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| RESEARCH ARTICLE

Efficacy of Bu-Shen Gu-Chi-Wan Combined with Collagen Sponge-Loaded Basic Fibroblast Growth Factor on Periodontal Bone Defects and Gingival Papillae Loss

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| ABSTRACT

The study aimed to evaluate the efficacy and molecular mechanisms of Bu-Shen Gu-Chi-Wan (BSGC) combined with a collagen sponge loaded with basic fibroblast growth factor (bFGF) in treating severe periodontitis. Sixty patients with severe periodontitis were enrolled and randomly assigned to either the bFGF-collagen sponge group (BFGF group) or the BSGC + bFGF-collagen sponge group (BSGC-BFGF group). Both groups underwent open-flap debridement and implantation of a bFGF-collagen sponge; the BSGC-BFGF group additionally received oral BSGC 4 g twice daily for 3 months. Periodontal pocket depth (PD), clinical attachment loss (CAL), gingival index (GI), cone-beam CT bone density (BD), bone height (BH), gingival papilla height (GPH), black-triangle area (BTA), as well as osteocalcin (OCN) and osteoprotegerin (OPG) levels in gingival crevicular fluid were assessed at baseline and at 6 and 12 months post-surgery. The study found that all postoperative parameters improved significantly compared with baseline in both groups ($P < 0.05$). The BSGC-BFGF group exhibited significantly greater reductions in PD, CAL, and GI, and greater increases in BD, BH, and GPH, along with a more pronounced reduction in BTA, than the BFGF group at both 6 and 12 months ($P < 0.05$). OCN and OPG levels peaked at 6 months and remained elevated at 12 months, with levels in the combined group consistently higher than those in the control group ($P < 0.05$). The study concluded that BSGC synergizes with bFGF by suppressing inflammation and activating osteogenic signaling pathways, markedly promoting regeneration of severe periodontal bone defects and reconstruction of the gingival papilla, thus providing a novel strategy for integrative periodontal regenerative therapy.

| KEYWORDS

Bu-Shen Gu-Chi-Wan; basic fibroblast growth factor; severe periodontitis; bone defect; gingival papilla recession

| ARTICLE INFORMATION

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1. Introduction

In 2021, the age-standardized prevalence of severe periodontitis among individuals aged 15 years and older was 12.5% globally, rising to 17.57% in South Asia; WHO concurrently estimated the prevalence of severe periodontitis in those over 15 years old at 19% [1]. Severe chronic periodontitis is characterized by progressive alveolar bone resorption, periodontal attachment loss, and gingival papilla recession, often leading to tooth mobility, impaired masticatory function, and esthetic defects in the anterior

