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*Review Article*

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

**B.Dharani*[1], Suba.A[1]**

[1] *Department of Physiology, Faculty of Medicine, A.C.S Medical College and Hospital, Dr.M.G.R Educational and Research Institute, Chennai, India.*

* Correspondence, e-mail: doctordharanibhaskaran@gmail.com

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**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 remodeling. 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 multidimensional targeting of pathophysiological pathways using natural treatment options, while improving patient compliance by enhancing the safety profile. The current review focuses on a novel, innovative, and conceptual formulation that is designed by the authors with scientific-evidence-packed natural compounds for management of OA. This review aims 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 which 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 a reasonable safety profile, making it suitable for long-term use. This formulation has the potential to emerge as an effective and safer alternative 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 the synovium, subchondral remodeling of bone, and chronic intolerable pain. It leads to stiffness of the joint involved, associated with reduced joint mobility that causes a reduction in patient's quality of life [2]. Because of the rise in the aging population, obesity, and sedentary lifestyle, the prevalence of OA is predicted to increase. The currently 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 a risk of long-term complications. Recently, various studies are being conducted on Disease-Modifying Osteoarthritis Drugs (DMOADs) that have the potential to provide a curative treatment [5—7]. Consequently, there is an expanding interest in exploring multidimensional targeting of pathophysiological pathways using natural treatment options, while improving patient compliance by enhancing the safety profile. In recent years, 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 chondroprotective 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, primarily through 5-lipoxygenase (5-LOX) inhibition which is an important enzyme in leukotriene synthesis [11]. Propolis is a bee product that is rich in polyphenols, 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 cells [13,14]. Due to the intricate and multifaceted nature of OA, a combination strategy harnessing these bioactive compounds could offer a better treatment outcome compared to individual therapy. The current review focuses 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 aims to evaluate the rationale behind formulating a novel conceptual tablet consisting of *C. quadrangularis*, *B. serrata*, propolis, and PEA for definitive management of OA, which 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 besides 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 the context of long-term use. Even though this review was not written using software for systematic review, we have made efforts to reduce selection bias through a 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 joint disease that specifically affects the synovium, articular cartilage, and subchondral bone, eventually causing stiffness, pain, and impaired mobility of the 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 process 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 the 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), which cause formation of proteases such as Matrix Metalloproteinases and aggrecanases [20—23]. Consequently, this leads to degradation of the Extracellular Matrix (ECM) and 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 cause the pathological changes in the joint [26]. Also, another critical mediator of inflammation was found to be the 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) occurs in the 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 the 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 mechanisms causes cartilage degradation, which is known as the hallmark of OA [32, 33]. Chondrocytes are the crucial cells in regulating ECM homeostasis [34]. Increased catabolic processes are marked by excess production of catabolic enzymes like MMP-1, MMP-3, and MMP-13 and a disintegrin and metalloproteinase with thrombospondin motifs-4 & -5 (ADAMTS-4 & -5), which degrade essential components of the ECM like aggrecan and type II collagen [35]. The loss of proteoglycans secondary to destruction of cartilage matrix reduces

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

### 3.4. Synovial Inflammation

The inflammation of the 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. Due to this condition, the inflamed synovial tissue produces inflammatory mediators like IL-6, TNF-α, and PGE2, which leads to synovial vascularization and hyperplasia [38—40]. This, in turn, leads to excess joint effusion, joint stiffness, and further accelerated cartilage degradation.

### 3.5. Pain mechanisms

The pain in OA involves multiple pathomechanisms, which include peripheral sensitization, central sensitization, neuropeptides, and subchondral bone remodelling. In OA, the inflammatory mediators such as prostaglandins, bradykinin, and cytokines sensitize the pain receptors in the joint, leading to reduced pain threshold, which is called 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 cause increased response to pain and neurogenic inflammation [44]. As a result of chronic inflammation, remodeling of subchondral bone occurs, leading to appearance of osteophytes, which further aggravates the nociceptive signalling process [45—47].

