Therapeutic Potential of Eugenol for Muscle Pain Management in Athletes: A Scoping Review

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ABSTRACT

Muscle pain is a prevalent affliction experienced by athletes during training and competition. Eugenol, a natural compound found in cloves, exhibits considerable promise as a therapeutic agent for myalgia through multiple mechanisms of action. Eugenol has been shown to inhibit prostaglandin E2 production and reduce cyclooxygenase-2 (COX-2) expression, a process that plays a pivotal role in inflammation and pain. Furthermore, eugenol has been observed to interact with TRPV1, HVACC, and α2-adrenergic and opioidergic receptors, contributing to its analgesic effects. In addition, studies have demonstrated that eugenol possesses significant anti-inflammatory properties, as evidenced by its ability to reduce the expression of pro-inflammatory cytokines and augment the activity of antioxidant enzymes. In a preclinical context, eugenol-active topical formulations have demonstrated encouraging results, showing promise in the development of muscle pain relief preparations for athletes, with a superior safety profile compared to conventional drugs. However, further research is necessary to optimize the dosage, formulation, and the appropriate application method. This review underscores the potential of eugenol as a safe and effective muscle pain therapy for athletes, as well as opportunities for the development of innovative topical formulations.

Keywords: eugenol, muscle pain, topical formulation, pain management

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INTRODUCTION

Muscle pain represents a common issue frequently experienced by athletes during both training and competition. Pharmacological treatments for this condition typically involve the use of non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac, capsaicin, and combinations of menthol and methyl salicylate, which have long been used to manage muscle pain. However, several limitations are associated with these treatments. For instance, diclofenac has been reported to induce allergic contact dermatitis in some individuals (Gulin and Chiriac, 2016). Methyl salicylate often causes a burning and stinging sensation (Versteeg *et al.*, 2024), while capsaicin is known to produce primarily local side effects, including erythema, burning, stinging, or itching, which are particularly uncomfortable when applied to open wounds (Groninger and Schisler, 2012). These issues highlight the growing need for safer and more effective therapeutic alternatives.

Eugenol, a natural compound found in various plants such as clove and cinnamon, attracts considerable attention from researchers as a potential therapeutic agent for managing muscle pain in athletes (Khalil *et al.*, 2017).The mechanism of action of eugenol in alleviating muscle pain involves several pathways, including the inhibition of inflammatory mediators and the

modulation of pain receptors. Recent studies demonstrate that eugenol inhibits the production of prostaglandin E2 and reduces the expression of cyclooxygenase-2 (COX-2), both of which play critical roles in the inflammation and pain processes (Barboza *et al.*, 2018). Additionally, eugenol exhibits analgesic effects through its interaction with the TRPV1 receptor, which is involved in pain perception (Ye *et al.*, 2024).

The development of eugenol as a therapy for muscle pain shows promising outcomes. Topical formulations of eugenol demonstrate effectiveness in reducing post-exercise muscle pain in athletes, with an improved safety profile (Ratna *et al.*, 2020; Cherdchom *et al.*, 2021). However, further research remains necessary to optimize the dosage, formulation, and application methods of eugenol in specific sports contexts. Given eugenol's potential as a safe and effective alternative for muscle pain management in athletes, a comprehensive literature review is warranted to evaluate the current scientific evidence and to identify opportunities for innovation in its application. This review aims to examine and discuss the mechanisms of action of eugenol, its effectiveness across different types of sports, and the potential for developing optimal formulations and application methods for athletes. The findings from this review are expected to provide a strong scientific foundation for the further development of eugenol as an innovative therapeutic agent for muscle pain in the field of sports.

METHODS

This article employed a narrative literature review approach to explore the potential of eugenol as a therapeutic agent for muscle pain in athletes. The analyzed literature included experimental studies, clinical trials, and related publications that addressed muscle pain issues in athletes and discussed eugenol in terms of its mechanisms of action, effectiveness, and formulation development for muscle pain management. Data were collected through literature searches in leading academic databases such as Scopus.