region. Although periodontal basic therapy combined with guided tissue regeneration (GTR) or local application of growth factors has achieved certain progress, traditional approaches still fail to produce predictable bone gain and papilla reconstruction in advanced furcation grade III lesions or deep, narrow vertical bone defects with poor blood supply, and their clinical efficacy remains unsatisfactory [2-4]. Therefore, novel combination therapies are urgently needed to further enhance the regenerative potential of both hard and soft tissues. In recent years, the holistic concept of traditional Chinese medicine (TCM) of "tonifying the kidney, replenishing the marrow, invigorating blood, and promoting tissue regeneration" has shown unique advantages in periodontal tissue engineering[5]. Bu-Shen Gu-Chi-Wan (BSGC), composed of Rehmanniae Radix Praeparata (Shu Di Huang), Drynariae Rhizoma (Gu Sui Bu), Astragali Radix (Huang Qi), and other kidney-tonifying and blood-activating herbs, has been demonstrated by modern pharmacological studies to promote osteoblast proliferation and differentiation through activation of the Wnt/β-catenin and BMP-2/Smad signaling pathways while simultaneously inhibiting osteoclast activity [6]. Basic fibroblast growth factor (bFGF) exerts potent angiogenic, osteoinductive, and soft-tissue-repair effects; however, when used alone, it suffers from a short half-life, the need for repeated administration, and susceptibility to an inflammatory microenvironment [7]. Theoretically, BSGC can provide a sustained and favorable biological milieu for bFGF by systemically regulating bone metabolism and improving local blood supply, whereas bFGF can rapidly initiate cellular proliferation cascades locally. The complementary advantages of the two modalities may overcome current regenerative bottlenecks. Nevertheless, the clinical efficacy and molecular mechanisms of BSGC combined with bFGF-collagen sponge in treating severe periodontitis, and bone defects, and gingival papilla recession have not yet been reported. Yuce et al. [8] found that the extent of alveolar bone resorption in periodontitis patients is closely related to osteoprotegerin (OPG) levels in gingival crevicular fluid, indicating the key role of the OPG/RANKL axis in bone metabolism regulation. Osteocalcin (OCN), a classic marker of osteoblast activity, can also indirectly reflect the rate of bone formation [9]. Therefore, this study conducted a 12-month randomized controlled trial to evaluate the clinical and radiographic efficacy of BSGC combined with bFGF-collagen sponge in severe periodontal bone defects and gingival papilla recession, and to further explore its effects on OCN and OPG expression in gingival crevicular fluid, aiming to provide evidence-based support and a novel strategy for integrative periodontal regenerative therapy.

2. Materials and Methods

2.1 Patient Selection

Sixty-four patients diagnosed with severe periodontitis at the Department of Periodontics, Stomatology Center of the First Affiliated Hospital of Naval Medical University were enrolled from July 2018 to December 2023 (Figure 1). There were 31 males and 33 females, aged 32~65 years (mean age 46.5 years), randomly divided into two groups of 32 each, as shown in the clinical flowchart (Figure 2).

Inclusion criteria: (1) at least one quadrant with residual probing depth (PD) ≥ 6 mm and clinical attachment loss (CAL) ≥ 3 mm after completion of periodontal basic therapy and 1-month re-evaluation; (2) radiographic evidence of an infrabony defect; (3) one target defect per patient located at maxillary incisors, premolars, or mandibular first/second molars; (4) tooth mobility ≤ grade I, with occlusal trauma adjusted.

Exclusion criteria: systemic diseases; platelet count < 100 × 10^9/L; smoking; pregnancy or lactation; oral contraceptive use; intake of drugs affecting platelet function within 3 months. The study was approved by the Ethics Committee of the First Affiliated Hospital of Naval Medical University, and informed consent was obtained from all participants.

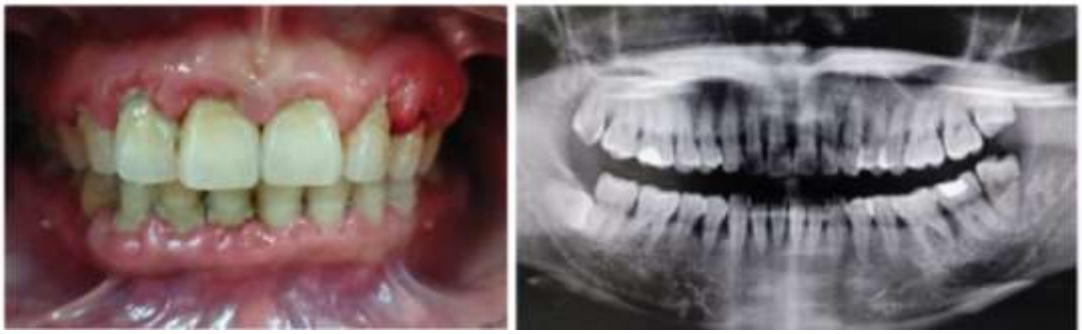

Figure 1. Severe periodontitis, female, 46 y. Gingival erythema and edema; PD= 4~9 mm, alveolar bone loss from grade 1 to 3.