## 4. Proposed drug combination

In the current review, the proposed combination (Fig. 1) of drugs for the rationally designed tablet comprises *C. quadrangularis, B. serrata,* propolis and PEA. It is formulated in such a way that it could target various pathways of OA pathophysiology such as inflammation, oxidative stress, degradation of cartilage, and chronic pain in a synergistic way. This can offer a safer and more effective option for treatment of OA, by helping 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.

### 4.1. *C. quadrangularis*

It is a commonly used Ayurveda medicine for management of fractures, osteoporosis, and joint disorders. It is also called the “Bone Setter’s” plant that was found to have anti-inflammatory, antioxidant, regenerative, and chondroprotective actions, through regulation of pro-inflammatory cytokines, suppressing 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 the matrix and proliferation of chondrocyte, thereby causing chondroprotective effects [52]. Further, it was found to decrease the 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 suppress inflammation in management of OA.

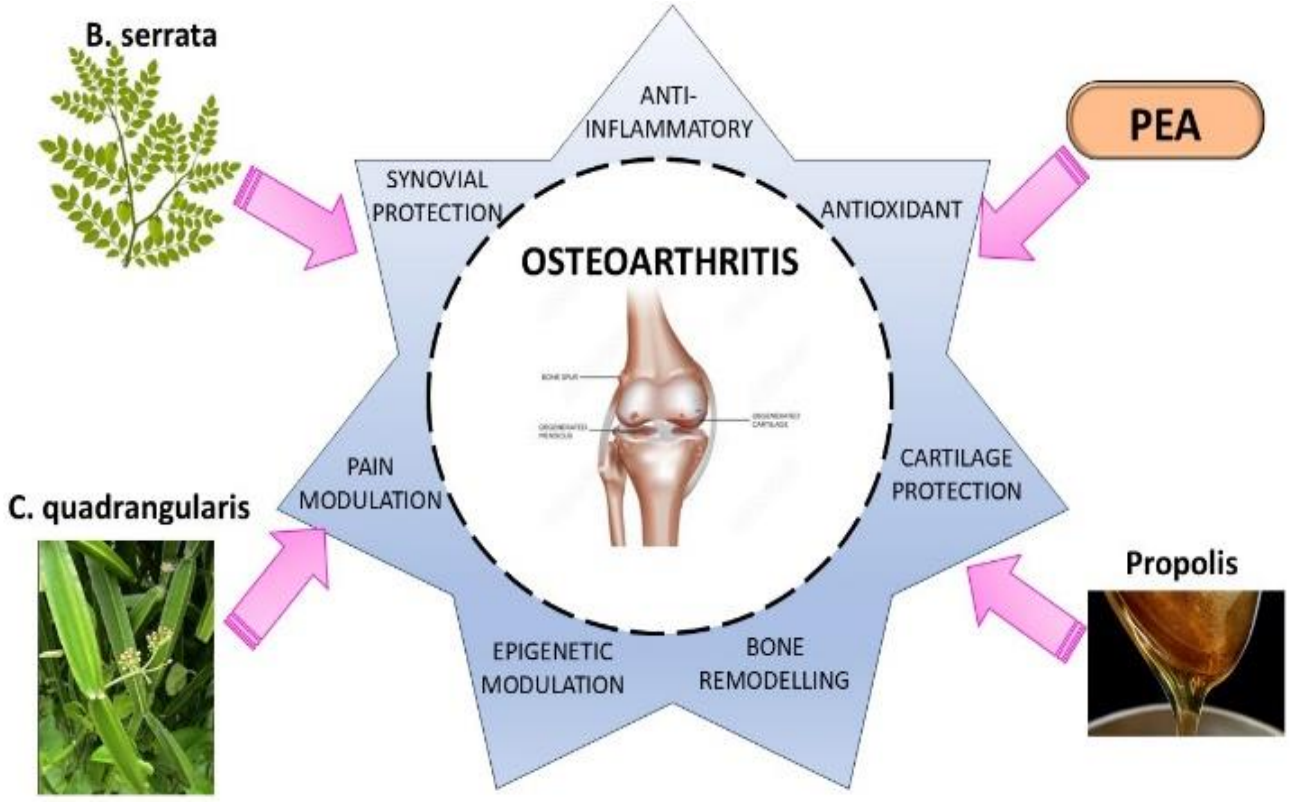


**Fig. 1.** Proposed drug combination.

**Table 1.** Evidence-based critical analysis of the 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:* inhibits MMP and protects cartilage from degradation | [82—86] |
| | | *C. quadrangularis*: enhances synthesis of glycosaminoglycans and collagen, increases chondrocyte proliferation | [87—90] |
| Decrease in oxidative stress | Propolis, *B. serrata*, PEA | Propolis: improves SOD, catalase and glutathione peroxidase activities | [91—95] |
| | | *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 cells 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] |
| Remodeling 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 the 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 the integrity of gut barrier and decreases microbial dysbiosis | [137—140] |
| | | PEA: modifies the composition of gut microbiota and suppresses 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] |

### 4.2. *B. serrata*

*B. serrata* is a medicinal plant, which is otherwise known as frankincense, and has been 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 has demonstrated inhibition of 5-lipoxygenase (5-LOX) and suppresses 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 significantly reduce pain and improve physical function [57]. It was shown to have disease-modifying effects, which were found by decreased levels of MMP-3, a marker of cartilage destruction [58]. Studies have shown that it prevents apoptosis of chondrocytes and improves cartilage integrity [59].

### 4.3. Propolis

It is a natural resin derived from bees that is rich in polyphenols, 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 suppressing 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 analgesic [64]. It acts by inducing PPAR-α, thereby reducing pro-inflammatory genes and consequently suppressing cytokine release. It also modulates mast cells, thereby preventing their degranulation and histamine-mediated 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 the 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 the potential to offer long-term benefit in OA.

