applied sciences

MDPI

Article

Diathermic Evaluation of Sustained Acoustic Medicine with Cannabidiol Coupling Gel

Ethan Bates [1,*], Makayla Cress [1], Rowan Paul [2] and Steven Sampson [3]

[1] Department of Biomedical Engineering, University of Cincinnati, Cincinnati, OH 45221, USA; cressml@mail.uc.edu
[2] Geisel School of Medicine, Dartmouth College, Hanover, NH 03755, USA; rowan_paul@alumni.brown.edu
[3] David Geffen School of Medicine, UCLA, Los Angeles, CA 90095, USA; drsampson@orthohealing.com
* Correspondence: ethanbates.samresearch@gmail.com

Featured Application

Sustained Acoustic Medicine (SAM) is an FDA-approved wearable long duration ultrasound device that is clinically effective at treating musculoskeletal injuries by delivering multi-hour, deep therapeutic heat, increasing local blood flow and promoting nutrient exchange though acoustic streaming. Cannabidiol (CBD) is a non-psychoactive small molecule that reduces inflammation and alleviates pain. This study shows that commercially available gel containing CBD can be used with SAM without reducing SAM's ultrasonic delivery or diathermic efficacy in deep musculoskeletal tissue. One potential clinical application of this approach is for enhancing CBD delivery to muscular tissue and tendons where it typically cannot easily penetrate due to its lipophilic nature.

Abstract

Musculoskeletal (MSK) pain is a prevalent clinical condition that significantly impairs quality of life, and current treatment options are not effective on all patients or have severe, long-term side effects. Sustained Acoustic Medicine (SAM) delivers therapeutic ultrasound, providing diathermic and mechanical stimulation to local tissue and facilitating healing. Additionally, therapeutic ultrasound has been shown to enhance transdermal drug delivery via sonophoresis. Cannabidiol (CBD) is a small molecule that has been shown to have anti-inflammatory effects drug delivery. However, CBD has never been studied in conjunction with therapeutic ultrasound, and its potential effects on ultrasound efficacy are unknown. Therefore, this study compares standard high viscosity ultrasound (US) gel and commercially available CBD gel both in terms of acoustic properties and in an ex vivo bovine muscle model with SAM treatment. The acoustic properties of CBD & US gels were measured using a hydrophone, an oscilloscope and a function generator. The function generator propagated a pulsed wave through each gel, and the time between the original and reflected waves was used to determine the acoustic coefficients. Then, a SAM transducer was positioned and placed into the coupling bandage and gel depot on the bovine muscle with 3 mL of US gel or CBD gel. Tissue was stimulated by SAM for 240 min with a 60-min cooldown, and internal muscle temperatures at 1 cm, 2 cm, and 5 cm were continuously monitored. US gel and CBD had no significant differences in their acoustic properties. There were no significant differences in the change in temperature for SAM treatment with CBD gel compared to SAM treatment with US gel at 1 cm ($\Delta 12.06 \pm 1.04$ °C vs. $\Delta 12.52 \pm 1.84$ °C, $p > 0.05$), 2 cm ($\Delta 8.13 \pm 1.01$ °C vs. $\Delta 8.97 \pm 1.04$ °C, $p > 0.05$), and 5 cm ($\Delta 4.83 \pm 0.91$ °C vs. $\Delta 3.83 \pm 0.66$ °C, $p > 0.05$). CBD gel does not compromise SAM's ultrasonic delivery and diathermic efficacy, making this combination a novel option for

Check for updates

Academic Editor: Vladislav Toronov

Received: 18 March 2026
Revised: 30 April 2026
Accepted: 2 May 2026
Published: 5 May 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

musculoskeletal rehabilitation. Future studies could explore changes in transdermal CBD delivery with SAM treatment for deep tissue delivery.

Keywords: Diathermic effects; Long duration ultrasound; Cannabidiol; Musculoskeletal pain; Sustained Acoustic Medicine; Transdermal Drug Delivery

1. Introduction

Despite significant advances in medical diagnostics and treatments, musculoskeletal (MSK) disorders and associated pain remain significant clinical challenges. These disorders, associated with inflammation, pain, tissue degradation, and neuromuscular disruption, include traumatic and degenerative pathologies with significant socioeconomic costs, and only an estimated 20% of costs are attributed to medical and related costs [1–3]. MSK disorder prevalence is projected to increase by 115% to an estimated 1 billion people worldwide by 2050 [4]. MSK-associated pain is a crucial aspect of these disorders that can affect bones, muscles, tendons, ligaments, and nerves and accounts for nearly 14% of disability-years lost worldwide [3].

Clinically, MSK pain is managed using a variety of treatment options. The first round of treatment options involves non-invasive, non-pharmaceutical options including rest, physical therapy, bracing, and rehabilitation. These treatments are often effective in the short-term and may even completely heal some patients, but for many patients they only provide temporary relief as their pain becomes more severe [5]. The next round of treatment options typically involves either pharmacological interventions, including nonsteroidal anti-inflammatory drugs (NSAIDS) and opioids, or more invasive techniques such as steroid injection, viscosupplementation, and surgery. While NSAIDs are clinically effective and some consider them to be a first-line therapy [6], their long term application has systemic adverse effects on the liver, kidney, and organs in the gastrointestinal system [7–10]. One of the main risk factors for GI complications due to NSAID use is age, which significantly hampers its usage on a geriatric population that is already suffering from MSK disorders at an increased rate [11].

Opioids are often an even worse treatment option for pain than other pharmaceutical options. Because opioids are very effective at reducing pain, excessive opioid use leading to patient addiction is very common. One systematic review suggest that the total societal cost of opioids to the United States has exceeded USD 50 billion per year [12]. Elevated nonmedical usage of opioids is also associated with serious adverse events and death, and it is widely recommended that chronic usage of opioids be closely monitored by physicians and other healthcare providers [13]. Chronic MSK pain leading to tissue damage often requires treatment with invasive procedures such as steroid injection, viscosupplemention, and surgery. Unfortunately, these treatment options also have long-term adverse effects, including infections, localized pain, and significant reduction in motion [5,14]. Finally, topical drugs provide a more targeted approach than injections, with overall reduced systemic adverse effects; however, efficacy is usually limited by the difficulty of crossing the skin barrier [15,16]. Drug penetration is affected by a variety of factors, including the site of application, local availability/depot of the drug, the drug formulation, and the specific properties of the active small molecule [17].

