soni, V.; Saini, C.; Mishra, P.K.; Srivastava, R.K. Cissus Quadrangularis (Hadjod) Inhibits RANKL-Induced Osteoclastogenesis and Augments Bone Health in an Estrogen-Deficient Preclinical Model of Osteoporosis via Modulating the Host Osteoimmune System. *Cells* 2023, *12*, 216, doi:10.3390/cells12020216.

10. Nath, R.; Kar, B.K.; Dhadiwal, R.K.; Daftary, G.V.; Khemnar, B.M.; Patil, N.N. Role of Cissus Quadrangularis in Bone Loss Pathologies. *Int J Orthop Sci* 2024, *10*, 196–201.

11. Alluri, V.K.; Kundimi, S.; Sengupta, K.; Golakoti, T.; Kilari, E.K. An Anti-Inflammatory Composition of Boswellia Serrata Resin Extracts Alleviates Pain and Protects Cartilage in Monoiodoacetate-Induced Osteoarthritis in Rats. *Evid. Based. Complement. Alternat. Med.* 2020, *2020*, 7381625, doi:10.1155/2020/7381625.

12. Kurek-Górecka, A.; Rzepecka-Stojko, A.; Górecki, M.; Stojko, J.; Sosada, M.; Swierczek-Zieba, G. Structure and Antioxidant Activity of Polyphenols Derived from Propolis. *Molecules* 2013, *19*, 78–101, doi:10.3390/molecules19010078.

13. Branković, M.; Gmizić, T.; Dukić, M.; Zdravković, M.; Daskalović, B.; Mrda, D.; Nikolić, N.; Brajković, M.; Gojgić, M.; Lalatović, J.; et al. Therapeutic Potential of Palmitoylethanolamide in Gastrointestinal Disorders. *Antioxidants (Basel)* 2024, *13*, 600, doi:10.3390/antiox13050600.

14. Costa, B.; Comelli, F.; Bettoni, I.; Colleoni, M.; Giagnoni, G. The Endogenous Fatty Acid Amide, Palmitoylethanolamide, Has Anti-Allodynic and Anti-Hyperalgesic Effects in a Murine Model of Neuropathic Pain: Involvement of CB(1), TRPV1 and PPARgamma Receptors and Neurotrophic Factors. *Pain* 2008, *139*, 541–550, doi:10.1016/j.pain.2008.06.003.

15. Yao, Q.; Wu, X.; Tao, C.; Gong, W.; Chen, M.; Qu, M.; Zhong, Y.; He, T.; Chen, S.; Xiao, G. Osteoarthritis: Pathogenic Signaling Pathways and Therapeutic Targets. *Signal Transduct. Target. Ther.* 2023, *8*, 56, doi:10.1038/s41392-023-01330-w.

16.Yunus, M.H.M.; Nordin, A.; Kamal, H. Pathophysiological Perspective of Osteoarthritis. *Medicina (Kaunas)* 2020, *56*, 614, doi:10.3390/medicina56110614.

17. Berenbaum, F. Osteoarthritis as an Inflammatory Disease (Osteoarthritis Is Not Osteoarthrosis!). *Osteoarthritis Cartilage* 2013, *21*, 16–21, doi:10.1016/j.joca.2012.11.012.

18. Wojdasiewicz, P.; Poniatowski, Ł.A.; Szukiewicz, D. The Role of Inflammatory and Anti-Inflammatory Cytokines in the Pathogenesis of Osteoarthritis. *Mediators Inflamm.* 2014, *2014*, 561459, doi:10.1155/2014/561459.

19. Zheng, L.; Zhang, Z.; Sheng, P.; Mobasheri, A. The Role of Metabolism in Chondrocyte Dysfunction and the Progression of Osteoarthritis. *Ageing Res. Rev.* 2021, *66*, 101249, doi:10.1016/j.arr.2020.101249.

20. Chen, C.; Xie, J.; Rajappa, R.; Deng, L.; Fredberg, J.; Yang, L. Interleukin-1ß and Tumor Necrosis Factor-α Increase Stiffness and Impair Contractile Function of Articular Chondrocytes. *Acta Biochim. Biophys. Sin. (Shanghai)* 2015, *47*, 121–129, doi:10.1093/abbs/gmu116.

21. Pratta, M.A.; Yao, W.; Decicco, C.; Tortorella, M.D.; Liu, R.-Q.; Copeland, R.A.; Magolda, R.; Newton, R.C.; Trzaskos, J.M.; Arner, E.C. Aggrecan Protects Cartilage Collagen from Proteolytic Cleavage. *J. Biol. Chem.* 2003, *278*, 45539–45545, doi:10.1074/jbc.M303737200.

22. Akkiraju, H.; Nohe, A. Role of Chondrocytes in Cartilage Formation, Progression of Osteoarthritis and Cartilage Regeneration. *J. Dev. Biol.* 2015, *3*, 177–192, doi:10.3390/jdb3040177.

23. Pulik, Ł.; Łęgosz, P.; Motyl, G. Matrix Metalloproteinases in Rheumatoid Arthritis and Osteoarthritis: A State of the Art Review. *Reumatologia* 2023, *61*, 191–201, doi:10.5114/reum/168503.

24. Tajdari, M.; Peyrovinasab, A.; Bayanati, M.; Ismail Mahboubi Rabbani, M.; Abdolghaffari, A.H.; Zarghi, A. Dual COX-2/TNF-α Inhibitors as Promising Anti-Inflammatory and Cancer Chemopreventive Agents: A Review. *Iran. J. Pharm. Res.* 2024, *23*, e151312, doi:10.5812/ijpr-151312.

25. Wang, Y.; Che, M.; Xin, J.; Zheng, Z.; Li, J.; Zhang, S. The Role of IL-1ß and TNF-α in Intervertebral Disc Degeneration. *Biomed. Pharmacother.* 2020, *131*, 110660, doi:10.1016/j.biopha.2020.110660.

26. Robinson, W.H.; Lepus, C.M.; Wang, Q.; Raghu, H.; Mao, R.; Lindstrom, T.M.; Sokolove, J. Low-Grade Inflammation as a Key Mediator of the Pathogenesis of Osteoarthritis. *Nat. Rev. Rheumatol.* 2016, *12*, 580–592, doi:10.1038/nrrheum.2016.136.

27. Link, T.M.; Li, X. Establishing Compositional MRI of

Cartilage as a Biomarker for Clinical Practice. *Osteoarthritis Cartilage* 2018, *26*, 1137–1139, doi:10.1016/j.joca.2018.02.902.

28. Lepetsos, P.; Papavassiliou, A.G. ROS/Oxidative Stress Signaling in Osteoarthritis. *Biochim. Biophys. Acta* 2016, *1862*, 576–591, doi:10.1016/j.bbadis.2016.01.003.

