Original Article

Efficacy of Complex Phytoadaptogens as an Adjunct to Non-surgical Treatment of Chronic Periodontitis: A Randomized Clinical Trial

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Received : 20-02-21
Revised : 08-03-21
Accepted : 12-04-21
Published : 10-06-21

ABSTRACT

Background: Many herbal formulas are used in dentistry in the complex treatment and prevention of periodontitis, but it is not always possible to achieve a long-term remission and stimulate regeneration of periodontal structures. **Aim:** The aim of this randomized clinical trial was to assess the efficacy of chronotherapy with complex phytoadaptogens (CFA) as an adjunct to non-surgical periodontal treatment (NSPT) and to achieve long-term remission. **Materials and Methods:** Forty systemically healthy patients with chronic generalized periodontitis (probing pocket depth ≥5 mm) were randomly divided into two groups: patients in one group received treatment with NSPT alone (group 2), whereas patients in another group received CFA in addition to NSPT (group 3). Twenty individuals with healthy periodontium (group 1) composed a control group. The clinical outcomes, Simplified Oral Hygiene Index (OHI-S), Sulcus Bleeding Index (SBI), Periodontal Index (PI), and Doppler ultrasound results, were assessed on baseline, after treatment, and 6 months after treatment. **Results:** There was a statistically significant difference between groups 2 and 3, in favor of group 3 in terms of microcirculation parameters—S ($P = 0.03$), M ($P = 0.02$), D ($P = 0.03$), and RI ($P = 0.005$); indicators of PI ($P = 0.005$), SBI ($P = 0.03$), and OHI-S ($P = 0.006$) were closer to the normal values during 6-month follow-up. Also there was a statistical difference ($P < 0.05$) at all time points compared with controls, for several parameters in intragroup comparison. **Conclusion:** The data obtained confirm the hypothesis that CFA application in chronic periodontitis treatment is more than appropriate for long-term prevention due to their immunomodulatory, anti-inflammatory, antioxidant, stress-limiting, chronotropic effects.

KEYWORDS: *Acantopanax senticosus, Glycyrrhiza glabra, microcirculation, periodontitis, Rhodiola rosea*

INTRODUCTION

Periodontitis is a common chronic inflammation of supporting tooth structures which is mainly associated with periodontal pathogens—*Porphiramonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia*.[1,2] Chronic periodontitis is the most difficult-to-treat disease of the maxillofacial region, which can be explained by its widespread prevalence in the population[3]; loss of a large number of intact teeth[4]; the development of chronic infection foci due to formation of gingival and periodontal pockets; and their role in the development of somatic pathology.[5,6]

Treatment of chronic periodontitis requires consideration of dental plaque microorganisms,

Access this article online

Quick Response Code:

Website: www.jispcd.org

DOI: 10.4103/jispcd.JISPCD_56_21

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How to cite this article: Dzampaeva ZV, Datieva FS, Esenova ZS, Takoeva EA. Efficacy of complex phytoadaptogens as an adjunct to non-surgical treatment of chronic periodontitis: A randomized clinical trial. J Int Soc Prevent Communit Dent 2021;11:348-56.

body response, as well as recovery and pathogenic mechanisms of the pathological process.[7-10] In routine practice, the treatment of inflammatory periodontal diseases is successfully performed by removing supra- and subgingival dental plaques, which allows only temporary elimination of the effect of pathogenic microorganisms on the periodontium.[11-13]

Currently, many herbal preparations are used in dentistry for complex treatment of periodontitis. However, it is not always possible to achieve long-term remission of periodontitis and to stimulate the regeneration of periodontal tissues.[14] We propose a new cocktail composed of complex phytoadaptogens (CFA), which includes *Glycyrrhiza glabra*, *Rhodiola rosea*, and *Acanthopanax senticosus* (RF Patent No. 2019137264). These are immunomodulators and antioxidants, possessing anti-stress activity—they modulate the synthesis of cortisol and adrenocorticotropic hormone under stress, increase neurohormone levels (endorphins and dopamine), and exhibit neuroprotective activity, thereby affecting the etiological factors and pathogenic mechanisms of periodontitis.[15-17] The use of CFA leads to non-specifically increased resistance.[18] CFA can be used for long-term prophylaxis and treatment, as they rarely cause side effects and are easily integrated in the biochemical processes of the body.[18,19]