Cannabidiol (CBD) is a non-psychoactive, lipophilic small molecule derived from cannabis sativa that is Food and Drug Administration (FDA)-approved in the United States for the treatment of seizures [18]. One group of receptors that can be targeted by CBD is the size transient receptor potential (TRP) cation channel, which includes TRP V1

(Vanilloid 1), TRP V2, TRP V4, TRP V5, TRP A1 (Ankyrin 1), and TRP M8 (Mucolipin 8); through modulating the activity of these receptors, CBD has an analgesic effect and is involved in regulating inflammatory hyperalgesia [18,19]. CBD inhibits pro-inflammatory pathways, including NF-κB, TNFα, IL-1β, IL-6, IL-12p40, and COX-2 [18,20–23]. CBD has also been shown to improve cell proliferation and migration in bone marrow-derived and adipose-derived stem cells [24], has reduced fibrosis activity by downregulating lipid peroxidation and ROS production [18], and has demonstrated immunosuppressive effects on immune cells and cytokines [22,25,26]. CBD's lipophilic nature and small structure allow it to penetrate deeply into highly vascularized tissues like the heart, brain, liver, and spleen, but it is much slower to enter ligaments and tendons which play a large role in MSK disorders [18]. There remains a need for a method to enhance transdermal delivery of CBD before it can be considered an effective treatment option for MSK pain.

Therapeutic ultrasound is a treatment method in which ultrasonic waves provide mechanical and thermal stimuli to local tissue [27–31]. The increases in temperature, cellular migration, and biomolecular activity enhance circulation, vasodilation, oxygenation, and nutrient exchange, boosting cellular metabolism and tissue regeneration [28,32]. During treatment, consistent and sustained heat penetrates deep into connective tissue and muscles, and mechanical motion loosens the fibrous extracellular matrix, modulating cellular and molecular activity with little to no adverse effects on the tissue itself [33–37]. Therapeutic ultrasound is non-invasive, non-ionizing, and has an independent mechanism of action from any concurrent pharmacological treatments, which makes ultrasound an attractive treatment option for healthcare providers to consider.

One interesting property of ultrasound therapy is sonophoresis, an increase in drug adsorption through the skin with concurrent ultrasound application. It is well-established that elevated local temperature and mechanical impetus increase skin porosity, facilitating transdermal drug delivery of small molecules and biologics through sonophoresis [36–40]. This allows for the enhanced delivery of drugs that typically have difficulty crossing the skin barrier, including diclofenac, a lipophilic small molecule with a similar molecular weight to CBD [40]. The ability to administer ultrasound and drug conjointly together over long periods of time is a powerful multi-modal and targeted approach to pain management and rehabilitation medicine. However, CBD delivery in conjunction with therapeutic ultrasound has never been studied, both in terms of enhanced delivery and in terms of synergistic effects.

Sustained acoustic medicine (SAM) is an effective wearable therapeutic ultrasound device for treating MSK injuries that has been approved by the United States FDA since 2013, with expanded FDA approvals for patient home-use in 2020 and for the treatment of knee osteoarthritis in 2023 [36,38,40,41]. In 2025, SAM treatment was the first non-pharmaceutical treatment approved by the USA Arthritis Foundation for ease-of-use and application for patients with chronic arthritis pain [42]. SAM provides long-duration continuous high-frequency ultrasound with two divergent beams at a total power of 1.3 W for 4 h, providing 18,000 joules of energy over the duration of the treatment [38,40,43]. SAM has been shown to be clinically effective in treating various MSK disorders in numerous studies, including myofascial pain, rotator cuff tendinopathy, knee osteoarthritis, and upper shoulder and neck pain [44–46]. Recent studies by Hendren et al. and Madzia et al. have demonstrated the diathermic and targeted drug delivery capabilities of SAM therapy for chronic joint pain with diclofenac sodium gel acting as an ultrasound and drug compiling depot over a 4 h treatment [38,47]. Jarit et al. also demonstrated the clinical efficacy of SAM therapy with 4 h of topical diclofenac gel used as a coupling depot in the patch reducing pain by over 4.4 points in 135 patients who failed to response to physical therapy alone [37]. SAM therapy is clinically demonstrated to reduce pain, improve joint function,

improve overall health quality scores, improve net health outcomes and be cost-effective for the healthcare system [38,45,48]. However, no studies have been conducted using SAM in conjunction with any CBD products. Developing a combination therapy that is non-invasive and non-addictive would be of significant interest to healthcare providers given the dearth of such options available clinically in the present. Therefore, the objective of this study is to determine the ultrasonic properties of a commercially available CBD gel and to test its diathermic effect with the SAM device in an ex vivo model.

2. Materials and Methods

Instrumentation & Materials: CBD gel (CBMD® PMT Pain Support CBD Topical Cream, CBMD, Irvine, CA, USA) is a topical agent with more than 20% CBD and less than 0.3% tetrahydrocannabinol (THC) available over the counter. The SAM device (model SAM-12, ZetrOZ Systems LLC., Trumbull, CT, USA) consists of a pair of small rechargeable transducer heads that clip onto an adhesive patch along with a controller. The SAM device produces a 3 MHz ultrasound wave with 0.65 W per transducer. High-viscosity US coupling gel (Aquasonic® 100 Ultrasound Transmission Gel, Parker Laboratories, Fairfield, NJ, USA), referred to as US gel hereafter, is widely used with ultrasound devices.

Acoustic Property Measurements. We first connected one piezoelectric disk used in the SAM transducer head to a function generator (AFG3021B, Tektronix, Beaverton, OR, USA), which was directly connected to a digital phosphor oscilloscope (DPO2014, Tektronix, Beaverton, OR, USA). The densities of US and CBD gel were determined using a digital scale and a syringe. We then connected a hydrophone (HNR-1000, Onda Corporation, Sunnyvale, CA, USA) to the oscilloscope and placed it on a ring stand. The piezoelectric disk was placed flat on the ring stand so that its voltage could be measured using the hydrophone. Then, we placed US gel or CBD gel above the piezoelectric disk to the height of a standardized object (d) measured with digital calipers, typically between 5 mm and 10 mm. The hydrophone was carefully lowered into the gel so that it was slightly below the gel's top surface (Figure 1a). The function generator was set to generate a pulsed sinusoidal wave with 3 MHz frequency, 0° phase, 7.4 V amplitude, 1 ms between pulses, and 5 cycles per waveform. The oscilloscope was set to use DC coupling mode, a bandwidth of 20 MHz, and a scale of 10× the probe voltage.

Once the experiment was initiated, the oscilloscope detected the initial wave directly from the function generator as well as the reflected wave transmitted through the gel to the hydrophone. Because the wave traveling through the gel is impeded by the medium it needs to travel through, it arrives later than the initial wave. The height of the initial wave (h_0), difference in time between the reflected wave and the initial wave (t) and the height of the reflected wave (h_1) were recorded from the oscilloscope. These values were used to calculate the acoustic impedance, the ability of a material to resist the propagation of sound waves, and the attenuation coefficient, the rate at which sound waves decrease in intensity as they travel through a material, for each gel. Acoustic impedance was calculated using the formula:

$$Z = \frac{\rho d}{t} \quad (1)$$

where Z is the acoustic impedance, ρ is the density of the gel, d is the height of the gel, and t is the time difference recorded from the oscilloscope. The values were also used to calculate the attenuation coefficient using the formula:

$$\alpha = \frac{20}{df} \log_{10} \frac{h_0}{h_1} \quad (2)$$

where α is the attenuation coefficient, d is the height of the gel, f is the testing frequency of 3 MHz, and h_0 and h_1 are the amplitudes of the initial wave and reflected wave, respectively. One run was the average of 64 readings on the oscilloscope, and three or four runs were conducted per treatment condition (n = 3–4 per treatment).

