RESEARCH PAPER

TARGETED THERAPY TO MAXIMIZE THE THERAPEUTIC BENEFITS WHILE MINIMIZING RISK: OSTEOARTHRITIS KNEE JOINT

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ABSTRACT

Musculoskeletal disorders (MSDs), particularly osteoarthritis (OA), are major causes of disability, impaired mobility, pain, and reduced quality of life worldwide. Conventional pharmacological and surgical treatments are often symptomatic and may be limited by adverse effects, contraindications, and patient ineligibility. Emerging evidence suggests that *Rhus toxicodendron* (Rhus tox) may help alleviate pain, stiffness, and inflammation, while knee orthotics can improve biomechanical function, reduce joint stress, and support knee stability. This narrative-integrative review explores a targeted approach combining *Rhus toxicodendron* therapy with knee orthotics to potentially enhance therapeutic outcomes while minimizing treatment-related risks. Evidence from preclinical, clinical, and rehabilitative studies published between 2000 and 2025 was synthesized, focusing on the pharmacological and clinical effects of *Rhus toxicodendron*, the biomechanical and functional benefits of knee orthotics, and their potential complementary effects. The synthesis indicates potential anti-inflammatory, antioxidant, and analgesic properties of *Rhus toxicodendron*, alongside pain reduction and biomechanical benefits associated with orthotic support. This dual-targeted strategy integrates biochemical modulation with biomechanical correction and may provide a promising conservative framework for OA management. However, standardized multidisciplinary clinical trials are required to establish its safety, efficacy, and clinical applicability.

Keywords*: Rhustoxicodendron, Knee Orthotics, Targeted Therapy, Musculoskeletal Disorders, Osteoarthritis*

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GRAPHICAL ABSTRACT:

1. INTRODUCTION

Musculoskeletal disorders (MSDs) are among the greatest contributors to chronic pain, disability, and socioeconomic burden in the world (Zhou et al., 2024). Knee osteoarthritis (OA) is one of the most common of them and is associated with almost half a billion of the global population, as well as one among the most common causes of years lived with disability (YLDs)(Liu, Wang, Lin, & Zhang, 2018). All these factors result in pain, stiffness, and a decrease in joint mobility due to the progressive degeneration of the articular cartilage, subchondral bone remodeling, and synovial inflammation (Sanchez-Lopez, Coras, Torres, Lane, & Guma, 2022). Not only do these symptoms limit physical activity, but they also diminish the quality of life and independence.

OA is a non-communicable musculoskeletal condition, which has been classified by the World Health Organization (WHO) as a major condition because it is becoming common in older populations and individuals who have been exposed to obesity, sedentary living, or repetitive strains on their joints (Shumnalieva, Kotov, & Monov, 2023). Disease burden will increase dramatically in the coming decades, as it can be observed due to the demographic transition and the consequent rise in life expectancy. OA, therefore, is currently a significant area of concern in international health-related approaches to ensure mobility and functional autonomy among the aging population.

The traditional approach to knee OA management is mainly the pharmacological, physical, and surgical management oriented at symptom management, as opposed to disease management (Uivaraseanu et al., 2022). Drugs like nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, or corticosteroid injections provide

temporary relief, but the drugs are usually restricted due to systemic side effects, which include gastrointestinal irritation, nephrotoxicity, and cardiovascular complications (Machado, Abdel-Shaheed, Underwood, & Day, 2021). Opioids, despite the sporadic prescriptions, are associated with potential dependence and tolerance.

Physiotherapy and exercise programs enhance the performance of the joints, but at the rehabilitative end, they need long-term compliance and personalized follow-ups. In extreme cases, the final option is total knee arthroplasty (TKA), which is very expensive, painful, and prone to infection, as well as the wear of the prosthesis (Bernasek, Gill, Herekar, & Lyons, 2023). Surgical options are not available to many patients, especially those who are aged with comorbidities.

Furthermore, although the number of treatments is enormous, the progression of the disease is not often stopped, and a large number of patients do not know how to cope with residual pain and a decrease in mobility. This reveals a serious therapeutic gap: the lack of a safe, cost-effective, and integrative approach that will cover both the biological and biomechanical components of OA pathophysiology.

The recent movement in musculoskeletal research has been towards integrative multimodal interventions that, in addition to reducing symptoms, it is also focused on curing the underlying processes of pain and joint degeneration (Behringer, Nagib, & Nagib, 2025). Two complementary therapeutic modalities have recently emerged as promising options

Rhustoxicodendron- a homeopathic substance reported to have anti-inflammatory, analgesic, and antioxidative activities; and Knee orthotics - Artificial aids (biomechanical), which correct the position of the joint, decrease joint load, and enhance functional stability.

The *Rhustoxicodendron*, an extract of the leaves of Toxicodendron radicans (poison ivy) has long been used in homeopathic medicine as a remedy for rheumatic pains, stiffness, and inflammation (especially rheumatic) as well as other diseases, especially those that respond to physical activity (Bondre & Agawane, 2023). Experimental and clinical evidence suggests that recent Rhus tox can regulate inflammatory cytokines, including TNF-α, IL-6, and IL-1β, while providing anti-oxidative stress and anti-inflammatory pain signals powered by prostaglandins (Khalil et al., 2021). It is safe and tolerable even when taken in long-term usage, unlike conventional NSAIDs and corticosteroids.

On the other hand, knee orthotics such as unloader, functional, and rehabilitative braces are evidence-based non-invasive treatments to redistribute load-bearing forces, increase stability of the joints, and alleviate pain during ambulation(Fernandes et al., 2025). Systematic reviews and meta-analyses have proven to be effective in enhancing the WOMAC and VAS scores in patients, especially in the medial compartment OA. They also enhance early mobility, postpone surgical intervention, and supplement physiotherapeutic programs.

