applied sciences

MDPI

Article

Measurement of the Clinical Effects of a Marine Fish Extract on Periodontal Healing—A Preliminary Clinical Interventional Study

Cristina Gabriela Pușcașu [1,*,†], Aureliana Caraiane [1,†], Elena Dumea [2,†], Erdogan Elvis Șachir [1,†], Gheorghe Raftu [1,†], Radu Andrei Pușcașu [3,†], Cristina Bartok-Nicolae [1,*,†], Eduard Radu Cernei [4,*,†], Liliana Sachelarie [5,*,†] and Liliana Loredana Hurjui [4,*,†]

1 Faculty of Dental Medicine, "Ovidius" University Constanta, 7 Ilarie Voronca Street, 900684 Constanța, Romania; drcaraiane@yahoo.com (A.C.); erdogan_sachir@yahoo.com (E.E.Ș.); gheorgheraftu@yahoo.com (G.R.)
2 Faculty of Medicine, "Ovidius" University Constanta, 1 Aleea Universității Corp B, 900470 Constanța, Romania; elenadumea@yahoo.com
3 Faculty of Medicine, University of Medicine and Pharmacy Carol Davila, 8, Bvld. Eroii Sanitari, 050474 Bucharest, Romania; radu.puscasu@stud.umfcd.ro
4 Faculty of Dental Medicine, "Grigore T. Popa" University of Medicine and Pharmacy, 700115 Iasi, Romania
5 Faculty of Dental Medicine, Apollonia University, Păcurari 11, 700511 Iasi, Romania
* Correspondence: cristinap@gmb.ro (C.G.P.); dr.cristina_nicolae@yahoo.com (C.B.-N.); eduard-radu.cernei@umfiasi.ro (E.R.C.); lisachero@yahoo.com (L.S.); loredana.hurjui@umfiasi.ro (L.L.H.)
† These authors contributed equally to this work.

Abstract: The aim of the study was to assess the clinical effects of periodontal healing using a Romanian pharmaceutical compound of marine fish extract (Alflutop®). Adults with periodontal disease were included in the study group. Gingival inflammation, the degree of tooth mobility, and probing depth (PD) were recorded for each patient before and after therapy. Patients were divided into two groups: group I—after scaling and root planing (SRP), patients followed therapy with marine fish extract, Alflutop®, group II—SRP therapy alone. Statistically significant differences between groups in terms of gingival inflammation reduction ($p = 0.045$) were found. Tooth mobility reduction, as well as PD improvement, were also noticed after the therapy ($p = 0.001$), but no statistically significant differences among PD reduction rates were found ($p = 0.356$). Alflutop® has proven a certain therapeutic efficiency in the treatment of periodontitis in terms of reduction in the clinical signs of inflammation and tooth mobility.

Keywords: periodontitis; periodontal healing; marine fish extract; Alflutop

check for updates

Citation: Pușcașu, C.G.; Caraiane, A.; Dumea, E.; Șachir, E.E.; Raftu, G.; Pușcașu, R.A.; Bartok-Nicolae, C.; Cernei, E.R.; Sachelarie, L.; Hurjui, L.L. Measurement of the Clinical Effects of a Marine Fish Extract on Periodontal Healing—A Preliminary Clinical Interventional Study. *Appl. Sci.* **2022**, *12*, 677. https://doi.org/10.3390/app12020677

Academic Editor: Gianrico Spagnuolo

Received: 23 December 2021
Accepted: 9 January 2022
Published: 11 January 2022

1. Introduction

Periodontal healing after specific anti-inflammatory and antimicrobial periodontal therapy can be supported by specific natural or synthetic compounds. This kind of therapy could be included as part of non-surgical therapy—and it is used after SRP (Scaling and Root Planing) therapy—in patients with periodontitis to help the healing process and possible clinical attachment gain [1]. In recent decades, periodontists have tried to find new non-invasive therapies to regenerate periodontal structures [2–4]. The periodontal regenerative process represents a dynamic tissue reaction, including different phenomena such as inflammation, cell proliferation, and the synthesis of extracellular matrix elements such as collagen fibers and elastic fibers [5,6]. Periodontal inflammation can be affected by poor oral hygiene, by immune response, the type of subgingival microbiota and other possible systemic diseases [7–9]. After full-mouth disinfection, periodontal non-surgical therapy can include the use of products having anti-inflammatory effects, increasing the host's defense, analgesic effects, the acceleration of cellular regeneration, an increase in protein synthesis,