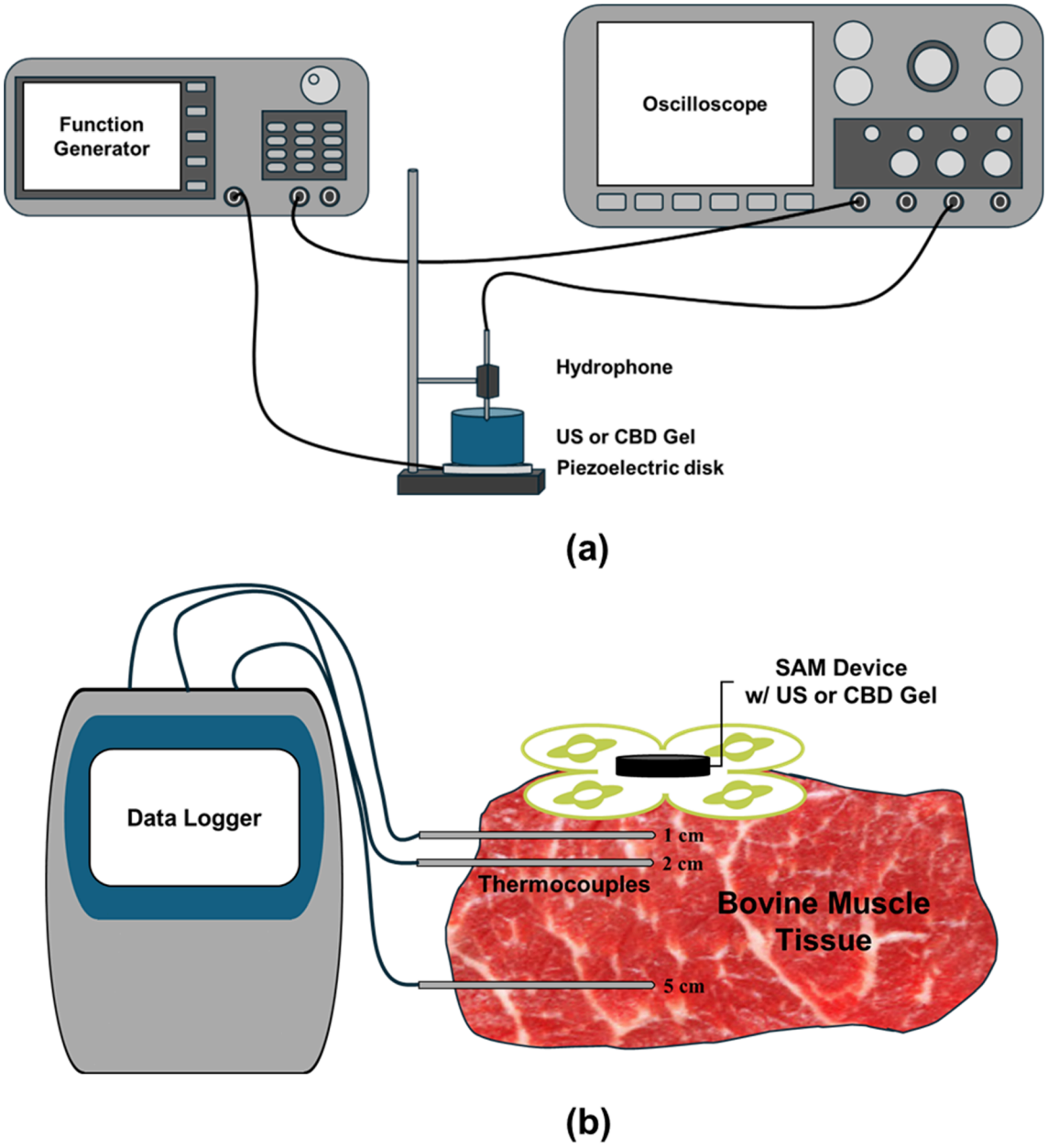

Figure 1. Experimental setups for (**a**) acoustic property testing and (**b**) bovine muscle diathermy testing.

Bovine Diathermy Measurements: We procured bovine muscle tissue, weighing approximately 800 g ± 200 g, from a local butcher and trimmed it using a scalpel, removing any excess fat or nonhomogeneous areas and cutting it to a roughly rectangular shape. The same cut of bovine muscle was used for all experiments, and the tissue was maintained under refrigeration and never frozen prior to use to minimize changes in material properties. The tissue was then wrapped and secured with plastic wrap to ensure it maintained its shape over the course of the experiment. The wrapped bovine tissue rested at room temperature overnight for approximately 16 h to equilibrate to room temperature and pressure. Then, we cut a small hole into the plastic wrap and applied 3 mL of ultrasound

(US) coupling gel or CBD gel to the tissue surface. The gel was then secured with SAM coupling devices to prevent lateral leakage. We positioned and placed a single SAM transducer into the coupling bandage on the bovine muscle. Stainless steel thermocouple probes (TJ36-ICSS-116G-6-GG, Omega Engineering, Thief River Falls, MN, USA) were inserted with stereotactic guidance 2.5 inches into the bovine muscle tissue directly beneath the center of the transducer at depths of 1 cm, 2 cm, and 5 cm (Figure 1b). The probes were securely held using a custom structure. Once the device and the probes were securely in place, we activated the SAM device.

Internal temperatures were continuously monitored using thermocouple probes, and data was recorded on a DAQPRO Data Logger (OM-DAQPRO-5300, Omega Engineering, Thief River Falls, MN, USA). During an initial heating period of approximately 5 min, we minimally adjusted the thermocouple probes horizontally to ensure proper and maximal temperature detection was occurring. SAM devices stimulated the tissue for a typical treatment duration of four hours, after which the tissue was allowed to cool down for an additional hour. The logger collected thermocouple K values every ten seconds throughout this procedure. At the end of the five-hour period, we stopped the data logger and downloaded the collected data to a computer via DAQLAB software (v1.40.01) for analysis and graphing. The experimental setup was repeated with US gel and CBD gel (n = 6 per treatment).

Statistical Analysis: Data are reported as mean ± SD. Equivalence between treatments was assessed by two one-sided tests (TOSTs) to determine the correct sample size for the study using an equivalence margin of 1.3 °C, 10% of the maximum difference typically seen at a 1 cm tissue depth, and an α of 0.05. We determined that n = 6 would be more than adequate to find any significant differences between the two treatment groups. The acoustic impedance and attenuation data were compared for each gel by Student's *t*-test. The temperature data were converted to Celsius and compared across depth and across treatment at each timepoint by two-way ANOVA with Tukey's HSD post hoc testing using GraphPad Prism 10.