Although both Rhus tox and orthotic therapy have shown some beneficial effects on their own, the possibility of using them together or in a synergistic effect has never been fully explored (Mizer, Rossettie, & Zumwalt, 2023). The combination of these interventions is based on the concept of target therapy that aims at maximizing the therapeutic effect by means of a multi-level modulation, i.e., biochemical, biomechanical, and functional, and reducing the risks of adverse effects.

Although the use of complementary and alternative medicine (CAM) in musculoskeletal management is gaining traction, there is no integrative paradigm that exists today in a systematic and evidence-based integrative model of *Rhustoxicodendron* therapy with knee orthotics. The literature offers a fairly isolated approach to these modalities, either as a pharmacological substitute (Rhus tox) or as a mechanical supplement (orthotics). This has led to the fact that the possibility of a synergistic relationship between molecular-level modulation and biomechanical correction has not been scrutinized(Xu, Xu, Zhang, & Luo, 2024).

Additionally, the available literature on Rhus tox is more interested in symptomatic relief without comparing their results to the joint mechanics or functional outcomes, and orthotic studies are, in general, more biomechanical, but they do not often consider the impact of biochemical or inflammatory factors. Closing this gap with a specifically integrative methodology of therapeutic approach might transform the ways of conservative management of OA, especially for patients who cannot receive long-term pharmacological or surgical treatment.

The current review aims to review and critically examine existing evidence regarding the therapeutic potential of *Rhustoxicodendron* and knee orthotics in the context of the conceptual framework of targeted therapy (Rajalekshmi & Agrawal, 2024). It will focus on analyzing the pharmacological and therapeutic profile of *Rhustoxicodendron* in musculoskeletal and rheumatic disease, with special emphasis on the mechanisms of action and clinical effectiveness(Kaur et al., 2024). Moreover, it addresses the biomechanical concepts, clinical, and outcome of knee orthotics in managing pain, functional mobility, and long-term joint preservation.

The review also examines the possibility of synergy between *Rhustoxicodendron* and knee orthotics in treating the two pathophysiological

aspects of osteoarthritis, which are biochemical inflammation and mechanical overloading. It also touches upon the overall idea of targeted therapy as a clinical model of the attainment of the highest therapeutic intervention with the minimum risks, with references to the personalization, safety, and patient-centered results. Lastly, the review determines the existing research gaps, methodological shortcomings, and possibilities of conducting further clinical trials and translational trials in the area of integrative musculoskeletal treatment. The review hopes to offer a scientific foundation that can be used in the combination of homeopathic and biomechanical interventions into one evidence-based therapeutic paradigm through these goals.

This review is narrative integrative in that it was conducted to synthesize and critically analyze evidence on both preclinical, clinical, and rehabilitative studies published within the period 2000-2025. The review consists of peer-reviewed trials, case reports and systematic reviews which assess the therapeutic effectiveness of *Rhustoxicodendron* in musculoskeletal disorders and those that discuss the design, biomechanics, and clinical effectiveness of knee orthotics. The information was thematically classified into four major areas (a) the pharmacological effects and biological mechanisms of the *Rhustoxicodendron*; (b) the biomechanical and rehabilitative principles of the knee orthotic therapy; (c) the synergistic and integrative potential of the combination of the two interventions; and (d) the conceptual framework of target therapy to play with the balance between the therapeutic efficacy of the interventions and safety.

This review will combine both pharmacological and biomechanical views in order to develop a holistic, evidence-based concept of integrative target therapy that can be implemented to improve the musculoskeletal health and functional recovery of patients with knee osteoarthritis. The synthesis is not only set to summarize current evidence to a greater extent but also present a direction of the translation to clinical practice, which will promote innovation in non-invasive, patient-centered treatment of musculoskeletal disorders.

2. LITERATURE REVIEW

Musculoskeletal disorders (MSDs) can be characterized as a dissimilar aggregate of diseases of the bones, muscles, joints, and connective tissues. Knee osteoarthritis (OA) is one of the conditions that is known to cause chronic pain and disability among them. According to Epidemiological data, it is estimated that some 500 million people are affected by OA at a global level, and most of the disease burden is caused by knee OA (Ouyang & Dai, 2025). This increasing prevalence has been linked to the aging of the population, obesity, and lifestyle issues that encourage the wear and tear of joints.

OA is not a degenerative wear and tear pathophysiologically, but a biomechanical and biochemical disease, and is associated with chronic low-grade inflammation, oxidative stress, and progressive cartilage degeneration (Yunus, Nordin, & Kamal, 2020). This bi-polarity of OA - the combination of mechanical stress and inflammatory mechanism - requires complex treatment. Nevertheless, the majority of the traditional therapies are directed at the inflammatory cascade (pharmacologically) or mechanical orientation (orthopedically) without much combination of both. This duality has created a void in holistic, patient-centered care and is the central argument behind the investigations of integrative targeted therapy with the *Rhustoxicodendron* and knee orthotics.

2.1. Homeopathic foundation and historical use

The *Rhustoxicodendron* (Rhus tox) a homeopathic remedy derived out of Toxicodendron radicans (poison ivy) has been used in traditional medicine since ancient times(Goswami, Saka, GV, & Biswas, 2022). Usually used to treat pain and stiffness caused by rest, and relieved by movement, Rhus tox has been extensively used in the treatment of rheumatism, arthritis, and musculoskeletal trauma. The therapeutic use of homeopathy is based on the rule, similia similibus curentur. This rule determines the use of homeopathy in joint stiffness and inflammation, and an increase in its mobility. Biochemical studies on the pharmacological effects of Rhus tox have just started to be investigated nowadays. The ability of Rhus tox to inhibit pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β), decrease cyclooxygenase-2 (COX-2) expression, and inhibit the production of prostaglandin E2 was proven by experimental models of inflammation, including carrageenan-induced paw edema and Freund adjuvant arthritis (Alhamedi et al., 2025). Besides, antioxidant effects have been demonstrated by increased activity of superoxide dismutase (SOD), catalase, and decreased lipid peroxidation.