The anti-inflammatory effect of *G. glabra* and *R. rosea* is due to several metabolites,[20,21] for example, glycyrrhetinic acid exerts a preconditioning effect in ischemic/reperfusion injury.[22-24]

A. senticosus regulates homeostatic responses via the neuroendocrine immune system (NEIM); they control stress-activated molecular chaperons (Hsp70), Forkhead Box Protein O DAF-16 transcription factor, cortisol, and nitric oxide.[15-17] Under stress conditions, adaptogens increase the functional activity of the pineal gland, with their effectiveness depending on the season.[25]

The mechanism of alveolar bone loss has been studied through the discovery of a receptor activator of nuclear factor-κb ligand (RANKL). RANKL is a ligand for RANK receptors on the surface of osteoclasts and functions as a key factor in osteoclast differentiation and activation. Osteoblasts also secrete osteoprotegerin, a glycoprotein that prevents RANKL from binding to RANK.[26] *G. glabra* glycyrrhizin is known to significantly inhibit RANKL-induced osteoclastogenesis and suppresses the expression of nuclear factor of activated T cells 1 (NFATc1) and acid phosphatase resistant to tartrate, cathepsin K, OSCAR (osteoclast-associated immunoglobulin-like receptor). Glycyrrhizin significantly reduces the secretion of tumor necrosis factor-α (TNF-α), IL-1β, and IL-6. In addition, glycyrrhizin reduces the production of reactive oxygen species (ROS) in osteoclasts by inducing AMPK (AMP-activated protein kinase) phosphorylation and NRF2 (nuclear factor-erythroid 2-related factor 2) nuclear transfer, which leads to an increase in the activity of antioxidant enzymes such as HO-1 (heme oxygenase-1), NQO-1 (quinone reductase), and GCLC (γ-glutamylcysteine ligase catalytic subunit).[27]

The aim was to increase the efficacy of chronic generalized periodontitis treatment and to achieve long-term remission by including chronotherapy with CFA in non-surgical periodontal treatment (NSPT).

Materials and Methods

Study design

This was a randomized controlled clinical trial. The study was conducted from February 2019 to September 2020. The study was approved by the Biomedical Ethics Committee (protocol number 6 on January 24, 2019) and also registered on Clinicaltrials.gov (NCT04623164). The study was conducted in accordance with the Helsinki Declaration. The sample size was calculated taking into account an effect size of 0.40, a significance level of 0.05, and a study power of 0.80; thus the sample size was 20.

The present study included 40 systemically healthy individuals with chronic generalized periodontitis (probing pocket depth (PPD) ≥5 mm, plaque index score <1.5, ability to maintain optimal oral hygiene after the initial phase of treatment) [Figure 1].

Each study participant with chronic generalized periodontitis was assigned a number, and then a random number generator divided all selected patients into two groups. Twenty individuals with healthy periodontium (group 1) composed a control group.

- Group 1—control (20 patients with healthy periodontium) (21.8±1.6 years);
- Group 2—20 patients who received NSPT (38.6 ± 2.5 years);
- Group 3—CFA application (20 patients who received NSPT + 28-day treatment with CFA) (39.6 ± 3.4years).

Inclusion criteria include

The presence of chronic periodontitis with PPD ≥5 mm; plaque index score <1.5; age from 20 to 45 years; without somatic pathology according to the patients.

Exclusion criteria include

Age under 20 and over 45; diabetes; chronic somatic diseases; infectious diseases; malignant neoplasms

