Extracorporeal Shockwave Applicator for Spinal Pain and Muscular Contracture: A New Design Approach

Lucian Daniel Dobreci 1, Valentin Zichil 2, Elena Nechita 3, Cosmin Constantin Grigoraș 2* and Vlad Andrei Ciubotariu 4

1 Department of Physical Therapy and Occupational Therapy, “Vasile Alecsandri” University of Bacău, 157 Calea Mărășești, 600115 Bacău, Romania; dobreci.lucian@ub.ro
2 Department of Engineering and Management, Mechatronics, “Vasile Alecsandri” University of Bacău, 157 Calea Mărășești, 600115 Bacău, Romania; valentinz@ub.ro
3 Department of Mathematics and Informatics, “Vasile Alecsandri” University of Bacău, 157 Calea Mărășești, 600115 Bacău, Romania; enechita@ub.ro
4 Department of Industrial Systems Engineering and Management, “Vasile Alecsandri” University of Bacău, 157 Calea Mărășești, 600115 Bacău, Romania; vlad.ciubotariu@ub.ro
* Correspondence: cosmin.grigoras@ub.ro

Received: 6 November 2020; Accepted: 3 December 2020; Published: 4 December 2020

Abstract: Shockwave therapy is a noninvasive treatment technique used in multidisciplinary fields, such as sports medicine, physical therapy, and orthopedics. This method of treatment is recommended for medical conditions, such as muscle contractions, intramuscular hematoma, or Dupuytren’s contracture. The shockwaves are high-energy pressure waves characterized by nonlinearity, high frequency, and peak pressure followed by low-pressure amplitude which are transmitted through an applicator to the affected tissue. In the case of spinal muscles, the conventional applicator can only be used on one side of the spinal cord at a time. Taking this into consideration, the approach suggested in this paper involves the design of a dedicated dual-tip applicator. This process implied predesign, finite element analysis, statistical analysis of the data, and optimization. We analyzed the input factors, such as frequency, pressure, applicator tip distance, shape, flatness, and material along with their effects, namely induced stress, tissue contact pressure, total strain energy, and propagation velocity. The proposed final design of the applicator uses geometric features suggested by the optimization analysis and also mechanical design features.

Keywords: shockwave therapy; spinal treatment; mathematical model; finite element analysis; statistical data

1. Introduction

The effect of shockwaves on human tissue was first observed during World War II for severe lung cracks in people exposed to the detonation of bombs in water as the shockwaves transmit high amounts of energy [1]. The transfer of this effect to a medical application has involved years of testing and research. The understanding of how to harness this natural behavior of shockwaves led to the introduction in practice, in 1980, of extracorporeal shockwave therapy (ESWT). First used to destroy kidney stones in humans [2], nowadays, it is considered a safe, nonsurgical, effective treatment [3] for multiple disorders in orthopedics, physical therapy, sports medicine, urology, and veterinary medicine, particularly used in chronic Achilles tendinopathy and plantar fasciitis, as well as bone defects [4]. ESWT is considered to be a fast pain relief and mobility restoration treatment while the noninvasive advantage ensures that no painkillers are needed [5]. Numerous investigations in sport-related injuries [6], knee osteoarthritis, upper limb diseases, treatment of plantar fasciitis, erectile dysfunction [4,7–9], musculoskeletal conditions, bone consolidation [10–12], human myofascial pain...
syndrome, fibromyalgia [13,14], and urinary or cardiovascular diseases [15–17] show that this method leads to a faster healing time and an improvement in functionality and quality of life [5,18,19].

The mechanism producing shockwaves consists of a ballistic device that uses compressed air to move a projectile at high velocity into the applicator, generating radial pressure waves. These shockwaves have a physical phase, which is composed of a maximum of 40 MPa positive pressure that transmits energy to the tissue and cells, lasting as long as 2–3 μs, and a minimum of −15 MPa negative pressure, as highlighted in Figure 1 [20], which induces physical effects (cavitation and increase of permeability in cell membranes) that last for 5 μs. Besides this mechanism, it is believed that other physicochemical, chemical, and biological phases take place during the treatment [12].