These results all support that Rhus tox has multi-targeted anti-inflammatory and antioxidant properties, which are consistent with the concept of targeted therapy, which tries to regulate as many biological processes as possible with low toxicity(Mohammed & Al-Shawi, 2025).

Figure 1 illustrates the dual-targeted therapeutic model integrating biochemical and biomechanical interventions for osteoarthritis. *Rhustoxicodendron* acts at the molecular level by downregulating inflammatory cytokines (TNF-α, IL-6, IL-1β), suppressing COX-2 expression.

Figure 1: Conceptual mechanistic Synergy between *Rhustoxicodendron* and knee orthotics

2.2. Preclinical Evidence and Mechanistic Insights

Mechanistic evidence has been considerable with regard to the anti-inflammatory

and antioxidant effects of *Rhustoxicodendron* in musculoskeletal diseases through experimental investigations. Rhus tox has exhibited very high anti-inflammatory effects on the inflammatory markers in vivo models, including carrageenan-induced paw edema and Freund's complete adjuvant arthritis (El-Shiekh, El-Mekkawy, Mouneir, Hassan, & Abdel-Sattar, 2021). These were explained by the decrease of pro-inflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) and the suppression of cyclooxygenase-2 (COX-2) and prostaglandin E_2 (PGE_2) synthesis.

One of the key mechanisms of action is also realized as oxidative stress modulation. Preclinical evidence shows that it increases the activity of antioxidant enzymes like superoxide dismutase (SOD) and catalase, and decreases lipid peroxidation, which means the restoration of the redox balance in inflamed tissues (de Lavor et al., 2018). Also, histopathological studies of arthritic joints demonstrated that synovial hyperplasia, leukocyte infiltration, cartilage erosion, etc., were attenuated, proving structural protection that is in accordance with its anti-inflammatory action.

Together, these preclinical data provide a molecular rationale for the therapeutic effect of *Rhustoxicodendron* by acting on both the inflammatory pathways and the oxidative pathways. This dual mechanism underlines the fact that it can be included in the conceptual framework of targeted therapy, which prioritizes multi-pathway control at a low level of toxicity to the organism.

2.3. Clinical Trials and Human Evidence

The therapeutic potential of *Rhustoxicodendron* has been investigated in several clinical studies regarding its effectiveness in the treatment of musculoskeletal disorders, especially in diseases that are characterized by pain, stiffness, and inflammation, like osteoarthritis and rheumatoid arthritis(El Gendy et al., 2024). These diverse studies all come to the same conclusion that Rhus tox is a safe and effective symptomatic and functional agent in the treatment of affected patients.

As an example, Mohanty et al. (2023) carried out a randomized controlled trial that assessed the effect of *Rhustoxicodendron* on pain, stiffness, and physical function with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale using 80 cases of knee OA (Mohanty, Sahoo, Gautam, & Ghosh, 2023). The treatment group was statistically found to have statistically significant pain and stiffness scores change in favour of treatment as compared to placebo, and enhanced joint flexibility and overall mobility. In a similar study, Karp et al. (2016) conducted an observational study on patients with rheumatoid arthritis and indicated that inflammatory biomarkers, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), were reduced after the Rhus tox administration (Karp et al., 2016). The changes noticed in these biochemicals were followed by significant clinical improvement in joint tenderness and swelling.

(Oberai et al., 2018) conducted another study in which *Rhustoxicodendron* was investigated in the context of chronic lower back pain with an open-label study. The patients who underwent the intervention reported that their range of motion was improved, their pain on the Visual Analog Scale (VAS) had been reduced, and their daily functional capacity had improved. It is important to note that none of these studies found any influential adverse effects, which supports the idea that Rhus tox is safe, and there is no adverse effect even when administered over a long period(Ward, Patel, Sayari, & Singh, 2025).

All these data suggest that *Rhustoxicodendron* is a potentially safe, low-risk, and effective adjunctive treatment that can be effective in musculoskeletal disorders(dos Santos, Perazzo, Cardoso, & Carvalho, 2007). Although most of the literature focuses on the symptomatic advantages, new facts also point to the biochemical regulation of inflammatory and oxidative cascades as the latent action of the substance (Kulinsky, 2007). However, it is necessary to note that the current trials are usually limited by small sample sizes, non-randomization/non-blinding, and non-uniform potency formulations, and this limits the external validity of the findings. Multi-center randomized controlled trials that have high quality with the use of standard dosing schedules can be used to validate these initial observations and make Rhus tox a proven integrative intervention in musculoskeletal pain management.

2.4. Safety and tolerability

In comparison to NSAIDs and corticosteroids, Rhus tox has a great safety profile, and the adverse effects are not widely reported (Birnesser, Oberbaum, Klein, & Weiser, 2004). Homeopathic dilutions, which usually range between 6C to 30C, are not toxic pharmacologically but biologically active, through immunomodulatory pathways (Bellavite, Ortolani, & Conforti, 2006). This allows chronic administration with no systemic risk, and as a result, Rhus is especially helpful with elderly patients having OA and those with comorbidities.

2.5. Research limitations

Although promising results were obtained, there are significant gaps. The existing evidence is mostly a result of small-scale, non-homogeneous studies of variable methodological rigor. The non-existence of standard outcome measures, less mechanistic validation, and less integration of biomechanical outcomes are barriers to translating the results into standard clinical protocols(Butler et al., 2009). Also, the synergistic effect of Rhus tox

when used together with biomechanical intervention has not been empirically established.