29. Ansari, M.Y.; Ahmad, N.; Haqqi, T.M. Oxidative Stress and Inflammation in Osteoarthritis Pathogenesis: Role of Polyphenols. *Biomed. Pharmacother.* 2020, *129*, 110452, doi:10.1016/j.biopha.2020.110452.

30. Bolduc, J.A.; Collins, J.A.; Loeser, R.F. Reactive Oxygen Species, Aging and Articular Cartilage Homeostasis. *Free Radic. Biol. Med.* 2019, *132*, 73–82, doi:10.1016/j.freeradbiomed.2018.08.038.

31. Guo, P.; Alhaskawi, A.; Adel Abdo Moqbel, S.; Pan, Z. Recent Development of Mitochondrial Metabolism and Dysfunction in Osteoarthritis. *Front. Pharmacol.* 2025, *16*, 1538662, doi:10.3389/fphar.2025.1538662.

32. Li, S.; Xiong, Y.; Zhu, H.; Ma, T.; Sun, X.; Xiao, J. Microenvironment-Responsive Nanosystems for Osteoarthritis Therapy. *Engineered Regeneration* 2024, *5*, 92–110, doi:10.1016/j.engreg.2023.12.002.

33. Kim, J.-H.; Jeon, J.; Shin, M.; Won, Y.; Lee, M.; Kwak, J.-S.; Lee, G.; Rhee, J.; Ryu, J.-H.; Chun, C.-H.; et al. Regulation of the Catabolic Cascade in Osteoarthritis by the Zinc-ZIP8-MTF1 Axis. *Cell* 2014, *156*, 730–743, doi:10.1016/j.cell.2014.01.007.

34. Fox, S.; Bedi, A.J.; Rodeo, A. The Basic Science of Articular Cartilage: Structure, Composition, and Function. *Sports Health* 2009, *1*, 461–468.

35. Troeberg, L.; Nagase, H. Proteases Involved in Cartilage Matrix Degradation in Osteoarthritis. *Biochim. Biophys. Acta* 2012, *1824*, 133–145, doi:10.1016/j.bbapap.2011.06.020.

36. Ur Rehman, S.; Iqbal, S.; Shahid, U.; Jahangir, S.; Malik, L. Cartilage: Structure, Function, and the Pathogenesis of Osteoarthritis. In *Advancements in Synovial Joint Science - Structure, Function, and Beyond. IntechOpen*; 2024.

37. Henao-Murillo, L.; Pastrama, M.-I.; Ito, K.; van Donkelaar, C.C. The Relationship between Proteoglycan Loss, Overloading-Induced Collagen Damage, and Cyclic Loading in Articular Cartilage. *Cartilage* 2021, *13*, 1501S-1512S, doi:10.1177/1947603519885005.

38. Mukherjee, A.; Das, B. The Role of Inflammatory Mediators and Matrix Metalloproteinases (MMPs) in the Progression of Osteoarthritis. *Biomater. Biosyst.* 2024, *13*, 100090, doi:10.1016/j.bbiosy.2024.100090.

39. Sanchez-Lopez, E.; Coras, R.; Torres, A.; Lane, N.E.; Guma, M. Synovial Inflammation in Osteoarthritis Progression. *Nat. Rev. Rheumatol.* 2022, *18*, 258–275, doi:10.1038/s41584-022-00749-9.

40. Mathiessen, A.; Conaghan, P.G. Synovitis in Osteoarthritis: Current Understanding with Therapeutic Implications. *Arthritis Res. Ther.* 2017, *19*, 18, doi:10.1186/s13075-017-1229-9.

41. Schaible, H.-G.; Ebersberger, A.; Natura, G. Update on Peripheral Mechanisms of Pain: Beyond Prostaglandins and Cytokines. *Arthritis Res. Ther.* 2011, *13*, 210, doi:10.1186/ar3305.

42. Eitner, A.; Hofmann, G.O.; Schaible, H.-G. Mechanisms of Osteoarthritic Pain. Studies in Humans and Experimental Models. *Front. Mol. Neurosci.* 2017, *10*, 349, doi:10.3389/fnmol.2017.00349.

43. Volcheck, M.M.; Graham, S.M.; Fleming, K.C.; Mohabbat, A.B.; Luedtke, C.A. Central Sensitization, Chronic Pain, and Other Symptoms: Better Understanding, Better Management. *Cleve. Clin. J. Med.* 2023, *90*, 245–254, doi:10.3949/ccjm.90a.22019.

44. Wen, B.; Pan, Y.; Cheng, J.; Xu, L.; Xu, J. The Role of Neuroinflammation in Complex Regional Pain Syndrome: A Comprehensive Review. *J. Pain Res.* 2023, *16*, 3061–3073, doi:10.2147/JPR.S423733.

45. Yang, D.; Xu, J.; Xu, K.; Xu, P. Skeletal Interoception in Osteoarthritis. *Bone Res.* 2024, *12*, 22, doi:10.1038/s41413-024-00328-6.

46. Hu, Y.; Chen, X.; Wang, S.; Jing, Y.; Su, J. Subchondral Bone Microenvironment in Osteoarthritis and Pain. *Bone Res.* 2021, *9*, 20, doi:10.1038/s41413-021-00147-z.

47. Zhu, S.; Zhu, J.; Zhen, G.; Hu, Y.; An, S.; Li, Y.; Zheng, Q.; Chen, Z.; Yang, Y.; Wan, M.; et al. Subchondral Bone Osteoclasts Induce Sensory Innervation and Osteoarthritis Pain. *J. Clin. Invest.* 2019, *129*, 1076–1093, doi:10.1172/JCI121561.

48. Singh, P.; Gupta, A.; Qayoom, I.; Singh, S.; Kumar, A. Orthobiologics with Phytobioactive Cues: A Paradigm in Bone Regeneration. *Biomed. Pharmacother.* 2020, *130*, 110754, doi:10.1016/j.biopha.2020.110754.

49. Mishra, G.; Srivastava, S.; Nagori, B.P. Pharmacological and Therapeutic Activity of Cissus Quadrangularis: An Overview. *International Journal of PharmTech Research* 2010, *2*, 1298–1310.

50. Bhujade, A.M.; Talmale, S.; Kumar, N.; Gupta, G.; Reddanna, P.; Das, S.K.; Patil, M.B. Evaluation of Cissus Quadrangularis Extracts as an Inhibitor of COX, 5-LOX, and Proinflammatory Mediators. *J. Ethnopharmacol.* 2012, *141*, 989–996, doi:10.1016/j.jep.2012.03.044.