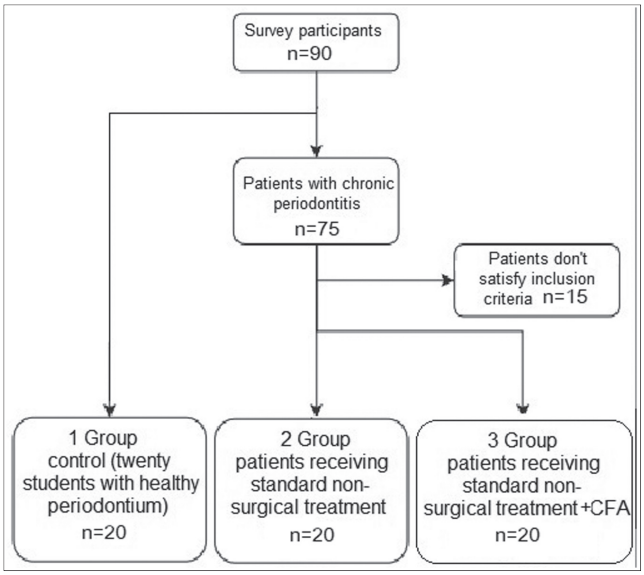

Figure 1: Participant flow diagram

of various organs and systems; viral infections; autoimmune diseases; mental illness; pregnancy and lactation in women.

Patients of all groups received recommendations on oral hygiene (including brushing techniques, use of interdental floss, and/or brushes), teeth scaling with a UDS-L LED ultrasonic scaler (Woodpecker, China), and Graceys curettes (Hu Friedy, Chicago, IL, USA). Periodontal pockets were irrigated with 0.12% chlorhexidine gluconate. Patients were advised to rinse their mouth three times a day for 14 days using 0.12% chlorhexidine gluconate, eliminating traumatic occlusion.[11] If necessary, antimicrobial therapy was prescribed in group 2 according to the standard scheme: amoxicillin + clavulanic acid by mouth, 625 mg 2 times a day for 7–10 days.

Control examinations were performed on baseline, after treatment, and 6 months after treatment. After each study time point, the patients were able to visit the dental office to assess the periodontal status.

The examination included:

1. Östberg's questionnaire to determine the chronotype once before treatment;
2. Primary outcome measures—Simplified Oral Hygiene Index (1964) (OHI-S); Sulcus Bleeding Index (SBI) (1975); Periodontal Index (PI) (1956) (baseline, after treatment, and 6 months after treatment);
3. Secondary outcome measures—systolic (S), diastolic (D), mean (M) blood flow velocity, PI—pulsatility index (Gosling index), RI—resistivity index (Pourcelot index), SD—Stewart index (baseline, after treatment, and 6 months after treatment).

CFA application

The cocktail of CFA is composed of 70% alcoholic extract of *G. glabra* and 40% alcoholic extracts of *R. rosea* and *A. senticosus* in a 2:1:1 ratio.[19] The CFAs were used in group 3 after NSPT. Following NSPT, the patient filled out Östberg's questionnaire to determine the chronotype for the selection of the CFA treatment regimen. Treatment with CFA was carried out during periods of exacerbation of chronic periodontitis for 28 days, with the dosage of CFA depending on the person's chronotype—45 drops in the morning before 10.00 o'clock for morning chronotype; 20 drops three times a day for mixed chronotype; 30 drops at 14.00 o'clock and 20 drops at 19.00 o'clock for evening chronotype.

Ultrasonic dopplerography

Doppler ultrasound (Angiodin-PC, Russia, 16 MHz probe) was used to diagnose microcirculation disorders. In the attached gingiva of the mucobuccal fold near the lower incisors, we selected an area without large blood vessels to study fluid exchange in tissues—systolic (S), diastolic (D), mean (M) blood flow velocity, PI—pulsatility index (Gosling index), RI—resistivity index (Pourcelot index), and SD—Stewart index.[28] The examination was performed before and after treatment and 6 months after treatment in each experimental group.

Statistical analysis

Statistical analysis was performed using the Statistica 10.0 software (StatSoft, Inc., Russia). The data were analyzed using a non-parametric method with the determination of the median (Md) and interquartile range (25th and 75th percentiles) due to the small number of variants in the sample. Comparison between groups was performed using the Kruskal–Wallis test. Results in the same group before and after the study were assessed using the Wilcoxon test. The comparison was performed by comparing data obtained before and after completion of treatment and 6 months after treatment. Correlation analysis was carried out using Spearman's method. Significance level was $P < 0.05$.

Results

After processing the data collected from Östberg's questionnaires, the following distribution of the patients by chronotype was found [Figure 2], which determined the mode of CFA application.

Changes in the Simplified Oral Hygiene Index (OHI-S) (1964); Sulcus Bleeding Index (SBI) (1975); and

Periodontal Index (PI) (1956) in group 3 clinically prove the preventive effect of CFA during follow-up for 6 months [Table 1].

