



ORIGINAL RESEARCH

DEVELOPMENT AND EVALUATION OF *ANGELICA DAHURICA*-BASED MEDICATED CHEWING GUM: A NOVEL APPROACH TO TREATING ORAL SUBMUCOUS FIBROSIS

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ABSTRACT

Background: Oral Submucous Fibrosis (OSMF) is a chronic, progressive disorder characterized by inflammation and fibrosis of the oral mucosa, resulting in restricted mouth opening, pain, and burning sensations. Current interventions for OSMF are limited by suboptimal efficacy and poor patient compliance, emphasizing the need for alternative therapeutic strategies. The present study aimed to develop and evaluate a novel medicated chewing gum formulation incorporating *Angelica dahurica*, a medicinal herb recognized for its anti-inflammatory and hepatoprotective properties, as a potential management approach for OSMF.

Objective: A medicated chewing gum was formulated using *Angelica dahurica* extract as the primary active ingredient. Characterization was carried out using Fourier-transform infrared spectroscopy (FTIR) to confirm the presence of functional groups, Thermogravimetric analysis (TGA) to determine the thermal stability of the product, Contact angle measurements, to evaluate surface wettability and Antimicrobial efficacy against *Enterococcus faecalis*, *Candida albicans*, and *Streptococcus mutans* was assessed using standard assay protocols.

Materials and Methods: A prospective research of the next ten cases treated under the same circumstances (7 men, 3 women, average age of 20.8 +2.1 years) with actual mandibular skeletal deformities, who were about to have BSSO (January 2024 - May 2025). Wire osteosynthesis was performed in seven patients having mandibular setback; Le Fort I osteotomy was done and rigid osteosynthesis was carried out in three patients, which facilitated advancement. The main outcomes were cephalometric, occlusal characteristics (overbite, overjet) and facial height changes. Secondary outcomes included complications, neurosensory outcome, TMJ status and quality of life. Stability was measured by using extended follow up (mean of 18.2 6.3months).

Results: FTIR analysis confirmed the presence of functional groups such as carbonyl and aromatic groups within the gum formulation. Thermogravimetric analysis revealed that the gum maintains structural stability up to 300°C, with thermal decomposition apparent at higher temperatures. The contact angle findings indicated a distinctly hydrophilic surface, suggesting suitability for effective mucosal delivery of the active ingredient. Antimicrobial testing revealed significant inhibitory activity against the tested pathogenic microorganisms.

Conclusions: The study demonstrates that medicated chewing gum formulated with *Angelica dahurica* possesses favorable chemical, thermal, surface, and antimicrobial properties that provides a promising alternative therapeutic option for treating OSMF.

Keywords: Oral sub mucous fibrosis, Medicated chewing gum, *Angelica Dahurica*

1. INTRODUCTION

Oral Submucous Fibrosis (OSMF) is a scarring disease of the oral cavity with the potential to progress into malignancy with a malignant transformation rate ranging from 1.5% to 15%. The primary goal of treatment is to prevent its transformation into cancer¹. Recent studies highlight areca nut as the chief inducer of the disease. Arecoline, a key component in areca nut, drives fibroblast proliferation and their transformation into myofibroblasts, leading to the proposed term "Areca-Nut Induced Fibrosis (AIOF)"². Excessive accumulation of extracellular matrix (ECM) proteins, particularly collagen, contributes to fibrosis and may trigger carcinogenic processes like epithelial-mesenchymal transition (EMT), resulting in symptoms such as ulceration, xerostomia, and restricted mouth opening³.

The disease progresses through a cascade of events, including defective collagen homeostasis, increased collagen synthesis, reduced collagen clearance, heightened inflammatory cytokines, altered growth factors, hypoxia, and EMT⁴. Collagen deposition in the buccal mucosa, palate, retromolar region, or pharynx restricts mouth opening and movement, significantly impacting patients' quality of life⁵.

Treatment strategies for OSMF involve a combination of conservative, medical, and surgical approaches, with physiotherapy playing a crucial role⁶. Key therapeutic agents, such as lycopene, beta-carotene, alpha-lipoic acid, vitamin E, selenium, and zinc, help combat inflammation, oxidative stress, and fibroblast activity, promoting immune function and cellular stability. Additional treatments include steroids, hyaluronidase, collagenase, placental extracts, interferon-gamma, aloe vera, turmeric, and pentoxifylline, which work to reduce fibrosis, manage symptoms, and enhance oral function and tissue healing⁷.