3. Results

The CBD gel had approximately the same density as the US gel (1020 vs. 1044 kg/m^3). When examining their acoustic properties, there were no significant differences in acoustic impedance (1.4 ± 0.017 vs. 1.4 ± 0.040 MRayls, $p > 0.05$) or attenuation coefficients (1.95 ± 0.20 vs. 1.14 ± 0.62, $p > 0.05$ dB/cm/MHz) between these two gels (Figure 2).

The diathermic analysis in the bovine tissue showed a distinct diathermic profile at each intramuscular depth. The highest temperature increase and change rate was recorded closest to the transducer surface, at a depth of 1 cm (Figure 3). In the US gel group, temperature increased from a baseline of 19.05 ± 0.54 °C and peaked at approximately 31.42 ± 2.00 °C ($p < 0.0001$) after 240 min of treatment at a depth of 1 cm. In contrast, the temperature of the bovine tissue rose from 19.13 ± 0.54 °C to 23.83 ± 0.87 °C at a depth of 5 cm, a change of Δ4.70 ± 1.08 °C compared to Δ12.31 ± 2.87 °C at 5 cm (Figure 3). The highest rate of temperature change was recorded in the first 60 min of stimulation, from 19.05 ± 0.54 °C to 28.08 ± 1.47 °C, with a relatively gradual change over the next 180 min up to 31.3 ± 2.00 °C. At the conclusion of SAM therapy, heat loss and bulk tissue equalization were observed in the next 60 min, with the temperature equilibrating to between 23.58 ± 0.94 °C and 23.01 ± 0.91 °C depending on the depth (Figure 3a). Even one hour after treatment, the tissue temperature was still significantly higher than baseline at all measured tissue depths ($p < 0.001$–$p < 0.0001$).

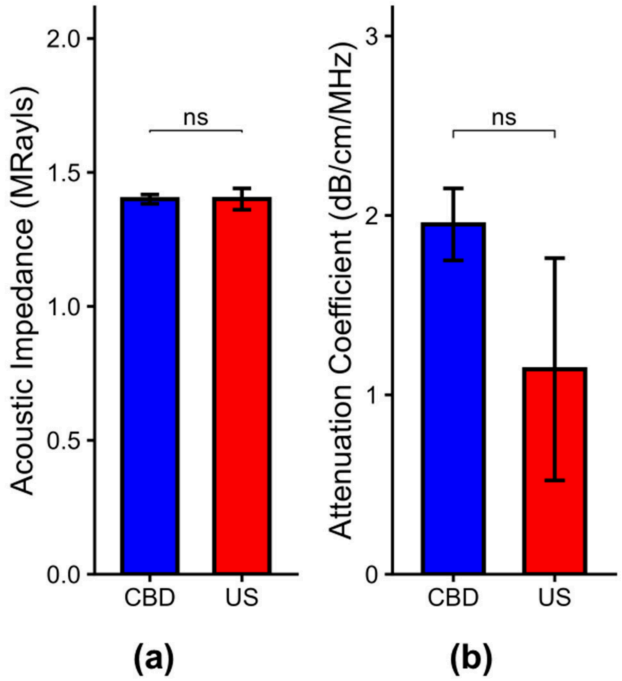

Figure 2. (**a**) Acoustic impedance and (**b**) attenuation coefficient of US and CBD gels measured by oscilloscope.

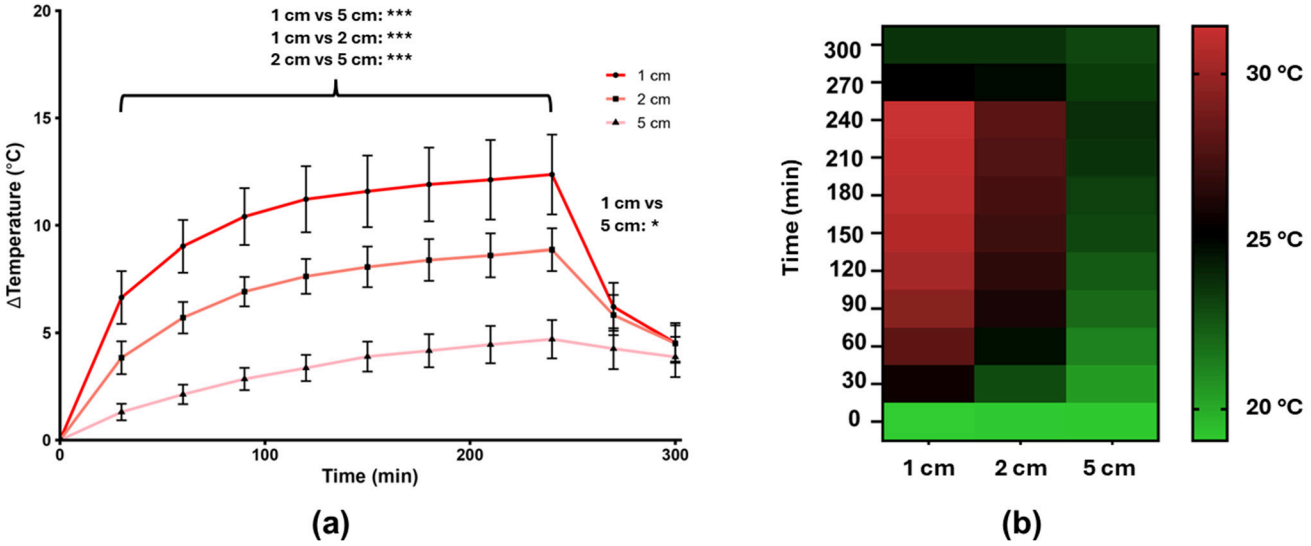

Figure 3. Diathermic profile of SAM treatment with US gel. (**a**) Temperature changes at 1 cm, 2 cm, and 5 cm depths in bovine tissue using US gel. (**b**) Heatmap showing average temperatures at 1 cm, 2 cm, and 5 cm depth in bovine tissue with SAM and US gel treatment. n = 6, * $p < 0.05$, *** $p < 0.0001$.

A similar pattern of temperature change and equilibration was observed with the CBD gel group, with the highest change at a depth of 1 cm, 19.19 ± 0.75 °C to 31.09 ± 1.02 °C (Δ11.90 ± 1.77 °C), and the lowest change at a depth of 5 cm, 19.14 ± 0.84 °C to 22.68 ± 0.23 °C, (Δ3.54 ± 1.07 °C) (Figure 4). In both groups, the rate of thermal change decreased after one hour of treatment but remained significantly higher than the baseline temperature (Figures 3 and 4). Comparatively, both US gel and CBD gel followed a similar diathermic profile. At all three tissue depths, there were no statistically significant differences between both groups (Figure 5).