and the acceleration of tissue healing or bone regeneration [9]. The main objective of non-surgical periodontal regeneration treatment involves the obtainment of a biologically active complex of natural compounds [10–12] aimed at assisting periodontal healing. In this context, natural biological chemical compounds are increasingly preferred as treatment alternatives. One of these compounds is Alflutop®, a Romanian pharmaceutical bioactive concentrate of marine fish, from the Black Sea, which is widely used in the treatment of degenerative osteoarticular diseases, inflammatory rheumatism or post-traumatic osteitis [13]. In vitro, Alflutop® has antioxidant and anti-inflammatory activity [14,15] and improves the proliferative status of chondrocytes [16]. Additionally, studies proved its effectiveness in reducing inflammatory cascade progression by inhibiting the release of pro-inflammatory cytokines such as interleukins (IL 6 and IL 8) and tumor necrosis factor-alpha (TNF^{α}) and is similar to the anti-inflammatory effect of dexamethasone [14]. According to previous research, the pharmaceutical properties of Alflutop® also include analgesic effects [17]. Past studies used the marine fish extract (Alflutop®) in dentistry, in endodontics, and in chronic periapical periodontitis after cleaning and shaping the root canal. The results showed the regenerative properties of Alflutop® used in endodontic temporary root canal treatment [18].

The aim of this research was to assess the clinical effects of the marine fish extract Alflutop® in periodontal therapy. Substances composing Alflutop® are natural and, according to the manufacturer, aimed at enhancing the proper metabolism at the joint's level and repairing the cartilage.

2. Materials and Methods

2.1. Study Population

A clinical interventional study was conducted in Constanța—on adults selected randomly from those who required periodontal therapy—in the Periodontology Department of Dentistry Faculty, Ovidius University of Constanța, during August–December, 2021. Ethical approval for the study was obtained from the Bioethics committee of Ovidius University (nr. 10788/30.08.2021). The study was conducted following the Helsinki declaration revised in 2013. All the patients selected and diagnosed with periodontitis, stages II–III—according to the classification which was presented at the 2017 World Workshop by the American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP) [19]—had no comorbidities or previously known allergies to any drug, were considered eligible and were included in the study group after having signed the informed consent for the research. The identity of all treated subjects was kept anonymous.

2.2. Clinical Protocol

A previously standardized dentist performed the oral examinations of the patients using a Williams probe (Hu-Friedy) and a flat dental mirror. The first clinical exam recorded the degree of periodontal involvement, assessed by the Gingival Index (GI), Papilla Bleeding Index (PBI), degree of tooth mobility probing depth (PD), and clinical attachment loss (CAL). The evaluation of pathologic tooth mobility was based on the usual scoring system [2]: 0—no mobility, 1—horizontal mobility less than 1 mm, 2—horizontal tooth mobility exceeding 1 mm, and 3—axial tooth mobility. Periodontal probing was carried out with a Williams probe (Hu-Friedy), in 6 points for each tooth. Maximum PD was recorded as the distance from the gingival margin to the deepest site reached by the blunt end of the periodontal probe. Bleeding on probing, expressed by PBI, was recorded simultaneously with PD measurements. The scores for PBI [2] were: 0—no bleeding, 1—single bleeding point, 2—multiple bleeding points, 3—bleeding filling interdental space, and 4—profuse bleeding or blood drop. GI (Löe & Silness 1963) scores were [2]: 0—normal aspect, 1—slight change in color and texture of the gingiva, no bleeding, 2—inflammation and bleeding on probing, 3—advanced inflammation and severe bleeding on probing. A periodontitis case was defined according to the new classification proposed by consensus in the last World Workshop on the Classification of Periodontal and Peri-Implant Diseases and

Conditions in 2017 [19]. A periodontitis case was considered when: there was interproximal clinical attachment loss (CAL) in ≥2 non-adjacent teeth, or ≥2 teeth with buccal or palatal site affected by CAL ≥ 3 mm and PD > 3 mm (in the same site) were detected, and PD ≥ 4 mm [19].

2.3. Subject Eligibility

Subjects qualifying for the study met the following inclusion criteria:

- Over 25 years of age;
- No known systemic pathology;
- No known allergy;
- Not alcohol or vitamin consumers;
- No periodontal treatment in the last 6 months.

Patients were excluded for one of the following conditions:

- Smoking;
- Pregnancy;
- Antibiotic intake within 8 weeks of the baseline examination.