The reviewed articles were selected based on inclusion criteria, which consisted of original research articles available in English and addressing the pharmacological aspects, mechanisms of action, and potential applications of eugenol in the context of muscle pain therapy. This review did not apply a time restriction for article selection, as it aimed to examine all relevant publications aligned with the objectives of the study. Meanwhile, exclusion criteria included articles that were irrelevant to the topic, studies with unclear methodologies, and publications not sourced from indexed journals. The selection of articles was conducted using a flowchart adapted from PRISMA (2020), as illustrated in Figure 1.

RESULT AND DISCUSSION

Based on the results of the article search that met the inclusion criteria, several relevant studies were identified and reviewed, as outlined in Table 1. Eugenol, a compound found in clove (*Syzygium aromaticum* L.), demonstrated substantial potential as a therapeutic agent for muscle pain. One of the mechanisms of eugenol's action was through its analgesic effect, which had been proven in various animal pain models (Lugo-Lugo *et al.*, 2019). In a study using mice, eugenol exhibited significant antinociceptive effects in reducing pain responses induced by acetic acid (Daniel *et al.*, 2009). According to Park *et al.* (2011), this antinociceptive effect was believed to be associated with interactions between

eugenol and α2-adrenergic and opioidergic receptors, but not serotonergic receptors.

The mechanism of eugenol in relieving muscle pain also involved the inhibition of ion channels related to pain transmission. Lee *et al.* (2005) found that eugenol inhibited high-voltage-activated calcium channels (HVACC), which likely contributed to its analgesic effect. Similarly, Seo *et al.* (2013) reported that T-type Ca^{2+} ion channels served as molecular targets contributing to eugenol's pain-relieving activity.

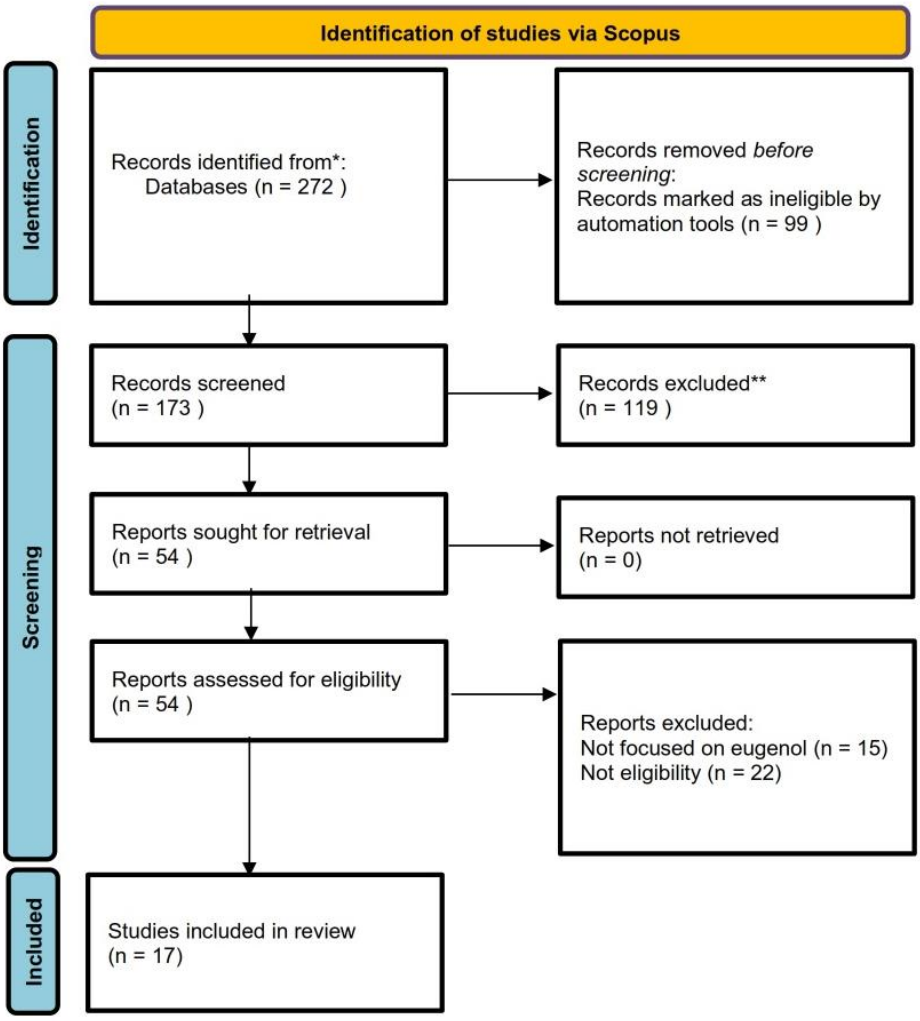

Figure 1. Flowchart of article selection.