Table 1 summarizes the pharmacological basis, clinical findings, and safety profile of *Rhustoxicodendron* in musculoskeletal disorders. The evidence collectively highlights its multi-targeted anti-inflammatory and antioxidant actions, clinical efficacy in reducing pain and stiffness, and excellent tolerability, supporting its potential as a safe adjunct in osteoarthritis and rheumatoid arthritis management.

Table 1: Summary of Pharmacological Basis, Clinical Evidence, and Safety of *Rhustoxicodendron*

Aspect	Key Findings	References
Homeopathic Foundation and Traditional Use	*Rhustoxicodendron (Rhus tox)* derived from poison ivy, is used in homeopathy for pain and stiffness relieved by motion; widely applied in rheumatism, arthritis, and musculoskeletal trauma. Based on the principle similia similibus curentur.	Goswami et al., 2022
Pharmacological Actions	Exhibits anti-inflammatory, antioxidant, and immunomodulatory properties. Inhibits TNF-α, IL-6, IL-1β, COX-2, and PGE_2; enhances SOD and catalase activity; reduces lipid peroxidation. Reflects multi-targeted action consistent with targeted therapy concept.	Alhamedi et al., 2025; Mohammed & Al-Shawi, 2025
Preclinical Evidence	Demonstrated significant reduction in inflammation in carrageenan-induced paw edema and Freund's adjuvant arthritis models; improved oxidative stress markers.	Alhamedi et al., 2025
Clinical Evidence (OA & RA)	RCT (Mohanty et al., 2023): 80 knee OA patients – significant improvement in pain, stiffness, and mobility (WOMAC scale). Observational study (Karp et al., 2016):	Mohanty et al., 2023; Karp et al., 2016; Oberai et al., 2018

	Reduction in ESR and CRP in RA patients; clinical improvement in tenderness and swelling. Open-label (Oberai et al., 2018): Chronic low back pain – improved range of motion and reduced VAS pain.	
Safety and Tolerability	Excellent safety profile compared to NSAIDs/corticosteroids. High dilutions (6C–30C) are biologically active but non-toxic. No major adverse effects reported even with long-term use. Suitable for elderly and comorbid patients.	Birnesser et al., 2004; Bellavite et al., 2006; Ward et al., 2025
Limitations of Current Evidence	Small sample sizes, lack of randomization/blinding, and inconsistent dosing limit generalizability. Need for standardized, multicenter RCTs to confirm efficacy.	dos Santos et al., 2007; Kulinsky, 2007

2.6. Evolution and Classification

Knee orthotics that include unloader braces, functional supports, rehabilitative devices, and prophylaxis braces are a mandatory part of the conservative management of musculoskeletal conditions(Dzidotor et al., 2024; Khan, Ahmad, Yunus, & Samad, 2023). They are mostly used to redistribute joint or mechanical loads, decrease joint stress, and increase knee degenerative or injury-related alignment and stability in individuals(Park & Kim, 2025). The biomechanical concept of orthotic therapy is the fact that it can alter the ground reaction forces and moment arms across the knee joint and, as a result, reduce the pressure on the involved compartments and enhance the overall gait efficiency.

In the last 20 years, orthotic technology has experienced significant changes and has introduced lightweight composite materials, adjustable hinges, and ergonomic designs that can be customized(Michalec, Schusser, Weidner, & Brandstötter, 2024). Not only have these innovations increased the mechanical performance but have also increased the comfort, compliance, and aesthetic appeal of orthoses and serve as a good long-term treatment option as patients with chronic joint disorders like osteoarthritis.

The knee orthotics are usually classified according to the mechanical action and the clinical use (Beaudreuil et al., 2009). Unloading braces are mostly applied in redistributing the load on the affected compartment, usually the medial side, of patients with varus or valgus deformities, thus alleviating pain and slowing the disease progression(Ramsey & Russell, 2009). Functional braces are created to induce ligamentous stability, especially when there are ruptures in the anterior cruciate ligament (ACL) or posterior cruciate ligament (PCL), and are commonly used during post-surgical rehabilitation (Romeyn, Jennings, & Davies, 2008). Rehabilitative braces are used to contain the range of motion after surgical procedures or acute injuries to allow joint function to be restored gradually, with the greatest amount of evaluated risk of reinjury reduced (Wang & Li, 2025). Lastly, prophylaxis braces are applied in sports or work

environments to avoid strain on the ligaments and high-risk knee injuries in physically active persons(Rishiraj et al., 2009).

Taken together, these types of categories are indicative of the multifaceted clinical uses of knee orthotics, which go beyond pain relief to also include functional restoration, prevention of injuries, and joint protection (Rishiraj et al., 2009). The development of orthotics design into more active and patient-adjusted systems marks an important step in non-invasive orthopedic treatment, which is an evidence-based biomechanical alternative to pharmacological and rehabilitative therapy. Knee orthotics are divided by their biomechanical mechanism, design, and treatment goals, as a key form of non-invasive intervention that can be used to treat osteoarthritis and joint instability in Table 2. The table below provides the overview of the main knee orthosis types, their key mechanisms of action, and the general clinical use.