![Figure 1. Schematic representation of a ballistic shockwave source [20].](image)

Although numerous studies have been conducted in the field of ESWT, they are focused on the effects the therapeutic benefits induce, only summary information regarding the applicator optimization being available. Distinct clinical studies mention the shape of the applicator (convex or concave), but not the way it can be improved. Therefore, we consider that present applicators can be developed so that they can be used in more than only one application area at a time. Taking into consideration the spinal pain and muscle contracture treatment, which implies applying the shockwaves successively on each side of the spinal cord, a dual-tip applicator would increase the application area, by targeting both sides of the tissue (in this case, the efficiency in terms of the number of shocks distributed will be double—in comparison with the standard protocol). The main objective is to design a tool that can allow simultaneous passes along both sides of the spinal cord while offering improved results compared to the classical applicator.

2. Methodology for the Statistical Data Interpretation and Finite Element Analysis

2.1. General Methodology

This experimental study was conducted as structured in Figure 2. An experimental plan was designed to compute the simulation data from a statistical perspective, thus indicating if the study can be considered significant or not. The generated experimental plan was used as an input data plan in the nonlinear dynamic analysis. The resulting data were analyzed for significance with the Design-Expert software, by using the Response Surface Optimal design and ANOVA tools. Following the analyzed data, a perspective on the final dual-tip design emerged. The new design underwent another series of simulations to validate if the results were the desired ones.
2.2. ESWT Mechanics

The ESWT equipment consists of a main unit and handpiece. From the main unit, the pressure and frequency are controlled. The shockwaves are produced in the handpiece, which is shown in Figure 3 [21]; through an air inlet, pressure accumulates and propels the projectile with high velocity towards the applicator, transferring its kinetic energy. At this moment, the applicator is in direct contact with the soft tissue, therefore, the energy is passed as pressure waves, which propagate into the human body [22], as it is indicated in Figure 4. The area of interest, in this case, is the spinal cord lumbar intervertebral disc (near L4/L5 lumbar vertebrae) and the propagation mechanics are presented as compression and rarefaction waves, produced at a pressure of 4 bar [23]. This action is repeated at a given frequency. Depending on the pressure variation, different areas can be treated. Low pressure affects soft tissue only (ligaments and muscles), while a high pressure has a stronger penetration, up to the bones [24].

![Figure 3. Schematic representation of a ballistic shockwave source, adapted from “Extracorporeal Shockwave Therapy” by L. Gerdesmeyer & L. Weil, 2007 [21].](image)

![Figure 4. Shockwave propagation through the soft tissue to the spinal cord; simulation using finite element analysis; (a) indicates the location where the analysis was performed; (b) indicates the area of interest of the spinal cord; (c) shows a conventional applicator in direct contact with soft tissue and the induced shockwaves propagation [23].](image)
2.3. Predesign of the Applicator and Finite Element Analysis Methodology

This challenge implied undergoing an investigation of the mechanics of the shockwave process, skin mechanical reaction, applicator design, and process parameters. Understating the full extent of the process allowed us to perform a finite element analysis (FEA) by using various process conditions. The results were analyzed statistically and consequently, the conclusions were drawn regarding the efficiency of the new applicator and the possibility of machining it by metal cutting techniques.

The starting point of this experimental study was a conventional shockwave applicator, made out of stainless steel (SAE 316). In Figure 5a, it can be noted that the applicator has three distinct zones: the impact of the projectile takes place in zone I; zone II is designed for fixture purposes, while zone III is designed as a 15 mm diameter cylinder having a convex or concave 55 [mm] radius. This part comes in direct contact with the skin. Before performing any experimental study, we had proven, based on practical experience, that this part has to be perpendicular to the skin, for maximum treatment efficiency. This assumption was necessary for simulation orientation and final design purposes.

![Figure 5](image)

**Figure 5.** Conventional (a) and predesigned dual-tip (b) shockwave applicator schematic representation and dimensions in millimeters.