The initial study group included 88 subjects, divided into two groups of 44 subjects each (group I—test and group II—control). Because of the reduced sample size, the simple randomization method was used with computer-generated numbers assigned initially for every subject, then the numbers were associated randomly, either within the test or control groups. Group I (test) received Alflutop® after scaling, root planning, and debridement (SRP), and group II (control) only received SRP therapy. After SRP, group I cases received infiltrations with Alflutop® solution into the mobile mucosa of the affected sites, or, in case of generalized periodontitis, into the mobile mucosa of the canine–premolar area, 2–3 times per week until all 10 vials were finished (approximately 3–4 weeks). A topical anesthetic was previously administered. Periodontal status was assessed for both cases and controls, before and after one month of periodontal therapy, by a single-blinded examiner who did not discuss with the patients the type of periodontal treatment they received. The evolution of inflammation indices, tooth mobility, and maximum PD were recorded in the database for all subjects. Appointments were made for all patients, for every treatment visit, as well as one month after the last infiltration with Alflutop® (test group). Patients from the control group were scheduled for the second periodontal examination one month after SRP treatment. Both groups of patients received oral hygiene instructions, and the use of antiseptic solution or antimicrobial treatment was forbidden until the final clinical examination.

The active ingredients of Alflutop® are based on anchovy (*Engraulis encrassicholus ponticus*), sprot (*Sprattus sprattus sprattus*), and puzanka (*Rizeafca nordmanni*) extracts, purified and deproteinated. The chemical composition of this bioactive small marine fish concentrate is extremely complex, represented by glycosaminoglycans (GAG), proteoglycans, glycoproteins, hyaluronic acid ($C_{14}H_{21}NO_{11}$), chondroitin 6-sulfate ($C_{28}H_{42}N_2O_{28}S_2$), chondroitin 4-sulfate ($C_{13}H_{21}NO_{15}S$), dermatan sulfate ($C_{14}H_{21}NO_{15}S$), keratan sulfate ($C_{28}H_{48}N_2O_{32}S_4$), low-molecular-weight polypeptides, free amino acids, myoinositol, glycerol-phospholipids, nitrogen, sulfur, phosphorus and microelements (Na, K, Fe, Ca, Mg, Cu, Mn, Zn), and distilled water and phenol used as excipients [20].

From the test group, only 35 patients could finalize the research. The other 9 patients did not finalize the protocol for other reasons which were unrelated to the therapy results (2 patients did not present in time and could not finish all 10 infiltrations, and 7 patients finished the infiltrations, but they did not present for the final assessment one month after therapy). Among the test group, after SRP therapy, 14 patients did not come for the final clinical examination. One month after therapy, 9 patients did not come, and 5 patients presented some days later than scheduled, so their data were not included in the evaluation (Figure 1). The final study groups are group I (test) with 35 cases and control group II with 30 patients.

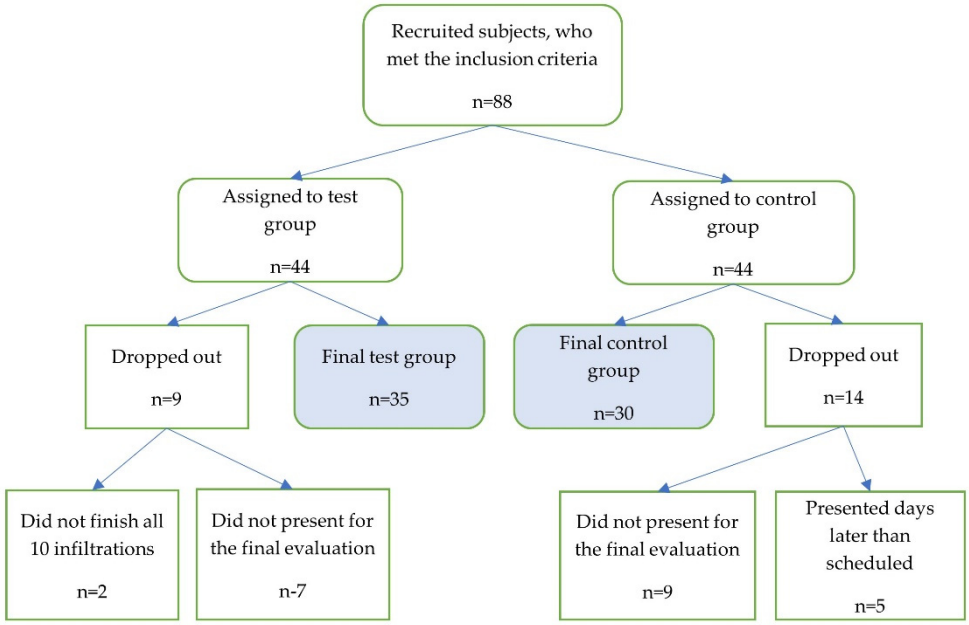

Figure 1. Flow chart with study group characteristics.