Table 1. Results of Selected Articles According to Criteria

Authors	Title	Source and Year	Objective	Study Design	Test Species	Dosage / Formulation	Findings
Lugo-Lugo DE, Pozos-Guillén A de J, Zapata-Morales JR, Rodríguez-Chong A, Rangel-López A de J, Saavedra-Leos MZ, et al.	Antinociceptive local activity of 4-allyl-1-hydroxy-2-methoxybenzene (eugenol) by the formalin test: an anti-inflammatory effect	Brazilian Journal of Pharmaceutical Sciences. 2019	To determine the analgesic/ anti-inflammatory effect of eugenol compared to diclofenac, naproxen, and tramadol using the formalin test.	In vivo experiment	Mice	Pure eugenol, local injection	The study showed that eugenol had moderate activity during the acute pain phase and stronger activity during inflammatory pain, with effects comparable to diclofenac and less than those of naproxen and tramadol in the formalin test.
Daniel AN, Sartoretto SM, Schmidt G, Caparroz-Assef SM, Bersani-Amado CA, Cuman RKN.	Anti-inflammatory and antinociceptive activities of eugenol essential oil in experimental animal models.	Revista Brasileira de Farmacognosia. 2009	To evaluate the anti-inflammatory and antinociceptive activities of eugenol for dental medicine after oral administration in vivo.	In vivo experiment	Rats	Oral essential oil	The study demonstrated that eugenol exhibited peripheral anti-inflammatory and antinociceptive activities.
Park SH, Sim YB, Lee JK, Kim SM, Kang YJ, Jung JS, et al.	The analgesic effects and mechanisms of orally administered eugenol	Archives of Pharmacal Reseaunrch. 2011	To understand the analgesic effects and mechanisms of oral	In vivo experiment	Mice	Oral eugenol	The study showed that eugenol exhibited antinociceptive properties in various

Authors	Title	Source and Year	Objective	Study Design	Test Species	Dosage / Formulation	Findings
			eugenol administration.				pain models, and its effects could be mediated by α2-adrenergic and opioid receptors, but not serotonergic receptors.
Lee MH, Yeon KY, Park CK, Li HY, Fang Z, Kim MS, et al.	Eugenol Inhibits Calcium Currents in Dental Afferent Neurons.	J Dent Res. 2005	To explain the molecular mechanism underlying the analgesic activity of eugenol and investigate its effects on high-voltage activated calcium currents (HVACC) in primary dental afferent neurons using heterologous expression systems.	In vitro electrophysiology	Rat neurons	Eugenol in electrophysiology medium	The study revealed that inhibition of HVACC by eugenol in primary dental afferent neurons was not mediated by TRPV1 activation, which could contribute to the analgesic effects of eugenol.
Seo H, Li HY, Perez-Reyes E, Lee JH.	Effects of eugenol on T-type Ca2+ channel isoforms.	The Journal of Pharmacology and Experime	To investigate how eugenol affects cloned T-	In vitro electrophysiology	HEK293 cells	Eugenol in patch-clamp solution	The study indicated that T-type Ca2+ channels are an additional