Table 2: Functional Classification of Knee Orthotics Based on Mechanism of Action and Clinical Utility

Type of Orthotic	**Primary Mechanism of Action**	**Typical Clinical Applications**
Unloading braces	Redistribute load away from the affected (medial or lateral) knee compartment to reduce joint stress and correct alignment	Medial compartment osteoarthritis, varus or valgus deformities
Functional braces	Provide external stabilization to compensate for ligament insufficiency and maintain joint kinematics during movement	ACL or PCL injuries, post-surgical rehabilitation, sports-related instability
Rehabilitative braces	Control range of motion during recovery and protect healing tissues by limiting excessive joint mobility	Postoperative management, acute ligamentous or meniscal injuries
Prophylactic braces	Prevent excessive joint loading or hyperextension under high-impact or repetitive stress conditions	Athletic training, occupational knee protection, high-risk physical activities

2.7. Clinical effectiveness

Several randomized controlled trials and systematic reviews have established that knee orthotics are effective in reducing pain and enhancing the function of patients with OA (Rodriguez-Merchan & De La Corte-Rodriguez, 2019). The studies indicate an enhancement in the WOMAC, VAS, and 6-minute walk test (6MWT) scores, and a reduction of about 20-40% in the intensity of pain. The Cochrane Review (2021) on knee bracing in OA found that unloading braces have moderate evidence of pain relief and

improvement of functionality over usual care (Görtz, Bugbee, & Eckersley, 2025).

2.8. Compliance and patient experience

The determinant of success is patient adherence. The enhancements in the brace design, lighter materials, and aesthetics have promoted long-term usage. It has been found that compliance is 65-80% especially in patients who are educated about the brace functionality (Law, Cheung, Yip, Yick, & Wong, 2017). Notably, orthotics puts patients in a situation to be self-managed, non-pharmacological, which encourages self-reliance and participation in recovery.

2.9. Limitations and adverse effects

The likely side effects involve skin irritation, pain, and muscle lassitude in the case of long-term use (Yiannakopoulou, 2015). Also, the fitness of the brace and alignment should be periodically reviewed in order to avoid disruptions in gait mechanics. Still, such disadvantages are nothing in comparison with the risk of pharmacological or surgical measures, which highlights the importance of orthotics as a low-risk supplement in the overall OA treatment.

2.10. Integrative Rationale: Synergy Between *Rhustoxicodendron* and Knee Orthotics

The combination of biological modulation (Rhus tox) and mechanical correction (orthotics) can be considered as a targeted approach, i.e., the inflammatory, oxidative, and mechanical components of OA are addressed in parallel (Batarfi, Yunus, Hamid, Maarof, & Abdul Rani, 2025). Theoretically, when Rhus tox works at the molecular level to decrease inflammatory mediators and oxidative stress, knee orthotics can work at the biomechanical level to redistribute joint load, limit cartilage wear, and stabilize the movement in Figure 2.

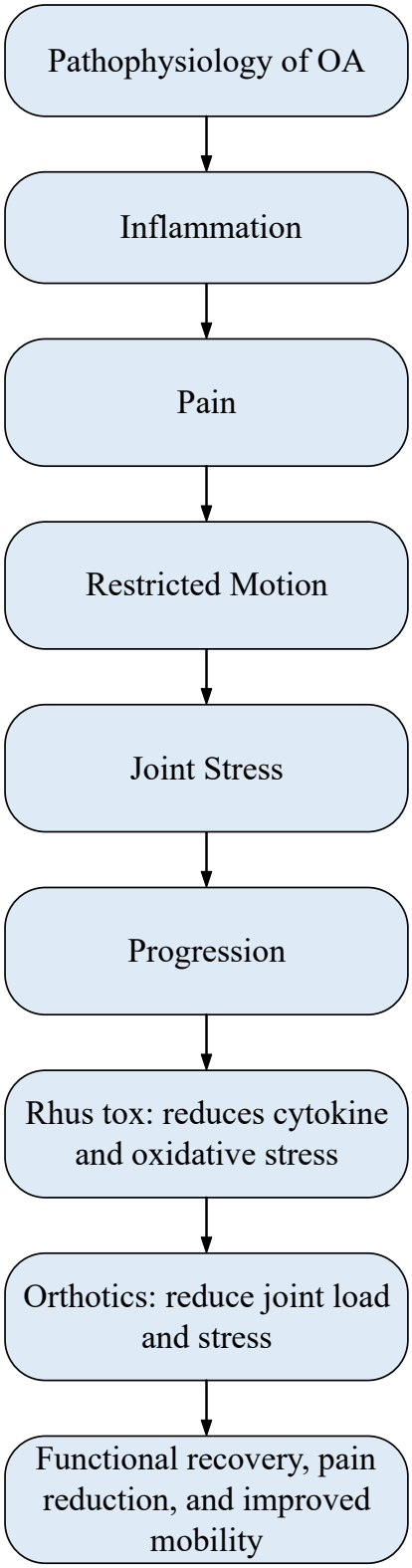


Figure 2: Conceptual mechanistic synergy between *Rhustoxicodendron* and knee orthotics

2.11. Evidence for multimodal therapy

Even though no studies have used Rhus tox and orthotic therapy concomitantly, other similar multimodal interventions (e.g., physiotherapy and homeopathy; herbal therapy and orthotic rehabilitation) suggest synergistic gains. A meta-

analysis of integrative musculoskeletal therapies in 2022 has determined that combined pharmacologic-mechanical interventions have better pain relief and functional recovery than monomodal interventions (Invernizzi et al., 2022). This would indicate that combination therapies, such as Rhus tox and orthotics, would yield an additive or synergistic result.

2.12. Advantages of an integrative framework

The integrative framework is unanimous in its management approach because it involves treating both major pathophysiological axes, inflammatory and mechanical, and offers a comprehensive approach to managing disease (Kalariya et al., 2023). It minimizes the side effects of the system and improves patient safety by counterbalancing or partially replacing traditional pharmacotherapy. The rate of patient compliance is enhanced since orthotic devices offer visual mechanical relief, and *Rhustoxicodendron* assists the system recovery, which encourages patients to continue taking medicines (Sapkota, Shrestha, Sahukhala, & Poudel, 2021). It is also economical, and thus this approach would be most appropriate in low-resource environments where both long-term pharmacotherapy and surgery may be unavailable. Moreover, the framework enables individualized interventions by the customization of orthotics and homeopathic dosing depending on the patterns of the symptoms and biomechanical requirements of an individual in Table 3.