Computer-aided design and FEA were made using the SolidWorks 2019. A total number of six concave and convex applicators had been conceived. The predesign of the dual-tip applicator is shown in Figure 5b and was used for the finite element analysis. The distance between the applicator tips was the essential part of this study as it had to satisfy the distance between the spinal muscles, which varies by gender, age, and body fat [25], therefore, this distance was set between 40 and 80 [mm]. The tip flatness was designed either concave or convex, as this feature may influence the wave dissipation (radial or focused). Since they are known to be widely used in the medical equipment industry, three common materials were analyzed: stainless steel SAE 316, titanium alloy Ti6Al4V, and cobalt–chrome alloy R30075. The alloys' mechanical data used within the finite element analysis are shown in Table 1.

| Material   | Material Model Type       | Property and Value             |
|------------|--------------------------|--------------------------------|
| SAE 316    | Linear elastic isotropic | $E = 193$ GPa, $\nu = 0.28$, $\rho = 7870$ kg/m$^3$ |
| Ti6Al4V    | Linear elastic isotropic | $E = 113.8$ GPa, $\nu = 0.34$, $\rho = 4430$ kg/m$^3$ |
| R30075     | Linear elastic isotropic | $E = 210$ GPa, $\nu = 0.29$, $\rho = 8400$ kg/m$^3$ |

Taking into consideration the technical data in the field of human skin mechanical properties, the soft tissue thickness was set to 5 mm [26,27]. This was necessary to understand how the soft tissue reacts and how the applicator shape influences the shockwave propagation. Thus, for the applicator,
a linear elastic isotropic model was applied, as highlighted in Table 1, while for the soft tissue, a hyperplastic material that imitates human skin was defined using the Mooney–Rivlin model, with the constants \( C_0 = C_1 = 0.1 \text{ MPa} \), Poisson’s coefficient \( \nu = 0.48 \), and density \( \rho = 1020 \text{ kg/m}^3 \) [26–29].

The assembly of the applicator and soft tissue implied placing them in direct contact, tangent by the tip radius, as shown in the left side of Figure 6. The soft tissue was fully fixed, while the applicator could move only in the vertical direction. The finite element simulation was performed by using a nonlinear dynamic 2D analysis. The connection between the applicator and the soft tissue had been defined by two contact sets, with no penetration conditions. The first one involved selecting the geometry of the components that came in direct or indirect contact. The second one defined a self-contact for the soft tissue. The discretization of the 2D model was made by using mesh controls with an element size of 0.4 mm, as a refined mesh leads to accurate results. Each study lasted for 3 s, with a 0.01 s increment, and it can be divided into three distinct time intervals: during the interval 0–1 s, the applicator was moved 2 mm into the skin, the second step was the actual simulation, while the last second was necessary to observe how the soft tissue behaved and how the shockwave propagated.

On zone I of the applicator, pressure was exercised at a given frequency. The results obtained from the finite element analysis were the von Mises stress MPa, total strain energy J/m\(^3\), contact pressure MPa, and wave propagation velocity mm/s. The von Mises stress was measured both for the applicator and for the soft tissue as maximum recorded values, while the total strain energy, contact pressure, and wave velocity were measured from within the soft tissue only. The stress accumulated in the applicator reached values no greater than 10% of the yield strength, therefore, the statistical interpretation was orientated on the effects that were induced in the soft tissue, while the main goal was to replicate the effects produced by the conventional applicator with dual-tip.

2.4. Statistical Analysis Methodology

A Response Surface Method (RMS) was implemented, by using the optimal (custom) design. When building the design of the analysis, the “Best” search option was selected along with an “I-optimal” design type. The input factors taken into consideration are highlighted in Table 2. The frequency and pressure were set according to the ESWT equipment. The proposed experimental plan included both conventional and dual-tip applicator, thus a relationship between them could be established. Considering the experimental plan, 25 simulations were indicated for the conventional applicator and 23 for the dual-tip one, out of which 11 were related to the 40 [mm] tip distance.
The statistics were based on the two-way analysis of variance (ANOVA). In a statistical hypothesis, a model is significant if the calculated p-value is below 0.05 and indicates a nonlinear relationship between factors and responses. Furthermore, if the p-value is smaller than 0.0001, it indicates that the outcome is highly possible [30,31]. Thus, this is an effective means for validating the inserted data. Moreover, the coefficient of determination (R²) and its extensions, adjusted and predicted (R²), were determined. If the values are above 0.80, then a high level of confidence in the generated mathematical models is ensured. The ANOVA takes into consideration also the interaction between the input factors and their influence on the response, therefore the equations are general, as parameters such as material, tip shape, and tip flatness cannot be quantifiable. Thus, a series of coefficients (c₁, c₂, c₃, c₄) have been added; however, they have small values, in the range of 10⁻¹ to 10⁻⁴ and do not affect the overall estimations.