In group 2, the systolic, diastolic, and mean blood flow velocities were reduced in comparison with the control group (healthy periodontium). After non-surgical treatment of periodontitis, the parameters of microcirculation approached the control values. There were differences between microcirculation parameters in patients 6 months after treatment and the control group [Figure 3].

In group 3, after 28-day treatment of periodontitis with CFA, the systolic (S) ($P = 0.005$), diastolic (D) ($P = 0.01$), and mean (M) ($P = 0.009$) blood flow velocities increase relative to the baseline level. Six months after 28 days of treatment with CFA parameters of microcirculation approached control values.

There were no statistically significant differences between the microcirculation parameters after treatment in groups 2 and 3, but they returned to the control range 6 months after treatment in group 3 compared with the patients in group 2, who did not receive CFA treatment: S ($P = 0.03$), D ($P = 0.02$), and M ($P = 0.03$), RI ($P = 0.005$) were closer to the control, which is evidence of greater efficacy of NSPT with CFA (cases of exacerbation of chronic periodontitis within 6 months after treatment were not observed, in contrast to patients from group 2) [Figure 3].

Consider the data of the correlation intrasystemic analysis of microcirculation parameters by the Spearman method in control group and baseline, after treatment, and 6 months after treatment in groups 2 and 3 [Table 2].

Discussion

The obtained results demonstrate that 28-day treatment with CFA in group 3 in the absence of side effects significantly reduces the inflammatory process and prevents damage to periodontal structures and the negative effects of periodontal pathogens—*Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*.[1,2] It is important to note that clinical parameters (PI, SBI, OHI-S) and microcirculation parameters 6 months after treatment were significantly closer to the control values after CFA in group 3 compared with group 2, which is evidence of the treatment effect prolongation and proves the presence of a preventive effect [Table 1].

The dominant pathomorphological process of periodontitis is inflammation, and inflammation mechanisms are deployed with the direct involvement of the microcirculation system. In groups 2 and 3, baseline, systolic (S), diastolic (D), and mean (M)

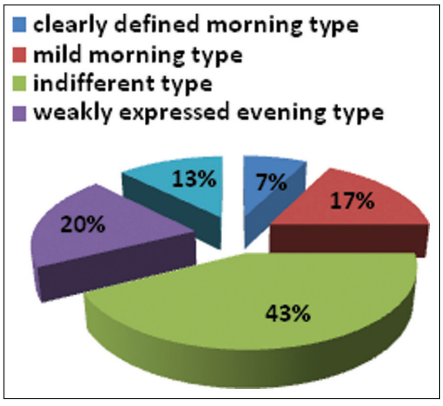

Figure 2: The results of Östberg's questionnaire

Table 1: Comparison of the clinical parameters at varying time intervals between test sites

	Group 2	Group 3
	OHI-S	
Baseline	2.3 (2; 2.5)	2.2 (2; 2.4)
After treatment	1.4 (1.3; 1.6)	1.15 (2; 2.3)
	$P^{*(\dagger)}$=0.005	$P^{*(\dagger)}$=0.005
		$P^{***(\ddagger)}$=0.006
6 months	1.25 (1.2; 1.9)	1 (1; 1.1)
	$P^{*(\dagger)}$=0.005	$P^{*(\dagger)}$=0.005
		$P^{**(\dagger)}$=0.02
		$P^{***(\ddagger)}$=0.007
	SBI	
Baseline	1.7 (1.5; 2)	1.75 (1.6; 2)
After treatment	0.85 (0.7; 1)	0.6 (0.5; 0.7)
	$P^{*\dagger}$=0.005	$P^{*\dagger}$=0.005
		$P^{***\ddagger}$=0.007
6 months	1.1 (0.9; 1.3)	0.7 (0.6; 0.9)
	$P^{*\dagger}$=0.005	$P^{*\dagger}$=0.005
	$P^{**\dagger}$=0.005	$P^{***\ddagger}$=0.005
	PI	
Baseline	3.4 (2.88; 3.6)	3.2 (2.9; 3.6)
After treatment	2 (1.9; 2)	1.3 (1.2; 1.9)
	$P^{*\dagger}$=0.005	$P^{*\dagger}$=0.005
6 months	1.8 (1.7; 1.9)	1.1 (1; 1.2)
	$P^{*\dagger}$=0.005	$P^{*\dagger}$=0.005
	$P^{***\ddagger}$=0.005	$P^{***\ddagger}$=0.005

