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Palm mixed-carotenes promote viability and exhibit non-cytotoxic effects on human oral mucosal fibroblasts

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Abstract

Palm mixed-carotenes (PMC), a carotenoid-rich fraction obtained from crude palm oil, contain provitamin A compounds with reported antioxidant and cell-protective activities. However, limited information is available on their biological effects in oral soft tissue cells. This study evaluated the effects of PMC on the viability of human oral mucosal fibroblasts (HOMFs) under in vitro conditions. Primary HOMFs were isolated from healthy donors and exposed to PMC at concentrations of 1.56 –100 µg/mL for 72 hours. Cell viability was determined using the MTT assay. Serum-free medium containing 0.1% dimethyl sulfoxide served as the negative control, while medium supplemented with 10% fetal bovine serum was used as the positive control. Data were analyzed using SPSS version 29.0, and group comparisons were performed using one-way ANOVA followed by Tukey's post hoc test, with significance set at $p < 0.05$. PMC treatment maintained or increased HOMF viability across all tested concentrations. The greatest viability response was observed at 6.25 µg/mL, which was significantly higher than the negative control ($p = 0.005$). All PMC-treated groups showed viability values above the 70% cut-off specified by ISO 10993-5, indicating that the tested concentrations were non-cytotoxic. These findings suggest that PMC are biocompatible with HOMFs and may support cellular viability, particularly at lower to intermediate concentrations. This study provides early in vitro evidence to support further investigation of PMC in oral soft tissue research.

Keywords: *carotenes, cell viability, cytotoxicity, human oral mucosal fibroblasts, palm oil*

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Introduction

Fibroblasts are important connective tissue cells that contribute to extracellular matrix production, tissue repair, immune regulation, and interactions within the tumor microenvironment. Although fibroblasts may appear similar morphologically, their biological behavior varies according to their tissue origin (Nanci, 2013). Oral fibroblasts are derived from neural crest ectomesenchyme and differ from fibroblasts found in skin and other connective tissues (Vijayashree & Sivapathasundharam, 2022). Within the oral cavity, these cells contribute to the development and maintenance of structures such as dentin, cementum, alveolar bone, salivary glands, and the oral mucosa by producing collagen, proteoglycans, glycoproteins, matrix metalloproteinases, cytokines, and other regulatory molecules (Vijayashree & Sivapathasundharam, 2022). Oral mucosal fibroblasts (OMFs) are of particular interest in regenerative research

because of their distinctive wound-healing properties. Compared with cutaneous fibroblasts, OMFs have been reported to show greater proliferative potential, enhanced collagen production in response to transforming growth factor-β1, and a fetal-like phenotype that may contribute to rapid healing with minimal scar formation (Toma *et al.,* 2021). Clinically, oral wounds often repair faster and with less scarring than skin wounds, partly due to intrinsic differences in fibroblast and keratinocyte behavior (El Ghalbzouri *et al.,* 2020). OMFs also display a shorter population doubling time and tend to stop proliferating once confluence is reached, in contrast to cutaneous fibroblasts, which may continue to divide (Okazaki *et al.,* 2002). These features support the use of OMFs as a relevant cellular model for oral tissue engineering and regenerative dentistry.

Given the importance of oxidative stress and inflammation in oral tissue repair, naturally derived bioactive compounds such as carotenoids have gained attention for their potential protective effects. Carotenoids may influence oral tissue repair through antioxidant and anti-inflammatory mechanisms. Kajiura *et al.* (2018) have documented that β-carotene suppressed *Porphyromonas gingivalis* lipopolysaccharide-induced production of inflammatory mediators in human monocytes via nuclear factor-kappa B inactivation, suggesting a potential anti-inflammatory role in periodontal infection-related responses. In human gingival fibroblasts exposed to high glucose, astaxanthin significantly reduced reactive oxygen species (ROS) levels, improved cell viability, and enhanced wound closure, suggesting that its antioxidant properties may support gingival wound-healing responses under oxidative stress (Aras-Tosun *et al*., 2022). More recently, astaxanthin was reported to promote proliferation, migration, collagen production, and osteogenic differentiation in human periodontal ligament fibroblasts while reducing ROS levels and increasing nuclear factor erythroid 2-related factor 2 expression under hyperglycemic condition (Chantadul *et al*., 2026). These findings suggest that carotenoid-based antioxidants may influence cellular behaviors relevant to oral wound healing and periodontal repair.