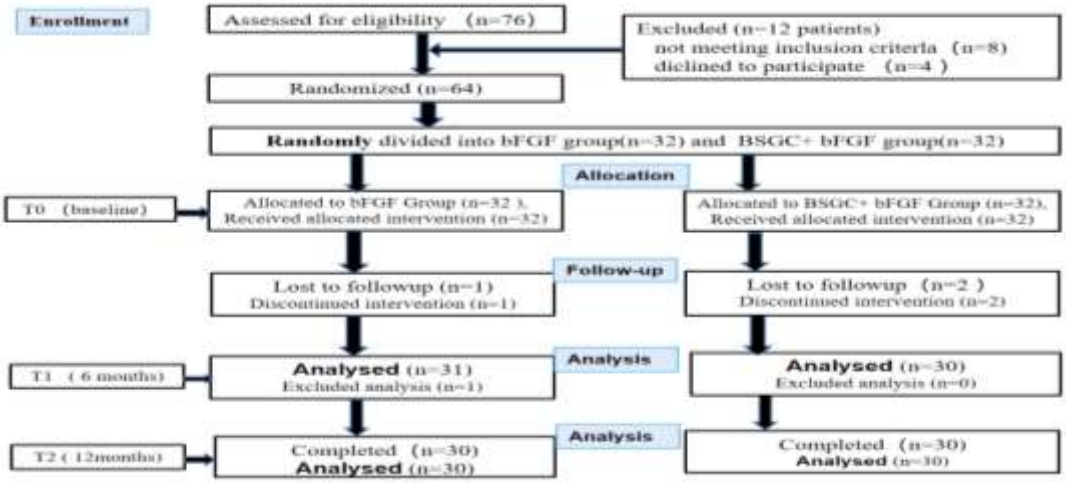

Figure 2. Flow chart of the study design, representing each group at different time schedules.

2.2 Materials

•Bu-Shen Gu-Chi-Wan (BSGC): Chengdu Jiuzhitang Jinding Pharmaceutical Co., Ltd.
• bFGF: Zhuhai Yisheng Bio-Pharmaceutical Co., Ltd.
•Medical-grade collagen sponge: Wuxi Bide Biomedical Engineering Co., Ltd.

2.3 Treatment Protocol

All subjects received oral-hygiene instructions and completed full-mouth supragingival scaling, subgingival debridement, and occlusal adjustment. After periodontal stabilization, a standardized flap procedure was performed to expose the bone defect. Following thorough debridement, the root surface was conditioned with minocycline for 3 min and irrigated with sterile saline.

(1) BFGF group: A bFGF-loaded collagen sponge (6 mm × 25 mm × 2 mm) was prepared by adding 300 μL of bFGF solution (4,375 IU/mL), delivering a total of 1,312 IU bFGF and yielding a final concentration of 4.375 IU/mm^3. The sponge was placed into the defect, the flap was repositioned and sutured, and a periodontal dressing was applied. Postoperatively, patients received metronidazole 0.2 g t.i.d. for 7 days.

(2) BSGC-BFGF group: The same bFGF-collagen sponge was implanted. In addition, oral BSGC 4 g was prescribed twice daily for 3 months. Sutures were removed at 2 weeks; patients were instructed to avoid hard-food contact for 4 weeks and to refrain from subgingival probing for 6 months.

2.4 Outcome Measurements

All parameters were recorded at baseline (pre-op) and at 6 and 12 months post-surgery.

(1) Periodontal clinical indices • Gingival index (GI) scored 0~3.
• Probing depth (PD): distance from the gingival margin to the bottom of the pocket, measured to the nearest 1 mm with a Williams probe.
• Clinical attachment loss (CAL): distance from the cemento-enamel junction to the bottom of the pocket.

(2) Bone density assessment CBCT scans (i-CAT 17-19, Kavo, USA) were acquired at baseline and at 6 and 12 months. Bone density (BD) in Hounsfield units (HU) was measured in the surgical site using iCATVision software (v1.9.3.14).