OHI-S: Simplified Oral Hygiene Index John C. Greene, Jack R. Vermillion; SBI: Sulcus Bleeding Index H.R. Muhleman; PI: Periodontal Index A.L. Rusell (1956) on baseline, after treatment, and 6 months after treatment; n=20 for each group; †Wilcoxon test, ‡Kruskal–Wallis test. Groups: Group 2: non-surgical periodontal treatment; Group 3: non-surgical periodontal treatment + 28-day use of complex phytoadaptogens (CFA). *Statistically significant difference (P<0.05) compared with indicators to baseline in the same group; **to the indicators after treatment in the same group;***indicators of group 3 in relation to group 2 on identical day.

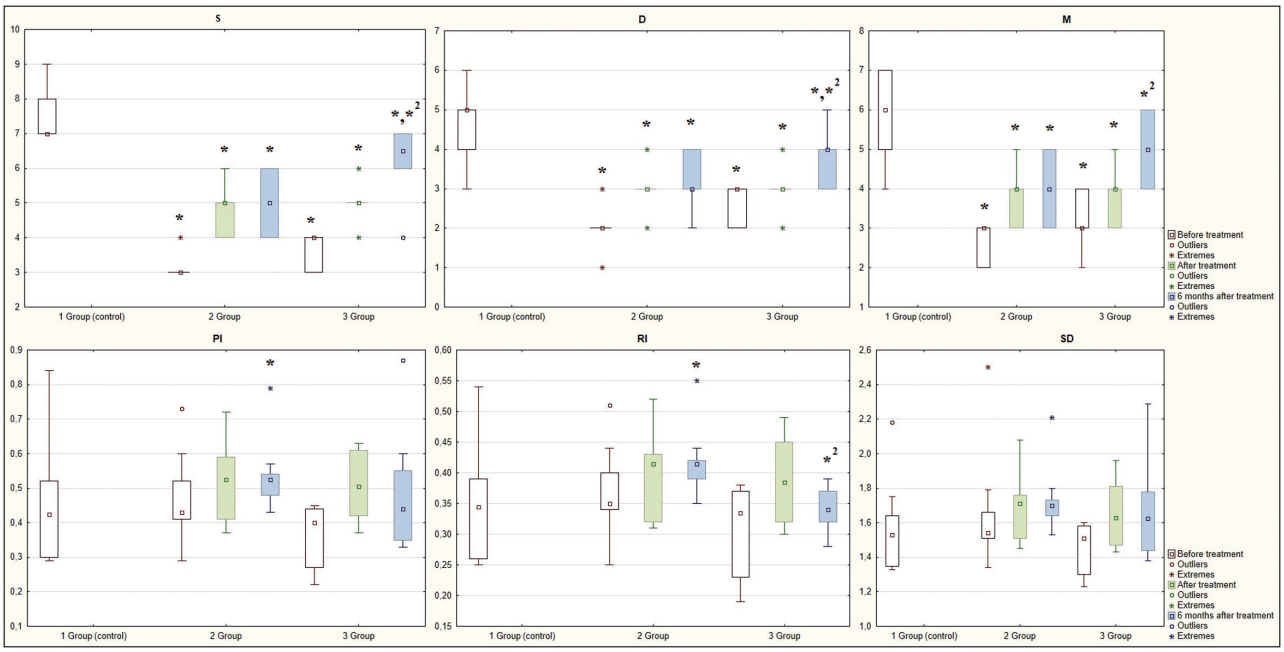

Figure 3: Dynamics of microcirculation disorders in all groups (box plot of multiple variables, $n = 20$ for each group). S, systolic (Vas, mm/s); M, mean (Vam, mm/s), D, diastolic (Vad, mm/s) blood flow velocity; PI, pulsatility index (Gosling index); RI, resistivity index (Pourcelot index); SD, Stewart index in the region of attached gingiva of transitional fold. Groups: Group 1: control (healthy periodontium); Group 2: NSPT; Group 3: NSPT + 28-day use of CFA. *to control; *^{n} to the group in relevant day; n the number of groups; $P < 0.05$