51. Bloomer, R.J.; Farney, T.M.; McCarthy, C.G.; Lee, S.-R. Cissus Quadrangularis Reduces Joint Pain in Exercise-Trained Men: A Pilot Study. *Phys. Sportsmed.* 2013, *41*, 29–35, doi:10.3810/psm.2013.09.2021.

52. Kanwar, J.; Samarasinghe, R.; Kumar, K.; Arya, R.; Sharma, S.; Zhou, S.-F.; Sasidharan, S.; Kanwar, R. Cissus Quadrangularis Inhibits IL-1β Induced Inflammatory Responses on Chondrocytes and Alleviates Bone Deterioration in Osteotomized Rats via P38 MAPK Signaling [Corrigendum]. *Drug Des. Devel. Ther.* 2017, *11*, 2683–2684, doi:10.2147/dddt.s148615.

53. Banu, J.; Varela, E.; Bahadur, A.N.; Soomro, R.; Kazi,

N.; Fernandes, G. Inhibition of Bone Loss by Cissus Quadrangularis in Mice: A Preliminary Report. *J. Osteoporos.* 2012, *2012*, 101206, doi:10.1155/2012/101206.

54. Iram, F.; Khan, S.A.; Husain, A. Phytochemistry and Potential Therapeutic Actions of Boswellic Acids: A Mini-Review. *Asian Pac. J. Trop. Biomed.* 2017, *7*, 513–523, doi:10.1016/j.apjtb.2017.05.001.

55. Siddiqui, M.Z. Boswellia Serrata, a Potential Antiinflammatory Agent: An Overview. *Indian J. Pharm. Sci.* 2011, *73*, 255–261, doi:10.4103/0250-474X.93507.

56. Sengupta, K.; Alluri, K.V.; Satish, A.R.; Mishra, S.; Golakoti, T.; Sarma, K.V.; Dey, D.; Raychaudhuri, S.P. A Double Blind, Randomized, Placebo Controlled Study of the Efficacy and Safety of 5-Loxin for Treatment of Osteoarthritis of the Knee. *Arthritis Res. Ther.* 2008, *10*, R85, doi:10.1186/ar2461.

57. 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.

58. Vishal, A.A.; Mishra, A.; Raychaudhuri, S.P. A Double Blind, Randomized, Placebo Controlled Clinical Study Evaluates the Early Efficacy of Aflapin in Subjects with Osteoarthritis of Knee. *Int. J. Med. Sci.* 2011, *8*, 615–622, doi:10.7150/ijms.8.615.

59. Sukhikh, S.; Noskova, S.; Ivanova, S.; Ulrikh, E.; Izgaryshev, A.; Babich, O. Chondroprotection and Molecular Mechanism of Action of Phytonutraceuticals on Osteoarthritis. *Molecules* 2021, *26*, 2391, doi:10.3390/molecules26082391.

60. Hossain, R.; Quispe, C.; Khan, R.A.; Saikat, A.S.M.; Ray, P.; Ongalbek, D.; Yeskaliyeva, B.; Jain, D.; Smeriglio, A.; Trombetta, D.; et al. Propolis: An Update on Its Chemistry and Pharmacological Applications. *Chin. Med.* 2022, *17*, 100, doi:10.1186/s13020-022-00651-2.

61. Oršolić, N.; Jazvinšćak Jembrek, M. Potential Strategies for Overcoming Drug Resistance Pathways Using Propolis and Its Polyphenolic/Flavonoid Compounds in Combination with Chemotherapy and Radiotherapy. *Nutrients* 2024, *16*, doi:10.3390/nu16213741.

62. Altabbal, S.; Athamnah, K.; Rahma, A.; Wali, A.F.; Eid, A.H.; Iratni, R.; Al Dhaheri, Y. Propolis: A Detailed Insight of Its Anticancer Molecular Mechanisms. *Pharmaceuticals (Basel)* 2023, *16*, doi:10.3390/ph16030450.

63. Arias, C.; Vásquez, B.; Salazar, L.A. Propolis as a Potential Therapeutic Agent to Counteract Age-Related Changes in Cartilage: An in Vivo Study. *Int. J. Mol. Sci.* 2023, *24*, doi:10.3390/ijms241814272.

64. Petrosino, S.; Marzo, D. The Pharmacology of Palmitoylethanolamide and First Data on the Therapeutic Efficacy of Some of Its New Formulations: Palmitoylethanolamide and Its New Formulations. *Br J Pharmacol* 2017, *174*, 1349–1365.

65. Skaper, S.D.; Facci, L.; Fusco, M.; Della Valle, M.F.; Zusso, M.; Costa, B.; Giusti, P. Palmitoylethanolamide, a Naturally Occurring Disease-Modifying Agent in Neuropathic Pain. *Inflammopharmacology* 2014, *22*, 79–94, doi:10.1007/s10787-013-0191-7.

66. Gabrielsson, L.; Mattsson, S.; Fowler, C.J. Palmitoylethanolamide for the Treatment of Pain: Pharmacokinetics, Safety and Efficacy. *Br. J. Clin. Pharmacol.* 2016, *82*, 932–942, doi:10.1111/bcp.13020.

67. Sengupta, K.; Kolla, J.N.; Krishnaraju, A.V.; Yalamanchili, N.; Rao, C.V.; Golakoti, T.; Raychaudhuri, S.; Raychaudhuri, S.P. Cellular and Molecular Mechanisms of Anti-Inflammatory Effect of Aflapin: A Novel Boswellia Serrata Extract. *Mol. Cell. Biochem.* 2011, *354*, 189–197, doi:10.1007/s11010-011-0818-1.

68. Sengupta, K.; Krishnaraju, A.V.; Vishal, A.A.; Mishra, A.; Trimurtulu, G.; Sarma, K.V.S.; Raychaudhuri, S.K.; Raychaudhuri, S.P. Comparative Efficacy and Tolerability of 5-Loxin and AflapinAgainst Osteoarthritis of the Knee: A Double Blind, Randomized, Placebo Controlled Clinical Study. *Int. J. Med. Sci.* 2010, *7*, 366–377, doi:10.7150/ijms.7.366.

69. Bannuru, R.R.; Osani, M.C.; 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.

70. Umar, S.; Umar, K.; Sarwar, A.H.M.G.; Khan, A.; Ahmad, N.; Ahmad, S.; Katiyar, C.K.; Husain, S.A.; Khan, H.A. Boswellia Serrata Extract Attenuates Inflammatory Mediators and Oxidative Stress in Collagen Induced Arthritis. *Phytomedicine* 2014, *21*, 847–856, doi:10.1016/j.phymed.2014.02.001.

71. Riva, A.; Ronchi, M.; Petrangolini, G.; Bosisio, S.; Allegrini, P. Improved Oral Absorption of Quercetin from Quercetin Phytosome®, a New Delivery System Based on Food Grade Lecithin. *Eur. J. Drug Metab. Pharmacokinet.* 2019, *44*, 169–177, doi:10.1007/s13318-018-0517-3.