Medicated chewing gum (MCG) is an innovative drug delivery system that combines a gum base with active ingredients for localized oral treatment or systemic absorption, serving as a versatile vehicle for pharmaceuticals and nutraceuticals⁸. A study evaluating gum-chewing exercises in older adults reported significant improvements in tongue pressure, bite force, saliva flow, and tongue and lip mobility after one month of regular use, highlighting its potential in enhancing oral health⁹. Additionally, massage techniques such as kneading and soft tissue manipulation improve the flexibility of fibrous tissues and enhance temporomandibular joint (TMJ) mobility in OSMF patients. Exercises like tongue stretches, cheek puffs, and ice cream sticks practice further aid in improving tongue movement and increasing mouth

opening¹⁰. This underscores the dual role of medicated chewing gums—not only as a drug delivery system but also as an exercise aid to improve oral function in OSMF patients.

Angelica dahurica is a traditional medicinal plant known for its bioactive compounds, including coumarins, polysaccharides, and volatile oils, which exhibit anti-inflammatory, antimicrobial, antioxidant, and anticancer properties¹¹. *A. dahurica* promotes wound healing in diabetes through its antimicrobial and anti-inflammatory effects, particularly by regulating macrophage polarization, as demonstrated in network pharmacology and in vivo studies¹². Notably, previous studies have explored the impact of *A. dahurica* extract (AD) and bergapten (BG)—its active compound—on hepatic fibrosis and related mechanisms. Findings indicate that AD and BG suppress fibrotic and inflammatory markers in hepatic stellate cells (HSCs), with AD mitigating fibrosis by modulating ECM deposition and inflammation, while FXR signaling via BG plays a key role¹³.

The present study aims to develop a plant-based medicated chewing gum using *Angelica dahurica* extract and evaluate its pharmaceutical and functional properties for the treatment of OSMF. By integrating drug delivery with therapeutic exercise, this novel approach may offer an effective, non-invasive intervention to improve oral function and quality of life in OSMF patients.

2. MATERIALS AND METHODS:

2.1 Preparation of Plant extract:

Angelica dahurica was sourced in the form of ready-made extract powder of 100g (Vedik Herbal, Shipra Ayurvedic, India). To prepare the plant extract, 2 g of *Angelica dahurica* powder (Vedik Herbal, Shipra Ayurvedic, India) was subjected to extraction using 50 mL of ethanol (analytical grade) as a solvent. The mixture was heated to 80°C and maintained under reflux for 30 minutes to ensure efficient solubilization of bioactive compounds. After the heating process, the solution was allowed to cool to room temperature and subsequently filtered through Whatman No. 1 filter paper to remove particulate matter, yielding a clear ethanolic extract of the plant.

2.3 Formulation of chewing gum:

For the preparation of a wax-based formulation, 10 g of beeswax was melted by heating to 80°C in a thermostatically controlled water bath. Once liquefied, 500 µL of glycerol (analytical grade) was added dropwise to the molten wax with continuous stirring using a magnetic stirrer to ensure uniform dispersion and homogenization. The prepared components were then used for subsequent experimental procedures. Subsequently, 5 mL of the previously prepared *Angelica dahurica* ethanolic extract was gradually introduced into the molten wax-glycerol mixture under continuous

stirring to ensure uniform integration of the extract into the matrix. The blending process was maintained at 80°C to prevent premature solidification and ensure homogeneity. Once fully mixed, the formulation was poured into molds or allowed to cool and solidify at room temperature, resulting in the final chewing gum preparation (Figure 1). The formulation was then stored in a desiccator to prevent moisture absorption

and maintain its stability for further analysis.



Figure 1. Fabricated *Angelica dahurica*-mediated medicated chewing gum prepared using beeswax as the gum base. The image displays the final form of the formulated gum, highlighting its uniform texture and consistent shape, suitable for therapeutic oral delivery.