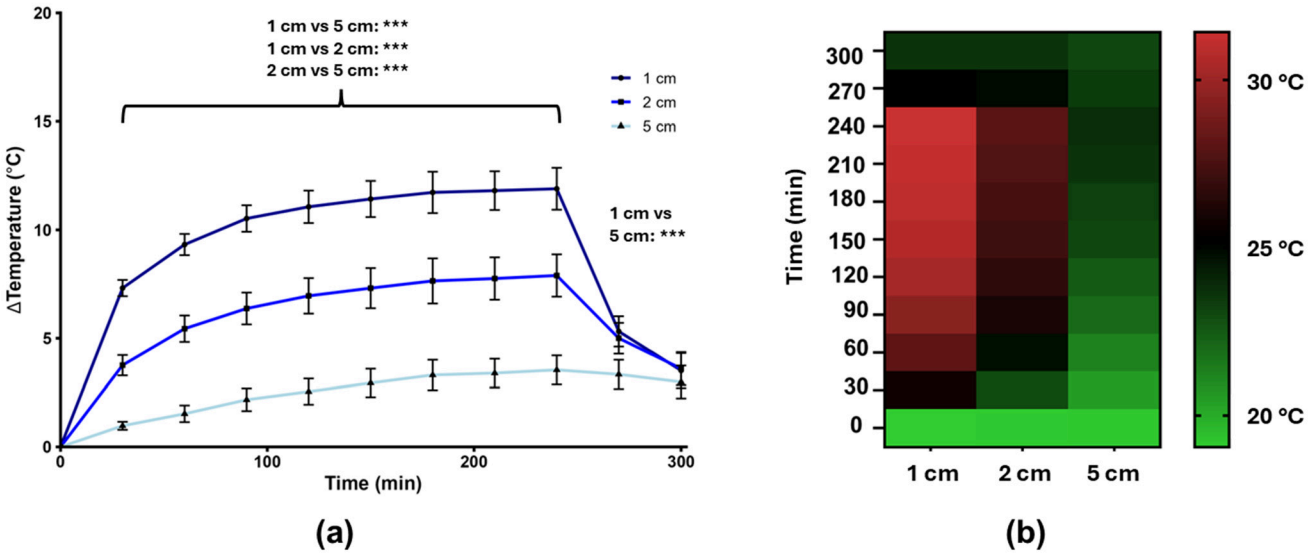

Figure 4. Diathermic profile of SAM treatment with CBD gel. (**a**) Temperature changes at 1 cm, 2 cm, and 5 cm depths in bovine tissue using CBD gel. (**b**) Heatmap showing average temperatures in bovine tissue at 1 cm, 2 cm, and 5 cm depths with SAM and CBD gel treatment. n = 6, *** $p < 0.0001$.

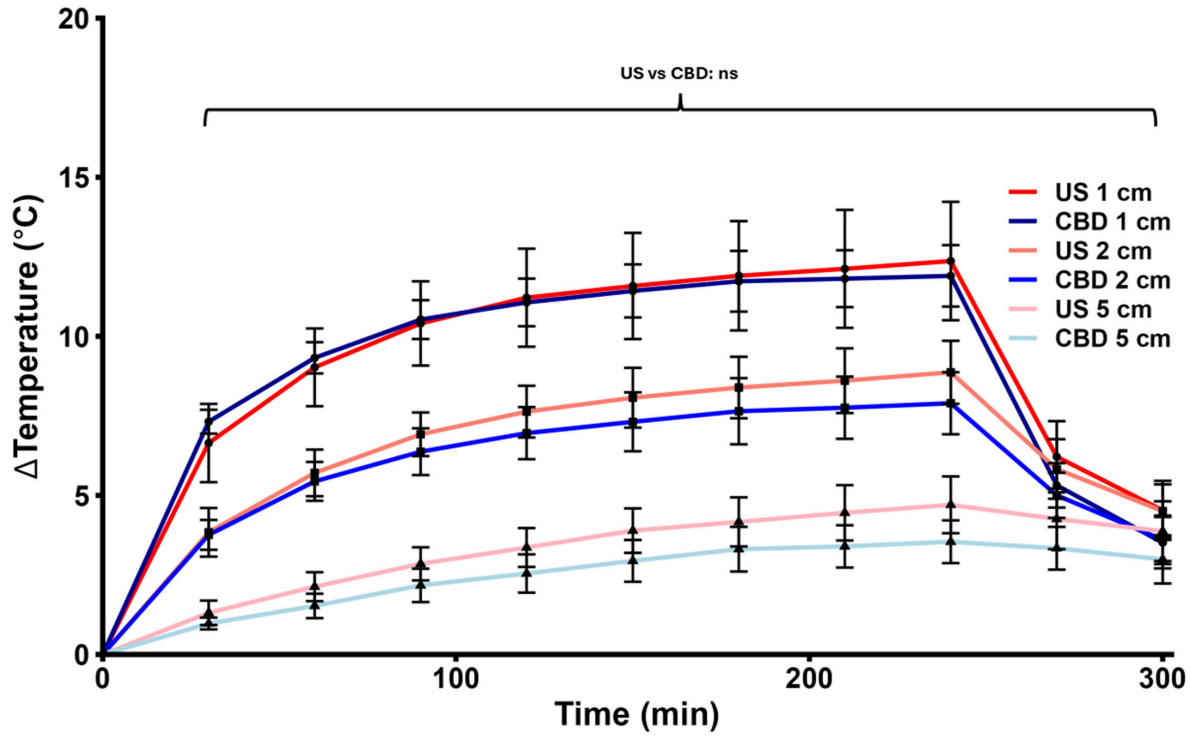

Figure 5. Comparison of diathermic profiles for SAM device with US gel and CBD gel at 1 cm, 2 cm, and 5 cm depths in bovine tissue. n = 6, ns not significant ($p > 0.05$).

4. Discussion

MSK disorders and their associated pain present a significant clinical challenge, and they are only increasing in prevalence over time [1]. Current treatment options for MSK pain have significant drawbacks, including long-term adverse effects, increased health costs, patient addiction, and in the case of surgical intervention, increased likelihood of revision surgery being required [7,11,49]. Recent advancements in the efficacy of CBD in treating MSK conditions offer a promising alternative therapy by inhibiting inflammatory pathways and reducing pain [21–23,25,26]. Studies have shown that CBD interacts with TRPV, 5HTC,

and PPAR receptors, which regulate multiple inflammatory pathways, including NF-κB, TNF α, IL-1β, IL-6, IL-12p40, and COX-2 [18,22,25,26]. However, CBD's lipophilic nature significantly limits its bioavailability in tissue with limited vascularization, and limited skin porosity hinders transdermal delivery methods [18].

Sonophoresis, which utilizes ultrasound's thermal and mechanical properties, can enhance transdermal drug delivery by increasing skin porosity [40,50,51]. Masterson et al. demonstrated that SAM establishes a diathermic profile and enhances transdermal delivery of diclofenac sodium through skin analogs, increasing total flux more than three-fold over diffusion alone [40]. Hendren et al. further showed that 3 MHz continuous SAM maintains its intensity and effectiveness up to 5 cm deep into tissue in human subjects [47]. Jarit et al. administered SAM and diclofenac treatment to 135 patients who failed conservative MSK treatment and found SAM a viable treatment option to reduce pain improve function, and enhance quality of life [37]. Walters et al., in a 2025 review of long duration sonophoresis in sports medicine applications, found that SAM therapy provides multi-modal thermal and mechanical stimuli to enhance drug delivery and activation of agents in biological tissue [52].