Authors	Title	Source and Year	Objective	Study Design	Test Species	Dosage / Formulation	Findings
		ntal Therapeutics. 2013	type calcium channel isoforms expressed in HEK293 cells using the whole-cell patch-clamp technique.				molecular target for eugenol's analgesic effects.
Takahashi K, Yoshida T, Wakamori M.	Mode-selective inhibitory effects of eugenol on the mouse TRPV1 channel.	Biochemical and Biophysical Research Communications. 2021	To identify the underlying mechanism of eugenol's antagonistic effects on TRPV1 activation induced by three modes of activation.	In vitro	Mouse TRPV1 channels	Eugenol in medium solution	The study showed that eugenol is a mode-selective TRPV1 antagonist and could be evaluated as a key analgesic compound targeting TRPV1 without serious side effects.
Ye H, Lin Q, Mei Q, Liu Q, Cao S.	Study on mechanism of transdermal administration of eugenol for pain treatment by network pharmacology and molecular docking technology.	Heliyon. 2024	To explore the pharmacological mechanisms of transdermal administration of eugenol (EUG) for pain treatment.	In silico + molecular docking	—	Transdermal eugenol	The study demonstrated that the initial application of eugenol leads to transient TRPV1 receptor stimulation and increased TRPV1 expression. Eugenol also

Authors	Title	Source and Year	Objective	Study Design	Test Species	Dosage / Formulation	Findings
							acts as a TRPV1 agonist, increasing intracellular Ca2+ levels, which may be related to the desensitization of pain sensation.
Kim SS, Oh OJ, Min HY, Park EJ, Kim Y, Park HJ, et al.	Eugenol suppresses cyclooxygenase-2 expression in lipopolysaccharide-stimulated mouse macrophage RAW264.7 cells.	Life Sciences. 2003	To investigate eugenol's ability to suppress cyclooxygenase-2 expression in lipopolysaccharide-stimulated RAW264.7 mouse macrophage cells.	In vitro	Mouse macrophages (RAW264.7)	Eugenol in culture medium	The study found that eugenol is a promising candidate for further development of COX-2 inhibitors as anti-inflammatory or chemopreventive agents.
Raghavenra H, Diwakr BT, Lokesh BR, Naidu KA.	Eugenol—The active principle from cloves inhibits 5-lipoxygenase activity and leukotriene-C4 in human PMNL cells.	Prostaglandins, Leukotrienes and Essential Fatty Acids. 2006	To investigate eugenol from cloves' ability to inhibit 5-lipoxygenase activity and leukotriene-C4 formation in human PMNL cells.	In vitro	Human PMNL cells	Eugenol in DMSO solution	The study showed that eugenol inhibited 5-LO through a non-competitive mechanism and also inhibited LTC4 formation in human PMNL cells, possibly playing a

Authors	Title	Source and Year	Objective	Study Design	Test Species	Dosage / Formulation	Findings
							beneficial role in modulating the 5-LO pathway in human PMNL cells.
de Andrade F das CP, Mendes AN.	Computational analysis of eugenol inhibitory activity in lipoxygenase and cyclooxygenase pathways.	Scientific Reports. 2020	To verify the pharmacokinetics of eugenol and its chemical interactions with COX-2 and 5-LOX, comparing it to other NSAIDs such as diclofenac and aspirin.	In silico	—	Computational model	The study found that eugenol could be used as a pharmacological compound similar to diclofenac and aspirin.
Adefegha SA, Oyeleye SI, Okeke BM, Oboh G.	Influence of eugenol on oxidative stress biomarkers in the liver of carrageenan-induced arthritis rats.	Journal of Basic and Clinical Physiology and Pharmacology. 2019	To evaluate the influence of eugenol on oxidative stress biomarkers in the liver of carrageenan-induced arthritis rats.	In vivo	Rats	Oral eugenol	The study showed that eugenol improved carrageenan-induced oxidative stress in the liver of arthritis rats.
Wang M, Dai T, Li S, Wang W.	Eugenol suppresses the proliferation and	Biochemical and Biophysical Research	To investigate the effects and molecular	In vitro	Human RA synoviocytes	Eugenol in DMSO solution	The study showed that eugenol may be a novel drug to