The statistical analysis was performed using IBM SPSS statistics software version 20. Data are presented as mean ± standard deviation (SD) or percentage for categorical variables. Descriptive statistics were performed within the two groups of cases and controls before and after therapy. Two-proportion z-tests that allow the comparison of the two proportions to see if they are the same were used to evaluate the evolution of the GI, PBI, and the degree of pathologic tooth mobility in both control and test groups, before and after therapy. The null hypothesis (H_0) for the test is that the proportions are the same. The Wilcoxon signed-rank test and the Mann–Whitney U test were used to compare the differences between probing depth (max) before and after therapy in both the tests and the controls. Levene's test for the equality of variances was used to assess the age and sex distribution among the subjects in both groups. The subject was the unity of analysis for all statistical comparisons with the level of statistical significance set at $p < 0.05$. Sample selection bias, confirmation bias, and publishing bias could influence the results. The non-significant improvements of the clinical parameters were reported together with relevant correlations to address potential publishing and confirmation bias. The loss of participants could influence the study results, as the control group lost more participants than the test group. The performance bias was addressed by providing the same treatment protocol in both groups (SRP), followed by an additional 10 infiltrations with the active ingredient in the test group. The patients that could not present for all 10 injections were excluded from the final evaluation. Additionally, smokers were excluded from the study participants.

3. Results

Sixty-five patients with periodontitis were divided into group I with 35 cases, mean aged 50.4 ± 10.6 years old (limits: 34–67 years), and group II with 30 controls, mean aged 44 ± 19 years old (limits: 25–81 years). No statistically significant difference was found between the age of subjects from the two groups (t = 1.321, df = 28.35, $p = 0.197$).

The distribution by age and gender revealed a similar mean age of males and females in the group of cases and younger females in the control group (Table 1).

Table 1. Age (mean) by group and by sex of the final study groups.

Group	Sex	N	Minimum	Maximum	Mean	Std. Deviation
Alflutop	Female/Age	19	40	67	51.57	8.31
	Male/Age	16	34	64	49	13.42
Control	Female/Age	19	25	46	33.36	8.88
	Male/Age	11	50	81	69.33	9.20

For group I (test), no statistically significant difference was noted among the mean age group of males and females (t = 0.589, df = 23, $p = 0.561$). For group II (control), statistically significant differences were noted among the mean age group of males and females (t = −8.219, df = 18, $p < 0.001$) (Levene's test for equality of variances).

After finishing the administration of all 10 Alflutop® vials and SRP, respectively, all patients were examined, and the final measurements were compared with the initial ones. No side effects of Alflutop® were reported, even pain at the infiltration sites.

The Gingival Index (GI), measured before and after therapy in both groups and analyzed using a two-proportion z-test, noticed no statistically significant differences for score 0 (normal aspect) registered in more than a half of cases and controls (n I = 14; 56% vs. n II = 13; 65%; $p = 0.540$), and score 1 (mild inflammation and no bleeding) was 2 times greater in cases (n I = 11; 44% vs. n II = 4; 20%; $p = 0.090$). Statistically significant differences were recorded between cases with a score of 2 of the GI (moderate inflammation, bleeding on probing) after Alflutop®, who presented a statistically significant reduction of GI score to 1 or even zero after therapy ($p = 0.045$) compared to controls (Figure 2).

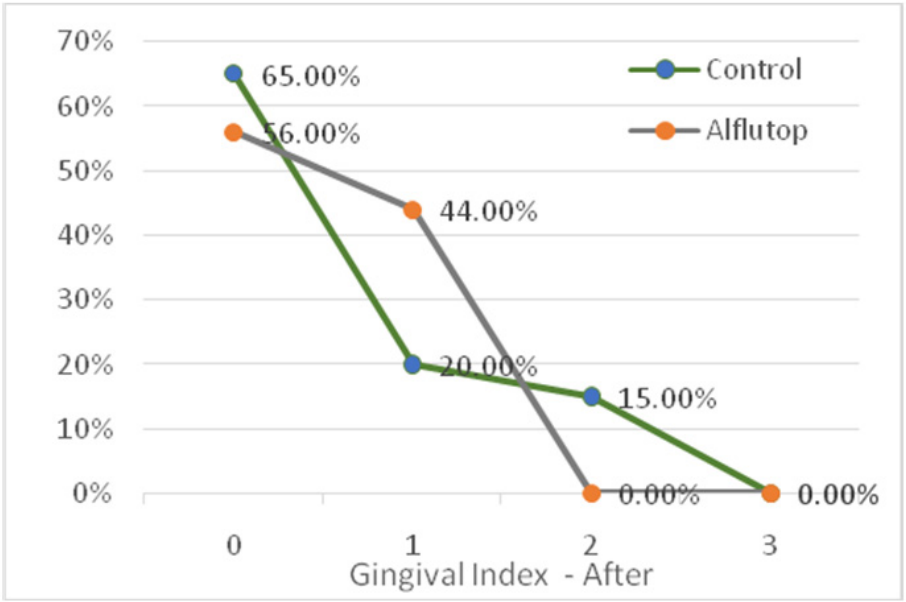

Figure 2. Evolution of Gingival Index in cases compared to controls (percentage of cases exhibiting GI reduction in both control and test group).