2.4 Characterization of chewing gum:

The prepared chewing gum was characterized using thermogravimetric analysis (TGA), Fourier-transform infrared spectroscopy (FTIR), contact angle measurements and antimicrobial assay. TGA was employed to evaluate the thermal stability and decomposition profile of the chewing gum. FTIR analysis was conducted to identify the functional groups and confirm the presence of components in the formulation. Contact angle measurements were performed to assess the surface wettability and hydrophobicity of the chewing gum. The antimicrobial assay was utilized to evaluate the chewing gum's efficacy in inhibiting microbial growth, providing insights into its potential as a functional product with antimicrobial properties.

3. RESULTS

3.1 Contact Angle Analysis

Contact angle measurements revealed the gum's hydrophobic properties, with significant C–H stretching vibrations at 2916.38 cm^{-1} and 2848.70 cm^{-1} , suggesting the presence of aliphatic hydrocarbons. A prominent carbonyl stretch at 1735.77 cm^{-1} confirmed the existence of functional groups like esters or ethers. Peaks at 1463.11 cm^{-1} and 1194.95 cm^{-1} further indicated alkanes and aromatic compounds (Figure 2). These findings demonstrated the gum's ability to repel water, which is critical for stability and bioadhesion. The surface characteristics suggest an optimal balance between moisture resistance and controlled release of active ingredients, enhancing its effectiveness in an oral environment.

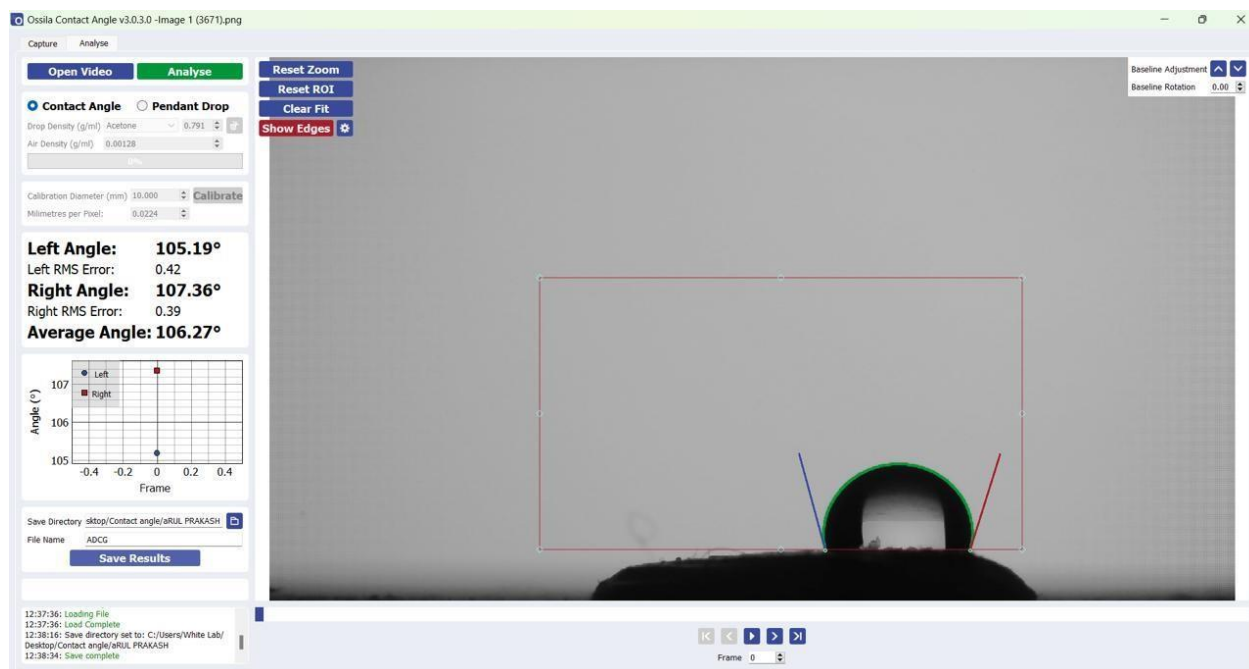


Figure 2. Contact angle analysis of the *Angelica dahurica*-mediated medicated chewing gum, illustrating its hydrophobic surface characteristics. The measured angle reflects limited wettability, which supports moisture resistance.