**Table 2.** Comparison of the existing OA treatment with the 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] |

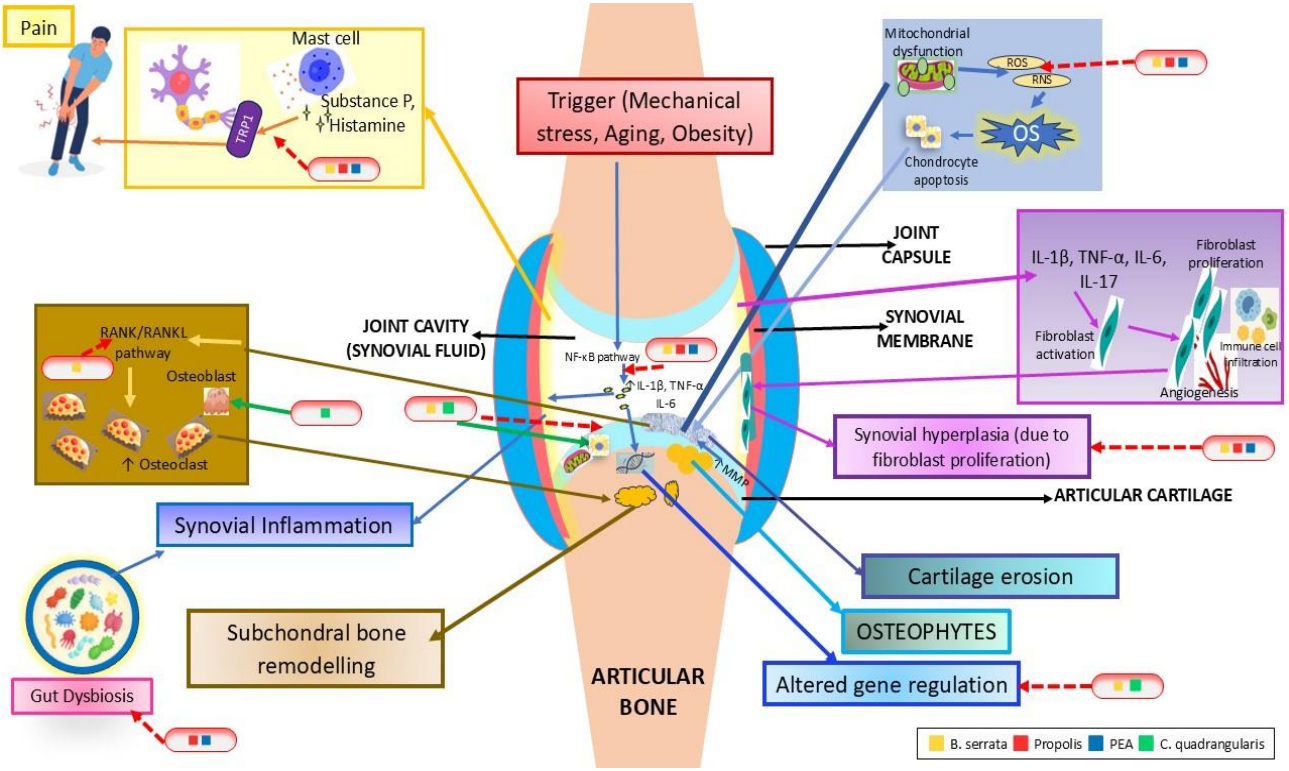


**Fig. 2.** Combined mechanistic action of the components of the drug. **Abbreviations:** OA — Osteoarthritis; PEA — *palmitoylethanolamide*; IL-1β — Interleukin 1β, NF-κB — Nuclear Factor kappa-light-chain-enhancer of activated B cells; IL-6 — Interleukin 6; IL-17— Interleukin-17; MMPs — Matrix Metalloproteinases; 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

As depicted in Fig. 2, the pathogenesis of OA is triggered and maintained by obesity, mechanical stress and aging, that drives oxidative stress and mitochondrial dysfunction.

Furthermore, Fig. 3 illustrates a wider intergrated perspective on how this conceptual combination focuses diverse yet interconnected components of OA pathophysiology, comprising oxidative stress, chronic inflammation, cartilage degradation, synovial inflammation, pain signalling, epigenetic dysregulation, and gut-joint axis dysfunction. The pathways involved in the 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) suppresses 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 multidimensional strategy to treat OA by its anti-inflammatory, antioxidant, cartilage-integrity- improving, matrix regeneration, and pain reduction properties based on existing scientific evidence.