Table 3: Integrative Comparison of *Rhustoxicodendron* and Knee Orthotics for Osteoarthritis Treatment

Aspect	***Rhustoxicodendron***	**Knee Orthotics**	**Combined Integrative Effect**
Mechanism of Action	Regulates inflammatory cytokines (TNF-α, IL-6, IL-1β); antioxidant activity (↑SOD, catalase).	Redistributes joint load; improves alignment; stabilizes knee mechanics.	Dual-targeted modulation addressing biochemical and biomechanical axes of OA.
Primary Benefits	Reduces pain, stiffness, and inflammation; enhances flexibility.	Decreases joint stress and pain; improves gait and mobility.	Comprehensive symptom relief and improved function.
Safety Profile	Non-toxic at homeopathic dilutions; minimal adverse effects.	Low-risk, non-invasive; minor skin irritation possible.	High safety and tolerability; suitable for elderly and comorbid patients.
Evidence Type	Small-scale RCTs and observational studies.	Strong clinical and biomechanical evidence.	Theoretical synergy; requires empirical validation.
Limitations	Small sample sizes; non-	Compliance issues;	Lack of combined studies

	standardized potency.	periodic adjustments needed.	and mechanistic trials.

Even with a well-conceived theoretical backbone, the implementation of integrative approaches in the clinical setting is difficult because of a number of research gaps. It is interesting to note that none of the studies have directly compared the effect of *Rhustoxicodendron* and knee orthotics, so no research has investigated the effectiveness of this type of therapy (Dillard & Knapp, 2005). Mechanistic knowledge is partial, with the majority of the homeopathic research being restricted to biochemical results without considering biomechanical counterparts, e.g. gait analysis or load distribution. The reproducibility is further undermined by methodological inconsistencies such as variability in potency, formulation, and study design. Moreover, the time span of the follow-up is most likely brief (6-12 months), which limits long-term joint preservation information. Inadequate interdisciplinary cooperation of homeopathy, orthopedic, and rehabilitation medicine to facilitate the development of standardized protocols is also a limitation to integration (Bernardini, Cracolici, Ferreri, Rinaldi, & Pulcri, 2015). These gaps will be addressed with properly designed prospective randomized controlled trials that will apply standardized *Rhustoxicodendron* preparations, objective biomechanical outcome measurements, and valid patient-reported outcome (WOMAC and KOOS) and translational biomarkers like inflammatory cytokine profiles and oxidative stress indices to elucidate underlying pathways of mechanism.

2.13. Synthesis and Conceptual Model for Targeted Musculoskeletal Therapy

All literature reviewed is pointing towards the same conclusion that both *Rhustoxicodendron* and knee orthotics have independent roles in the reduction of pain, improved functionality, and enhanced quality of life in cases of musculoskeletal disorders (Rajalekshmi & Agrawal, 2024). Their combination into the principle of target therapy, which aims at achieving the greatest efficacy and reducing the risks of the system, offers a new impetus in managing OA.

Integrative target therapy presents a personalized, non-invasive, and sustainable intervention that integrates molecular and biomechanical interventions using unified delivery, which has the potential to transform the conservative care of OA (Mohammadinejad et al., 2020). The framework has also been in line with the overall objectives of current rehabilitation medicine: recovery, disease prevention, and empowering patients via self-management. The below figure 3 shows the Proposed framework of integrative Target therapy for knee osteoarthritis.

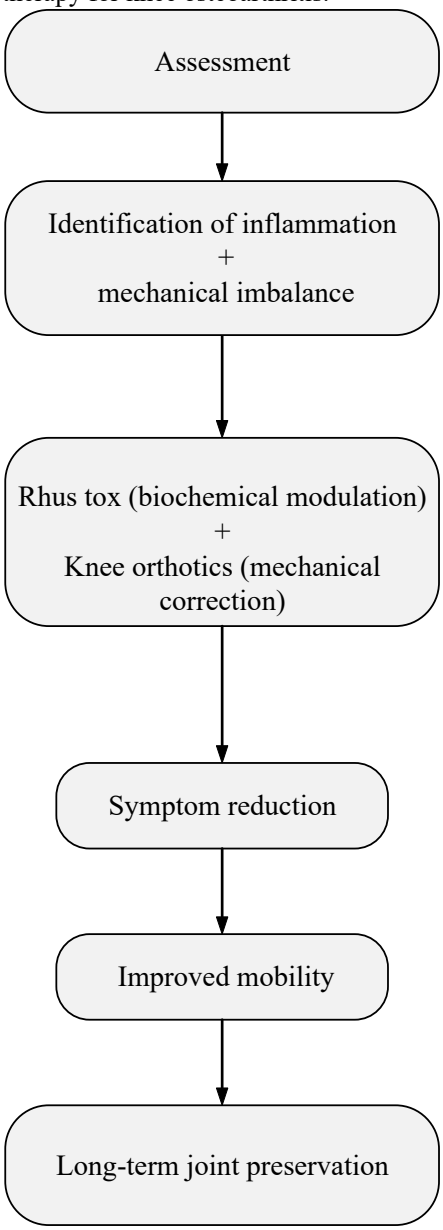


Figure 3: Proposed framework of integrative Target therapy for knee osteoarthritis

Finally, current literature gives credible evidence to the use of *Rhustoxicodendron* and knee orthotics as an individual therapy agent in musculoskeletal management. Nevertheless, the synergy between the two modalities has not been studied, and it is an obvious and clinically significant gap in research. A combination of the two interventions in the framework of target therapy is consistent with the emerging paradigm of precision and integrative medicine, providing a moderate, patient-centered approach to knee osteoarthritis (Luo, Wang, & Guo, 2025). The design of biochemical and biomechanical interventions can create the path to new translational research, which

can possibly rebrand conservative musculoskeletal care.

