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Phytochemicals as Modulators of TRPV1 in Pain and Inflammation a Review

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ABSTRACT

Background: Pain and inflammation are complex physiological responses that significantly impact the quality of life for millions of individuals worldwide. Current pharmacological treatments often present substantial risks, underscoring the need for safer and more effective therapeutic options.

Aim: This review aims to comprehensively explore the potential of phytochemicals as modulators of the Transient Receptor Potential Vanilloid 1 (TRPV1) channel, a key player in pain and inflammation pathways.

Material and Methods: A detailed examination of the mechanisms of action, therapeutic benefits, and current research status of various phytochemicals was conducted. Special attention was given to bioactive compounds derived from plants such as capsaicin, curcumin, gingerol, eugenol, and piperine, alongside cocoa constituents like theobromine and epicatechin.

Results: Phytochemicals exhibit diverse mechanisms of action on TRPV1, offering analgesic and anti-inflammatory benefits with potentially fewer adverse effects compared to conventional medications. Capsaicin, curcumin, gingerol, eugenol, and piperine have demonstrated significant therapeutic potential. However, the application of cocoa constituents in pain and inflammation management requires further exploration and preclinical testing.

Conclusion: This study underscores the promising therapeutic potential of phytochemicals as TRPV1 modulators. A multidisciplinary approach involving healthcare providers, researchers, and regulatory agencies is essential for the effective integration of phytochemical-based therapies into clinical practice. Future research should focus on elucidating molecular mechanisms, exploring synergistic interactions, and conducting large-scale clinical trials to establish long-term safety and efficacy, thereby enhancing pain and inflammation management and overall patient care.

Keywords: Bioactive compounds, inflammation, pain, phytochemicals, Transient Receptor Potential Vanilloid 1 (TRPV1)

1. Introduction

Pain and inflammation are complex physiological responses that significantly impact the quality of life for millions of individuals worldwide. Current pharmacological treatments, including nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, often carry substantial risks such as gastrointestinal issues, addiction, and tolerance, highlighting the urgent need for safer and more effective therapeutic alternatives (Amaechi et al., 2021; Bach-Rojecky et al., 2019; Pergolizzi et al., 2021). One promising avenue is the modulation of the Transient Receptor Potential Vanilloid 1 (TRPV1) channel, a key player in pain and inflammation pathways (J. Yang et al., 2017).

Phytochemicals, which are bioactive compounds derived from plants, have garnered attention for their potential to modulate TRPV1. These natural compounds, found in a wide variety of fruits, vegetables, herbs, and spices, offer a rich reservoir of therapeutic agents with diverse biological activities (Behl et al., 2021). Phytochemicals such as capsaicin and curcumin have been shown to interact with TRPV1, providing relief from pain and inflammation through mechanisms that are distinct from conventional drugs (Naik et al., 2021).

Therefore, this review aims to provide a comprehensive exploration of the potential of phytochemicals as modulators of TRPV1, detailing their mechanisms of action, therapeutic benefits, and the current state of research in this area. By synthesizing the available evidence, this review underscores the importance of considering phytochemicals in the development of novel pain and inflammation therapies. By advancing our understanding of the interaction between phytochemicals and TRPV1, this review hope to pave the way for innovative treatments that leverage the benefits of nature to enhance human health and well-being.

2. Results and Discussion

TRPV1 Receptors Overview

1) Structure and Function of TRPV1 Receptors

The TRPV1 receptor is a non-selective cation channel that is part of the broader TRP family of ion channels (Baker et al., 2016). TRPV1 is composed of four subunits, forming a tetramer. Each subunit is made up of six transmembrane domains and a pore area that facilitates the movement of ions. This receptor is predominantly found in sensory neurons, namely nociceptive neurons which are responsible for detecting pain. TRPV1 is triggered by various stimuli including elevated temperatures (over 43°C), acidic environments (low pH), and capsaicin, the active compound found in chili peppers (Brito et al., 2014; Chen et al., 2022; F. Yang & Zheng, 2017). TRPV1 activation results in the entry of cations, specifically calcium (Ca^{2+}), into the cell, triggering a series of intracellular signaling cascades (Shah et al., 2020). These pathways ultimately lead to the perception of pain and the production of substances that promote inflammation, emphasizing the receptor's ability to contribute to both the sensing of pain and the occurrence of inflammation.

2) Role of TRPV1 in Pain Sensation

TRPV1 receptors are essential for the perception and communication of pain. When stimulated by harmful stimuli, TRPV1 receptors on pain-sensing neurons initiate the opening of the channel, enabling positively charged ions to enter the cell (Benítez-Angeles et al., 2020). This process causes depolarization of the neuron, resulting in the production of action potentials that are conveyed to the central nervous system, where they are interpreted as pain (Li & Wang, 2021). This process is crucial for the body's capacity to perceive and react to detrimental stimuli, offering a safeguarding mechanism against potential harm. Nevertheless, in pathological circumstances, such as persistent pain, TRPV1 receptors have the potential to become hypersensitive and excessively active. This sensitization can occur as a consequence of continuous exposure to inflammatory mediators or nerve damage, resulting in increased pain sensitivity and the occurrence of spontaneous pain (Matsuda et al., 2019). Gaining a comprehensive understanding of the mechanisms that drive the activation and sensitization of

TRPV1 is crucial in order to design precise and focused therapies for pain control.

3) TRPV1 in Inflammatory Processes

In addition to its function in perceiving pain, TRPV1 is also deeply implicated in inflammatory processes. Stimulation of TRPV1 on sensory neurons not only initiates pain signals but also results in the secretion of neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) (Iyengar et al., 2017). These neuropeptides have a strong ability to widen blood vessels and act as pro-inflammatory agents, which play a role in the body's inflammatory response. They facilitate the expansion of blood vessels, heightened permeability of blood vessels, and the mobilization of immune cells to the location of injury or infection. In addition, the activation of TRPV1 might induce the synthesis of cytokines and chemokines, so intensifying the inflammatory response (Bujak et al., 2019). TRPV1, when consistently activated, has been associated with many inflammatory disorders such as arthritis, inflammatory bowel disease, and neuropathic pain (Choi et al., 2016; Qu et al., 2023; Toledo-Mauriño et al., 2018). Hence, regulating the activity of TRPV1 holds great potential as a therapeutic approach to alleviate pain and manage inflammation in these circumstances.