72. Lang-Illievich, K.; Klivinyi, C.; Lasser, C.; Brenna, C.T.A.; Szilagyi, I.S.; Bornemann-Cimenti, H. Palmitoylethanolamide in the Treatment of Chronic Pain: A Systematic Review and Meta-Analysis of Double-Blind Randomized Controlled Trials. *Nutrients* 2023, *15*, doi:10.3390/nu15061350.

73. Steels, E.; Venkatesh, R.; Steels, E.; Vitetta, G.; Vitetta, L. A Double-Blind Randomized Placebo Controlled Study Assessing Safety, Tolerability and Efficacy of Palmitoylethanolamide for Symptoms of Knee Osteoarthritis. *Inflammopharmacology* 2019, *27*, 475–485, doi:10.1007/s10787-019-00582-9.

74. Jung, J.I.; Lee, H.S.; Jeon, Y.E.; Kim, S.M.; Hong, S.H.; Moon, J.M.; Lim, C.Y.; Kim, Y.H.; Kim, E.J. Anti-Inflammatory Activity of Palmitoylethanolamide Ameliorates Osteoarthritis Induced by Monosodium Iodoacetate in Sprague-Dawley Rats. *Inflammopharmacology* 2021, *29*, 1475–1486, doi:10.1007/s10787-021-00870-3.

75.Gugliandolo, E.; Fusco, R.; Biundo, F.; D'Amico, R.; Benedetto, F.; Di Paola, R.; Cuzzocrea, S.

Palmitoylethanolamide and Polydatin Combination Reduces Inflammation and Oxidative Stress in Vascular Injury. *Pharmacol. Res.* 2017, *123*, 83–92, doi:10.1016/j.phrs.2017.06.014.

76.Marini, I.; Bartolucci, M.L.; Bortolotti, F.; Gatto, M.R.; Bonetti, G.A. Palmitoylethanolamide versus a Nonsteroidal Anti-Inflammatory Drug in the Treatment of Temporomandibular Joint Inflammatory Pain. *J. Orofac. Pain* 2012, *26*, 99–104.

77.Berretta, A.A.; Silveira, M.A.D.; Cóndor Capcha, J.M.; De Jong, D. Propolis and Its Potential against SARS-CoV-2 Infection Mechanisms and COVID-19 Disease: Running Title: Propolis against SARS-CoV-2 Infection and COVID-19. *Biomed. Pharmacother.* 2020, *131*, 110622, doi:10.1016/j.biopha.2020.110622.

78.Kurek-Górecka, A.; Górecki, M.; Rzepecka-Stojko, A.; Balwierz, R.; Stojko, J. Bee Products in Dermatology and Skin Care. *Molecules* 2020, *25*, 556, doi:10.3390/molecules25030556.

79.Pahlavani, N.; Malekahmadi, M.; Firouzi, S.; Rostami, D.; Sedaghat, A.; Moghaddam, A.B.; Ferns, G.A.; Navashenaq, J.G.; Reazvani, R.; Safarian, M.; et al. Molecular and Cellular Mechanisms of the Effects of Propolis in Inflammation, Oxidative Stress and Glycemic Control in Chronic Diseases. *Nutr. Metab. (Lond.)* 2020, *17*, 65, doi:10.1186/s12986-020-00485-5.

80.Xuan, H.; Yuan, W.; Chang, H.; Liu, M.; Hu, F. Anti-Inflammatory Effects of Chinese Propolis in Lipopolysaccharide-Stimulated Human Umbilical Vein Endothelial Cells by Suppressing Autophagy and MAPK/NF-κB Signaling Pathway. *Inflammopharmacology* 2019, *27*, 561–571, doi:10.1007/s10787-018-0533-6.

81.Zulhendri, F.; Lesmana, R.; Tandean, S.; Christoper, A.; Chandrasekaran, K.; Irsyam, I.; Suwantika, A.A.; Abdulah, R.; Wathoni, N. Recent Update on the Anti-Inflammatory Activities of Propolis. *Molecules* 2022, *27*, 8473, doi:10.3390/molecules27238473.

82.Majeed, M.; Majeed, S.; Narayanan, N.K.; Nagabhushanam, K. A Pilot, Randomized, Double-Blind, Placebo-Controlled Trial to Assess the Safety and Efficacy of a Novel Boswellia Serrata Extract in the Management of Osteoarthritis of the Knee: A Novel B. Serrata Extract for Knee Osteoarthritis. *Phytother Res* 2019, *33*, 1457–1468.

83.Minoretti, P.; Santiago Sáez, A.; Liaño Riera, M.; Gómez Serrano, M.; García Martín, Á. Efficacy and Safety of Two Chondroprotective Supplements in Patients with Knee Osteoarthritis: A Randomized, Single-Blind, Pilot Study. *Cureus* 2024, *16*, e57579, doi:10.7759/cureus.57579.

84.Hussain, H.; Wang, D.; El-Seedi, H.R.; Rashan, L.; Ahmed, I.; Abbas, M.; Mamadalieva, N.Z.; Sultani, H.N.; Hussain, M.I.; Shah, S.T.A. Therapeutic Potential of Boswellic Acids: An Update Patent Review (2016-2023). *Expert Opin. Ther. Pat.* 2024, *34*, 723–732, doi:10.1080/13543776.2024.2369626.

85.Villalvilla, A.; da Silva, J.A.; Largo, R.; Gualillo, O.; Vieira, P.C.; Herrero-Beaumont, G.; Gómez, R. 6-Shogaol Inhibits Chondrocytes' Innate Immune Responses and Cathepsin-K Activity. *Mol. Nutr. Food Res.* 2014, *58*, 256–266, doi:10.1002/mnfr.201200833.

86.Shin, M.-R.; Kim, H.-Y.; Choi, H.-Y.; Park, K.S.; Choi, H.J.; Roh, S.-S. Boswellia Serrata Extract, 5-Loxin®, Prevents Joint Pain and Cartilage Degeneration in a Rat Model of Osteoarthritis through Inhibition of Inflammatory Responses and Restoration of Matrix Homeostasis. *Evid. Based. Complement. Alternat. Med.* 2022, *2022*, 3067526, doi:10.1155/2022/3067526.

87.Potu, B.K.; Bhat, K.M.R.; Rao, M.S.; Nampurath, G.K.; Chamallamudi, M.R.; Nayak, S.R.; Muttigi, M.S. Petroleum Ether Extract of Cissus Quadrangularis (Linn.) Enhances Bone Marrow Mesenchymal Stem Cell Proliferation and Facilitates Osteoblastogenesis. *Clinics (Sao Paulo)* 2009, *64*, 993–998, doi:10.1590/S1807-59322009001000010.