The PBI score of 1 underwent a statistically significant reduction in the Alflutop® group vs. the SRP groups ($p = 0.045$) (Figure 3).

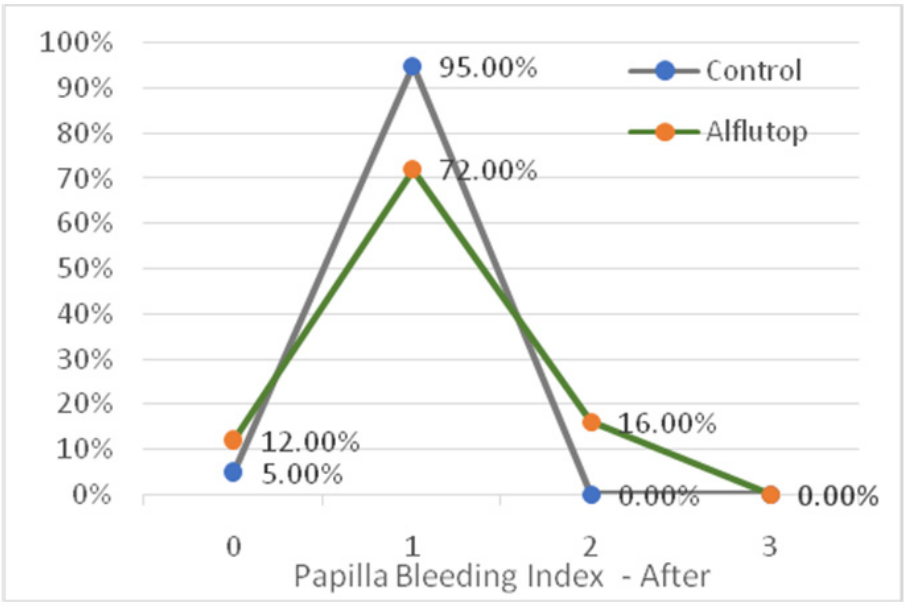

Figure 3. Evolution of Papilla Bleeding Index in cases compared to controls.

A statistically significant reduction in pathologic tooth mobility was observed in patients from group I, compared to the control group, for cases with first-degree tooth mobility ($p = 0.02$), as well as for lesions exhibiting second-degree tooth mobility ($p = 0.045$) (Figure 4).

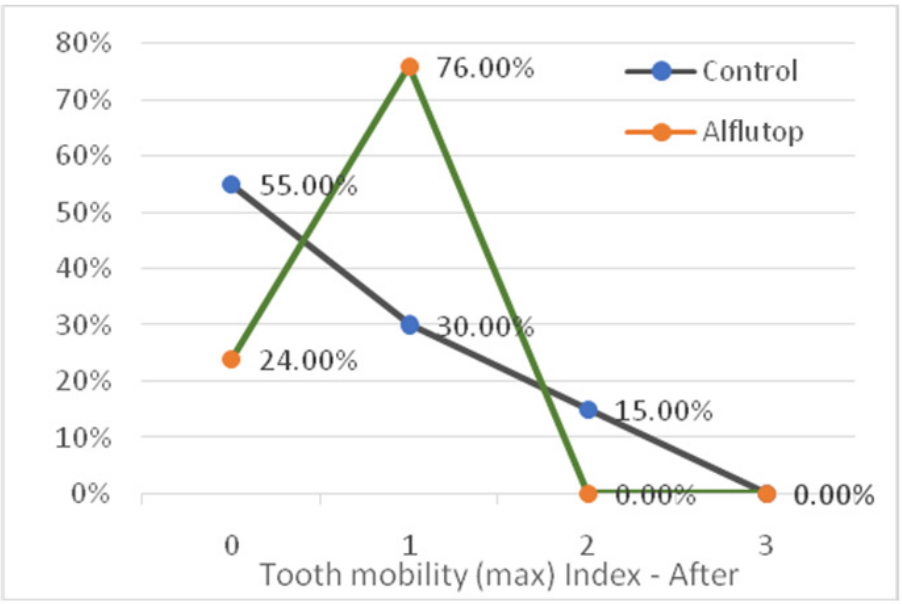

Figure 4. Evolution of tooth mobility in both groups after therapy.

Maximum PD significantly reduced in both groups when comparing initial and final measurements (before and after therapy) ($p = 0.001$), but the reduction rate was not statistically significant among cases vs. controls ($p = 0.356$).