Phytochemicals Targeting TRPV1

Phytochemicals are inherent substances present in plants that possess diverse biological actions that are advantageous to human health (Harrison et al., 2015). While not classified as essential nutrients like vitamins or minerals, these chemicals are recognized for their ability to prevent disease and enhance health due to their antioxidant, anti-inflammatory, and anti-cancer capabilities (Chang et al., 2019; Usman et al., 2022; Zhu et al., 2018). Phytochemicals regulate the function of TRPV1 receptors through several ways, impacting their involvement in pain and inflammation. Certain phytochemicals function as agonists by directly stimulating TRPV1 receptors. As an illustration, capsaicin, which is present in chili peppers, attaches to TRPV1 and triggers a structural alteration that unlocks the channel, resulting in the entry of ions and the subsequent transmission of pain signals (Braga Ferreira et al., 2020; Cortés-Ferré et al., 2021). Some phytochemicals serve as antagonists, which means they suppress the activation of TRPV1 and hence decrease pain and inflammatory reactions (Abbas, 2020). In addition, many phytochemicals indirectly regulate TRPV1 by affecting signaling pathways that control receptor sensitivity and expression (Premkumar, 2014). These interactions may include the regulation of intracellular calcium levels, suppression of protein kinases, or alterations in gene expression.

Implications for Treating Pain and Inflammation

Phytochemicals have the potential to modulate TRPV1, which could be a promising strategy for effectively treating pain and inflammation. Phytochemicals can provide analgesic and anti-inflammatory effects by either activating or inhibiting TRPV1 receptors, which can be advantageous in treating certain clinical diseases (Abbas, 2020). Phytochemicals such as capsaicin, curcumin, gingerol, eugenol, and piperine are frequently utilized for their analgesic and anti-inflammatory effects, as shown in Table 1.

Capsaicin from chili peppers is extensively used in topical creams and patches (Anantaworasakul et al., 2020; Sultana et al., 2020). When capsaicin activates TRPV1 on sensory neurons, it can lead to an initial sensation of burning pain followed by prolonged desensitization and reduced pain signaling, contributing to its analgesic effects. Low doses of topical capsaicin can produce reversible desensitization without long-term effects, while high doses have been shown to cause degeneration of nerve fibers and could potentially provide long-term pain relief (Hall et al., 2020). Based on Anand et al. (2022), capsaicin particularly in high concentrations such as an 8% patch, has been found to be effective in providing pain relief for individuals with painful diabetic neuropathy by desensitizing pain receptors and may also contribute to the regeneration and restoration of nerve fibers, which can lead to prolonged analgesic effects. Capsaicin has also been used in the management of painful conditions such as painful menses, toothache, muscle pain, neuralgia, diabetic neuropathy, osteoarthritis, and

rheumatoid arthritis due to its analgesic properties (Frias & Merighi, 2016). Clinical evidence suggests that capsaicin can significantly reduce pain and improve sensory perception, with some patients experiencing pain relief for up to 12 months after a single application (Fattori et al., 2016). Similarly, curcumin when interacts with TRPV1, downregulating its expression and signaling pathways, thereby offering significant anti-inflammatory and analgesic benefits. The study by Hüseyin et al. (2022), shows the effects of curcumin in preclinical models of neuropathic and postoperative pain, which curcumin can reduce neuropathic pain behaviors, downregulate proinflammatory cytokines, and attenuate pain via various biochemical pathways. The curcumin demonstrates both protective effects against injured neurons and anti-hyperalgesic activity in the context of postoperative pain, providing pain relief and potentially facilitating recovery. Study by M. Yang et al. (2017), shows that curcumin supplementation in rats reduced visceral pain and the activity of pain receptors, indicating its potential as a pain management agent for ulcerative colitis. However, when curcumin encounters capsaicin, it may slightly reduce the ability of capsaicin to activate the TRPV1 channel because they are both trying to bind to the same place on the protein (Wang, 2021). Instead of working together with capsaicin to enhance the activation of TRPV1, curcumin appears to be in competition with it.

Ginger, which contains gingerol, acts as a mild agonist of TRPV1, providing warmth and desensitization to reduce pain signaling. Since gingerol can bind to the same site on these receptors as the pain-relieving capsaicin, this suggests that gingerol and similar ginger compounds might have analgesic or pain-relieving properties (Yin et al., 2019). Gingerol, particularly 6-gingerol, interacts with transient receptor potential vanilloid-1 channels similarly to capsaicin. It inhibits the human TRPV1 channel by interacting with its various domains, which can lead to a decrease in the activity and expression of these receptors and thus affect pain perception (Andrei et al., 2022). Based on Fajrin et al. (2020), 6-shogaol, another active compound of ginger has a strong affinity toward TRPV1 and its administration reduced the expression of TRPV1 in the spinal cord of mice with painful diabetic neuropathy, leading to alleviated hyperalgesia and allodynia. While eugenol has been found to function as a weak, partial agonist of the TRPV1 receptor and as a competitive antagonist to capsaicin (Ye et al., 2024). It exhibits an inhibitory effect on TRPV1, which requires the channel to be activated. Eugenol does not impact heat induced TRPV1 channel activity, and its TRPV1 activation requires a higher concentration compared to capsaicin due to the absence of an amide group and a long aliphatic tail in its structure. Additionally, eugenol could increase the expression of TRPV1 in cells and activate TRPV1 to induce intracellular calcium influx, which might be associated with the desensitization of pain sensations upon continued exposure (Andrei et al., 2023). Study by Al-ameedi et al. (2017), shows that Eugenol, found in clove bud extract have pain-relieving and anti-inflammatory effects in mice. It reduces pain by blocking certain neural channels and appears to lessen pain responses, as seen in tests. Based on Takahashi et al (2021), eugenol effects are concentration dependent; at low pH, lower concentrations of eugenol enhance TRPV1 activity, whereas higher concentrations first enhance and then suppress it. Thus, eugenol does not affect TRPV1 when activated by heat.

Lastly, the commonly used of phytochemical for pain relief and inflammation is piperine which also have warming sensation. Piperine activate the pain-related TRPV1 receptor, causing calcium to enter cells and potentially enhancing the body's pain response. The study by Panthong et al. (2020), observed that these substances enhanced contact sensitization in a contact hypersensitivity model in mice, suggesting potential analgesic and adjuvant effects that could be useful in the development of herbal analgesic drugs. Furthermore, based on Sánchez-Trujillo et al. (2020), Piperine from black pepper was found to alleviate pain from normally non-painful stimuli (allodynia) in rats with neuropathic pain. Administered in larger doses, it appears to work by activating TRPV1 and GABA A receptors, showing promise as a treatment for human neuropathic pain. These compounds offer a natural and often safer alternative to conventional pain medications as shown in Table 1.