3. Results

The results were analyzed from two perspectives. The first one refers to the numeric values obtained from the FEA and the second one refers to the data obtained from the statistical analysis.

Stress developed in the soft tissue, when using the lowest dual-tip applicator, ranged between 0.108 and 0.527 MPa. When using the conventional applicator, stress increased by more than 310%, at a maximum value of 1.654 MPa. The same pattern was observed when comparing the contact pressure obtained by the two applicators. The measurements ranged from 2.8 and 9.92 MPa for the conventional applicator to 1.22 and 2.76 MPa for the dual-tip type, thus, the soft tissue recorded lower contact pressures, as much as 580% when using the new applicator. The total strain energy J/m³ represents the energy that was needed to deform the soft tissue. Due to its nature, which is easily deformable, the values obtained were between 10⁻⁴ and 10⁻³ J/m³. As in the previous cases, higher values corresponded to the conventional applicator, while the lower ones to the dual-tip applicator.

The pressure wave propagation velocity followed the same tendency; it was shown that slower propagation velocities resulted when using a large tip distance. The experimental data indicate that the dual-tip design provided up to 130% slower pressure wave propagation velocity, with values in the range of 1.53 and 6.96 mm/s, while the conventional applicator induced speeds up to 15.92 mm/s.

Table 3 shows the ANOVA results for each model. Taking into consideration that the p-values for each model were below 0.0001 and that coefficients of determination were above 0.89, we concluded that the model was significant, meaning that the input factors had a strong impact on the responses. For each of the input factors, a Box–Cox analysis was performed and a transformation was recommended (sst–natural logarithm, cp–inverse square root, tse and wv–square root). Therefore, the equations for each mathematical model are highlighted below in Equations (1)–(4) and expressed accordingly.

| Table 2. Response surface method optimal design matrix. |
|-------|-----|-----|-----|-----|-----|-----|
| Name       | Units | Type      | Levels | Level 1 | Level 2 | Level 3 |
| Frequency  | Hz    | Continuous | -     | 2      | 14     | -      |
| Pressure   | bar   | Continuous | -     | 1      | 6      | -      |
| Tip distance | mm    | Discrete   | 3     | 0      | 40     | 80     |
| Tip shape  | -     | Nominal    | 2     | conventional | dual-tip   | -      |
| Tip flatness | -     | Nominal    | 2     | concave | convex   | -      |
| Material   | -     | Nominal    | 3     | SAE 316 | Ti6Al4V   | R30075 |

| Table 3. Response surface method—ANOVA results. |
|-------|-----|-----|-----|-----|-----|
| Source                  | F-Value | p-Value | R²   | Adj-R²  | Pred-R²  |
| Soft tissue stress (sts) model | 386.69 | <0.0001 | 0.9730 | 0.9704 | 0.9658 |
| Contact pressure (cp) model   | 51.64  | <0.0001 | 0.9244 | 0.9065 | 0.8886 |
| Total strain energy (tse) model | 75.55  | <0.0001 | 0.8999 | 0.8800 | 0.9134 |
| Wave velocity (wv) model      | 31.35  | <0.0001 | 0.9864 | 0.9852 | 0.9831 |
\ln(s_{t_d}) = c_1 + 0.056P - 0.0309T_d \tag{1}

\frac{1}{\sqrt{c_p}} = c_2 + 0.0151f - 0.0011P + 0.0014T_d \tag{2}

\sqrt{t_{s_e}} = c_3 + 0.0004P \tag{3}

\sqrt{w_{r_t}} = c_4 + 0.0076f + 0.0194P - 0.0296T_d \tag{4}

The input factors had a variable influence on the responses. The analysis was orientated through developing a new dual-tip applicator by analyzing the effects this tool had on the soft tissue. Therefore, the graphs from Figure 7; Figure 8 highlight the relevant factors for this design process.