Authors	Title	Source and Year	Objective	Study Design	Test Species	Dosage / Formulation	Findings
	invasion of TNF-α-induced fibroblast-like synoviocytes via regulating NF-κB and COX-2.	Communications. 2022	mechanisms of eugenol on the fibroblast-like synoviocyte phenotype in rheumatoid arthritis (RA).				suppress RA progression by inhibiting NF-κB signaling and COX-2 expression in fibroblast-like synoviocytes.
Abdou A, Ennaji H, Maaghloud FE, Azhary KE, Badou A, Elmakssoudi A, et al.	In silico and in vivo anti-inflammatory effect of eugenol and acetyleugenol.	Scientific African. 2024	To assess the anti-inflammatory effects of the volatile compounds (eugenol) derived from clove buds in vivo and in silico.	In silico + in vivo	Mice	Eugenol and acetyleugenol	The study showed that eugenol and acetyleugenol exhibited better binding properties when interacting with the COX-2 enzyme, indicating their potential as anti-inflammatory agents.
Prasad SN, Muralidhara.	Neuroprotective Efficacy of Eugenol and Isoeugenol in Acrylamide-Induced Neuropathy in rats: Behavioral and	Neurochemical Research. 2013	To assess the neuroprotective efficacy of eugenol (Eug) and isoeugenol (IE) in acrylamide-induced neuropathy	In vivo	Rats	Oral eugenol and isoeugenol	The study demonstrated that eugenol mitigated acrylamide-induced neuropathy in rats and showed potential for therapeutic use as an

Authors	Title	Source and Year	Objective	Study Design	Test Species	Dosage / Formulation	Findings
	Biochemical evidence.		(ACR) in rats.				adjunct in managing other forms of neuropathy in humans.
Jesudasan JS, Wahab PUA, Sekhar MRM.	Effectiveness of 0.2% chlorhexidine gel and a eugenol-based paste on postoperative alveolar osteitis in patients having third molars extracted: a randomised controlled clinical trial.	The British Journal of Oral & Maxillofacial Surgery. 2015	To compare the effects of 0.2% chlorhexidine gel, eugenol-based paste, and a control group on postoperative alveolar osteitis incidence in patients who had third molars extracted.	Randomized controlled trial	Humans	Eugenol paste	The study showed that eugenol reduced pain, inflammation, infection, and wound healing more effectively than the control group in cases of alveolar osteitis.
Cavallaro A.	Gel for topical application of clove essential oil with broad spectrum anti-inflammatory action and method of preparing same	Patent US20150182578A1, 2015	To patent a topical gel formulation of clove essential oil.	Patent/technical	—	Topical clove oil gel	The patent demonstrated that clove essential oil gel containing eugenol exhibits anti-inflammatory and analgesic effects.

Authors	Title	Source and Year	Objective	Study Design	Test Species	Dosage / Formulation	Findings
Cherdchom S, Keawsongsaeng W, Buasorn W, Rimsueb N, Pienpinijtham P, Sereemaspun A, et al.	Development of Eugenol-Embedded Calcium Citrate Nanoparticles as a Local Anesthetic Agent.	ACS Omega. 2021	To investigate the potential use of calcium citrate nanoparticles as carriers for the topical application of eugenol.	In vitro formulation study	Human cells (keratinocytes and fibroblasts) and human skin samples	Eugenol-loaded nanoparticles	The study revealed that eugenol-loaded calcium citrate nanoparticles have shown potential as a carrier for the topical administration of eugenol. These new nanoparticles represent a promising alternative for the topical application of local anesthetics with natural pain relief.

In addition, eugenol was found to inhibit the Transient Receptor Potential Vanilloid 1 (TRPV1) receptor, which plays a role in pain stimulation (Takahashi *et al.*, 2021). TRPV1 is known to have a critical role in molecular mechanisms contributing to pain and injury-induced hyperalgesia. Ye *et al.* (2024) reported that eugenol acted as a TRPV1 agonist, increasing intracellular Ca^{2+} levels, which may contribute to desensitizing pain sensations, thus providing new evidence for the application of topical transdermal eugenol in pain therapy. These findings indicated that eugenol offers potential as an effective muscle pain therapy agent through multiple pathways.

Beyond its analgesic effects, eugenol also possessed significant anti-inflammatory properties, which helped reduce muscle pain associated with inflammation. Since inflammation often accompanied muscle pain, its reduction could help relieve discomfort. In a study using a carrageenan-induced inflammation model, eugenol was shown to reduce edema and leukocyte migration, demonstrating its anti-inflammatory effectiveness (Daniel *et al.*, 2009).