Table 1. Key Phytochemicals Modulating TRPV1

Key Phytochemicals	Clinical Implications	Clinical Applications	Result	Source
Capsaicin	Potential non-opioid option with varied mechanisms, possible cancer cytotoxicity.	Nasal sprays, oral ingestion for weight management, dysphagia improvement, topical pain relief, high-dose patches for neuropathic pain, diagnostic capsules for dyspepsia.	Effective in weight loss, swallowing improvement, pain relief, long-term neuropathic pain relief, and predicting dyspepsia.	(Braga Ferreira et al., 2020)
Capsaicin	Inhibits skin melanogenesis, potential for treating hyperpigmentation.	Topical application for pigmentation and chronic pain relief.	Reduces melanin synthesis in cultured melanocytes and melanogenic enzyme levels.	(Wu et al., 2020)
Capsaicin	Interacts with TRPV1 receptor for lipid regulation, atherosclerosis prevention, and gastrointestinal protection.	Analgesic for neuropathic, arthritic pain, itch, gastrointestinal disorders, dietary inclusion.	Reduces lipid storage, protects gastric mucosa, effective in chronic pain management.	(Zhang et al., 2021)
Capsaicin	Anti-inflammatory, beneficial for cardiovascular health.	Pain management in neuralgia, diabetic neuropathy.	Effective analgesic with minimal side effects, anti-cancer potential.	(Munjuluri et al., 2022)
Capsaicin	Neuroprotective in various conditions like brain injury, Parkinson's, Alzheimer's.	-	Reduces neurological impairments, protects neurons from toxic insults.	(Abdel-Salam & Mózsik, 2023)
Capsaicin	Manages neuropathic, musculoskeletal pain, pruritus.	Creams, gels, patches, sprays, injectable forms for various pain conditions.	Reduces pain in osteoarthritis, rheumatoid arthritis, minimal systemic absorption, few side effects.	(Basith et al., 2016)
Capsaicin	Directs development of TRPV1-targeting analgesics, identifies drug development challenges.	Pain and itch treatment, musculoskeletal pain management.	Significant pain relief for arthritis, high-concentration patches reduce adverse effects.	(F. Yang & Zheng, 2017)
Capsaicin	Therapeutic for inflammatory skin	Formulations for atopic dermatitis, antioxidant,	Reduces skin inflammation and edema,	(Basharat et al., 2021)

Key Phytochemicals	Clinical Implications	Clinical Applications	Result	Source
	conditions, pain management.	anticancer properties, pain relief.	beneficial for Alzheimer's disease symptoms.	
Curcumin	Antioxidant, anti-inflammatory, antinociceptive for pain relief.	Treats neuropathic, postsurgical, inflammatory pain.	Potential in pain management, bioavailability improvement needed.	(Sun et al., 2018)
Curcumin	Anti-inflammatory, anticancer, antinociceptive properties.	Traditional medicine uses for inflammation, pain, antioxidants.	Conflicting efficacy and safety reports, further studies needed.	(Nalli et al., 2017)
Curcumin	-	-	Activates blood circulation, pain relief, treats qi stagnation and blood stasis.	(Peng et al., 2022)
Gingerol	Potential in Type 2 diabetes mellitus (T2DM) treatment, improves glucose control, lipid profile.	Dietary management, traditional remedy for T2DM.	Improves glucose control, insulin sensitivity, lipid profiles; further studies needed.	(Pagano et al., 2021)
Gingerol	Analgesic for various pain types, potential Non-steroidal anti-inflammatory drugs (NSAID) alternative.	-	Treats migraine, dysmenorrhea, osteoarthritis pain.	(Kim et al., 2022)
Gingerol	Analgesic effects for pain conditions like oral mucositis.	-	Relieves pain by targeting sodium channels in sensory neurons.	(Hitomi et al., 2017)
Eugenol	Antinociceptive, anti-inflammatory, COX-2 inhibition.	Dental pain relief, analgesic for various conditions.	Significant analgesic and anti-inflammatory effects.	(Déciga-Campos et al., 2021)
Eugenol	Analgesic, local anesthetic, alternative to opioids, NSAIDs.	Transdermal treatment, dental care, topical therapeutic formulations.	Activates TRPV1 receptors, induces TRPV1 expression, effective pain management.	(Kopustinskiene et al., 2022)
Piperine	Antinociceptive, anti-inflammatory, TRPV1 receptor involvement.	-	Reduces nociceptive effects, engages cholinergic and vanilloid systems, no toxicity.	(Oliveira et al., 2018)

Other than that, Cocoa which are starting to be considered as Dietary supplements, functional foods, on the other hand is less commonly used specifically for pain management despite its promising therapeutic potential. The primary active compounds in cocoa, theobromine and epicatechin, have demonstrated various health benefits, including anti-inflammatory and analgesic properties (Dutra et al., 2024). However, its clinical applications have been largely focused on general health and wellness, particularly in the form of dietary supplements and functional foods aimed at improving cardiovascular health and overall inflammatory markers.

Based on study by Aprila Fajrin et al. (2024), the ethanol extract of cocoa pod husk (EECPH), has significant effects on the management of diabetic neuropathy in mice. EECPH treatment demonstrated repair properties on the histology of the pancreas, improving the number and diameter of Langerhans cells while decreasing degeneration and necrosis. The treatment also improved nerve morphology in the mice, indicating potential benefits for diabetic neuropathy. The expression of the TRPV-1 protein in the pancreas and spinal cord was modulated by EECPH, with decreased expression correlating with reduced hyperalgesia and blood glucose levels. Despite these promising attributes, cocoa remains underutilized in clinical pain management (De Feo et al., 2020; Sá & Castor, 2023). This underutilization highlights the urgency for more focused research on cocoa's analgesic properties. Conducting comprehensive clinical trials to evaluate the efficacy and safety of cocoa compounds in pain management can provide the necessary evidence to support its use in clinical practice. Such research can also help identify the optimal dosages and formulations for maximizing therapeutic benefits. Furthermore, expanding research on cocoa can lead to the discovery of novel mechanisms through which its compounds alleviate pain and inflammation. Understanding these mechanisms can pave the way for the development of new, targeted pain therapies that leverage cocoa's natural properties.