Figure 7. Effects of tip distance on soft tissue stress (a) and contact pressure (b).

Figure 8. Effects of tip distance on total strain energy (a) and wave propagation velocity (b).

High amounts of stresses induced in the soft tissue are specific to low tip distances. Figure 7a indicates that a larger tip distance induced considerably less stress. The optimal tip distance was above 40 mm and the estimated stress was lower than 0.5 MPa. The contact pressure, as shown in Figure 7b, was slightly influenced by the tip distance, however, a contact pressure of 3 MPa was estimated. Figure 8a offers the same positive tendency for the dual-tip applicator, but in this case, the required strain energy was insignificantly small. The velocity of the pressure wave through the soft
tissue had average values when using a dual-tip design, with a distance between 40 and 60 mm, as it can be seen in Figure 8b.

4. Applicator Design Optimization

Present studies in the field of extracorporeal shockwave therapy indicate the use of high frequency (>10 Hz) with low pressure (from 1.8 to 3.2 bar) [4,6]. Considering that the new applicator has to deliver at least the same overall results and also the hands-on experience, we have concluded that a tip distance of over 40 mm was a starting solution. Thus, a numerical optimization was performed. The criteria used, presented in Figure 9, consider the obtained results along with the objectives of this study. Therefore, we considered that for optimizing the tip distance, the maximum values for both input factor and responses had to be taken into consideration. It can be identified in Figure 9, regarding the numerical optimization proposed solution for the optimal tip distance, that, with a desirability factor of 0.951, the optimization suggests a tip distance of 50.2 mm. The numerical optimization was validated by using the second set of finite element simulations. This was performed with the numerical optimization proposed data and by applying the changes to the applicator design.

![Figure 9](image1.png)

**Figure 9.** Numerical optimization proposed solution regarding the optimal tip distance.

The numerical optimization was validated by using the second set of finite element simulations by applying the changes to the applicator design. The proposed tip distance was set to 50 mm with a convex radius of 55 mm, a diameter of 15 mm, and an overall height of the applicator of 47.5 mm, as pointed out in Figure 10.

![Figure 10](image2.png)

**Figure 10.** The final design and schematic representation (dimensions in millimeters) of the dual-tip applicator, using the proposed solution.
The behavior of the nonlinear dynamic simulations was, regarding improvements in the levels of stress, contact pressure, strain energy, and velocity, as expected. One particular aspect came forward: the shockwaves produced by the new applicator propagated through the soft tissue at longer lengths than those produced by the conventional one. This comparison is outlined in Figure 11, where a series of 10 consecutive frames, each at 0.03 seconds apart, were captured. The velocity and spread of the shockwave are indicated as a color gradient. The data indicate that near the tip of both the applicators, the shockwave propagated with high velocity, indicated by the red color, and gradually lost intensity, coloring into blue as it traveled through soft tissue. It can be noted that as the shockwaves were spread over a larger area, their velocity decreased significantly. The simulation was carried out by using a frequency of 8 Hz, combined with a pressure of 6 bar. The timer started at the first impulse given to the applicator. The propagation, from its start to complete dispersion, in the case of the conventional applicator, lasted for 0.27 s, whereas the wave propagation obtained by the new applicator was still widely spread through the soft tissue. It can be observed that the peak for the shockwaves induced by the conventional applicator was at 0.15 s, compared to our solution, which presented intense values from 0.12 s to 0.18 s. From second 0.21 a sharp decrease in the shockwave velocity and dispersal can be observed for the conventional applicator.

**Figure 11.** Comparison between the conventional (a) and dual-tip (b) applicator shockwave velocity and spreading through soft tissue, at a pressure of 6 bar, frequency of 8 Hz, and the time interval between two frames at 0.03 s.

### 5. Discussion

Given the numerical data obtained from the finite element analysis, statistical analysis, and design optimization, we consider that the objective of this study was successfully achieved along with the future research directions in the field of ESWT.