3.2 Thermogravimetric Analysis (TGA)

TGA results highlighted the gum's thermal stability up to 300°C. A major decomposition phase was observed between 300°C and 450°C, indicating the breakdown of volatile and organic components. Beyond 450°C, weight loss stabilized, suggesting minimal residue and confirming that the gum primarily consists of decomposable substances (Figure 3). This analysis demonstrated that the gum is thermally robust under typical storage and usage conditions. The absence of significant residues highlights the natural and biodegradable nature of the product, ensuring safety and environmental compatibility while maintaining its therapeutic properties.

Figure 3:

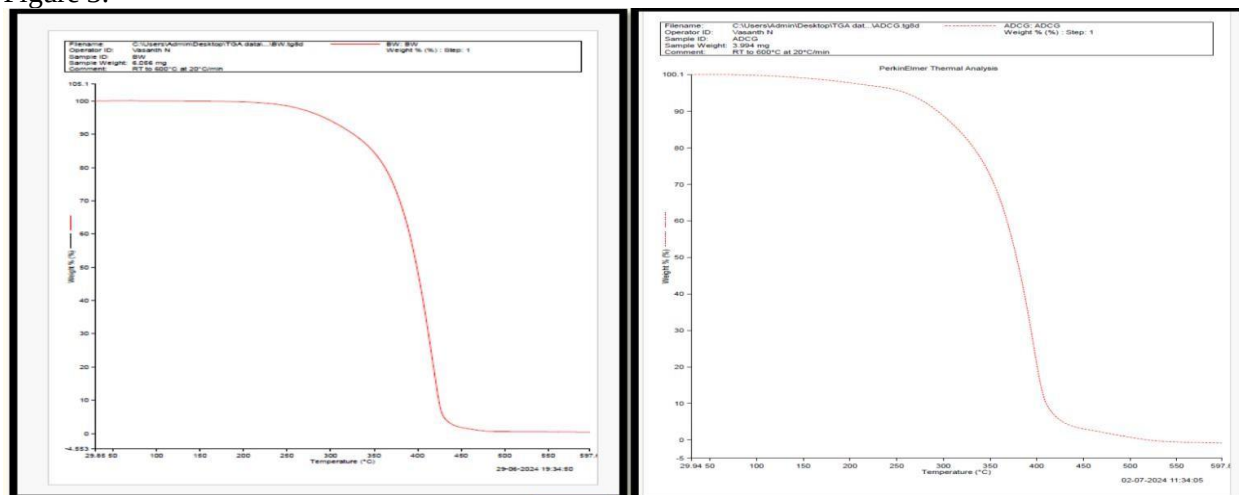
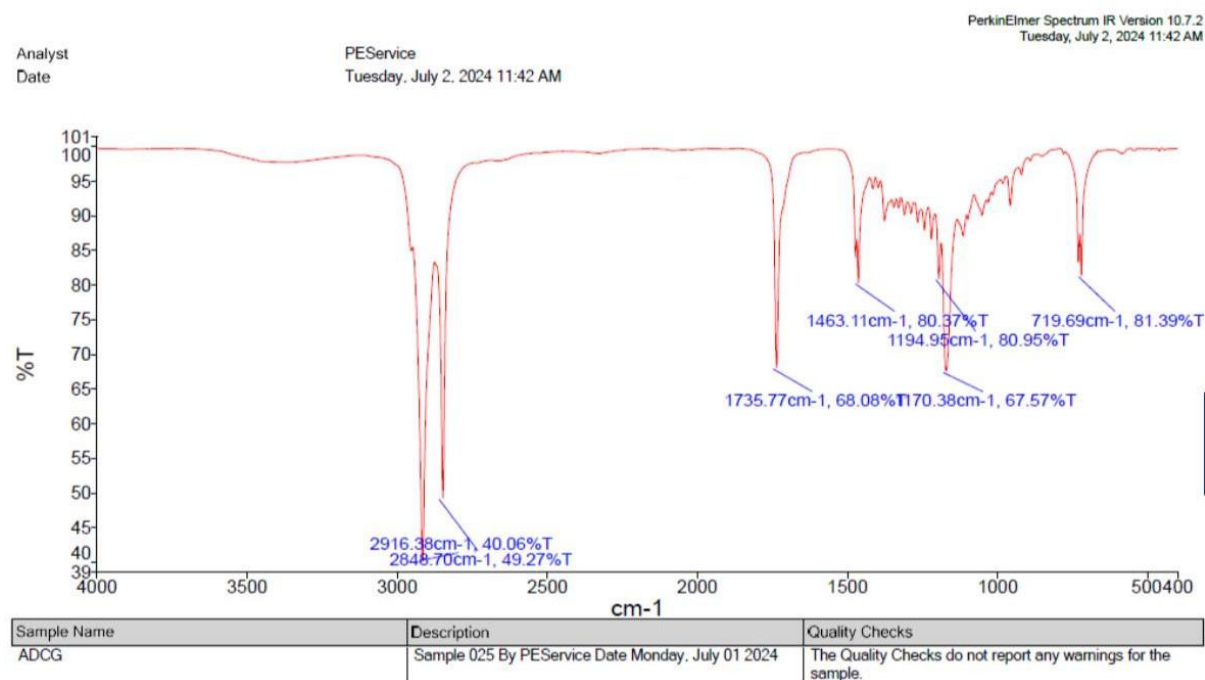