Discussion

Phytochemicals targeting TRPV1 offer several potential therapeutic benefits for treating pain and inflammation. These natural compounds provide analgesic and anti-inflammatory effects with relatively fewer adverse effects compared to conventional medications. They offer a holistic approach to pain management, addressing both the symptoms and underlying mechanisms of pain and inflammation. Moreover, phytochemicals present diverse chemical structures and mechanisms of action, allowing for the development of novel therapeutics tailored to specific patient needs (Lagoa et al., 2020; Mazurakova et al., 2022). However, there are limitations to consider, including variability in bioavailability, efficacy, and safety profiles among different phytochemicals. Additionally, challenges related to standardization, formulation, and regulatory approval pose hurdles to their widespread clinical use (Hossain et al., 2022). Further research is needed to address these limitations and optimize the therapeutic potential of phytochemicals in pain and inflammation management.

The integration of phytochemicals targeting TRPV1 into clinical practice requires a multidisciplinary approach involving healthcare providers, researchers, and regulatory agencies as shown in Figure 1. Clinicians or Healthcare providers play a crucial role by incorporating phytochemical-based therapies as adjuncts or alternatives to conventional treatments, particularly for patients with chronic pain conditions or those seeking natural remedies (Choudhari et al., 2020). Essential to this process is patient education, ensuring that patients are well-informed about the potential benefits, risks, and interactions of phytochemicals with other medications (Dores et al., 2023; Ekor, 2014; Grellier et al., 2017). Continuous education is vital for healthcare providers to stay updated on the latest research findings and guidelines for the use of phytochemicals in pain and inflammation management. Researchers are tasked with advancing the understanding of phytochemicals targeting TRPV1 by conducting rigorous studies on their efficacy and safety, as well as exploring their mechanisms of action. Collaboration with industry stakeholders is critical for developing standardized, safe, and effective phytochemical formulations (Cordell, 2015). Furthermore, researchers are responsible for generating the evidence needed to create and support practice

guidelines, which are then shared with healthcare providers to inform clinical practice. Regulatory agencies are responsible for the regulation and oversight of phytochemical-based therapies, ensuring they meet established safety and efficacy standards. These agencies also develop and enforce guidelines for the clinical use of phytochemicals based on the latest research (Bahorun et al., 2019). Additionally, they play a key role in promoting public awareness about the benefits and risks associated with phytochemical use, ensuring that accurate and transparent information is accessible to the public.

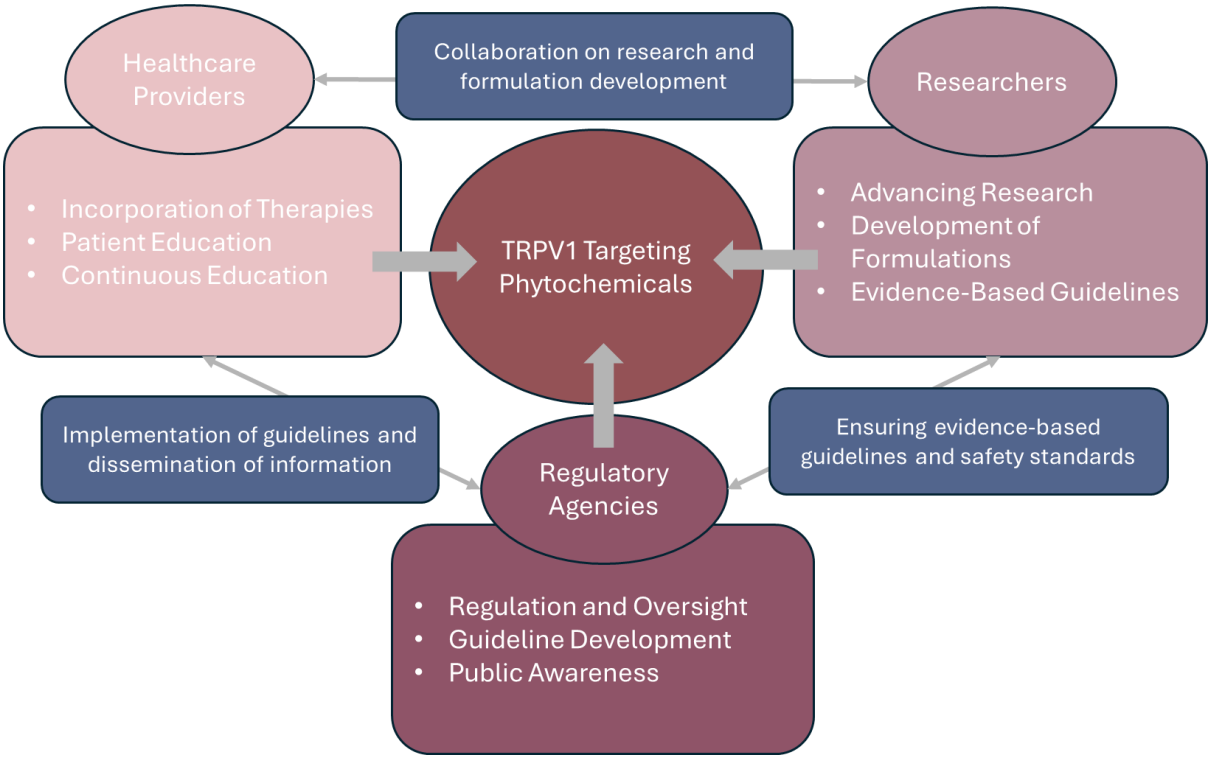

Figure 1. Integration approach of implementing phytochemical targeting TRPV1

Future research in the field of phytochemical modulation of TRPV1, especially cacao which still less implemented should focus on several key areas to further elucidate their therapeutic potential and optimize clinical outcomes. This includes investigating the mechanisms of action of phytochemicals on TRPV1 receptors at the molecular level, exploring synergistic interactions between phytochemicals and other therapeutic agents, and evaluating their long-term safety and efficacy in large-scale clinical trials.

3. Conclusion

In conclusion, the exploration of phytochemicals as modulators of TRPV1 presents a promising avenue for the effective treatment of pain and inflammation. Phytochemicals such as capsaicin, curcumin, gingerol, eugenol, and piperine exhibit diverse mechanisms of action, including both agonistic and antagonistic effects on TRPV1 receptors, offering analgesic and anti-inflammatory benefits with potentially fewer adverse effects compared to conventional medications. Meanwhile, it is crucial to underscore the urgent need for further exploration and preclinical testing regarding the constituents of cocoa and their active compounds. Despite the promising therapeutic potential demonstrated by compounds like theobromine and epicatechin in various studies, their application in pain and inflammation management remains incompletely understood. Further investigation into the mechanisms of action of these compounds on TRPV1, coupled with preclinical research to elucidate their efficacy and safety profiles, is imperative. Furthermore, a multidisciplinary approach involving healthcare providers, researchers, and regulatory agencies is essential to integrate phytochemical-based therapies into clinical practice effectively. Future research should focus on elucidating the

molecular mechanisms of action of phytochemicals on TRPV1, exploring synergistic interactions with other therapeutic agents, and conducting large-scale clinical trials to establish their long-term safety and efficacy. By addressing these challenges and advancing the understanding of phytochemical modulation of TRPV1, it can harness the therapeutic potential of natural compounds to improve pain and inflammation management and enhance overall patient care.