The experimental plan, suggested by the statistical analysis, was a useful tool in organizing the numerical trials. Moreover, the assembly of all the inspected data was interpreted with ease. The analysis of variation has shown that each input factor has a significant impact on the response. This study pointed out the mathematical models that link the input factors to the response, and to what extent. The mathematical solution can be classified as very good, as the finite element analysis data confirmed the optimization results.

During the simulations, low stress values were developed in the applicator and no critical areas were detected. This aspect was useful for shape optimization, as large areas of the applicator have a
low material use coefficient. A direct link between the tip distance and the soft tissue stress highlights that the conventional applicator has local results while the dual-tip one induces shockwaves that are scattered on larger areas. The dual-tip design proved that it can deliver optimum results in terms of soft tissue stress and shockwave propagation velocity. Lower values of strain energy are consistent with high frequency, low contact pressure, and decreased tip distances, while strain energy and contact pressure were optimal in the case of the dual-tip applicator.

This study shows the possibility of improving medical equipment by using finite element analysis and statistical data interpretation. It had pointed out how the effects of the shockwave propagate through the soft tissue, by comparing the two applicators. The dual-tip applicator design leads to slower velocities of the shockwaves but they are spread out through a larger area. It can be stated that this new design induces effects with higher propagation lengths.

From the treatment point of view, the applicator can reduce the overall treatment time, with benefits both for the therapist and for the patient. The fact that the contact pressure has significantly lower values comes with the benefit of a more bearable treatment from the patient’s point of view, while, if necessary, this can be increased by raising the air pressure.

Future directions of research in this field can relate to aspects such as variable tip distance, technology for manufacturing (casting, assembling, five-axis milling), new materials (polymers), new technologies, such as metal printing (selective laser melting (SLM) or direct metal laser sintering (DMLS)), or further optimization of the dual-tip applicator.

6. Conclusions

Although the conventional applicator produced fast propagated shockwaves, they were not as effective as the ones produced by the new design. This was because the dual-tip applicator effect covers a larger area, taking a long time to dissipate. We consider that this improvement will lead to efficient treatment and faster healing time.

**Author Contributions:** Conceptualization, L.D.D.; methodology, V.Z., E.N., and C.C.G.; software, V.Z., E.N., C.C.G., and V.A.C.; validation, L.D.D., V.Z., and E.N.; formal analysis, V.Z., E.N., C.C.G., and V.A.C.; investigation, L.D.D., V.Z., and C.C.G.; resources, E.N., V.Z., and L.D.D.; data curation, C.C.G. and E.N.; writing—original draft preparation, C.C.G.; writing—review and editing, C.C.G.; visualization, L.D.D., V.Z., E.N., and C.C.G.; supervision, V.Z., L.D.D., and E.N. All authors have read and agreed to the published version of the manuscript.

**Funding:** The research was funded by the Ministry of Education and Research, through the National Council for the Financing of Higher Education, Romania, grant number CNFIS-FDI-2020-0461.

**Conflicts of Interest:** The authors would like to declare no conflicts of interest.

**References.**

1. Lohrer, H.; Nauck, T.; Korakakis, V.; Malliaropoulos, N.; Historical ESWT paradigms are overcome: A narrative review. *BioMed Res. Int.* 2016, 2016, 3850461. doi:10.1155/2016/3850461.

2. Chaussy, C.H.; Brendel, W.; Schmiedt, E. Extracorporeally induced destruction of kidney stones by shock waves. *Lancet* 1980, 316, 1265–1268, doi:10.1016/S0140-6736(80)92335-1.

3. Magdy, H.; Ahmad, M. Extracorporeal shockwave therapy in the treatment of chronic plantar fasciitis. *Zagazig Univ. Med. J.* 2009, 1, 73–82.

4. Testa, G.; Vescio, A. Perez, S.; Consoli, A.; Costarella, L.; Sessa, G.; Pavone, V; Extracorporeal shockwave therapy treatment in upper limb diseases: A systematic review. *J. Clin. Med.* 2020, 9, 453, doi:10.3390/jcm9020453.