Table 2: Correlation intrasystemic analysis of microcirculation parameters using Spearman's method

Baseline								
	Control			Group 2			Group 3	
	P	*P*-value		*P*	*P*-value		*P*	*P*-value
S&D	0.68	0.029*	D&RI	−0.64	0.04*	S&M	0.69	0.016*
S&M	0.81	0.004*	D&SD	−0.67	0.03*	PI&RI	0.81	0.000002*
D&RI	−0.63	0.04*	PI&RI	0.79	0.0004*	PI&SD	0.94	0.00003*
D&M	0.95	0.00002*	PI&SD	0.91	0.0003*	RI&SD	0.99	0.0000*
PI&RI	0.99	0.00003*	RI&SD	0.99	0.0000*			
RI&SD	0.99	0.0000*						
After treatment								
	Control			Group 2			Group 3	
	P	*P*-value		*P*	*P*-value		*P*	*P*-value
S&D	0.68	0.029*	S&D	0.74	0.01*	S&M	0.84	0.001*
S&M	0.81	0.004*	D&M	0.74	0.01*	D&PI	−0.71	0.019*
D&RI	−0.63	0.04*	D&PI	−0.71	0.01*	D&RI	−0.8	0.004*
D&M	0.95	0.00002*	PI&RI	0.95	0.000019*	PI&RI	0.95	0.000014*
PI&RI	0.99	0.00003*	PI&SD	0.95	0.000014*	D&SD	−0.8	0.004*
RI&SD	0.99	0.0000*	RI&SD	0.99	0.0000*	PI&SD	0.95	0.000014*
6 months after treatment								
	Control			Group 2			Group 3	
	P	*P*-value		*P*	*P*-value		*P*	*P*-value
S&D	0.68	0.029*	D&M	0.72	0.01*	S&M	0.78	0.006*
S&M	0.81	0.004*	RI&SD	0.82	0.0001*	D&RI	−0.65	0.008*
D&RI	−0.63	0.04*				D&M	0.80	0.02*
D&M	0.95	0.00002*				PI&RI	0.76	0.03*
PI&RI	0.99	0.00003*				RI&SD	0.84	0.002*
RI&SD	0.99	0.0000*						

S, systolic (Vas, mm/s); M, mean (Vam, mm/s); D, diastolic (Vad, mm/s) blood flow velocity; PI, pulsatility index (Gosling index); RI, resistivity index (Pourcelot index); SD, Stewart index. *Statistically significant correlations (P<0.05)

blood flow velocities significantly decreased compared with controls, which is associated with the loss of the ability to actively contract due to spasm of arterioles and venous stasis in the microvasculature with pronounced rheological disturbances and stasis (decreased perfusion) [Figure 3]. Analysis of changes in microcirculation parameters before treatment demonstrates that changes in microcirculation sharply disrupt the tissue homeostasis, self-regulation of cells, which leads to an exacerbation of the inflammatory process in the periodontium.[29] Ischemia causes metabolic disorders (increased lipid peroxide content).

Polymorphonuclear leukocytes (PMNLs) are the first line of defense against periodontal pathogens [Figure 4A–C]. As part of an oxygen-dependent mechanism, PMNL produces large amounts of ROSs during phagocytosis of periodontal pathogens. ROSs are highly toxic substances that are produced under normal physiological conditions and are subsequently removed by antioxidant systems to prevent tissue damage. The cells and intercellular matrix of the connective tissue have a low level of antioxidant defense enzymes, lipids, and water-soluble antioxidants, and therefore, they are not resistant to an excess of lipid peroxidation products. Thus, ROS suppresses collagen synthesis. That is why an increased ROS content and oxidative stress play a significant role in the progression of alveolar bone loss.[30] The use of CFA prevents the accumulation of lipid peroxidation products in the periodontium, exerting an antioxidant effect. By activating protein kinase A through the conversion of ATP into c-AMP, they stimulate the enzymatic systems of metabolism, which leads to the accumulation of high-energy compounds and increased energy metabolism [Figure 4D].[31-34]