4. References

1. Abbas, M. A. (2020). Modulation of TRPV1 channel function by natural products in the treatment of pain. In *Chemico-Biological Interactions* (Vol. 330). https://doi.org/10.1016/j.cbi.2020.109178
2. Abdel-Salam, O. M. E., & Mózsik, G. (2023). Capsaicin, The Vanilloid Receptor TRPV1 Agonist in Neuroprotection: Mechanisms Involved and Significance. *Neurochemical Research*, *48*(11), 3296–3315. https://doi.org/10.1007/s11064-023-03983-z
3. Al-ameedi, A., Faris, J., Rabee, A., Naji, H., Obayes, A., & Obaid, W. (2017). Analgesic and Anti- Inflammatory Effects of Hydro Alcoholic Extract of (Syzygium aromaticum) in Albino Mice. *Kufa Journal For Veterinary Medical Sciences*, *8*(2), 56–62. https://doi.org/10.36326/kjvs/2017/v8i24124
4. Amaechi, O., Huffman, M. M. C., & Featherstone, K. (2021). Pharmacologic Therapy for Acute Pain. In *American family physician* (Vol. 104, Issue 1).
5. Anand, P., Privitera, R., Donatien, P., Fadavi, H., Tesfaye, S., Bravis, V., & Misra, V. P. (2022). Reversing painful and non-painful diabetic neuropathy with the capsaicin 8% patch: Clinical evidence for pain relief and restoration of function via nerve fiber regeneration. *Frontiers in Neurology*, *13*. https://doi.org/10.3389/fneur.2022.998904
6. Anantaworasakul, P., Chaiyana, W., Michniak-Kohn, B. B., Rungseevijitprapa, W., & Ampasavate, C. (2020). Enhanced transdermal delivery of concentrated capsaicin from chili extract-loaded lipid nanoparticles with reduced skin irritation. *Pharmaceutics*, *12*(5). https://doi.org/10.3390/pharmaceutics12050463
7. Andrei, C., Zanfirescu, A., Nițulescu, G. M., & Negreș, S. (2022). Understanding the Molecular Mechanisms Underlying the Analgesic Effect of Ginger. *Nutraceuticals*, *2*(4), 384–403. https://doi.org/10.3390/nutraceuticals2040029
8. Andrei, C., Zanfirescu, A., Nițulescu, G. M., Olaru, O. T., & Negreș, S. (2023). Natural Active Ingredients and TRPV1 Modulation: Focus on Key Chemical Moieties Involved in Ligand–Target Interaction. *Plants*, *12*(2). https://doi.org/10.3390/plants12020339
9. Aprila Fajrin, F., Holidah, D., Nurhidayah, H., Suci Wulansari, P., Pudji Restanto, D., Azkiyah, L., Witono, Y., & Satia Nugraha, A. (2024). The ethanol extract of cocoa pod husk minimizes hyperalgesia and blood glucose levels in diabetic neuropathy model through transient receptor protein vanilloid (TRPV)-1. *Saudi Pharmaceutical Journal*, *32*(6), 102097. https://doi.org/10.1016/j.jsps.2024.102097
10. Bach-Rojecky, L., Vadunec, D., Žunić, K., Kurija, J., Šipicki, S., Gregg, R., Mikula, I., & Primorac, D. (2019). Continuing war on pain: A personalized approach to the therapy with nonsteroidal anti-inflammatory drugs and opioids. In *Personalized Medicine* (Vol. 16, Issue 2). https://doi.org/10.2217/pme-2018-0116
11. Bahorun, T., Aruoma, O. I., & Neergheen-Bhujun, V. S. (2019). Phytomedicines, nutraceuticals, and functional foods regulatory framework: The African context. In *Nutraceutical and Functional Food Regulations in the United States and around the World*. https://doi.org/10.1016/B978-0-12-816467-9.00032-0
12. Baker, K., Raemdonck, K., Dekkak, B., Snelgrove, R. J., Ford, J., Shala, F., Belvisi, M. G., & Birrell, M. A. (2016). Role of the ion channel, transient receptor potential cation channel subfamily V member 1 (TRPV1), in allergic asthma. *Respiratory Research*, *17*(1). https://doi.org/10.1186/s12931-016-0384-x
13. Basharat, S., Gilani, S. A., Iftikhar, F., Murtaza, M. A., Basharat, A., Sattar, A., Qamar,

M. M., & Ali, M. (2021). Capsaicin: Plants of the Genus Capsicum and Positive Effect of Oriental Spice on Skin Health. *Skin Pharmacology and Physiology*, *33*(6), 331–341. https://doi.org/10.1159/000512196