Kim *et al.* (2003) and Raghavenra *et al.* (2006) found that eugenol inhibited the synthesis of prostaglandins and leukotrienes, which are inflammatory mediators involved in pain

transmission. This finding was further supported by de Andrade and Mender (2020), who showed that eugenol exerted anti-inflammatory effects through the inhibition of lipoxygenase and cyclooxygenase enzymes. Moreover, eugenol was found to reduce the expression of pro-inflammatory cytokines such as TNF-α and COX-2 while enhancing the expression of antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX). By reducing inflammation and oxidative stress, eugenol helped alleviate muscle pain related to inflammatory conditions (Adefegha *et al.*, 2019; Wang *et al.*, 2022; Abdou *et al.*, 2024).

Research conducted by Prasad and Muralidhara (2013) also revealed that eugenol was effective in alleviating neuropathy. Neuropathy results from damage to the nervous system due to trauma, toxins, or metabolic disorders affecting peripheral or central neurons. In athletes, neuropathic pain can result from direct or indirect injuries to central (brain and spinal cord) or peripheral (nerves and small fibers) nervous structures. Using an acrylamide-induced neuropathy model, both eugenol and isoeugenol were shown to reduce oxidative stress in the sciatic nerve, lower cytosolic calcium levels, and inhibit acetylcholinesterase activity. These results suggested that eugenol may serve as an effective alternative for managing neuropathic pain.

In the context of clinical use, further investigations were required to determine the effective and safe dosage of eugenol as a therapeutic agent for muscle pain. Although eugenol had shown substantial potential in various animal models, human studies were still needed to ensure its safety and efficacy. Nevertheless, with its multiple identified mechanisms of action, eugenol offered new hope as a more natural and safer alternative for muscle pain therapy.

The development of topical formulations containing eugenol for managing muscle pain in athletes showed considerable promise, as eugenol present in clove leaf oil had demonstrated significant analgesic and anti-inflammatory properties (Daniel *et al.*, 2009). Jesudasan *et al.* (2015) found that a paste formulation containing eugenol provided superior pain relief in postoperative alveolar osteitis compared to 0.2% chlorhexidine gel. In a gel formulation, Cavallaro (2015) patented a clove essential oil-based topical gel in which eugenol was the main active component with proven anti-inflammatory and analgesic activity.

One of the most recent approaches was developed by Cherdchom *et al.* (2021), who formulated eugenol into a calcium citrate nanoparticle-based topical delivery system that exhibited good stability and high biocompatibility. Their study demonstrated that this formulation provided an effective transdermal drug delivery system due to its ability to penetrate the skin and reach targeted areas. They also reported that the formulated eugenol nanoparticles had potential as a local topical anesthetic for pain management.

In the development of such topicals, determining the optimal formulation of eugenol was essential to ensure product safety and effectiveness. Special attention must be given to the fact that direct application of eugenol to the skin still required further investigation due to its potential to cause local irritation and its low solubility in water (Tammannavar *et al.*, 2013). Nevertheless, the development of topical formulations containing eugenol holds great potential for muscle pain management in athletes. With its proven analgesic and anti-inflammatory effects, eugenol may be formulated into a topical

product that aids athletes in recovering more quickly from injuries while reducing reliance on synthetic drugs. However, further studies are needed to confirm the safety and efficacy of such formulations.

CONCLUSION

Eugenol presented substantial potential as a therapeutic agent for muscle pain in athletes due to its significant analgesic and anti-inflammatory effects. Various mechanisms of action had been identified, including the inhibition of inflammatory mediators, modulation of pain receptors, and reduction of oxidative stress. Topical formulations containing eugenol showed promising results in alleviating post-exercise muscle pain, with a favorable safety profile. Nevertheless, further research was required to determine the optimal dosage, ensure long-term safety, and develop effective application methods. Given this potential, eugenol could serve as a more natural and safer therapeutic alternative for athletes, supporting faster recovery and reducing reliance on synthetic medications. It is hoped that the findings of this review may serve as a foundation for further investigations into the application of eugenol in the management of muscle pain in athletes.

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Author Contribution

All authors participated to all aspects of this work, including preparation, research, data collecting and analysis, manuscript drafting, and publication approval.

Competing Interest

None.

Ethical Approval

None.

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