4. Discussion

This preliminary study aimed to evaluate the clinical effects of treatment with SRP and Alflutop®, compared with the clinical effects of SRP alone. All the participants from group I tolerated the Alflutop® therapy well, and no side effects were noticed as other studies mentioned before [21,22]. The clinical effects of the Alflutop® solution used in

the test study group in conjunction with SRP resulted in a reduction in GI and PBI scores. Additional therapy with Alflutop® can also contribute to a reduction in inflammation not only in gingival tissues but also at the level of the periodontal ligament fibers, suggested by the decrease in pathologic tooth mobility, supporting the hypothesis of anti-inflammatory action in both gingival tissues and periodontal ligament fibers. This reduction in pathologic tooth mobility after Alflutop® therapy was noticed more often in sites with severe inflammation than in sites with advanced bone loss.

Periodontal disease could have some characteristics similar to osteoarticular diseases, being characterized by the loss of tooth-supporting tissues (alveolar bone and periodontal ligaments) induced by an immune response activated by periodontal pathogens. This is the reason why we used Alflutop® infiltrations as an adjuvant for periodontal treatment. The elimination of pathogen microbiota from periodontal pockets is crucial, but the need for arresting bone loss mechanisms led to the use of different healing methods and the use of different compounds, such as marine-derived biomaterials, to provide healing [23–25].

The stimulation of the chondrocyte proliferation could be considered a therapeutic solution for periodontal disease as it was revealed in osteoarticular diseases [22]. Periodontal tissues are supporting structures of both alveolar bone and periodontal ligaments, which can be considered a relatively inflexible joint.

This was the main aspect that led us to choose marine fish extract (Alflutop®) for periodontal anti-inflammatory and regeneration therapy.

Periodontal disease involves both alveolar bone and periodontal ligament resorption, as well as endodontic periapical lesions. Histological investigations have shown the osteoregenerative abilities of Alflutop® can possess a significant clinical efficiency for temporary placement into root canals in the treatment of periapical bone defects and for stimulating the regeneration of the damaged periapical tissues [18,26]. For periodontal therapy, the active substance should be administrated via infiltration, in the mobile mucosa, in front of the periodontally compromised teeth. If the periodontal destruction is generalized, the product will be injected into the mobile mucosa in front of canine–premolar teeth [1]. Therapeutic efficacy at the periodontal level could be improved by delivering drugs directly to the oral mobile mucosa [27] or by using other marine-derived drug-delivery biomaterials, such as chitosan [28].

Several studies [18,29,30] have shown that, in the case of periapical endodontic lesions, Alflutop® solution, applied intracanally, had regenerative properties observed one month after treatment.

Because both periodontal disease and rheumatoid arthritis have similar pathways [25,29], natural compounds with anti-inflammatory effects and regenerative properties are needed in order to arrest inflammation and to stimulate an organism to regenerate lost tissues. If the regenerative effects proven by studies [21,24] can be expanded on periodontal lesions, we expect Alflutop® therapy to have a long-term stimulation effect on the alveolar bone's regeneration, but this will be a subject of future research. It has been shown that biomaterials for the periodontal ligament and bone regeneration provide good results in terms of maintaining bone volume, also offering a high percentage of vitality, safety, and lack of complications [24,26,31].

The strength of the study might be that it includes both men and women of different ages. Additionally, no similar study has been published before; this could reflect its originality, but could also be a limitation because the comparison of the study results with similar research is currently impossible. A limitation of the study is the random selection of the participants among the patients addressed for periodontal examination. Due to the current pandemic variations, the addressability of patients to dental care decreased, and an invitation for study participation could have a very low response rate. Furthermore, the level of oral hygiene varied between the subjects during the study. The low number of study participants is one final limitation; this could be the consequence of the current pandemic because 23 of the initially enrolled patients did not finalize the protocol, even though the study protocol did not require a long-term commitment. Those 9 patients from

the test group and 14 patients from the control group presented similar initial periodontal conditions to the rest of the patients, but their periodontal condition after treatment could not be recorded, which might influence the final findings.

5. Conclusions

The marine fish extract Alflutop® is a natural chondroprotective product with anti-inflammatory effects, contributing to regeneration at the cartilage level.This clinical investigation suggests that the marine fish extract (Alflutop®) could have a certain therapeutic efficiency in periodontal healing in terms of reductions in clinical signs of inflammation and tooth mobility. This study is limited to a number of patients but provides information that can be used in future research on the therapeutic efficacy of Alflutop® marine fish extract. Further research is also needed on product compliance and acceptance by different populations and age groups.