Figure 3. Thermogravimetric analysis (TGA) curve of the formulated medicated chewing gum incorporating *Angelica dahurica*, illustrating mass loss as a function of temperature. Initial stability was maintained up to 300°C, followed by a significant degradation phase between 300°C and 450°C, indicating thermal decomposition of organic components. The plateau beyond 450°C reflects minimal residual content, supporting the formulation's biodegradable nature and thermal resilience under standard processing and storage conditions.

3.3 Fourier-Transform Infrared Spectroscopy (FTIR)

FTIR analysis identified key functional groups in the gum matrix, confirming the successful incorporation of *Angelica dahurica*. Peaks in the range of 2916.38 cm^{-1} and 2848.70 cm^{-1} indicated the presence of aliphatic hydrocarbons, while a strong carbonyl stretch at 1735.77 cm^{-1} suggested esters or related compounds. Peaks below 1000 cm^{-1} (719.69 cm^{-1}) highlighted aromatic compounds (Figure 4). These results validated the stability of the extract and its interaction with the gum base. FTIR confirmed the structural integrity of the active ingredients, ensuring their therapeutic efficacy and compatibility within the formulation.



FTIR

Figure 4. spectrum of the formulated gum matrix showing characteristic absorption bands at 2916.38 cm^{-1} and 2848.70 cm^{-1} , corresponding to C–H stretching vibrations, a distinct peak at 1735.77 cm^{-1} associated with carbonyl group stretching, and a band at 719.69 cm^{-1} attributed to out-of-plane bending of aromatic C–H bonds.

3.4 Antimicrobial assay:

The antimicrobial assay demonstrated the gum's effectiveness against *Enterococcus faecalis*, *Candida albicans*, and *Streptococcus mutans*. Clear zones of inhibition were observed, indicating significant antimicrobial activity. The results confirmed the presence of active compounds in *Angelica dahurica*, capable of combating microorganisms associated with oral infections. This finding supports the gum's potential in promoting oral health by reducing bacterial and fungal populations. The size of the inhibition zones validates the gum's therapeutic efficacy, emphasizing its suitability as a medicated product for managing conditions like oral submucous fibrosis while preventing microbial-related complications.

4. DISCUSSION

Oral submucous fibrosis (OSMF) causes a drastic change in the quality of life (QoL), leaving them compromised for the rest of their lives. Advanced stages of OSMF were identified to be the major risk factor in complicating QoL. The patients have functional disabilities and physical pain, in spite of being addressed with various therapeutic modalities¹⁴. The current study successfully formulated and evaluated an *Angelica dahurica*-based medicated

chewing gum, demonstrating significant potential in alleviating symptoms of oral submucous fibrosis. The optimized formulation exhibited satisfactory mechanical and antimicrobial properties.

The plant-based chewing gum formulation incorporating *Angelica dahurica* extract, developed using a beeswax base, exhibited favorable elasticity, thermal stability, notable antimicrobial activity and therapeutic potential.

These findings are consistent with previous studies on biodegradable medicated chewing gum formulations utilizing natural gum bases, such as those derived from *Triticum aestivum* (wheat) ¹⁵. The chewing gum formulation enhances bioavailability and provides sustained local delivery, improving treatment outcomes and patient compliance [16]. This offers sustainable treatment options for OSMF wherein a combination of exercise (chewing) along with medication can aid in a better prognosis and improved results. Thus emphasizing the use of combined therapy in a single formulation.