14. Basith, S., Cui, M., Hong, S., & Choi, S. (2016). Harnessing the therapeutic potential of capsaicin and its analogues in pain and other diseases. *Molecules*, *21*(8). https://doi.org/10.3390/molecules21080966
15. Behl, T., Rocchetti, G., Chadha, S., Zengin, G., Bungau, S., Kumar, A., Mehta, V., Uddin, M. S., Khullar, G., Setia, D., Arora, S., Sinan, K. I., Ak, G., Putnik, P., Gallo, M., & Montesano, D. (2021). Phytochemicals from Plant Foods as Potential Source of Antiviral Agents: An Overview. *Pharmaceuticals*, *14*(4). https://doi.org/10.3390/ph14040381
16. Benítez-Angeles, M., Morales-Lázaro, S. L., Juárez-González, E., & Rosenbaum, T. (2020). TRPV1: Structure, endogenous agonists, and mechanisms. *International Journal of Molecular Sciences*, *21*(10). https://doi.org/10.3390/ijms21103421
17. Braga Ferreira, L. G., Faria, J. V., dos Santos, J. P. S., & Faria, R. X. (2020). Capsaicin: TRPV1-independent mechanisms and novel therapeutic possibilities. *European Journal of Pharmacology*, *887*(July), 173356. https://doi.org/10.1016/j.ejphar.2020.173356
18. Brito, R., Sheth, S., Mukherjea, D., Rybak, L. P., & Ramkumar, V. (2014). TRPV1: A potential drug target for treating various diseases. In *Cells* (Vol. 3, Issue 2). https://doi.org/10.3390/cells3020517
19. Bujak, J. K., Kosmala, D., Szopa, I. M., Majchrzak, K., & Bednarczyk, P. (2019). Inflammation, Cancer and Immunity—Implication of TRPV1 Channel. In *Frontiers in Oncology* (Vol. 9). https://doi.org/10.3389/fonc.2019.01087
20. Chang, S. K., Alasalvar, C., & Shahidi, F. (2019). Superfruits: Phytochemicals, antioxidant efficacies, and health effects–A comprehensive review. In *Critical Reviews in Food Science and Nutrition* (Vol. 59, Issue 10). https://doi.org/10.1080/10408398.2017.1422111
21. Chen, Z., He, Y., Tao, X., Ma, Y., Jia, J., & Wang, Y. (2022). Thermal Nociception of Ionic Skin: TRPV1 Ion Channel-Inspired Heat-Activated Dynamic Ionic Liquid. *Journal of Physical Chemistry Letters*, *13*(43). https://doi.org/10.1021/acs.jpclett.2c02952
22. Choi, S. I., Lim, J. Y., Yoo, S., Kim, H., & Hwang, S. W. (2016). Emerging Role of Spinal Cord TRPV1 in Pain Exacerbation. In *Neural Plasticity* (Vol. 2016). https://doi.org/10.1155/2016/5954890
23. Choudhari, A. S., Mandave, P. C., Deshpande, M., Ranjekar, P., & Prakash, O. (2020). Phytochemicals in cancer treatment: From preclinical studies to clinical practice. In *Frontiers in Pharmacology* (Vol. 10). https://doi.org/10.3389/fphar.2019.01614
24. Cordell, G. A. (2015). Phytochemistry and traditional medicine - The revolution continues. *Phytochemistry Letters*, *10*. https://doi.org/10.1016/j.phytol.2014.06.002
25. Cortés-Ferré, H. E., Guajardo-Flores, D., Romero-De La Vega, G., & Gutierrez-Uribe, J. A. (2021). Recovery of Capsaicinoids and Other Phytochemicals Involved With TRPV-1 Receptor to Re-valorize Chili Pepper Waste and Produce Nutraceuticals. In *Frontiers in Sustainable Food Systems* (Vol. 4). https://doi.org/10.3389/fsufs.2020.588534
26. De Feo, M., Paladini, A., Ferri, C., Carducci, A., Del Pinto, R., Varrassi, G., & Grassi, D. (2020). Anti-Inflammatory and Anti-Nociceptive Effects of Cocoa: A Review on Future Perspectives in Treatment of Pain. In *Pain and Therapy* (Vol. 9, Issue 1). https://doi.org/10.1007/s40122-020-00165-5
27. Déciga-Campos, M., Beltrán-Villalobos, K. L., Aguilar-Mariscal, H., González-Trujano, M. E., Ángeles-López, G. E., & Ventura-Martínez, R. (2021). Synergistic Herb-Herb Interaction of the Antinociceptive and Anti-Inflammatory Effects of Syzygium aromaticum and Rosmarinus officinalis Combination. *Evidence-Based Complementary and Alternative Medicine*, *2021*. https://doi.org/10.1155/2021/8916618
28. Dores, A. R., Peixoto, M., Castro, M., Sá, C., Carvalho, I. P., Martins, A., Maia, E.,

Praça, I., & Marques, A. (2023). Knowledge and Beliefs about Herb/Supplement Consumption and Herb/Supplement–Drug Interactions among the General Population, including Healthcare Professionals and Pharmacists: A Systematic Review and Guidelines for a Smart Decision System. In *Nutrients* (Vol. 15, Issue 10). https://doi.org/10.3390/nu15102298

29. Dutra, N. S., da Silva D'Ávila, C. M., da Silva, T. C., de Oliveira Mendes, T., Livinalli, I. C., Bertoncelli, A. C. Z., Saccol, F. K., & Cadoná, F. C. (2024). Biological properties of caffeine, (+)-catechin, and theobromine: an in silico study. *3 Biotech*, *14*(4). https://doi.org/10.1007/s13205-024-03934-7
30. Ekor, M. (2014). The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. In *Frontiers in Neurology: Vol. 4 JAN*. https://doi.org/10.3389/fphar.2013.00177
31. Fajrin, F. A., Nugroho, A. E., Nurrochmad, A., & Susilowati, R. (2020). Ginger extract and its compound, 6-shogaol, attenuates painful diabetic neuropathy in mice via reducing TRPV1 and NMDAR2B expressions in the spinal cord. *Journal of Ethnopharmacology*, *249*. https://doi.org/10.1016/j.jep.2019.112396
32. Fattori, V., Hohmann, M. S. N., Rossaneis, A. C., Pinho-Ribeiro, F. A., & Verri, W. A. (2016). Capsaicin: Current understanding of its mechanisms and therapy of pain and other pre-clinical and clinical uses. In *Molecules* (Vol. 21, Issue 7). https://doi.org/10.3390/molecules21070844
33. Frias, B., & Merighi, A. (2016). Capsaicin, nociception and pain. In *Molecules* (Vol. 21, Issue 6). https://doi.org/10.3390/molecules21060797
34. Grellier, J., White, M. P., Albin, M., Bell, S., Elliott, L. R., Gascón, M., Gualdi, S., Mancini, L., Nieuwenhuijsen, M. J., Sarigiannis, D. A., Van Den Bosch, M., Wolf, T., Wuijts, S., & Fleming, L. E. (2017). BlueHealth: A study programme protocol for mapping and quantifying the potential benefits to public health and well-being from Europe's blue spaces. *BMJ Open*, *7*(6). https://doi.org/10.1136/bmjopen-2017-016188
35. Hall, O. M., Broussard, A., Range, T., Carroll Turpin, M. A., Ellis, S., Lim, V. M., Cornett, E. M., & Kaye, A. D. (2020). Novel Agents in Neuropathic Pain, the Role of Capsaicin: Pharmacology, Efficacy, Side Effects, Different Preparations. *Current Pain and Headache Reports*, *24*(9). https://doi.org/10.1007/s11916-020-00886-4
36. Harrison, A. M., Heritier, F., Childs, B. G., Bostwick, J. M., & Dziadzko, M. A. (2015). Systematic Review of the Use of Phytochemicals for Management of Pain in Cancer Therapy. In *BioMed Research International* (Vol. 2015). https://doi.org/10.1155/2015/506327
37. Hitomi, S., Ono, K., Terawaki, K., Matsumoto, C., Mizuno, K., Yamaguchi, K., Imai, R., Omiya, Y., Hattori, T., Kase, Y., & Inenaga, K. (2017). [6]-gingerol and [6]-shogaol, active ingredients of the traditional Japanese medicine hangeshashinto, relief oral ulcerative mucositis-induced pain via action on Na+ channels. In *Pharmacological Research* (Vol. 117, Issue 16). Elsevier Ltd. https://doi.org/10.1016/j.phrs.2016.12.026
38. Hossain, C. M., Gera, M., & Ali, K. A. (2022). Current Status And Challenges Of Herbal Drug Development And Regulatory Aspect: A Global Perspective. *Asian Journal of Pharmaceutical and Clinical Research*. https://doi.org/10.22159/ajpcr.2022.v15i12.46134
39. Hüseyin, G., Ceren, G. Ö., & Suat, Ö. İ. (2022). Curcumin Enhanced the Anti-proliferative Effect of Cetixumab Through TRPV1 Channels in Human Larynx Cancer Cells. *Egyptian Journal of Ear, Nose, Throat and Allied Sciences*, *23*(23), 1–13. https://doi.org/10.21608/ejentas.2022.111505.1448
40. Iyengar, S., Ossipov, M. H., & Johnson, K. W. (2017). The role of calcitonin gene-related peptide in peripheral and central pain mechanisms including migraine. In *Pain* (Vol. 158, Issue 4). https://doi.org/10.1097/j.pain.0000000000000831
41. Kim, S., Cheon, C., Kim, B., & Kim, W. (2022). The Effect of Ginger and Its Sub-Components on Pain. *Plants*, *11*(17), 1–17. https://doi.org/10.3390/plants11172296
42. Kopustinskiene, D. M., Bernatonyte, U., Maslii, Y., Herbina, N., & Bernatoniene, J.