88.Bafna, P.S.; Patil, P.H.; Maru, S.K.; Mutha, R.E. Cissus Quadrangularis L: A Comprehensive Multidisciplinary Review. *J. Ethnopharmacol.* 2021, *279*, 114355, doi:10.1016/j.jep.2021.114355.

89.Sawangjit, R.; Puttarak, P.; Saokaew, S.; Chaiyakunapruk, N. Efficacy and Safety of Cissus Quadrangularis L. in Clinical Use: A Systematic Review and Meta-Analysis of Randomized Controlled Trials: Efficacy and Safety of Cissus in Clinical Use. *Phytother Res* 2017, *31*, 555–567.

90.Sen, M.; Dash, B. A Review on Phytochemical and Pharmacological Aspects ofCissus quadrangularisL. *Int. J. Green Pharm.* 2012, *6*, 169, doi:10.4103/0973-8258.104924.

91.Martinotti, S.; Ranzato, E. Propolis: A New Frontier for Wound Healing? *Burns Trauma* 2015, *3*, 9, doi:10.1186/s41038-015-0010-z.

92.Bolfa, P.; Vidrighinescu, R.; Petruta, A.; Dezmirean, D.; Stan, L.; Vlase, L.; Damian, G.; Catoi, C.; Filip, A.; Clichici, S. Photoprotective Effects of Romanian Propolis on Skin of Mice Exposed to UVB Irradiation. *Food Chem. Toxicol.* 2013, *62*, 329–342, doi:10.1016/j.fct.2013.08.078

93. Miryan, M.; Soleimani, D.; Dehghani, L.; Sohrabi, K.; Khorvash, F.; Bagherniya, M.; Sayedi, S.M.; Askari, G. The Effect of Propolis Supplementation on Clinical Symptoms in Patients with Coronavirus (COVID-19): A Structured Summary of a Study Protocol for a Randomised Controlled Trial. *Trials* 2020, *21*, 996, doi:10.1186/s13063-020-04934-7.

94.Nazari-Bonab, H.; Jamilian, P.; Radkhah, N.; Zarezadeh, M.; Ebrahimi-Mameghani, M. The Effect of Propolis Supplementation in Improving Antioxidant Status: A Systematic Review and Meta-Analysis of Controlled Clinical Trials. *Phytother. Res.* 2023, *37*, 3712–3723, doi:10.1002/ptr.7899.

95.Hori, J.I.; Zamboni, D.S.; Carrão, D.B.; Goldman, G.H.; Berretta, A.A. The Inhibition of Inflammasome by Brazilian Propolis (EPP-AF). *Evid. Based. Complement. Alternat. Med.* 2013, *2013*, 418508, doi:10.1155/2013/418508.

96.Dalmonte, T.; Andreani, G.; Rudelli, C.; Isani, G. Efficacy of Extracts of Oleogum Resin of Boswellia in the

Treatment of Knee Osteoarthritis: A Systematic Review and Meta-Analysis. *Phytother. Res.* 2024, *38*, 5672–5689, doi:10.1002/ptr.8336.

97.Abdel-Tawab, M.; Werz, O.; Schubert-Zsilavecz, M. Boswellia Serrata: An Overall Assessment of in Vitro, Preclinical, Pharmacokinetic and Clinical Data: An Overall Assessment of in Vitro, Preclinical, Pharmacokinetic and Clinical Data. *Clin Pharmacokinet* 2011, *50*, 349–369.

98.Doaee, P.; Rajaei, Z.; Roghani, M.; Alaei, H.; Kamalinejad, M. Effects of Boswellia Serrata Resin Extract on Motor Dysfunction and Brain Oxidative Stress in an Experimental Model of Parkinson's Disease. *Avicenna J. Phytomed.* 2019, *9*, 281–290.

99.Sailer, E.R.; Subramanian, L.R.; Rall, B.; Hoernlein, R.F.; Ammon, H.P.; Safayhi, H. Acetyl-11-Keto-Beta-Boswellic Acid (AKBA): Structure Requirements for Binding and 5-Lipoxygenase Inhibitory Activity. *Br. J. Pharmacol.* 1996, *117*, 615–618, doi:10.1111/j.1476-5381.1996.tb15235.x.

100.Hesselink, K.; De Boer, J.M.; Witkamp, T. Palmitoylethanolamide: A Natural Body-Own Anti-Inflammatory Agent, Effective and Safe against Influenza and Common Cold. *Int J Inflam* 2013.

101.Clayton, P.; Subah, S.; Venkatesh, R.; Hill, M.; Bogoda, N. Palmitoylethanolamide: A Potential Alternative to Cannabidiol. *J. Diet. Suppl.* 2023, *20*, 505–530, doi:10.1080/19390211.2021.2005733.

102.Varrassi, G.; Rekatsina, M.; Leoni, M.L.G.; Cascella, M.; Finco, G.; Sardo, S.; Corno, C.; Tiso, D.; Schweiger, V.; Fornasari, D.M.M.; et al. A Decades-Long Journey of Palmitoylethanolamide (PEA) for Chronic Neuropathic Pain Management: A Comprehensive Narrative Review. *Pain Ther.* 2025, *14*, 81–101, doi:10.1007/s40122-024-00685-4.

103.Petrosino, S.; Cordaro, M.; Verde, R.; Schiano Moriello, A.; Marcolongo, G.; Schievano, C.; Siracusa, R.; Piscitelli, F.; Peritore, A.F.; Crupi, R.; et al. Oral Ultramicronized Palmitoylethanolamide: Plasma and Tissue Levels and Spinal Anti-Hyperalgesic Effect. *Front. Pharmacol.* 2018, *9*, 249, doi:10.3389/fphar.2018.00249.

104.Passavanti, M.B.; Alfieri, A.; Pace, M.C.; Pota, V.; Sansone, P.; Piccinno, G.; Barbarisi, M.; Aurilio, C.; Fiore, M. Clinical Applications of Palmitoylethanolamide in Pain Management: Protocol for a Scoping Review. *Syst. Rev.* 2019, *8*, 9, doi:10.1186/s13643-018-0934-z.

105.Artukoglu, B.B.; Beyer, C.; Zuloff-Shani, A.; Brener, E.; Bloch, M.H. Efficacy of Palmitoylethanolamide for Pain: A Meta-Analysis. *Pain Physician* 2017, *20*, 353–362.

106.Nestmann, E.R. Safety of Micronized Palmitoylethanolamide (microPEA): Lack of Toxicity and Genotoxic Potential. *Food Sci. Nutr.* 2017, *5*, 292–309, doi:10.1002/fsn3.392.