Author Contributions: Conceptualization, C.G.P. and A.C.; methodology, C.B.-N.; software, E.E.Ș.; validation, C.G.P.; formal analysis, E.D. and G.R.; investigation, R.A.P.; data curation, A.C. and G.R.; writing—original draft preparation, E.R.C. and C.G.P.; writing—review and editing, L.L.H. and R.A.P.; visualization, E.D.; writing—review, editing and validation, L.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Ovidius University Constanta, Romania (protocol code10788/30.08.2021).

Informed Consent Statement: Written informed consent was obtained from all subjects involved in the study.Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: Not applicable.

Acknowledgments: The findings expressed in this paper are those of the authors.

Conflicts of Interest: All authors have equal contribution and declare no conflict of interest.

References

1. Dumitriu, H.T. *Tratat de Parodontologie*; ViațaRomânească: București, Romania, 2015; pp. 548–550.
2. Lindhe, J.; Karring, T.; Lang, P. *Clinical Periodontology and Implant Dentistry*, 4th ed.; Blackwell Munksgaard: Oxford, UK, 2003; pp. 50–60, 403–413.
3. Rusu, D.; Boariu, M.; Stratul, Ș.; Bojin, F.; Paunescu, V.; Calniceanu, H.; Șurlin, P.; Roman, A.; Milicescu, Ș.; Caruntu, C. Interaction between a 3D collagen matrix used for periodontal soft tissue regeneration and T-lymphocytes: An in vitro pilot study. *ExpTher. Med.* **2019**, *17*, 990–996. [CrossRef]
4. An, S.; Huang, X.; Gao, Y.; Ling, J.; Huang, Y.; Xiao, Y. FGF-2 induces the proliferation of human periodontal ligament cells and modulates their osteoblastic phenotype by affecting Runx2 expression in the presence and absence of osteogenic inducers. *Int. J. Mol. Med.* **2015**, *36*, 705–711. [CrossRef]
5. Pugliese, L.S.; Merado, A.P.; Reis, S.R.; Andrade, Z.A. The influence of low-level laser therapy on biomodulation of collagen and elastic fibers. *PesquiOdontol. Bras.* **2003**, *17*, 307–313. [CrossRef] [PubMed]
6. Rab, A.; Siraj, K.; Irshad, M.; Latif, A.; Naz, S.; Bashir, S.; Rafique, M.S. Laser irradiation effects on structural, morphological and mechanical properties of ZirCAD dental ceramic. *Dig. J. Nanomater. Biostruct.* **2021**, *16*, 677–684.
7. Pușcașu, C.G.; Dumea, E.; Petcu, L.C. Cardiovascular disease and diabetes, potential risk factors for periodontal disease. *Acta Med. Mediterr.* **2019**, *35*, 3177–3182. [CrossRef]
8. Puşcaşu, C.G.; Ștefănescu, C.L.; Murineanu, R.M.; Grigorian, M.; Petcu, L.C.; Dumea, E.; Sachelarie, L.; Puşcaşu, R.A. Histological Aspects Regarding Dental Pulp of Diabetic Patients. *Appl. Sci.* **2021**, *11*, 9440. [CrossRef]
9. Marques, M.M.; Preira, A.N.; Fujihara, N.A.; Nogueira, F.N.; Eduardo, C.P. Effect of low-power laser irradiation on protein synthesis and ultrastructure of human gingival fibroblasts. *Lasers Surg. Med.* **2004**, *34*, 260–265. [CrossRef] [PubMed]
10. Apetroaei, M.; Rau, I.; Paduretu, C.C.; Lilios, G.; Schroder, V. Pharmaceutical Applications of Chitosan Extracted from Local Marine Sources. *Rev. Chim.* **2019**, *70*, 2618–2621. [CrossRef]
11. Bucur, L.; Ionus, E.; Moise, G.; Gîrd, C.; Schroder, V. GC-MS Analysis and bioactive properties of zingiberisrhizoma essential oil. *Farmacia* **2020**, *68*, 280–287. [CrossRef]
12. Ohtani, M.; Nishimura, T. The preventive and therapeutic application of garlic and other plant ingredients in the treatment of periodontal diseases (Review). *ExpTher. Med.* **2020**, *19*, 1507–1510. [CrossRef] [PubMed]