(2022). Natural Herbal Non-Opioid Topical Pain Relievers—Comparison with Traditional Therapy. *Pharmaceutics*, *14*(12), 1–17. https://doi.org/10.3390/pharmaceutics14122648

43. Lagoa, R., Silva, J., Rodrigues, J. R., & Bishayee, A. (2020). Advances in phytochemical delivery systems for improved anticancer activity. In *Biotechnology Advances* (Vol. 38). https://doi.org/10.1016/j.biotechadv.2019.04.004
44. Li, F., & Wang, F. (2021). TRPV1 in Pain and Itch. In *Advances in Experimental Medicine and Biology* (Vol. 1349). https://doi.org/10.1007/978-981-16-4254-8_12
45. Matsuda, M., Huh, Y., & Ji, R. R. (2019). Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain. In *Journal of Anesthesia* (Vol. 33, Issue 1). https://doi.org/10.1007/s00540-018-2579-4
46. Mazurakova, A., Koklesova, L., Samec, M., Kudela, E., Kajo, K., Skuciova, V., Csizmár, S. H., Mestanova, V., Pec, M., Adamkov, M., Al-Ishaq, R. K., Smejkal, K., Giordano, F. A., Büsselberg, D., Biringer, K., Golubnitschaja, O., & Kubatka, P. (2022). Anti-breast cancer effects of phytochemicals: primary, secondary, and tertiary care. In *EPMA Journal* (Vol. 13, Issue 2). https://doi.org/10.1007/s13167-022-00277-2
47. Munjuluri, S., Wilkerson, D. A., Sooch, G., Chen, X., White, F. A., & Obukhov, A. G. (2022). Capsaicin and TRPV1 channels in the cardiovascular system: The role of inflammation. *Cells*, *11*(1), 1–21. https://doi.org/10.3390/cells11010018
48. Naik, G. G., Uniyal, A., Chouhan, D., Tiwari, V., & Sahu, A. N. (2021). Natural Products and some Semi-synthetic Analogues as Potential TRPV1 Ligands for Attenuating Neuropathic Pain. *Current Pharmaceutical Biotechnology*, *23*(6). https://doi.org/10.2174/1389201022666210719155931
49. Nalli, M., Ortar, G., Schiano Moriello, A., Di Marzo, V., & De Petrocellis, L. (2017). Effects of curcumin and curcumin analogues on TRP channels. *Fitoterapia*, *122*(September), 126–131. https://doi.org/10.1016/j.fitote.2017.09.007
50. Oliveira, P. de A., de Almeida, T. B., de Oliveira, R. G., Gonçalves, G. M., de Oliveira, J. M., Alves dos Santos, B. B., Laureano-Melo, R., Côrtes, W. da S., França, T. do N., Vasconcellos, M. L. A. de A., & Marinho, B. G. (2018). Evaluation of the antinociceptive and anti-inflammatory activities of piperic acid: Involvement of the cholinergic and vanilloid systems. *European Journal of Pharmacology*, *834*(July), 54–64. https://doi.org/10.1016/j.ejphar.2018.07.022
51. Pagano, E., Souto, E. B., Durazzo, A., Sharifi-Rad, J., Lucarini, M., Souto, S. B., Salehi, B., Zam, W., Montanaro, V., Lucariello, G., Izzo, A. A., Santini, A., & Romano, B. (2021). Ginger (Zingiber officinale Roscoe) as a nutraceutical: Focus on the metabolic, analgesic, and antiinflammatory effects. *Phytotherapy Research*, *35*(5), 2403–2417. https://doi.org/10.1002/ptr.6964
52. Panthong, S., Imai, Y., Matsuoka, T., Suzuki, W., Watanabe, T., Terada, Y., Kurohane, K., Sekiguchi, K., Ogawa, E., Endo, Y., & Itharat, A. (2020). The role of Piper chaba Hunt. and its pure compound, piperine, on TRPV1 activation and adjuvant effect. *BMC Complementary Medicine and Therapies*, *20*(1), 1–9. https://doi.org/10.1186/s12906-020-02917-4
53. Peng, S., Li, J., Huo, M., Cao, Y., Chen, Z., Zhang, Y., & Qiao, Y. (2022). Identification of the material basis of the medicinal properties in Curcuma Longa L. to enhance targeted clinical application. *Journal of Traditional Chinese Medical Sciences*, *9*(4), 374–382. https://doi.org/10.1016/j.jtcms.2022.07.001
54. Pergolizzi, J. V., Magnusson, P., LeQuang, J. A., Breve, F., Taylor, R., Wollmuth, C., & Varrassi, G. (2021). Can NSAIDs and Acetaminophen Effectively Replace Opioid Treatment Options for Acute Pain? *Expert Opinion on Pharmacotherapy*, *22*(9). https://doi.org/10.1080/14656566.2021.1901885
55. Premkumar, L. S. (2014). Transient receptor potential channels as targets for phytochemicals. In *ACS Chemical Neuroscience* (Vol. 5, Issue 11). https://doi.org/10.1021/cn500094a
56. Qu, Y., Fu, Y., Liu, Y., Liu, C., Xu, B., Zhang, Q., & Jiang, P. (2023). The role of