107.Schweiger, V.; Schievano, C.; Martini, A.; Polati, L.; Del Balzo, G.; Simari, S.; Milan, B.; Finco, G.; Varrassi, G.; Polati, E. Extended Treatment with Micron-Size Oral Palmitoylethanolamide (PEA) in Chronic Pain: A Systematic Review and Meta-Analysis. *Nutrients* 2024, *16*, 1653, doi:10.3390/nu16111653.

108.Shamraiz, U.; Hussain, H.; Ur Rehman, N.; Al-Shidhani, S.; Saeed, A.; Khan, H.Y.; Khan, A.; Fischer, L.; Csuk, R.; Badshah, A.; et al. Synthesis of New Boswellic Acid Derivatives as Potential Antiproliferative Agents. *Nat. Prod. Res.* 2020, *34*, 1845–1852, doi:10.1080/14786419.2018.1564295.

109.Sharma, S.; Gupta, S.; Khajuria, V.; Bhagat, A.; Ahmed, Z.; Shah, B.A. Analogues of Boswellic Acids as Inhibitors of Pro-Inflammatory Cytokines TNF-α and IL-6. *Bioorg. Med. Chem. Lett.* 2016, *26*, 695–698, doi:10.1016/j.bmcl.2015.11.035.

110.Mbiantcha, M.; Khalid, R.; Atsamo, D.A.; Njoku, I.S.; Mehreen, A.; Ateufack, G.; Hamza, D.; Nana, W.Y.; Naeem, R.U.; Izhar, A. Anti-Hypernociceptive Effects of Methanol Extract of Boswellia Dalzielii on STZ-Induced Diabetic Neuropathic Pain. *Advances in Traditional Medicine* 2020, *20*, 405–417, doi:10.1007/s13596-019-00411-y.

111.Majeed, A.; Majeed, S.; Satish, G.; Manjunatha, R.; Rabbani, S.N.; Patil, N.V.P.; Mundkur, L. 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.

112.Roy, N.K.; Parama, D.; Banik, K.; Bordoloi, D.; Devi, A.K.; Thakur, K.K.; Padmavathi, G.; Shakibaei, M.; Fan, L.; Sethi, G.; et al. An Update on Pharmacological Potential of Boswellic Acids against Chronic Diseases. *Int. J. Mol. Sci.* 2019, *20*, 4101, doi:10.3390/ijms20174101.

113.Machado, J.L.; Assunção, A.K.M.; da Silva, M.C.P.; Dos Reis, A.S.; Costa, G.C.; Arruda, D. de S.; Rocha, B.A.; Vaz, M.M. de O.L.L.; Paes, A.M. de A.; Guerra, R.N.M.; et al. Brazilian Green Propolis: Anti-Inflammatory Property by an Immunomodulatory Activity. *Evid. Based. Complement. Alternat. Med.* 2012, *2012*, 157652, doi:10.1155/2012/157652.

114.Kasote, D.; Bankova, V.; Viljoen, A.M. Propolis: Chemical Diversity and Challenges in Quality Control. *Phytochem. Rev.* 2022, *21*, 1887–1911, doi:10.1007/s11101-022-09816-1.

115.Katiyar, D. Propolis: A Natural Biomaterial. *Mater. Today* 2023, doi:10.1016/j.matpr.2023.05.522.

116.Xu, W.; Lu, H.; Yuan, Y.; Deng, Z.; Zheng, L.; Li, H. The Antioxidant and Anti-Inflammatory Effects of Flavonoids from Propolis via Nrf2 and NF-κB Pathways. *Foods* 2022, *11*, 2439, doi:10.3390/foods11162439.

117.Muthusami, S.; Ramachandran, I.; Krishnamoorthy, S.; Govindan, R.; Narasimhan, S. Cissus Quadrangularis Augments IGF System Components in Human Osteoblast like SaOS-2 Cells. *Growth Horm. IGF Res.* 2011, *21*, 343–348, doi:10.1016/j.ghir.2011.09.002.

118.Dhanasekaran, S. Phytochemical Characteristics of Aerial Part of Cissus Quadrangularis (L) and Its in-Vitro Inhibitory Activity against Leukemic Cells and

Antioxidant Properties. *Saudi J. Biol. Sci.* 2020, *27*, 1302–1309, doi:10.1016/j.sjbs.2020.01.005.

119.Guerra, J.M.; Hanes, M.A.; Rasa, C.; Loganathan, N.; Innis-Whitehouse, W.; Gutierrez, E.; Nair, S.; Banu, J. Modulation of Bone Turnover by Cissus Quadrangularis after Ovariectomy in Rats. *J. Bone Miner. Metab.* 2019, *37*, 780–795, doi:10.1007/s00774-018-0983-3.

120.Tasadduq, R.; Gordon, J.; Al-Ghanim, K.A.; Lian, J.B.; Van Wijnen, A.J.; Stein, J.L.; Stein, G.S.; Shakoori, A.R. Ethanol Extract of Cissus Quadrangularis Enhances Osteoblast Differentiation and Mineralization of Murine Pre-Osteoblastic MC3T3-E1 Cells: Effect of Herbal Extract on Osteoblast Differentiation. *J. Cell. Physiol.* 2017, *232*, 540–547, doi:10.1002/jcp.25449.

121.Liao, L.; Zhu, W.; Tao, C.; Li, D.; Mao, M. Cissus Quadrangularis L Extract-Loaded Tricalcium Phosphate Reinforced Natural Polymer Composite for Guided Bone Regeneration. *J. Mater. Sci. Mater. Med.* 2023, *34*, 33, doi:10.1007/s10856-023-06739-x.

122.Sadeghnia, H.R.; Arjmand, F.; Ghorbani, A. Neuroprotective Effect of Boswellia Serrata and Its Active Constituent Acetyl 11-Keto-β-Boswellic Acid against Oxygen-Glucose-Serum Deprivation-Induced Cell Injury. *Acta Pol. Pharm.* 2017, *74*, 911–920.

123.Nakhaei, K.; Bagheri-Hosseini, S.; Sabbaghzade, N.; Behmadi, J.; Boozari, M. Boswellic Acid Nanoparticles: Promising Strategies for Increasing Therapeutic Effects. *Rev. Bras. Farmacogn.* 2023, *33*, 713–723, doi:10.1007/s43450-023-00405-7.

124.Li, W.; Ren, L.; Zheng, X.; Liu, J.; Wang, J.; Ji, T.; Du, G. 3-O-Acetyl-11-Keto- β -Boswellic Acid Ameliorated Aberrant Metabolic Landscape and Inhibited Autophagy in Glioblastoma. *Acta Pharm. Sin. B.* 2020, *10*, 301–312, doi:10.1016/j.apsb.2019.12.012.