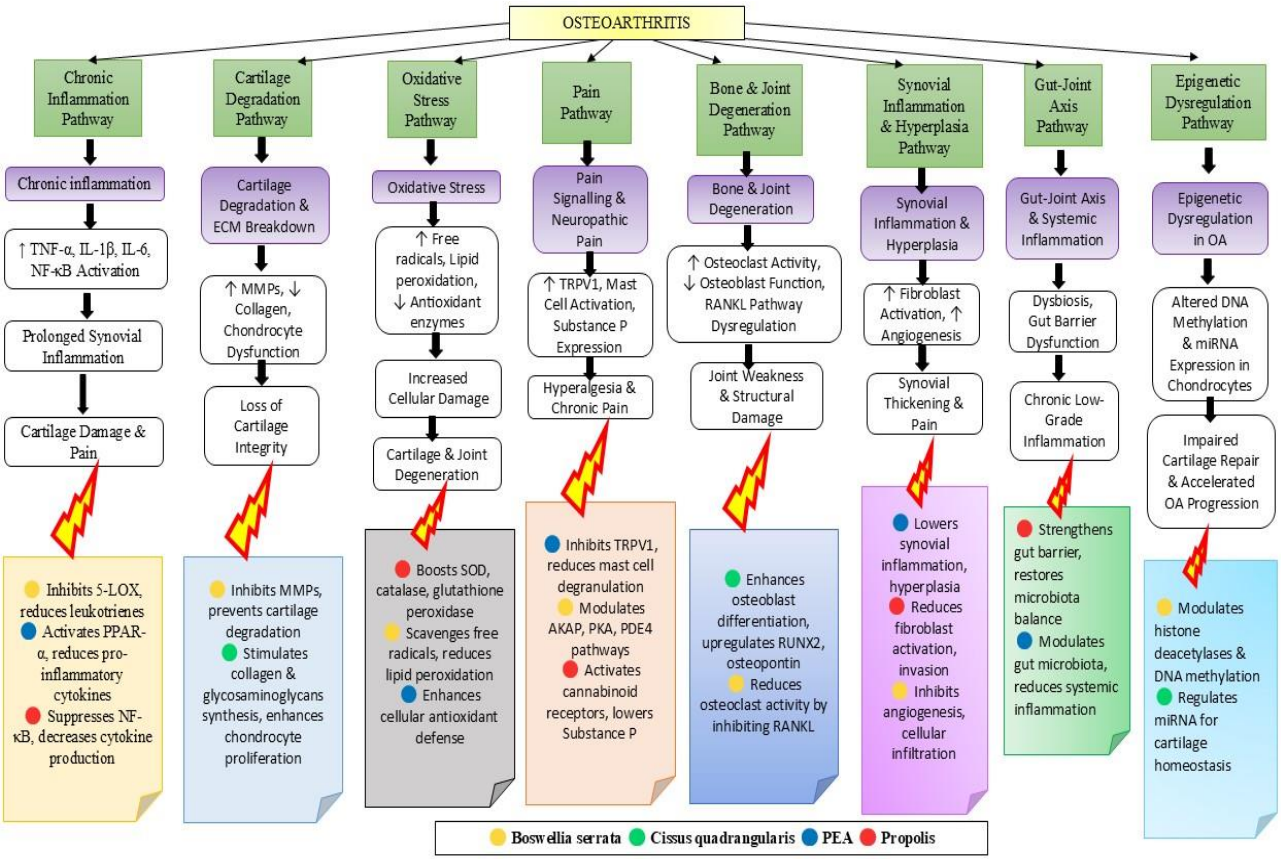


**Fig. 3.** Combined mechanistic action of the components of the drug. This infographic depicts the interrelated pathways that contribute to the pathophysiology of OA and the specific actions of *B. serrata*, *C. quadrangularis*, PEA and propolis in targeting these pathways to execute therapeutic effects in OA.

## 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 need proper consideration. Firstly, this formulation is purely 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 have potential variability in terms of bioavailability, quality, and standardization that could significantly affect formulation and thereby pose a regulatory challenge. Also, other aspects of this combination formulation on long-term safety and drug interactions are yet to be explored. These limitations emphasize the need for a large-scale clinical trial on this formulation for 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. 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.

## 8. Purpose of this review

The current review was proposed in the 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. Even though the proposed formulation has not yet been evaluated clinically, it is entirely built upon existing robust preclinical and clinical studies on mechanistic evidence. The principal goal of this review article is not to recommend the proposed formulation for immediate clinical application, but rather to offer a scientifically sound rational basis for the purpose of further translational research and robust evidence-based drug development. Through presenting an evidence-based novel formulation strategy, the authors aim for future clinical translation of this conceptual formulation by further research collaboration and clinical validation.