(3) Bone height Periapical radiographs were taken at baseline, 6 and 12 months. Images were imported into Digimizer 6.0 (MedCalc, Belgium), normalized by setting tooth length to 10 units, and Bone height (BH) was measured.

(4) Gingival papilla height and black-triangle area [10] Standardized digital photographs were taken perpendicular to the labial surface before and 12 months after treatment. After calibration with a 10-mm scale within the image, Gingival papilla height (GPH) was determined by dropping a perpendicular from the papilla tip to a line connecting the mesial and distal CEJs. The black-triangle area (BTA) was automatically calculated by Digimizer 6.0. Two examiners performed the measurements independently, and the mean value was used.

(5) Osteocalcin and osteoprotegerin in gingival crevicular fluid Gingival crevicular fluid (GCF) was collected at baseline and at 6 and 12 months using the method of Chen TL et al. [11] Pre-weighed filter strips (10 mm × 2 mm) were inserted into the deepest part of the pocket for 30 s, repeated three times. The strips were re-weighed, and volume was calculated assuming 1 mg ≈ 1 μL. Samples were placed in 500 μL PBS, stored at -80 °C, thawed, sonicated, centrifuged (5,000 rpm, 5 min, 4 °C), and

analyzed for Osteocalcin (OCN) and osteoprotegerin (OPG) using commercial ELISA kits (Shanghai Jier dun Biotechnology) at 450 nm.

2.5 Statistical Analysis

All analyses were performed with SPSS 23.0 (IBM Corp., Armonk, NY, USA). Normally distributed data are presented as mean ± SD. Paired t-tests compared baseline, 6- and 12-month values for GI, PD, CAL, BD, BH, GPH, BTA, OCN, and OPG; independent t-tests compared between-group differences at each time point. The Wilcoxon rank-sum test was used for GI. $P < 0.05$ was considered statistically significant.

3. Results

3.1 Periodontal Clinical Parameters (Figure 3)

At 6 and 12 months, GI, PD, and CAL were significantly lower than baseline in both groups ($P < 0.01$). The BSGC-BFGF group showed significantly greater reductions at all time points compared with the BFGF group ($P < 0.05$, Table 1).

Table 1. Comparison of the GI, PD, AL between groups at different time points ♦

Groups	GI	PD（mm）	CAL（mm）
BFGF			
Baseline	2.25 ± 0.30	6.65 ± 1.00	6.72 ±0.90
6M post-therapy	0.90 ± 0.15**	3.40 ± 0.80**	3.75 ± 0.45**
12M post-therapy	1.05 ± 0.10**	3.55 ± 0.75**	3.79 ± 0.40**
BSGC-BFGF			
Baseline	2.30 ± 0.25	6.69 ± 0.50	6.74 ± 1.05
6M post-therapy	0.65± 0.05**#	2.70 ± 0.40**#	3.05 ± 0.35**#
12M post-therapy	0.80 ± 0.10**	2.65 ± 0.45**#	3.00 ± 0.25**#

Significant differences compared with baseline, ** $p<0.01$. Significant differences compared with BFGF group, # $p<0.05$. ♦ Numbers are mean ±standard deviations. Abbreviations: BFGF: basic fibroblast growth factor; BSGC: Bu Shen Gu Chi Wan; M: month; GI: gingival index; PD: Probing depth; CAL: clinical attachment loss.