3. METHODOLOGY

The literature search was systematic to obtain the studies that are pertinent to the therapeutic effects of *Rhustoxdendron* and the use of knee orthotics in musculoskeletal disorders, and especially in knee osteoarthritis (Rajgurav & Aphale, 2017). Based on the search and selection of the literature, a PRISMA 2020-type flow diagram (Figure 4) was created to summarize the literature search and selection. The figure has identified the number of studies that were identified, screened, excluded, and included in the final synthesis.

One thousand five hundred four records were identified with the help of electronic databases (PubMed = 342, Scopus = 286, Web of Science = 228, Cochrane Library = 98, Google scholar = 200). On eliminating 326 duplicates, 828 distinct records were left to be screened by title and abstract. Out of them, 700 studies were filtered out as irrelevant or insufficient musculoskeletal coverage. 128 of the full-text studies were then evaluated as eligible, of which 70 were removed due to not meeting inclusion criteria (non-OA populations, lack of data, or missing text). In conclusion, 60 articles were incorporated in the qualitative synthesis, and 36 were employed to make thematic synthesis and critical appraisal.

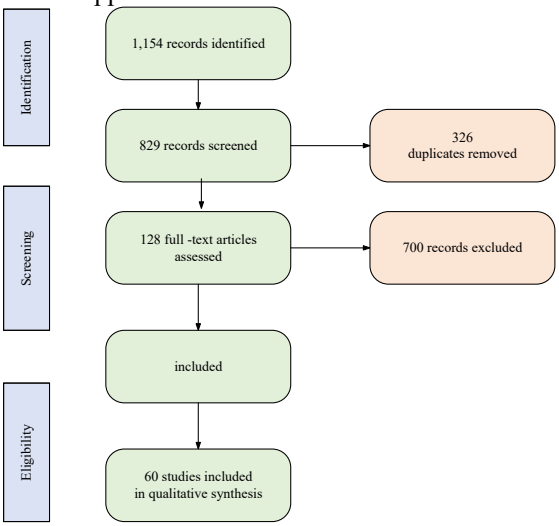


Figure 4: PRISMA Flowchart of study identification and selection on *Rhustoxicodendron* and knee orthotics

It was a review of preclinical and clinical trials on *Rhustoxdendron* in musculoskeletal diseases, and studies on the design, use, and efficacy of knee orthotics. Articles that spoke about the use of integrative or targeted therapy were also taken into account. Original research, case reports, systematic reviews, and meta-analyses were eligible as types of study. The research that was not related to musculoskeletal applications, or publications that did not provide any methodological details or results, were skipped. Based on the included studies, data were pulled out regarding the type of study, population (in case of clinical studies), intervention, outcomes, safety and significant findings. These results were then tabulated in terms of themes in order to determine the individual and combined effect of *Rhustoxdendron* and knee orthotics as well as knowledge gaps and future directions of research.

4. RESULTS AND DISCUSSION

The combining of literature provided the consistent evidence that testifies to the efficiency of *Rhustoxicodendron* and knee orthotics as effective non-invasive and low-risk interventions used to manage the symptoms of knee osteoarthritis (OA) and other musculoskeletal disorders. Although the results confirm the therapeutic independence of the two modalities, there is a critical gap therein: empirical validation of the combination of modalities. This part provides the synthesized findings and discusses them in comparison to each other, and places the integration of the two modalities in context with the proposed Integrative Target Therapy.

4.1. Biochemical Modulation: Therapeutic Profile of *Rhustoxicodendron*

Preclinical and clinical data reviewed indicate strongly the suitability of *Rhustoxicodendron* (Rhus tox) as a multi-targeted biological agent, having anti-inflammatory and anti-oxidative activity. It was also shown in preclinical models that it could reduce the inflammatory cascade through inhibition of pro-inflammatory cytokines, including TNF-α , IL-6, and IL-1β , as well as decreasing the expression of cyclooxygenase-2 (COX-2). What is more, its antioxidant phenotype, with its upsurged superoxide dismutase (SOD) and catalase activity, implies its active action against the oxidative stress in OA pathophysiology(Nam et al., 2003).

Rhus tox had positive symptomatic effects in clinical trials. Such as the randomized controlled trial (Bhattacharyya et al., 2024) found statistically significant pain, stiffness, and physical functions in patients with knee OA using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) measures. The observational evidence (Simeon, Beega, Abiola, Wofuru, & Eze, 2024) also associated the administration of Rhus tox with decreases in the levels of such inflammatory biomarkers as the Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP).

Compared to traditional pharmacological agents (such as NSAIDs), Rhus tox has an excellent safety and tolerability profile, which can be used in chronic therapy without any serious risk to the body system(Setty & Sigal, 2005). Nevertheless, the small size of the samples, divergent preparations of potency, and inconsistent rigor of methodology often undermine the existing clinical evidence. Importantly, all these studies have been almost solely based on biochemical and patient-reported

outcomes, with very little taking into consideration objective biomechanical measures such as gait analysis or joint load distribution.