Expanding on this research, this study shows that a similar diathermic profile can be achieved using commercially available CBD gel as a SAM ultrasound gel alternative. Based on our results, there was no significant difference in acoustic properties between CBD gel and US gel, even though the CBD gel was not specifically designed while taking into consideration its potential use with SAM ultrasound devices. The primary factor that influences the suitability of a gel for ultrasound applications is its effect on the ultrasound waves propagating through it. A gel that dissipates ultrasound waves too quickly or scatters the waves due to its nonhomogeneity would reduce the amount of ultrasound energy being applied to the targeted tissue. Since we were unable to detect any significant difference in acoustic impedance or attenuation coefficient between the US gel and the CBD gel, it would make sense that their diathermic profiles would be similar. Therefore, it is not surprising that there was no significant difference in diathermic profile between CBD gel and US with SAM treatment. The increases in temperature seen in this study are comparable to previous studies examining diathermy with a bovine muscle tissue model; Hendren et al. saw maximum temperature changes of approximately 14.68 °C at 1 cm and approximately 4.20 °C at 5 cm, while Masterson et al. noted a temperature increase of approximately 8 °C at 1 cm and approximately 2 °C at 5 cm [40,47]. SAM treatment, when used in conjunction with CBD, also retained a significantly higher temperature 60 min post-treatment, which could enhance blood flow and cellular and tissue regeneration beyond the treatment duration.

The key limitations of this study are the utilization of an ex vivo model. Since the bovine muscle tissue used here did not have a skin barrier or functional vasculature, it may not completely model thermal changes in human tissue with SAM treatment. Different tissues can have different acoustic properties, and it is established that skin attenuates ultrasound waves more rapidly than muscle [53]. In addition to this, active blood flow can account for a significant portion of heat dissipation in tissue [54]; the measured treatment temperatures seen in this study could be elevated compared to patient use. Therefore, future studies could examine the diathermic functionality of SAM with CBD gel in a mechanical, vascularized model with active blood flow and a skin-like barrier. Additionally, future studies with small-molecule modeling could explore how delivery of CBD is enhanced with the addition of SAM and whether there is any synergistic effect when both therapies are applied together. Finally, given that this study shows that an unconventional drug-containing gel can act as an effective coupling gel with therapeutic ultrasound devices,

researchers could also explore other gels containing a variety of different active components that could benefit from enhanced delivery through sonophoresis for multiple hours.

5. Conclusions

Our findings indicate that the CBD gel applied in this study can effectively be used as an ultrasound gel alternative without compromising deep tissue ultrasonic delivery and the diathermic profile generated during SAM treatment. Therefore, commercially available CBD gel is a safe and effective alternate coupling gel for SAM that has the potential to enhance pain relief for patients with MSK disorders through combined thermal therapy and targeted CBD delivery.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app16094544/s1, Table S1: Raw Data for Acoustic Properties Experiments; Table S2: Raw Data for Bovine Diathermy Experiments.

Author Contributions: Conceptualization, R.P. and S.S.; investigation, E.B. and M.C.; writing—original draft preparation, E.B. and M.C.; writing—review and editing, R.P. and S.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: The original contributions presented in this study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Acknowledgments: The authors thank the cooperative research program at the University of Cincinnati and ZetrOZ Systems for facilitating this research project.

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

Abbreviations

The following abbreviations are used in this manuscript:

MSK	Musculoskeletal
GDP	Gross Domestic Product
CBD	Cannabidiol
TRP	Transient Receptor Potential
SAM	Sustained Acoustic Medicine
US	Ultrasound
TOSTs	Two one-sided *t*-tests

References

1. Nguyen, A.T.; Aris, I.M.; Snyder, B.D.; Harris, M.B.; Kang, J.D.; Murray, M.; Rodriguez, E.K.; Nazarian, A. Musculoskeletal Health: An Ecological Study Assessing Disease Burden and Research Funding. *Lancet Reg. Health-Am.* **2024**, *29*, 100661. [CrossRef]
2. Greggi, C.; Visconti, V.V.; Albanese, M.; Gasperini, B.; Chiavoghilefu, A.; Prezioso, C.; Persechino, B.; Iavicoli, S.; Gasbarra, E.; Iundusi, R.; et al. Work-Related Musculoskeletal Disorders: A Systematic Review and Meta-Analysis. *J. Clin. Med.* **2024**, *13*, 3964. [CrossRef]
3. McSwan, J.; Gudin, J.; Song, X.J.; Plapler, P.G.; Betteridge, N.J.; Kechemir, H.; Igracki-Turudic, I.; Pickering, G. Self-Healing: A Concept for Musculoskeletal Body Pain Management—Scientific Evidence and Mode of Action. *J. Pain Res.* **2021**, *14*, 2943–2958. [CrossRef]
4. Gill, T.K.; Mittinty, M.M.; March, L.M.; Steinmetz, J.D.; Culbreth, G.T.; Cross, M.; Kopec, J.A.; Woolf, A.D.; Haile, L.M.; Hagins, H.; et al. Global, Regional, and National Burden of Other Musculoskeletal Disorders, 1990–2020, and Projections to 2050: A Systematic Analysis of the Global Burden of Disease Study 2021. *Lancet Rheumatol.* **2023**, *5*, e670–e682. [CrossRef]
5. Romero-Morales, C.; Bravo-Aguilar, M.; Abuín-Porras, V.; Almazán-Polo, J.; Calvo-Lobo, C.; Martínez-Jiménez, E.M.; López-López, D.; Navarro-Flores, E. Current Advances and Novel Research on Minimal Invasive Techniques for Musculoskeletal Disorders. *Disease-a-Month* **2021**, *67*, 101210. [CrossRef] [PubMed]