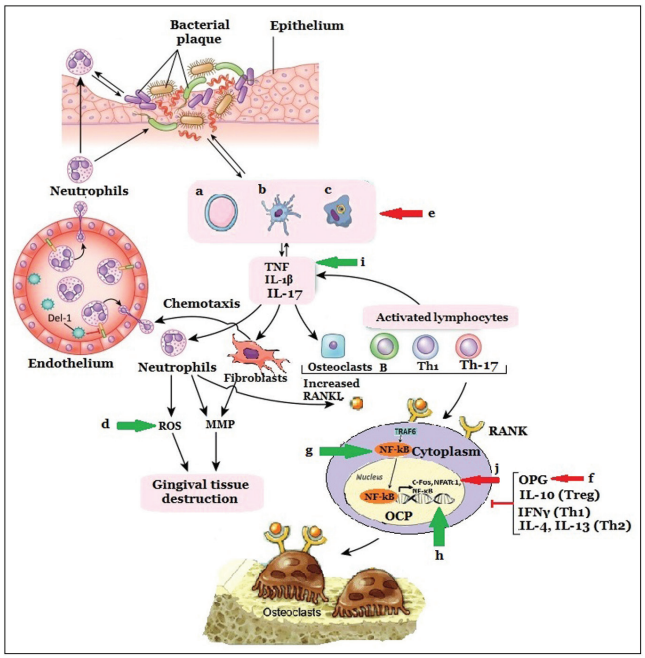

Figure 4: Alveolar bone loss mechanism and its correction with CFA. A. T-lymphocyte. B. Dendritic cell. C. Macrophage. The red arrows show effects of chronic stress (E, F, J) and the green arrows show effects of CFA (D, G, H, I). OCP, osteoclast precursor; OPG, osteoprotegerin; ROS, reactive oxygen species; MMP, matrix metalloproteinases; Th, T helper cells; TNF, tumor necrosis factor; RANKL, receptor activator of nuclear factor kappa-B ligand; NF-κB, receptor activator of nuclear factor kappa-B (RANK); TRAF6, tumor necrosis factor receptor-associated factors; NFATc1, nuclear factor of activated T-cells

Correlation analysis using the Spearman method demonstrated strong correlations between the velocity characteristics of blood flow (S, D, M) and a linear relationship between PI and RI in the control group. In groups 2 and 3, before treatment, functional relationships between the velocity characteristics of blood flow were impaired, and the strength of correlation between PI and RI decreased. In groups 2 and 3, the functional relationships between the velocity characteristics of blood flow are restored after treatment, and the strength of the correlation between PI and RI is close to the control value. In group 2, 6 months after treatment, there was an impairment of the functional relationships between the parameters of microcirculation, which was clinically manifested by an exacerbation of the inflammatory process in the periodontium. In the group 3, on the contrary, all functional relationships between the parameters were restored and close to the control ones in group 1 [Table 2]. Development of a pathological process associated with a deficit in the capillary blood flow volume results in impairment of the mechanisms that regulate transcapillary metabolism and metabolic processes in tissues.[35]

With the growth of civilization, more and more studies confirm the strong correlation between chronic stress and chronic periodontal disease.[36-39] In recent years, significant progress in understanding the mechanisms of osteoclastogenesis has been achieved due to the discovery of the receptor activator of nuclear factor-κb ligand (RANKL). RANKL is a ligand for RANK receptors on the surface of osteoclasts and functions as a key factor in osteoclast differentiation and activation. Osteoblasts also secrete osteoprotegerin, a glycoprotein that prevents RANKL from binding to RANK.[26] Glucocorticoids affect periodontal structures in different ways. On the one hand, during inflammation, glucocorticoids help maintain the integrity of the cell membrane even in the presence of toxins, which reduces edema of periodontal soft

tissues (enhances lipomodulin synthesis and decreases histamine secretion) [Figure 4E]. On the other hand, glucocorticoid exposure leads to rapid bone loss due to the combined effect of decreasing osteosynthesis and increasing bone resorption, as glucocorticoids promote osteoclastogenesis by inhibiting osteoprotegerin (OPG).[26,36]