4.2. Biomechanical Correction: Clinical Efficacy of Knee Orthotics

Knee orthotics, specifically unloader braces, have been proven to be an evidence-based biomechanical intervention (Rucinski et al., 2022). Its general principle is the non-invasive modification of joint kinetics aimed at redistribution of load-bearing forces, decreased load on the compartment that is affected (in most cases the medial one), and improved overall gait efficiency.

The Cochrane Review (2021) clinical findings, along with various other randomized controlled studies and systematic reviews, show the effectiveness of orthotic therapy. All these studies prove that bracing can generate a considerable decrease in pain severity and significant improvement in the functional scale (WOMAC, VAS, and 6-minute walk test). This renders orthotics as a supporting pillar of the non-pharmacological conservative management.

In contrast to Rhus tox studies, which tend to be inconsistent in methodology, orthopedic and rehabilitative medicine has a strong body of evidence to prove the efficacy of orthotics. Compliance of the patient is the biggest clinical problem with orthotics, which is enhanced by lightweight construction (reports of 65-80% compliance). In theory, the orthotic studies are usually incapable of incorporating the biochemical part of OA as the studies are exclusively concerned with mechanical results. This forms a definite dichotomy in the existing literature: there is one modality with respect to the inflammatory disease process (Rhus tox), and the other modality with respect to the mechanical failure (orthotics).

4.3. Discussion of Synergistic Potential and Integrative Target Therapy

The greatest literature synthesis discovery is the gap in the empirical research regarding the application of *Rhustoxicodendron* and knee orthotics. There are currently no studies aimed at proving the synergistic or additive action of modulation of the molecular environment at the same time and correction of joint mechanics.

Nevertheless, the conceptual ground on which this integration, the targeted approach, is based is strong and indirectly justified:

1. Treatment of OA Bi-polarity: OA is a disease that is a vicious cycle of inflammation, pain, mechanical imbalance, and progressive cartilage degeneration. With a molecular down-regulator (Rhus tox), the intervention targets both primary axes of the pathophysiology of the disease, in combination with a mechanical stabilizer (orthotics).
2. Multimodal Therapy Evidence: The results of a 2022 meta-analysis of integrative musculoskeletal therapy showed that a combination of pharmacologic-mechanical therapy is typically associated with a higher level of pain relief and functional recovery than monomodal therapies. This implies that the joint intervention of Rhus tox and orthotics will have increased therapeutic benefits compared to the individual intervention(Jang et al., 2023).
3. Increased Compliance and Safety: The integrative framework has a major benefit compared to traditional treatment, which is reducing systemic risks. Rhus tox offers a safe biochemical mechanism of pain and symptom alleviation, whereas the orthotic offers immediate and visible mechanical relief. This is a non-invasive and holistic relief that is expected to enhance patient adherence, particularly in geriatric patients with comorbidities with a high risk of NSAID and surgical interventions (Masiero, Mastrocostas, & Musumeci, 2018).

The final part of this discussion is the Integrative Target Therapy Framework that suggests an individualized and progressive intervention: assessment results in the identification of both inflammatory and mechanical imbalances that are treated simultaneously. The final implication of using such a framework is that it may lead to the realization of long-term joint preservation, which is uncommon with existing symptom-based monotherapies. To address the existing gap in the current research, with well-structured prospective studies, the biochemical biomarkers (cytokines) and objective biomechanical measurements (gait analysis) are the critical steps to transform this conceptual model into a conventional pattern of OA management at the conservative phase.

4.4. Future Directions: Bridging the Methodological Gap

In order to substantiate conclusively the integrative approach, future studies will require overcoming the methodological deficiencies that have been discovered throughout the literature. This includes:

- Standardization: Standard dosing protocols set up of Rhus tox and standardized and validated designs of knee orthotics.
- Interdisciplinary Outcomes: The ability to design trials that involve a set of outcome measures that is based on a combination of patient-reported data (WOMAC, KOOS) with translational biomarkers and objective biomechanical measures (e.g., the knee adduction moment (KAM) measurements).

- Long-Term Follow-up: Trials with the follow-up period longer than 12 months should be carried out to provide important data on the effect of the combined therapy on the progression of the disease and the preservation of the joint structure.

The combination of these two low-risk modalities into a specific framework provides a revolutionary way of conservative treatment of knee osteoarthritis to shift towards managing the symptoms instead of a disease-modifying treatment.

5. CONCLUSION

This review highlights the potential of combining *Rhustoxicodendron* and knee orthotics as dual-targeted therapy to the management of knee osteoarthritis in the context of targeted therapy. It identifies the independent hours of effectiveness of Rhus tox as a safe and multi-targeted biological agent with marked anti-inflammatory and antioxidant activities and also identifies the proven biomechanical advantages of knee orthotics in redistributing load and enhancing joint performance. These modalities jointly present the people with complementary mechanisms that are biochemical modulation and mechanical correction that complies with the principle of personalized and precision medicine. The existing literature however does not carry any empirical research that considers their synergetic capacity. Higher quality, longitudinal randomized controlled trials are necessary on a large scale in the future so as to confirm this integrative model, using standardized Rhus tox preparations, biomechanical outcomes, and molecular biomarkers. The creation of this evidence base would be the first step toward a paradigm shift of knee osteoarthritis conservative management methods, being symptomatic as opposed to holistically maintaining the joint, enhancing functionality, and maintaining a steady increase in patient quality of life.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

COMPETING INTERESTS

The authors have no competing financial or non-financial interests to disclose.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article. Further information is available from the corresponding author upon reasonable request.

ETHICS APPROVAL

This article is a review based on previously published studies and does not involve any new studies with human participants or animals performed by any of the authors. Therefore, ethical approval was not required.

CONSENT TO PARTICIPATE

Not applicable, as this article does not involve any human participants.

CONSENT FOR PUBLICATION

All authors have read and approved the final manuscript and consent to its publication.

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