TRPV1 in RA pathogenesis: worthy of attention. In *Frontiers in Immunology* (Vol. 14). https://doi.org/10.3389/fimmu.2023.1232013

57. Sá, M. C. I. de, & Castor, M. G. M. (2023). Therapeutic Use of Palmitoylethanolamide as an Anti-Inflammatory and Immunomodulator. *Future Pharmacology*, *3*(4), 951–978. https://doi.org/10.3390/futurepharmacol3040058
58. Sánchez-Trujillo, L. A., Mendoza-Monroy, J. L., Rocha-González, H. I., Quiñonez-Bastidas, G. N., Balderas-López, J. L., & Navarrete, A. (2020). Antiallodynic Effect of Piperine in Neuropathic Rats. *Revista Brasileira de Farmacognosia*, *30*(4), 482–487. https://doi.org/10.1007/s43450-020-00047-z
59. Shah, S., Carver, C. M., Mullen, P., Milne, S., Lukacs, V., Shapiro, M. S., & Gamper, N. (2020). Local Ca2+ signals couple activation of TRPV1 and ANO1 sensory ion channels. *Science Signaling*, *13*(629). https://doi.org/10.1126/scisignal.aaw7963
60. Sultana, A., Singla, R. K., He, X., Sun, Y., Alam, M. S., & Shen, B. (2020). Topical Capsaicin for the Treatment of Neuropathic Pain. *Current Drug Metabolism*, *22*(3). https://doi.org/10.2174/1389200221999201116143701
61. Sun, J., Chen, F., Braun, C., Zhou, Y. Q., Rittner, H., Tian, Y. K., Cai, X. Y., & Ye, D. W. (2018). Role of curcumin in the management of pathological pain. In *Phytomedicine* (Vol. 48). Elsevier GmbH. https://doi.org/10.1016/j.phymed.2018.04.045
62. Takahashi, K., Yoshida, T., & Wakamori, M. (2021). Mode-selective inhibitory effects of eugenol on the mouse TRPV1 channel. *Biochemical and Biophysical Research Communications*, *556*. https://doi.org/10.1016/j.bbrc.2021.03.126
63. Toledo-Mauriño, J. J., Furuzawa-Carballeda, J., Villeda-Ramírez, M. A., Fonseca-Camarillo, G., Meza-Guillen, D., Barreto-Zúñiga, R., & Yamamoto-Furusho, J. K. (2018). The transient receptor potential vanilloid 1 is associated with active inflammation in ulcerative colitis. *Mediators of Inflammation*, *2018*. https://doi.org/10.1155/2018/6570371
64. Usman, M., Khan, W. R., Yousaf, N., Akram, S., Murtaza, G., Kudus, K. A., Ditta, A., Rosli, Z., Rajpar, M. N., & Nazre, M. (2022). Exploring the Phytochemicals and Anti-Cancer Potential of the Members of Fabaceae Family: A Comprehensive Review. In *Molecules* (Vol. 27, Issue 12). https://doi.org/10.3390/molecules27123863
65. Wang, G. (2021). Lipid-dependent sequential allosteric activation of heat-sensing TRPV1 channels by anchor-stereoselective "hot" vanilloid compounds and analogs. *Biochemistry and Biophysics Reports*, *28*(September), 101109. https://doi.org/10.1016/j.bbrep.2021.101109
66. Wu, Q., Bai, P., Xia, Y., Xia, Y., Xu, B., Dai, K., Zheng, Z., Guo, M. S. S., Fung, K. W. C., Dong, T. T. X., & Tsim, K. W. K. (2020). Capsaicin Inhibits the Expression of Melanogenic Proteins in Melanocyte via Activation of TRPV1 Channel: Identifying an Inhibitor of Skin Melanogenesis. *Journal of Agricultural and Food Chemistry*, *68*(50), 14863–14873. https://doi.org/10.1021/acs.jafc.0c06321
67. Yang, F., & Zheng, J. (2017). Understand spiciness: mechanism of TRPV1 channel activation by capsaicin. *Protein and Cell*, *8*(3), 169–177. https://doi.org/10.1007/s13238-016-0353-7
68. Yang, J., Hsieh, C. L., & Lin, Y. W. (2017). Role of Transient Receptor Potential Vanilloid 1 in Electroacupuncture Analgesia on Chronic Inflammatory Pain in Mice. *BioMed Research International*, *2017*. https://doi.org/10.1155/2017/5068347
69. Yang, M., Wang, J., Yang, C., Han, H., Rong, W., & Zhang, G. (2017). Oral administration of curcumin attenuates visceral hyperalgesia through inhibiting phosphorylation of TRPV1 in rat model of ulcerative colitis. *Molecular Pain*, *13*, 1–11. https://doi.org/10.1177/1744806917726416
70. Ye, H., Lin, Q., Mei, Q., Liu, Q., & Cao, S. (2024). Study on mechanism of transdermal administration of eugenol for pain treatment by network pharmacology and molecular docking technology. *Heliyon*, *10*(8), e29722. https://doi.org/10.1016/j.heliyon.2024.e29722
71. Yin, Y., Dong, Y., Vu, S., Yang, F., Yarov-Yarovoy, V., Tian, Y., & Zheng, J. (2019).

Structural mechanisms underlying activation of TRPV1 channels by pungent compounds in gingers. *British Journal of Pharmacology*, *176*(17), 3364–3377. https://doi.org/10.1111/bph.14766

72. Zhang, D., Sun, X., Battino, M., Wei, X., Shi, J., Zhao, L., Liu, S., Xiao, J., Shi, B., & Zou, X. (2021). A comparative overview on chili pepper (capsicum genus) and sichuan pepper (zanthoxylum genus): From pungent spices to pharma-foods. *Trends in Food Science and Technology*, *117*(February), 148–162. https://doi.org/10.1016/j.tifs.2021.03.004
73. Zhu, F., Du, B., & Xu, B. (2018). Anti-inflammatory effects of phytochemicals from fruits, vegetables, and food legumes: A review. *Critical Reviews in Food Science and Nutrition*, *58*(8). https://doi.org/10.1080/10408398.2016.1251390

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