6. El-Tallawy, S.N.; Nalamasu, R.; Salem, G.I.; LeQuang, J.A.K.; Pergolizzi, J.V.; Christo, P.J. Management of Musculoskeletal Pain: An Update with Emphasis on Chronic Musculoskeletal Pain. *Pain Ther.* **2021**, *10*, 181–209. [CrossRef] [PubMed]
7. Bidaut-Russell, M.; Gabriel, S.E. Adverse Gastrointestinal Effects of NSAIDs: Consequences and Costs. *Best Pract. Res. Clin. Gastroenterol.* **2001**, *15*, 739–753. [CrossRef]
8. Roelofs, P.D.D.M.; Deyo, R.A.; Koes, B.W.; Scholten, R.J.P.M.; van Tulder, M.W. Nonsteroidal Anti-Inflammatory Drugs for Low Back Pain. *Spine* **2008**, *33*, 1766–1774. [CrossRef]
9. Wirth, T.; Lafforgue, P.; Pham, T. NSAID: Current Limits to Prescription. *Jt. Bone Spine* **2024**, *91*, 105685. [CrossRef] [PubMed]
10. Ghlichloo, I.; Gerriets, V. *Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)*; StatPearls Publishing: Treasure Island, FL, USA, 2025.
11. Sostres, C.; Gargallo, C.J.; Arroyo, M.T.; Lanas, A. Adverse Effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs, Aspirin and Coxibs) on Upper Gastrointestinal Tract. *Best Pract. Res. Clin. Gastroenterol.* **2010**, *24*, 121–132. [CrossRef]
12. Oderda, G.M.; Lake, J.; Rüdell, K.; Roland, C.L.; Masters, E.T. Economic Burden of Prescription Opioid Misuse and Abuse: A Systematic Review. *J. Pain Palliat. Care Pharmacother.* **2015**, *29*, 388–400. [CrossRef] [PubMed]
13. Biancuzzi, H.; Dal Mas, F.; Brescia, V.; Campostrini, S.; Cascella, M.; Cuomo, A.; Cobianchi, L.; Dorken-Gallastegi, A.; Gebran, A.; Kaafarani, H.M.; et al. Opioid Misuse: A Review of the Main Issues, Challenges, and Strategies. *Int. J. Environ. Res. Public Health* **2022**, *19*, 11754. [CrossRef]
14. Nemes, D.; Amaricai, E.; Tanase, D.; Popa, D.; Catan, L.; Andrei, D. Physical Therapy vs. Medical Treatment of Musculoskeletal Disorders in Dentistry—A Randomised Prospective Study. *Ann. Agric. Environ. Med.* **2013**, *20*, 301–306.
15. Bariguian, F.; Marina, R.; Hagen, F.M. Topical Diclofenac, an Efficacious Treatment for Osteoarthritis: A Narrative Review. *Rheumatol. Ther.* **2020**, *7*, 217–236. [CrossRef] [PubMed]
16. Drosopoulou, K.; Kosheleva, R.I.; Ofrydopoulou, A.; Tsoupras, A.; Mitropoulos, A. Topical and Transdermal Delivery of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) for Inflammation and Pain: Current Trends and Future Directions in Delivery Systems. *Processes* **2025**, *13*, 907. [CrossRef]
17. Pradal, J. Comparison of Skin Permeation and Putative Anti-Inflammatory Activity of Commercially Available Topical Products Containing Ibuprofen and Diclofenac. *J. Pain Res.* **2020**, *13*, 2805–2814. [CrossRef]
18. Martinez Naya, N.; Kelly, J.; Corna, G.; Golino, M.; Abbate, A.; Toldo, S. Molecular and Cellular Mechanisms of Action of Cannabidiol. *Molecules* **2023**, *28*, 5980. [CrossRef]
19. Szallasi, A.; Di Marzo, V. New Perspectives on Enigmatic Vanilloid Receptors. *Trends Neurosci.* **2000**, *23*, 491–497. [CrossRef]
20. Liou, G.I.; Auchampach, J.A.; Hillard, C.J.; Zhu, G.; Yousufzai, B.; Mian, S.; Khan, S.; Khalifa, Y. Mediation of Cannabidiol Anti-Inflammation in the Retina by Equilibrative Nucleoside Transporter and A2A Adenosine Receptor. *Investig. Ophthalmol. Vis. Sci.* **2008**, *49*, 5526–5531. [CrossRef]
21. Sunda, F.; Arowolo, A. A Molecular Basis for the Anti-Inflammatory and Anti-Fibrosis Properties of Cannabidiol. *FASEB J.* **2020**, *34*, 14083–14092. [CrossRef]
22. Cosentino, M.; Legnaro, M.; Luini, A.; Ferrari, M.; Sodergren, M.; Pacchetti, B.; Marino, F. Effect of Cannabidiol on Cyclooxygenase Type 1 and 2 Expression and Function in Human Neutrophils. *Cannabis Cannabinoid Res.* **2023**, *8*, 999–1007. [CrossRef]
23. Carrier, E.J.; Auchampach, J.A.; Hillard, C.J. Inhibition of an Equilibrative Nucleoside Transporter by Cannabidiol: A Mechanism of Cannabinoid Immunosuppression. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 7895–7900. [CrossRef]
24. Miller, H.; De Leo, N.; Badach, J.; Lin, A.; Williamson, J.; Bonawitz, S.; Ostrovsky, O. Role of Marijuana Components on the Regenerative Ability of Stem Cells. *Cell Biochem. Funct.* **2021**, *39*, 432–441. [CrossRef]
25. Wu, H.Y.; Chu, R.M.; Wang, C.C.; Lee, C.Y.; Lin, S.H.; Jan, T.R. Cannabidiol-Induced Apoptosis in Primary Lymphocytes Is Associated with Oxidative Stress-Dependent Activation of Caspase-8. *Toxicol. Appl. Pharmacol.* **2008**, *226*, 260–270. [CrossRef]
26. Baban, B.; Hoda, N.; Malik, A.; Khodadadi, H.; Simmerman, E.; Vaibhav, K.; Mozaffari, M.S. Impact of Cannabidiol Treatment on Regulatory T-17 Cells and Neutrophil Polarization in Acute Kidney Injury. *Am. J. Physiol.-Ren. Physiol.* **2018**, *315*, 1149–1158. [CrossRef] [PubMed]
27. Draper, D.O.; Castel, J.C.; Castel, C. Rate of Temperature Increase in Human Muscle During 1 MHz and 3 MHz Continuous Ultrasound. *J. Orthop. Sports Phys. Ther.* **1995**, *22*, 142–150. [CrossRef]
28. Draper, D.O.; Edvalson, C.G.; Knight, K.L.; Eggett, D.; Shurtz, J. Temperature Increases in the Human Achilles Tendon During Ultrasound Treatments With Commercial Ultrasound Gel and Full-Thickness and Half-Thickness Gel Pads. *J. Athl. Train.* **2010**, *45*, 333–337. [CrossRef] [PubMed]
29. Merrick, M.A.; Bernard, K.D.; Devor, S.T.; Williams, M.J.M. Identical 3-MHz Ultrasound Treatments with Different Devices Produce Different Intramuscular Temperatures. *J. Orthop. Sports Phys. Ther.* **2003**, *33*, 379–385. [CrossRef] [PubMed]
30. Feng, F.; Mal, A.; Kabo, M.; Wang, J.C.; Bar-Cohen, Y. The Mechanical and Thermal Effects of Focused Ultrasound in a Model Biological Material. *J. Acoust. Soc. Am.* **2005**, *117*, 2347–2355. [CrossRef]
31. Rigby, J.H.; Taggart, R.M.; Stratton, K.L.; Lewis, G.K.; Draper, D.O. Intramuscular Heating Characteristics of Multihour Low-Intensity Therapeutic Ultrasound. *J. Athl. Train.* **2015**, *50*, 1158–1164. [CrossRef]