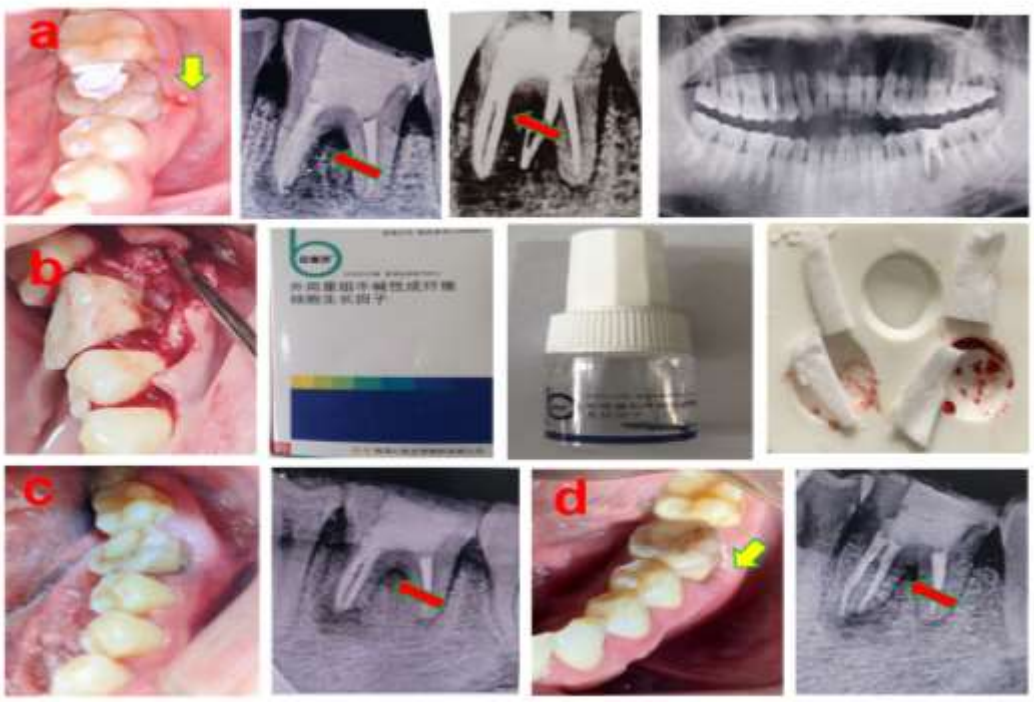

Figure 3. Clinical and radiographs of a 40 y male patient in the BSGC group. (a). Pre-operative: periodontal fistula with periodontal bone defect (root canal retreatment for periapical radiolucency). (b). During flap surgery, a collagen sponge loaded with bFGF was applied, combined with Bushen Guchi Pills for 3 months. (c). 6 months post-operative, the fistula healed and the bone defect good filling. (d).12 months post-operative, gingival and bone healed well.

3.2 Bone Density

At 6 and 12 months post-surgery, bone density(BD) was significantly higher than baseline in both groups ($P < 0.01$). At every time point, the BSGC-BFGF group exhibited markedly greater BD than the BFGF group ($P < 0.01$, Table 2).

Table 2. Comparison of the BD between groups at different time points（HU）♦

Groups	BD at different time points		
	baseline	6M post-therapy	12M post-therapy
BFGF	210.10±8.20	550.30±10.50**	510.50±15.60**
BSGC-BFGF	235.50±12.00	750.40±15.20**##	760.80±15.30**##

Significant differences compared with baseline ** $p<0.01$. Significant differences compared with BFGF group, ## $p<0.01$. ♦ Numbers are mean ±standard deviations. Abbreviations: BFGF: **basic fibroblast growth factor;** BSGC：Bu Shen Gu Chi Wan; M:month;BD:bone density.

3.3 Bone Height:

At 6 and 12 months postoperatively, Bone Height (BH) was significantly improved compared with baseline in both groups ($P < 0.01$). The BSGC-BFGF group exhibited superior BH at all time points compared with the BFGF group ($P < 0.01$, Table 3 and Figure 4).

Table 3. Comparison of the BH between groups at different time points（u）♦

Groups	BH at different time points		
	baseline	6M post-therapy	12M post-therapy
BFGF	5.45±0.15	8.65±0.35**	7.90±0.50**
BSGC-BFGF	5.68±0.10	11.25±0.75**##	11.95±0.90**##

Significant differences compared with baseline, ** p<0.01. Significant differences compared with BFGF group, ## p<0.01. ♦ Numbers are mean ±standard deviations. Abbreviations: BFGF: **basic fibroblast growth factor;** BSGC：Bu Shen Gu Chi Wan; M: month; u,units; BH:bone height.