5. Kalyvianakis, D.; Mykoniatis, I.; Memmos, E.; Kapoteli, P.; Memmos, D.; Hatzichristou, D.; Low-intensity shockwave therapy (LiST) for erectile dysfunction: A randomized clinical trial assessing the impact of energy flux density (EFD) and frequency of sessions. *Int. J. Impot. Res.* 2020, 32, 329–337, doi:10.1038/s41443-019-0185-0.

6. Leal, C.; Berumen E.; Fernandez A.; Bucci S.; Castillo A.; Extracorporeal shockwave therapy and sports-related injuries. *Shockwave Med.* 2018, 6, 70–86, doi:10.1159/000485063.
7. Hsu, C.-C.; Cheng, J.-H.; Wang, C.-J.; Ko, J.-Y.; Hsu S.-L.; Hsu, T.-C.; Shockwave therapy combined with autologous adipose-derived mesenchymal stem cells is better than with human umbilical cord Wharton’s jelly-derived mesenchymal stem cells on knee osteoarthritis. *Int. J. Mol. Sci.* 2020, 21, 1217, doi:10.3390/ijms21041217.

8. Vita, R.; Benveniga, S.; Giammusso, B.; La Vignera, S.; Determinants of early response to low-intensity extracorporeal shockwaves for the treatment of vasculogenic erectile dysfunction: An open-label, prospective study. *J. Clin. Med.* 2019, 8, 1017, doi:10.3390/jcm8071017.

9. Wang, Y.-C.; Chen, S.-J.; Huang, P.-P.; Huang, H.-T.; Cheng, Y.-M.; Shih, C.-L.; Efficacy of different energy levels used in focused and radial extracorporeal shockwave therapy in the treatment of plantar fasciitis: A meta-analysis of randomized placebo-controlled trials. *J. Clin. Med.* 2019, 8, 1497, doi:10.3390/jcm8091497.

10. Al-Abbad, H.; Allen, S.; Morris, S.; Reznik, J.; Biros, E.; Paulik, B.; Wright, A.; The effects of shockwave therapy on musculoskeletal conditions based on changes in imaging: A systematic review and meta-analysis with meta-regression. *BMC Musculoskelet. Disord.* 2020, 21, 275, doi:10.1186/s12891-020-02370-w.

11. Kertzman, P.; Lenza, M.; Pedrinelli, A.; Eijnsman, B.; Shockwave treatment for musculoskeletal diseases and bone consolidation: Qualitative analysis of the literature. *Revista Brasileira de Ortopedia* 2015, 50, 3–8, doi:10.1016/j.roe.2015.01.003.

12. Moya, D.; Ramón, S.; Schaden, W.; Wang, C.-J.; Guiloff, L.; Cheng, J.-H.; The role of extracorporeal shockwave treatment in musculoskeletal disorders. *BJB* 2018, 100, 251–263, doi:10.2106/BJB.17.00661.

13. Hansen, L.K.; Schroeder, H.D.; Lund, L.; Rajagopal, K.; Maduri, V.; Sellathurai, J.; The effect of low intensity shockwave treatment (Li-SWT) on human myoblasts and mouse skeletal muscle. *BMC Musculoskelet. Disord.* 2017, 18, 557, doi:10.1186/s12891-017-1879-4.

14. Ramon, S.; Gleitz, M.; Hernandez, L.; Romero, L.D.; Update on the efficacy of extracorporeal shockwave treatment for myofascial pain syndrome and fibromyalgia. *Int. J. Surg.* 2015, 24, 201–206, doi:10.1016/j.ijsu.2015.08.083.

15. Sun, C.K.; Yip, H.K. Mechanisms underlying extracorporeal shockwave treatment for ischemic cardiovascular disease. *Shockwave Med.* 2018, 6, 102–108, doi:10.1159/000485065.

16. Wang, H.J. Application of extracorporeal shockwave therapy on erectile dysfunction and lower urinary tract inflammatory diseases. *Shockwave Med.* 2018, 6, 127–139, doi:10.1159/000485070.

17. Yip H.-K.; Lee F.-Y.; Chen K.-H.; Sung P.-H.; Sun C.-K.; Preclinical and clinical application of extracorporeal shockwave for ischemic cardiovascular disease. *Shockwave Med.* 2018, 6, 87–101, doi:10.1159/000485064.