32. Gallo, J.A.; Draper, D.O.; Thein Brody, L.; Fellingham, G.W. A Comparison of Human Muscle Temperature Increases During 3-MHz Continuous and Pulsed Ultrasound With Equivalent Temporal Average Intensities. *J. Orthop. Sports Phys. Ther.* **2004**, *34*, 395–401. [CrossRef]
33. Ebadi, S.; Ansari, N.N.; Naghdi, S.; Jalaei, S.; Sadat, M.; Bagheri, H.; Vantulder, M.W.; Henschke, N.; Fallah, E. The Effect of Continuous Ultrasound on Chronic Non-Specific Low Back Pain: A Single Blind Placebo-Controlled Randomized Trial. *BMC Musculoskelet. Disord.* **2012**, *13*, 192. [CrossRef] [PubMed]
34. Choi, J.W.; Choi, B.H.; Park, S.H.; Pai, K.S.; Li, T.Z.; Min, B.H.; Park, S.R. Mechanical Stimulation by Ultrasound Enhances Chondrogenic Differentiation of Mesenchymal Stem Cells in a Fibrin-Hyaluronic Acid Hydrogel. *Artif. Organs* **2013**, *37*, 648–655. [CrossRef]
35. Izadifar, Z.; Babyn, P.; Chapman, D. Mechanical and Biological Effects of Ultrasound: A Review of Present Knowledge. *Ultrasound Med. Biol.* **2017**, *43*, 1085–1104. [CrossRef]
36. Uddin, S.M.Z.; Komatsu, D.E.; Motyka, T.; Petterson, S. Low-Intensity Continuous Ultrasound Therapies—A Systematic Review of Current State-of-the-Art and Future Perspectives. *J. Clin. Med.* **2021**, *10*, 2698. [CrossRef]
37. Jarit, P.; Klyve, D.; Walters, R. Long Duration Sonophoresis of Diclofenac to Augment Rehabilitation of Common Musculoskeletal Injuries. *Glob. J. Orthop. Res.* **2023**, *4*, 584. [CrossRef] [PubMed]
38. Madzia, A.; Agrawal, C.; Jarit, P.; Petterson, S.; Plancher, K.; Ortiz, R. Sustained Acoustic Medicine Combined with A Diclofenac Ultrasound Coupling Patch for the Rapid Symptomatic Relief of Knee Osteoarthritis: Multi-Site Clinical Efficacy Study. *Open Orthop. J.* **2020**, *14*, 176–185. [CrossRef]
39. Marathe, D.; Bhuvanashree, V.S.; Mehta, C.H.; Ashwini, T.; Nayak, U.Y. Low-Frequency Sonophoresis: A Promising Strategy for Enhanced Transdermal Delivery. *Adv. Pharmacol. Pharm. Sci.* **2024**, *2024*, 1247450. [CrossRef] [PubMed]
40. Masterson, J.; Kluge, B.; Burdette, A.; Lewis, G. Sustained Acoustic Medicine; Sonophoresis for Nonsteroidal Anti-Inflammatory Drug Delivery in Arthritis. *Ther. Deliv.* **2020**, *11*, 363–372. [CrossRef]
41. Draper, D.O.; Wells, A.; Wilk, K. Efficacy of Sustained Acoustic Medicine as an Add-on to Traditional Therapy in Treating Sport-Related Injuries: Case Reports. *Glob. J. Orthop. Res.* **2020**, *2*, 545.
42. Sam® 2.0 Device & Sam® Single Peel Gel Capture Patches. Available online: https://www.arthritis.org/partnership/ease-of-use-products/sam-2-device-single-peel-gel-capture-patches (accessed on 3 April 2026).
43. Draper, D.O. A Comparison of Traditional Ultrasound and Sustained Acoustic Medicine (SAM). *Orthop. Sports Med. Open Access J.* **2019**, *2*, 201–202. [CrossRef]
44. Best, T.M.; Moore, B.; Jarit, P.; Moorman, C.T.; Lewis, G.K. Sustained Acoustic Medicine: Wearable, Long Duration Ultrasonic Therapy for the Treatment of Tendinopathy. *Physician Sportsmed.* **2015**, *43*, 366–374. [CrossRef]
45. Draper, D.O.; Klyve, D.; Ortiz, R.; Best, T.M. Effect of Low-Intensity Long-Duration Ultrasound on the Symptomatic Relief of Knee Osteoarthritis: A Randomized, Placebo-Controlled Double-Blind Study. *J. Orthop. Surg. Res.* **2018**, *13*, 257. [CrossRef]
46. Winkler, S.L.; Urbisci, A.E.; Best, T.M. Sustained Acoustic Medicine for the Treatment of Musculoskeletal Injuries: A Systematic Review and Meta-Analysis. *BMC Sports Sci. Med. Rehabil.* **2021**, *13*, 159. [CrossRef] [PubMed]
47. Hendren, T.F.; Yeretzian, N.R.; Bavanasi, K. Clinical Diathermy Performance Evaluation of Multi-Hour Sustained Acoustic Medicine Treatment with 2.5% Diclofenac Ultrasound Coupling Patch. *Int. J. Phys. Med. Rehabil.* **2023**, *11*, 678.
48. Best, T.M.; Petterson, S.; Plancher, K. Sustained Acoustic Medicine as a Non-Surgical and Non-Opioid Knee Osteoarthritis Treatment Option: A Health Economic Cost-Effectiveness Analysis for Symptom Management. *J. Orthop. Surg. Res.* **2020**, *15*, 481. [CrossRef]
49. Crofford, L.J. Adverse Effects of Chronic Opioid Therapy for Chronic Musculoskeletal Pain. *Nat. Rev. Rheumatol.* **2010**, *6*, 191–197. [CrossRef]
50. Seah, B.C.Q.; Teo, B.M. Recent Advances in Ultrasound-Based Transdermal Drug Delivery. *Int. J. Nanomed.* **2018**, *13*, 7749–7763. [CrossRef] [PubMed]
51. Feiszthuber, H.; Bhatnagar, S.; Gyöngy, M.; Coussios, C.C. Cavitation-Enhanced Delivery of Insulin in Agar and Porcine Models of Human Skin. *Phys. Med. Biol.* **2015**, *60*, 2421–2434. [CrossRef]
52. Walters, R.; Snyder, D. Clinical Uses Of Long-Duration Ultrasound And Long-Duration Sonophoresis in Sports Medicine—Minireview. *J. Orthop.* **2025**, *9*, 1–8. [CrossRef]
53. Fernandez, S.V.; Kim, J.; Sadat, D.; Marcus, C.; Suh, E.; Mclntosh, R.; Shah, A.; Dagdeviren, C. A Dynamic Ultrasound Phantom with Tissue-Mimicking Mechanical and Acoustic Properties. *Adv. Sci.* **2024**, *11*, 2400271. [CrossRef] [PubMed]
54. Chiesa, S.T.; Trangmar, S.J.; González-Alonso, J. Temperature and Blood Flow Distribution in the Human Leg during Passive Heat Stress. *J. Appl. Physiol.* **2016**, *120*, 1047–1058. [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.