**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.<br>• Propolis: Liposomal encapsulation might improve flavonoid bioavailability.<br>• PEA: Micronization might increase the 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*.<br>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.<br>• Hydroxypropyl Methylcellulose (HPMC) might improve controlled release of polyphenolic compounds.<br>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.<br>• *B. serrata* may enhance anticoagulants and hence should be used in caution with aspirin or warfarin.<br>• PEA has low drug interaction risk but has theoretical interaction with some CNS depressants.<br>• 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.<br>• Possible oral delivery formats are capsule, tablet or softgel.<br>• The choice depends upon target release kinetics, stability and bioavailability. |
| Dosing strategy | • *B. serrata*: 100—250 mg/ day of standardized Boswellia extract.<br>• *C. quadrangularis*: 500—1000 mg/day of standardized ketosteroid containing cissus extract.<br>• PEA: 300—600 mg/day of micronized PEA.<br>• Propolis: 250—500 mg/day of standardized propolis extract. |
| Target patient group | • The potential target patient group include inflammatory OA phenotype, adjuvant OA therapy, patients contraindicated to NSAIDS.<br>• It has a strong conceptual potential to be used as a treatment of OA, as a part of early intervention. |

## 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 such as 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 a 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 for conventional NSAIDs. Based on existing evidence about treating OA by individual components from various studies on their rationale and safety profile, this current review suggests that this formulation has a strong translational potential.

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

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