13. Svetlova, M.S.; Ignatev, V.K. Use of Alflutop in the treatment of patients with osteoarthrosis. *Klinicheskaiameditsina* **2004**, *82*, 52–55.
14. Olariu, L.; Dumitriu, B.; Buse, E.; Rosoiu, N. The "in vitro" effect of Alflutop® product on some extracellular signaling factors involved in the osteoarthicular pathology inflammation. *Acad. Rom. Sci. Ann. Ser. Biol. Sci.* **2015**, *4*, 7–17.
15. Olariu, L.; Dumitriu, B.; Ene, D.M.; Pavlov, A.; Pyatigorskaya, N.; Rosoiu, N. Alflutop modulates "in vitro" relevant mechanisms of osteoarthritic pathology. *Acad. Rom. Sci. Ann.—Ser. Biol. Sci.* **2017**, *6*, 82–99.
16. Olariu, L.; Pyatigorskaya, N.; Dumitriu, B.; Pavlov, A.; Vacaru, A.M.; Vacaru, A. "In vitro" chondro-restitutive capacity of Alflutop® proved on chondrocytes cultures. *Rom. Biotechnol. Lett.* **2016**, *22*, 12047–12053.
17. Noskov, C.M.; Sherina, T.A.; Parula, O.M. The role of Alflutop in the treatment of primary osteoarthritis. *Therapy* **2016**, *2*, 32940–32945.
18. Borysenko, A.V.; Palamarciuk, S.I. Usage of paste for temporary placement in the treatment of chronic apical periodontitis. *IJMD* **2012**, *16*, 17–20.
19. Tonetti, M.S.; Greenwell, H.; Kornman, K.S. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. *J. Clin. Periodontol.* **2018**, *45* (Suppl. 20), S149–S161. [CrossRef]
20. Agasarov, L.G. Pharmacopuncture in Dorsopathy Treatment. *J. Acupunct. Meridian Stud.* **2008**, *2*, 110–113. [CrossRef]
21. Olariu, L.; Dumitriu, B.; Carciun, L.; Buse, E.; Rosoiu, N.; Bojinca, M.; Papacocea, T. The in vitro influence of a pharmaceutically active small sea fish extract on apoptosis and proliferation mechanisms amplified by inflammatory conditions. *Farmacia* **2018**, *66*, 524–529. [CrossRef]
22. Cherkasova, V.G.; Muravyev, S.V.; Chaynikov, P.N.; Kulesh, A.M.; Wetzler, M.V. Pathogenetic treatment of large joint osteoarthritis at the clinic for sports medicine. *GenijOrtopedii* **2019**, *25*, 413–423. [CrossRef]
23. Lee, H.-S.; Byun, S.-H.; Cho, S.-W.; Yang, B.-E. Past, Present, and Future of Regeneration Therapy in Oral and Periodontal Tissue: A Review. *Appl. Sci.* **2019**, *9*, 1046. [CrossRef]
24. Burlui, A.; Sachelarie, L.; Romila, L.E.; Farcas, D.M. Achievement of dental implant in patients with osteoporosis. *IJMD* **2019**, *23*, 134–137.
25. Sachelarie, L.; Farcas, D.M.; Dartu, L.; Vasiliu, M.; Daraba, O.; Nazarie, S.; Mocanu, C.; Burlui, V. Comparative study of diseases of the stomatognathic system and specific parameters of osteoporosis. *Osteoporos. Int.* **2016**, *27*, 845–848. [CrossRef]
26. Farcas, D.M.; Sachelarie, L.; Romila, L.; Burlui, A.; Șuteu, C. The correlation between low bone density and periodontal disease. *IJMD* **2020**, *23*, 537–540.
27. Vladu, A.F.; Marin, S.; Neacșu, I.A.; Trușcă, R.D.; Kaya, M.G.A.; Kaya, D.A.; Popa, A.M.; Poiană, C.; Cristescu, I.; Orlov, C.; et al. Spongious filler based on collagen -hydroxyapatite-eugenol acetate with therapeutic potential in bone cancer. *Farmacia* **2020**, *68*, 313–321. [CrossRef]
28. Cicciù, M.; Fiorillo, L.; Cervino, G. Chitosan Use in Dentistry: A Systematic Review of Recent Clinical Studies. *Mar. Drugs* **2019**, *17*, 417. [CrossRef] [PubMed]
29. Gordeev, A.V.; Galushko, E.A.; Savushkina, N.M.; Lila, A.M. Is periodontitis a harbinger of rheumatoid arthritis? *Rheumatol. Sci. Pract.* **2018**, *56*, 613–621.
30. Son, S.-J.; Jang, S.; Rah, H.; Choi, S. Characteristics of the Dental Pulp and Periodontal Ligament Stem Cells of the Yucatan Miniature Pig. *Appl. Sci.* **2021**, *11*, 9461. [CrossRef]
31. Sukhikh, S.; Babich, O.; Prosekov, A.; Patyukov, N.; Ivanova, S. Future of Chondroprotectors in the Treatment of Degenerative Processes of Connective Tissue. *Pharmaceuticals* **2020**, *13*, 220. [CrossRef] [PubMed]