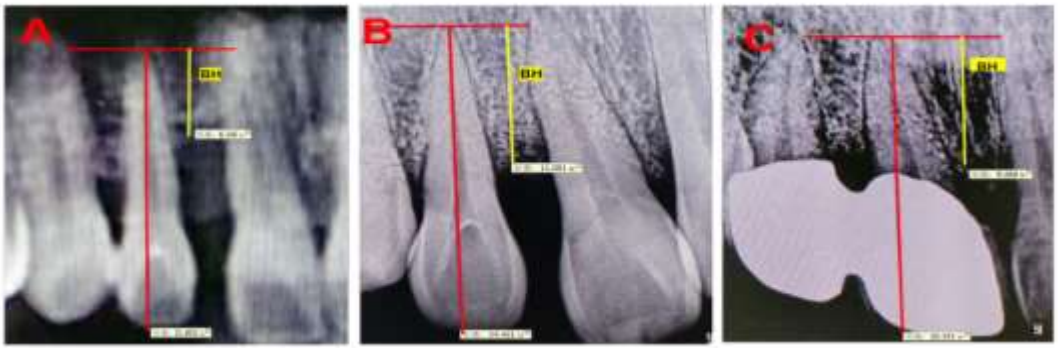

Figure 4. Diagram of BH measured by Digimizer 6.0 Image Program of BFGF+BSGC Group. Mr. Mo, male, 35 y, severe periodontitis. (A) Pre-therapy bone resorption is 2-3 degree between tooth 11 and tooth 12 , mesial BH of tooth12 is 6.166u; (B) Mesial BH of tooth 12 is 12.051u at 6 months;(C) Mesial BH of tooth 12 is 9.269u, bone regeneration improved at 12 months after treatment. Abbreviations: BH: bone height

Gingival Papilla Height and Black-Triangle Area (Figures 4 and 5): Twelve months post-surgery, both gingival papilla height (GPH) and black-triangle area (BTA) were significantly improved compared with baseline in each group ($P < 0.05$). The degree of improvement in the BSGC-BFGF group was significantly better than that in the BFGF group ($P < 0.05$, Table 4).

Table 4. Comparison of the GPH and BTA between groups at different time points ♦

Groups	GPH （u）		BTA （u^2）	
	Baseline	12M post-therapy	Baseline	12M post-therapy
BFGF	2.80±0.40	3.65±0.30*	1.13±0.15	0.60±0.10*
BSGC-BFGF	2.75±0.45	4.15±0.20*#	1.20±0.10	0.41±0.15*#

Significant differences compared with baseline, ** p<0.05. Significant differences compared with BFGF group, # p<0.05. ♦ Numbers are mean ±standard deviations. Abbreviations: BFGF: **basic fibroblast growth factor**, BSGC：Bu Shen Gu Chi Wan.;, M: month; GPH:Gingival papilla height; BTA: black triangle area; u: units.

Figure 5. The photograph was processed by Digimizer 6.0 Image Program to determine GPH and BTA. A. Measurement diagram of GPH and BTA.; B. Set the ruler to a scale of 10, and measure the GPH to be 2.850 u; C. Set the ruler to a scale of 10, and measure the BTA to be 1.025 u2. Abbreviations: a line: connecting CEJ on the labial surface of two adjacent teeth; BTA: black triangles area; GPH: gingival papilla height; u,units; CEJ: cemento-enamel junction.

3.4 OCN and OPG Levels in GCF:

At 6 and 12 months post-surgery, OCN and OPG concentrations in GCF were significantly higher than baseline in both groups ($P < 0.05$). The BSGC-BFGF group exhibited significantly higher levels at every time point compared with the BFGF group ($P < 0.05$, Table 5).