CFAs affect inflammation in the periodontium by several mechanisms: they modulate the synthesis of cortisol and adrenocorticotropic hormone during stress, increase levels of neurohormones ("happiness hormones"—endorphins, dopamine), exhibit neuroprotective activity, and prolong the stage of resistance of Selye's triad.[15,16,40] Secondary metabolites of adaptogens initiate adaptation of cells to stress, which is called the phenomenon of hormesis or preconditioning[17]; under the influence of Fapri and transcription factors NF-KB and FOXO, neurons adapt to stress that plays a role in the adaptation of the NEIM system to the photoperiod [Figure 4G].[41,42] Glycyrrhizin *G. glabra* significantly inhibits RANKL-induced osteoclastogenesis by suppressing the expression of nuclear factor-activated T cells 1 (NFATc1) [Figure 4H]. Glycyrrhizin significantly reduces the secretion of TNF-α, IL-1β, and IL-6 [Figure 4I] and reduces the production of ROS in osteoclasts, inducing phosphorylation of AMPK (AMP-activated protein kinase) and nuclear transfer of NRF2 (nuclear factor-erythroid 2-related factor 2), which leads to an increase in the activity of antioxidant enzymes.[27] The use of CFA makes it possible to obtain a synergistic effect in various pathological conditions.[16,43]

A chronotherapeutic approach to the use of CFA improves the clinical efficacy of NSPT.[44,45] It has been proven that pharmacokinetics and pharmacodynamics follow the circadian rhythms: optimizing the timing of medication administration taking into account that circadian fluctuations can increase the effectiveness of therapeutic measures.[45,46] Chronotherapy also reduces side effects and improves the overall drug safety. Gingival wound healing, angiogenesis, Smad-mediated transcriptional responses, and nuclear translocations are regulated by circadian rhythms.[47] Glucocorticoids are the most important factors in the transfer of circadian time from SCN to peripheral osteoclasts and that peripheral osteoclast clock can regulate the circadian rhythm of bone resorption by regulating the expression of cathepsin K (CTSK) and nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1).[26] The chronotropic effects of adaptogens enhance the therapeutic effect of CFA and NSPT through the pineal gland with the participation of melatonin and its receptors.[25,48] Melatonin has an anti-stress effect, altering biochemical and neurochemical processes in the hypothalamic structures of the brain.[46,49,50]

The strength of the study is the assessment of the CFA contribution to the clinical outcomes of periodontitis, which has never been studied before. A pronounced prophylactic effect of CFA was proven during the follow-up period (6 months). Also, the main advantage of using CFA is that there is no need to use antibacterial drugs, which eliminate the risk of gastrointestinal side effects.

The limitations of the study are that with a small number of patients in the sample, it is difficult to assess adherence to the treatment; therefore, in the future, we plan to examine a larger number of patients in order to more accurately assess the results of CFA chronotherapy in each individual chronotype. In the future, it is necessary to identify a chronotype more susceptible to chronic periodontitis, as chronostomatology opens up great opportunities for increasing the effectiveness of therapy and early diagnosis.

Conclusions

The data obtained confirm the concept that chronotherapy with CFA in patients with chronic periodontitis relieves clinical manifestations of inflammation in the periodontium without antimicrobial therapy with amoxicillin and clavulanic acid, which is confirmed by the beneficial changes in periodontal indices and microcirculation parameters. The use of CFA is more than advisable for long-term prophylaxis due to their immunomodulatory, anti-inflammatory, antioxidant, stress-limiting, chronotropic effects.

Future scope/clinical significance

It is planned to establish mass production of this herbal composition as a biologically active supplement for the prevention of chronic periodontitis and prolongation of the remission periods.

Acknowledgements

The authors express their appreciation to clinical managers who collaborated in and facilitated the data-collection process.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Authors contributions

All authors had contributed to study conception, data collection, data acquisition and analysis, data interpretation, and manuscript writing. All authors have read and approved the manuscript.

Ethical policy and institutional review board statement

The study received approval from the Biomedical Ethics Committee of Institute of Biomedical Investigations – the Affiliate of Vladikavkaz Scientific Centre of Russian Academy of Sciences (protocol number 6 on January 24, 2019) and also registered on Clinicaltrials.gov (NCT04623164). Study was conducted in accordance with the Declaration of Helsinki.

Patient declaration of consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. Participants were given freedom to withdraw from the trial at any point.

Data availability statement

Not applicable.

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