125. Bartolucci, M.L.; Marini, I.; Bortolotti, F.; Impellizzeri, D.; Di Paola, R.; Bruschetta, G.; Crupi, R.; Portelli, M.; Militi, A.; Oteri, G.; et al. Micronized Palmitoylethanolamide Reduces Joint Pain and Glial Cell Activation. *Inflamm. Res.* 2018, *67*, 891–901, doi:10.1007/s00011-018-1179-y.

126. Loi, S.; Pontis, E.; Cofelice, A.; Pirarba, V.; Fais, S.; Daniilidis, M.F. Effect of Ultramicronized-Palmitoylethanolamide and Co-Micronized Palmitoylethanolamide/Polydatin on Chronic Pelvic Pain and Quality of Life in Endometriosis Patients: An Open-Label Pilot Study. *Int J Womens Health* 2019, *11*, 443–449.

127.Lama, A.; Pirozzi, C.; Severi, I.; Morgese, M.G.; Senzacqua, M.; Annunziata, C.; Comella, F.; Del Piano, F.; Schiavone, S.; Petrosino, S.; et al. Palmitoylethanolamide Dampens Neuroinflammation and Anxiety-like Behavior in Obese Mice. *Brain Behav. Immun.* 2022, *102*, 110–123, doi:10.1016/j.bbi.2022.02.008.

128.Bueno-Silva, B.; Kawamoto, D.; Ando-Suguimoto, E.S.; Casarin, R.C.V.; Alencar, S.M.; Rosalen, P.L.; Mayer, M.P.A. Brazilian Red Propolis Effects on Peritoneal Macrophage Activity: Nitric Oxide, Cell Viability, pro-Inflammatory Cytokines and Gene Expression. *J. Ethnopharmacol.* 2017, *207*, 100–107, doi:10.1016/j.jep.2017.06.015.

129. Šuran, J.; Cepanec, I.; Mašek, T.; Radić, B.; Radić, S.; Tlak Gajger, I.; Vlainić, J. Propolis Extract and Its Bioactive Compounds-from Traditional to Modern Extraction Technologies. *Molecules* 2021, *26*, 2930, doi:10.3390/molecules26102930.

130.Javed, S.; Mangla, B.; Ahsan, W. From Propolis to Nanopropolis: An Exemplary Journey and a Paradigm Shift of a Resinous Substance Produced by Bees. *Phytother. Res.* 2022, *36*, 2016–2041, doi:10.1002/ptr.7435.

131.Lv, L.; Cui, H.; Ma, Z.; Liu, X.; Yang, L. Recent Progresses in the Pharmacological Activities of Caffeic Acid Phenethyl Ester. *Naunyn. Schmiedebergs. Arch. Pharmacol.* 2021, *394*, 1327–1339, doi:10.1007/s00210-021-02054-w.

132.Kumar, R.; Singh, S.; Saksena, A.K.; Pal, R.; Jaiswal, R.; Kumar, R. Effect of Boswellia Serrata Extract on Acute Inflammatory Parameters and Tumor Necrosis Factor-α in Complete Freund's Adjuvant-Induced Animal Model of Rheumatoid Arthritis. *Int. J. Appl. Basic Med. Res.* 2019, *9*, 100–106, doi:10.4103/ijabmr.IJABMR_248_18.

133.Choi, Y.-J.; Jung, J.I.; Bae, J.; Lee, J.K.; Kim, E.J. Evaluating the Anti-Osteoarthritis Potential of Standardized Boswellia Serrata Gum Resin Extract in Alleviating Knee Joint Pathology and Inflammation in Osteoarthritis-Induced Models. *Int. J. Mol. Sci.* 2024, *25*, 3218, doi:10.3390/ijms25063218.

134.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.

135.Ammon, H.P.T. 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.

136.De Carvalho Fm De, A.; Schneider, J.K.; De Jesus, C.; De Andrade, L.N.; Amaral, R.G.; David, J.M. Brazilian Red Propolis: Extracts Production, Physicochemical Characterization, and Cytotoxicity Profile for Antitumor Activity. *Biomolecules* 2020, *10*.

137.Fonseca, L.; Ribeiro, M.; Schultz, J.; Borges, N.A.; Cardozo, L.; Leal, V.O.; Ribeiro-Alves, M.; Paiva, B.R.; Leite, P.E.C.; Sanz, C.L.; et al. Effects of Propolis Supplementation on Gut Microbiota and Uremic Toxin Profiles of Patients Undergoing Hemodialysis. *Toxins (Basel)* 2024, *16*, 416, doi:10.3390/toxins16100416.

138.Okamoto, Y.; Hara, T.; Ebato, T.; Fukui, T.; Masuzawa, T. Brazilian Propolis Ameliorates Trinitrobenzene Sulfonic Acid-Induced Colitis in Mice by Inhibiting Th1 Differentiation. *Int. Immunopharmacol.* 2013, *16*, 178–183, doi:10.1016/j.intimp.2013.04.004.

139.Kurek-Górecka, A.; Keskin, Ş.; Bobis, O.; Felitti, R.;

Górecki, M.; Otręba, M.; Stojko, J.; Olczyk, P.; Kolayli, S.; Rzepecka-Stojko, A. Comparison of the Antioxidant Activity of Propolis Samples from Different Geographical Regions. *Plants* 2022, *11*, 1203, doi:10.3390/plants11091203.

140.Cristiano, C.; Pirozzi, C.; Coretti, L.; Cavaliere, G.; Lama, A.; Russo, R.; Lembo, F.; Mollica, M.P.; Meli, R.; Calignano, A.; et al. Palmitoylethanolamide Counteracts Autistic-like Behaviours in BTBR T+tf/J Mice: Contribution of Central and Peripheral Mechanisms. *Brain Behav. Immun.* 2018, *74*, 166–175, doi:10.1016/j.bbi.2018.09.003.

141.Roviezzo, F.; Rossi, A.; Caiazzo, E.; Orlando, P.; Riemma, M.A.; Iacono, V.M.; Guarino, A.; Ialenti, A.; Cicala, C.; Peritore, A.; et al. Palmitoylethanolamide Supplementation during Sensitization Prevents Airway Allergic Symptoms in the Mouse. *Front. Pharmacol.* 2017, *8*, 857, doi:10.3389/fphar.2017.00857.

142.Impellizzeri, D.; Di Paola, R.; Cordaro, M.; Gugliandolo, E.; Casili, G.; Morittu, V.M.; Britti, D.; Esposito, E.; Cuzzocrea, S. Adelmidrol, a Palmitoylethanolamide Analogue, as a New Pharmacological Treatment for the Management of Acute and Chronic Inflammation. *Biochem. Pharmacol.* 2016, *119*, 27–41, doi:10.1016/j.bcp.2016.09.001.