Table 5. Comparison of the levels of OCN、OPG in GCF between groups at different time points♦

Groups	OCN(ug/L)	OPG(pmol/L)
BFGF		
Baseline	10.15 ±1.20	310.15 ±2.50
6M post-therapy	15.30 ± 3.20*	340.40 ±3.10*
12M post-therapy	13.50 ±1.50	321.10 ±4.30
BSGC-BFGF		
Baseline	11.05 ±1.30	312.20 ±3.15
6M post-therapy	38.50 ±4.15**##	403.50 ±4.30**##
12M post-therapy	20.15 ±2.55*#	365.45 ±4.10*#

Significant differences compared with baseline,* $P < 0.05$,** $P < 0.01$ ； Significant differences compared with BFGF group, # $p<0.05$, # $p<0.01$. ♦ Numbers are mean ±standard deviations. Abbreviations: BFGF: basic fibroblast growth factor, BSGC：Bu Shen Gu Chi Wan. , M: month, OPG:Osteoprotegerin.OCN；Osteocalcin。

4. Discussion

This study is the first to combine Bu-Shen Gu-Chi-Wan (BSGC) with bFGF-collagen sponge for severe periodontal bone defects accompanied by gingival papilla recession. Compared with bFGF alone, the combination achieved superior clinical, radiographic, and molecular outcomes. Over 6- and 12-month follow-ups, the combined group showed sustained reductions in bleeding index, pocket depth, and clinical attachment loss; CBCT-verified bone density and defect fill were markedly higher than those of the control; gingival papilla height increased, and black triangles diminished, yielding improved esthetics. Persistently elevated OCN) and OPG in GCF suggest that a coordinated "anti-resorption—pro-formation" axis is central to the rebalanced bone metabolism [8,12].

Systemic regulation by BSGF creates a favorable microenvironment for bFGF. Catalpol and naringin from Rehmanniae Radix Praeparata and Drynariae Rhizoma activate Wnt/β-catenin and BMP-2/Smad signaling to drive osteoblast differentiation [13], whereas astragalus polysaccharides inhibit NF-κB via PI3K/Akt, down-regulating IL-1β and TNF-α and alleviating local inflammation [14]. After sustained release from the collagen sponge, bFGF binds to BSGC-induced FGFR1/2-positive progenitor cells, triggering MAPK/ERK cascades that accelerate angiogenesis and cell proliferation [15]. Peak OCN at 6 months indicates an earlier onset of osteogenesis, corroborating the early trigger by bFGF and the sustained amplification by BSGC [16]. Doğan reported that non-surgical therapy can elevate OPG [17]; our group also demonstrated that HBO-bFGF promotes calvarial defect healing with elevated OPG and CD34 [12]. Furthermore, we observed favorable clinical outcomes when calcined natural bovine bone (CBB) was combined with bFGF for periodontal bone repair [18].

In our previous work, periodontitis patients undergoing splinting therapy received oral BSGC 4 g twice daily for 3 months. Two years later, gingival bleeding index and PD improved, gingival blood flow and alkaline phosphatase increased markedly, and alveolar bone loss was reduced, indicating that BSGC combined with periodontal splinting enhances bone regeneration by improving gingival micro-circulation, regulating bone metabolism, and minimizing occlusal trauma [19].

On the translational level, a 3-month oral course of BSGC maintains bone gain and soft-tissue esthetics for more than 12 months, avoids repeated surgeries and costly barrier membranes, shows high compliance, and is suitable for community-based care. Limitations include a modest sample size, single-center design, and absence of a GTR-only control; mechanistically, only OPG and OCN were measured. Future multi-center RCTs integrating network pharmacology, metabolomics, and animal models are warranted to systematically dissect interactions among Wnt, BMP, PI3K, and other pathways and to clarify the key active ingredients and targets of BSGC.