The antimicrobial efficacy exhibited by chewing gum infused with *Angelica dahurica* extract shows good potential for localized management of OSMF. These findings share a therapeutic goal with research on Pentoxifylline (PTX), which has been proven to enhance mouth opening and reduce oral burning sensations. While both approaches address similar symptoms, the chewing gum stands out for its targeted delivery and ease of use, presenting a novel strategy for OSMF treatment ¹⁷.

Agents like spirulina have demonstrated greater efficacy compared to Pentoxifylline (PTX) [18], but with the limitation of being administered systemically. The chewing gum formulated in the present study provides a targeted, non-invasive delivery method.

Very limited data is available on the use of medicated chewing gums for OSMF. Study reporting caffeine-infused and Curcumin-infused medicated chewing gums shows sufficient anti-inflammatory, antioxidant, and tissue-repairing properties against OSMF ^{19, 20}. These properties were well established in herb *Angelina dahurica*, which stimulates blood flow, promote healing in the fibrous tissue and reduces inflammation associated with OSMF. The Bergapten compound present in *Angelica dahurica* extract reduces the extracellular matrix deposition and inflammation by activating the Farnesoid x receptor, thus showing antifibrotic activity¹². Additionally, the potential for local absorption via the oral mucosa provides a more direct and efficient way of delivering these compounds to the affected area compared to oral ingestion.

Recent evidence suggests that both nutritional deficiencies and molecular dysregulations contribute to the pathogenesis of oral submucous fibrosis. A case-control study revealed significantly reduced salivary Vitamin D3 levels in patients with Oral Submucous Fibrosis (OSMF), indicating a potential role of Vitamin D3 in modulating epithelial integrity, immune response, and fibrosis ²¹. Complementarily, another study profiling circulating exosomal microRNAs

(miRNAs) in leukoplakia, OSMF, and combined lesions identified distinct miRNA signatures associated with inflammation, fibrogenesis, and carcinogenic transformation [22]. Together, these findings underscore the multifactorial etiology of OPMDs, highlighting the interplay between micronutrient imbalance and epigenetic regulation, and propose both salivary Vitamin D3 and exosomal miRNAs as promising non-invasive biomarkers and therapeutic targets in early diagnosis and management.

While the present study successfully demonstrates the feasibility of incorporating *Angelica dahurica* into a stable, bioactive chewing gum, a few limitations remain. Notably, the biological relevance of the formulation's anti-fibrotic potential has not yet been explored in vitro using cellular models that mimic the pathophysiology of OSMF, such as TGF- β 1-induced fibrosis. Additionally, the absence of sustained release profiling under physiologically relevant conditions limits understanding of how effectively the active compounds are delivered during use. The study also lacks data on patient usability, taste acceptability, and long-term biocompatibility.

Future investigations should focus on validating anti-fibrotic efficacy in vitro using oral fibroblasts or keratinocytes under fibrogenic stimuli, coupled with release kinetics studies in simulated salivary environments. Eventually, clinical translation will require in vivo testing for safety, patient compliance, and therapeutic outcomes in individuals with early to moderate OSMF.

CONCLUSION

The development of a medicated chewing gum incorporating *Angelica dahurica* presents a novel and promising approach to managing Oral Submucous Fibrosis (OSMF). The formulation demonstrated favorable physicochemical properties, including thermal stability, hydrophilicity, and antimicrobial activity against key oral pathogens. These characteristics suggest that the chewing gum could offer symptomatic relief, inhibit microbial proliferation, and potentially slow disease progression. While these preliminary findings are encouraging, further in vivo studies and clinical trials are warranted to validate the therapeutic efficacy, safety, and patient compliance associated with this formulation. Overall, this study lays the groundwork for the use of herbal-based chewing gums as accessible and patient-friendly interventions in the early management of OSMF.

DECLARATIONS

Competing interest

The authors declare that there are no competing interest.

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Ethical Approval

“Not applicable”

Consent for publication

“Not applicable” No funding was received from any financially supporting body

Competing interests

The authors declare no competing interests.

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