18. Débora Ap, O. M.; da Silva, C.N.; Dolinocente, T.; Araújo, T.; Guidi, R.M.; Shock wave therapy associated with radio frequency in the treatment of abdominal skin flaccidity. *J. Dermatology Cosmetol.* 2019, 3, 69–73, doi:10.15406/jdc.2019.03.00116.

19. Dedes, V.; Stergioulas, A.; Kipreos, G.; Dedel, A.M.; Mitasea, A.; Panoutsopoulos, G.I.; Effectiveness and safety of shockwave therapy in tendinopathies. *Materia Socio-Medica* 2018, 30, 131–146, doi:10.5455/msm.2018.30.141-146.

20. Cleveland, R.; Mcateer, J. Physics of shock wave lithotripsy. *Smith’s Textb. Endourol.* 2012, 1, 17–322, doi:10.1002/9781444345148.ch49.

21. Gerdesmeyer, L.; Weil, L.S. Extracorporeal shock wave therapy: Technologies, basics, clinical results; Towson, Md.: Data Trace Pub.: Towson, Maryland, USA, 2007, 14-15.

22. d’Agostino, M.C.; Craig, K.; Tibalt, E.; Respizzi, S.; Shock wave as biological therapeutic tool: From mechanical stimulation to recovery and healing, through mechanotransduction. *Int. J. Surg.* 2015, 24, 147–153, doi:10.1016/j.ijsu.2015.11.030.

23. Liu, Y.; Chen, X.; Guo, A.; Liu, S.; Hu, G.; Quantitative assessments of mechanical responses upon radial extracorporeal shock wave therapy. *Adv. Sci.* 2018, 5, 1700797, doi:10.1002/advs.518.

24. Cheng, J.-H.; Wang, C.-J. Biological mechanism of shockwave in bone. *Int. J. Surg.* 2015, 24, 143–146, doi:10.1016/j.ijsu.2015.06.059.

25. Frostell, A.; Hakim, R.; Thelin, E.P.; Mattsson, P.; Svensson, M.; A review of the segmental diameter of the healthy human spinal cord. *Front. Neurol.* 2016, 7, 238–238, doi:10.3389/fneur.2016.00238.

26. Annaith, A.N.; Ottenio, M.; Bruyère, K.; Destrade, M.; Gilchrist, M.D.; Mechanical properties of excised human skin. In Proceedings of the 6th World Congress of Biomechanics (WCB 2010), Singapore, 1–6 August 2010; Springer: Berlin/Heidelberg, Germany, 2010, pp. 1000–1003, doi:10.1007/978-3-642-14515-5_255.

27. Yang, W.; Sherman, V.R.; Gludovatz, B.; Schaible, E.; Stewart, P.; Ritchie, R.O.; Meyers, M.A.; On the tear resistance of skin. *Nat. Commun.* 2015, 6, 6649, doi:10.1038/ncomms7649.
28. Alkhamaali, Z.K.; Crocombe, A.D.; Solan, M.C.; Cirovic, S.; Finite element modelling of radial shock wave therapy for chronic plantar fasciitis. *Comput. Methods Biomech. Biomed. Eng.* 2016, 19, 1069–1078, doi:10.1080/10255842.2015.1096348.

29. Liang, X.; Boppart, S.A. Biomechanical properties of in vivo human skin from dynamic optical coherence elastography. *IEEE Trans. Bio-Med. Eng.* 2010, 57, 953–959, doi:10.1109/TBME.2009.2033464.

30. Greenland, S.; Senn, S.J.; Rothman, K.J.; Carlin, J.B.; Poole, C.; Goodman, S.N.; Altman, D.G.; Statistical tests, P values, confidence intervals, and power: A guide to misinterpretations. *Eur. J. Epidemiol.* 2016, 31, 337–350, doi:10.1007/s10654-016-0149-3.

31. Roselan, M.A.A.; Ashari, S.E.; Faujan, N.H.; Mohd Faudzi, S.M.; Mohamad, R. Improved nanoemulsion formulation containing kojic monooleate: Optimization, characterization and in vitro studies. *Molecules* 2020, 25, 2616, doi:10.3390/app10238637.

**Publisher’s Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.