Gu-Chi-Gao (GCG) is derived from Liu-Wei-Di-Huang-Wan with added Lycium barbarum, Sophora subprostrata, Dendrobium, Ophiopogon, and Drynaria herbs that tonify kidney essence, clear heat, and detoxify, conferring effects of strengthening the teeth, reducing swelling, and alleviating pain. In vitro studies [20] show that Lycium and Drynaria at 10^{-5}~10^{-7} g/mL markedly promote human gingival fibroblast proliferation and migration, delay senescence, and enhance root-surface adhesion and collagen secretion. Dendrobium polysaccharides and Ophiopogon saponins synergistically stimulate hPDLC DNA synthesis, increasing S-phase fraction by 25 %, indicating accelerated periodontal ligament regeneration. Animal studies [21-23] demonstrate that (1) in rat and guinea-pig experimental periodontitis, GCG reduced gingival index and pocket depth by 42 % and 38 %

respectively, and preserved 0.35 mm more alveolar height versus controls; (2) gingival and alveolar PGE_2 decreased by >50%, indicating COX_2 mediated inhibition of prostaglandin-driven bone resorption; (3) osteoclast numbers fell 60 %, with degenerative ultrastructural changes and vacuolation rates reduced, while ALP-positive osteoblasts increased 1.8-fold, OCN expression rose, and bone formation rate improved. A clinical trial [24] of 72 adolescent periodontitis patients showed that 3 months of oral GCG achieved a 68.4 % improvement in mobility ≥ grade I, significantly better than controls ($P < 0.01$). Mechanistic studies [25,26] further revealed (1) elevated $CD3^+$ and $CD4^+$ T-cell proportions in peripheral blood, 35 % and 28 % increases in polymorphonuclear leukocyte phagocytic index and rate, and decreased bone-resorption marker CTX-I; (2) plasma cortisol rose within 1 week and remained elevated for 12 months, suggesting that GCG enhances glucocorticoid negative feedback via the HPA axis to suppress inflammatory cascades; (3) molecular down-regulation of gingival COX_2 and mPGES-1 with reduced PGE_2 and TXB_2, coupled with up-regulation of $Runx_2$ and Osterix, achieving dual "anti-inflammatory/ pro-regenerative" effects.

This study also found that the BSGC group exhibited greater improvements in GPH and BTA than the bFGF-only group, likely because the combined bFGF–BSGC treatment promoted alveolar-bone regeneration, thereby increasing bone height and density, which in turn elevated the measured gingival papilla height and reduced the black-triangle area. Whether GSGC can achieve gingival-tissue regeneration remains to be further investigated.

5. Conclusion

BSGC combined with bFGF-collagen sponge markedly promotes bone regeneration in periodontal osseous defects of severe periodontitis and also contributes to the recovery and reconstruction of lost gingival papillae. The underlying mechanism of its efficacy may involve up-regulation of OPG/OCN expression, suppression of osteoclast activity, and enhancement of osteogenesis. This study provides new evidence-based support for integrative periodontal regenerative therapy and demonstrates broad clinical potential, although the detailed mechanisms still require further investigation.

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Author Contributions: TC-conceived the ideas original draft preparation and manuscript review; HZ and BX -original draft preparation; YW and CH-case collection; PW and CH-Clinical treatment; ZQ and XG-interpretation of data; YZ- conceived the ideas; DT-manuscript review.

Abbreviations: GI: Gingival Index; PD: Probing Depth; AL: Attachment Loss; CBCT: Cone-Beam Computed Tomography; ELISA: Enzyme-Linked Immunosorbent Assay; OCN: osteocalcin; OPG: Osteoprotegerin; RANKL: Receptor Activator of Nuclear Factor-Kb Ligand; GCF: Gingival Crevicular Fluid; bFGF: Basic Fibroblast Growth Factor; BSGC: Bu Shen Gu-Chi-Wan; CBB: calcined natural bovine bone; GCG: Gu-Chi-Gao; GPH: Gingival Papilla Height; BTA: Black Triangle Area; BD: bone density; BH: bone heights; U: Units; M: Months.

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