143.Pirozzi, C.; Coretti, L.; Opallo, N.; Bove, M.; Annunziata, C.; Comella, F.; Turco, L.; Lama, A.; Trabace, L.; Meli, R.; et al. Palmitoylethanolamide Counteracts High-Fat Diet-Induced Gut Dysfunction by Reprogramming Microbiota Composition and Affecting Tryptophan Metabolism. *Front. Nutr.* 2023, *10*, 1143004, doi:10.3389/fnut.2023.1143004.

144.Wang, Z.; Singh, A.; Jones, G.; Aitken, D.; Laslett, L.L.; Hussain, S. *Boswellia for Osteoarthritis. Cochrane Libr*; 2022;

145.Ragab, E.A.; Abd El-Wahab, M.F.; Doghish, A.S.; Salama, R.M.; Eissa, N.; Darwish, S.F. The Journey of Boswellic Acids from Synthesis to Pharmacological Activities. *Naunyn. Schmiedebergs. Arch. Pharmacol.* 2024, *397*, 1477–1504, doi:10.1007/s00210-023-02725-w.

146.Shen, J.; Abu-Amer, Y.; O'Keefe, R.J.; McAlinden, A. Inflammation and Epigenetic Regulation in Osteoarthritis. *Connect. Tissue Res.* 2017, *58*, 49–63, doi:10.1080/03008207.2016.1208655.

147.Gong, Y.; Jiang, X.; Yang, S.; Huang, Y.; Hong, J.; Ma, Y.; Fang, X.; Fang, Y.; Wu, J. The Biological Activity of 3-O-Acetyl-11-Keto-β-Boswellic Acid in Nervous System Diseases. *Neuromolecular Med.* 2022, *24*, 374–384, doi:10.1007/s12017-022-08707-0.

148.Rajeshkumar, S.; Menon, S.; Kumar, V.; Ponnanikajamideen, M.; Ali, D.; Arunachalam, K. Anti-Inflammatory and Antimicrobial Potential of Cissus Quadrangularis-Assisted Copper Oxide Nanoparticles. *J. Nanomater.* 2021, *2021*, 1–11, doi:10.1155/2021/5742981.

149.Coutinho de Almeida, R.; Ramos, Y.F.M.; Mahfouz, A.; den Hollander, W.; Lakenberg, N.; Houtman, E.; van Hoolwerff, M.; Suchiman, H.E.D.; Rodríguez Ruiz, A.; Slagboom, P.E.; et al. RNA Sequencing Data Integration Reveals an miRNA Interactome of Osteoarthritis Cartilage. *Ann. Rheum. Dis.* 2019, *78*, 270–277, doi:10.1136/annrheumdis-2018-213882.

150.Muthusami, S.; Senthilkumar, K.; Vignesh, C.; Ilangovan, R.; Stanley, J.; Selvamurugan, N.; Srinivasan, N. Effects of Cissus Quadrangularis on the Proliferation, Differentiation and Matrix Mineralization of Human Osteoblast like SaOS-2 Cells. *J. Cell. Biochem.* 2011, *112*, 1035–1045, doi:10.1002/jcb.23016.

151.Awari, V.S.; Barvkar, V.T.; Ade, A.B.; Borde, M.Y. Endophytic Fungi from Cissus Quadrangularis Plant a Promising Source of Bioactive Compounds. *Braz. J. Microbiol.* 2024, *55*, 3733–3750, doi:10.1007/s42770-024-01500-0.

152.Abdel-Tawab, M.; Werz, O.; Schubert-Zsilavecz, M. Boswellia Serrata: An Overall Assessment of Its Clinical Efficacy and Safety. *Phytomedicine* 2011, *18*, 1207–1218.

153.Rajaab, K.M.; Surendran, S.; Vijayakumar, K. Efficacy of Boswellia Serrata Extract in Osteoarthritis Management: A Systematic Review. *Complement Ther Med* 2020, *50*.

154.Daily, J.W.; Yang, M.; Park, S. Natural Products for the Management of Osteoarthritis: A Comprehensive Review. *Evid Based Complement Alternat Med* 2016.

155.Takeda, S.; Yamada, N.; Inaba, T. Propolis-Derived Compounds Exhibit Anti-Inflammatory and Antioxidant Properties in Osteoarthritis Model. *Evid Based Complement Alternat Med* 2014.

156.Sforcin, J.M. Propolis and the Immune System: A Review. *J. Ethnopharmacol.* 2007, *113*, 1–14, doi:10.1016/j.jep.2007.05.012.

157.Mcalindon, T.E.; Lavalley, M.P.; Harvey, W.F. Effectiveness of Intra-Articular Corticosteroids for Knee Osteoarthritis: A Systematic Review. *Ann Intern Med* 2017, *166*, 255–266.

158.Gopukumar, K.; Raveendran, R.; Rao, M.N. Bone Healing Potential of Cissus Quadrangularis: A Systematic Review. *J Ayurveda Integr Med* 2019, *10*, 165–172.

159.Pande, S.; Pathak, P. Molecular Mechanisms of Cissus Quadrangularis in Bone Regeneration. *Phytother Res* 2016, *30*, 1517–1526.

160.Coxib and traditional NSAID Trialists' (CNT) Collaboration; Bhala, N.; Emberson, J.; Merhi, A.; Abramson, S.; Arber, N.; Baron, J.A.; Bombardier, C.; Cannon, C.; Farkouh, M.E.; et al. Vascular and Upper Gastrointestinal Effects of Non-Steroidal Anti-Inflammatory Drugs: Meta-Analyses of Individual Participant Data from Randomised Trials. *Lancet* 2013, *382*, 769–779, doi:10.1016/S0140-6736(13)60900-9.

161.Hesselink, J.M.K.; Hekker, T.A. Therapeutic Utility of Palmitoylethanolamide in the Treatment of Neuropathic Pain Associated with Various Pathological Conditions: A Case Series. *J. Pain Res.* 2012, *5*, 437–442, doi:10.2147/JPR.S32143.

162.Paladini, A.; Fusco, M.; Cenacchi, T.

Palmitoylethanolamide: A Potential Therapeutic Agent in Pain Management. *Clin Drug Investig* 2017, *37*, 729–737.

163.Oo, W.M.; Hunter, D.J. Disease-Modifying Treatments in Osteoarthritis: Current Status and Future Therapeutic Targets. *Drugs* 2018, *78*, 469–493.

164.Hunter, D.J.; Mcdougall, J.J.; Keefe, F.J. The Potential for Novel Disease-Modifying Pharmacological Therapies in Osteoarthritis. *Osteoarthr Cartil* 2017, *25*, 235–242.

165.Kalayil, N.; Budar, A.A.; Dave, R.K. Nanofibers for Drug Delivery: Design and Fabrication Strategies. *BIO Integr*. 2024, *5*, doi:10.15212/bioi-2024-0023.