Palm fruit is recognized as a rich natural source of carotenoids, particularly in terms of provitamin A activity (Choo, 1994). As humans cannot synthesize carotenoids, these compounds must be obtained through the diet (Eggersdorfer & Wyss, 2018). Carotenoid intake has been associated with several health-related benefits, including reduced risk of chronic diseases and support for tissue repair processes (Jiang *et al.*, 2021; Viaña-Mendieta *et al*., 2022; Wang *et al*., 2023). Palm mixed-carotenes (PMC) contain mainly α-carotene and β-carotene, together with smaller amounts of other carotenoids, and these components may act collectively to exert protective biological effects (Islam *et al*., 2024). However, the effects of PMC on human oral mucosal fibroblasts remain insufficiently explored. Considering the regenerative relevance of OMFs and the potential bioactivity of PMC, this study aimed to determine the effects of PMC on the viability of human oral mucosal fibroblasts (HOMFs) in vitro.

Materials and Methods

Materials

Most reagents and chemicals used in this study were purchased from Thermo Fisher Scientific, USA/UK. Reagents or chemicals obtained from other suppliers are stated in the relevant subsections.

Source of PMC

The PMC used in this study were obtained in the form of EVTene™ 8%, a commercially prepared natural mixed-carotene oil concentrate derived from Malaysian crude palm oil *(Elaeis guineensis)* and supplied by ExcelVite Sdn. Bhd. (Chemor, Perak, Malaysia). As this preparation was commercially supplied, extraction and concentration procedures were not performed in the present study. According to the product composition provided by the supplier, the preparation contained mainly β-carotene and α-carotene at approximately

67% and 32%, respectively, with minor amounts of γ-carotene and lycopene.

Sample collection

Primary HOMFs were obtained from oral soft tissue specimens collected from three healthy individuals who underwent surgical removal of impacted third molars. Donors were eligible if they were non-smokers, did not consume alcohol, had no visible oral lesions, and had no history of systemic medication use within the previous six months. A 4 mm tissue specimen was collected from clinically healthy oral mucosa adjacent to the extraction site. The specimen was immediately transferred into phosphate-buffered saline (PBS) supplemented with 1% antibiotic-antimycotic solution, consisting of 10,000 units/mL penicillin, 10,000 µg/mL streptomycin, and 25 µg/mL amphotericin B.

Isolation of HOMFs

The tissue specimens were minced into small fragments and enzymatically digested with 0.3% collagenase type I (Worthington Biochemical Corp., USA) at 37°C for 10 minutes in a shaker incubator to release cells from the extracellular matrix. The digested suspension was centrifuged at 600 × g for 10 minutes, and the resulting cell pellet was transferred into tissue culture flasks.

Cells were cultured in Dulbecco's Modified Eagle Medium/Nutrient Mixture F-12 (DMEM/F-12) supplemented with 10% fetal bovine serum (FBS), 1% antibiotic-antimycotic solution, 1% GlutaMAX, and 1% L-ascorbic acid (Sigma-Aldrich, USA). Cultures were maintained at 37°C in a humidified incubator containing 5% CO_2. To reduce passage-related variability, fibroblasts from passages 4 to 5 were used in all experiments (Azmi et al., 2023).

Cell seeding and treatment

HOMFs were seeded in 96-well plates at 5,000 cells per well, equivalent to 0.1 mL of a 5×10^5 cells/mL suspension. The seeded cells were incubated for 24 hours at 37°C in a humidified atmosphere containing 5% CO_2 to allow attachment. After incubation, the existing culture medium was aspirated and replaced with 0.1 mL of serum-free DMEM/F-12 supplemented with 1% antibiotic-antimycotic solution, 1% GlutaMAX, and 1% L-ascorbic acid. PMC solutions were prepared in serum-free DMEM/F-12 containing 0.1% dimethyl sulfoxide (DMSO). The cells were then treated with PMC at final concentrations of 1.56, 3.33, 6.25, 12.5, 25, 50, and 100 µg/mL. Serum-free DMEM/F-12 containing 0.1% DMSO was used as the negative control, while DMEM/F-12 supplemented with 10% FBS served as the positive control. The experiment was conducted using three independent biological replicates.

MTT assay for cell viability and cytotoxicity

Cell viability was evaluated using the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) assay as an indirect indicator of viable, metabolically active cells. The assay was used to assess the cellular response of HOMFs to PMC treatment and to identify any cytotoxic effect.

Following 72 hours of PMC treatment, 10 µL of MTT solution (5 mg/mL in PBS; Sigma-Aldrich, USA) was added to each well and incubated for 4 hours at 37°C. Formazan crystals were dissolved by adding 100 µL of DMSO, and absorbance was measured at 570 nm using a microplate reader (Riss et al., 2016). Background values were corrected, and cell viability was calculated relative to the negative control, which was set as 100%. Samples with viability of 70% or higher were considered non-cytotoxic according to ISO 10993-5 (ISO, 2009).

Statistical analysis

Data are reported as mean ± standard error of the mean. All statistical analyses were performed using SPSS version 29.0 (IBM Corp., USA). Differences between treatment groups were evaluated by one-way analysis of variance (ANOVA), with Tukey's HSD test

applied for post hoc comparisons. A *p*-value below 0.05 was considered statistically significant.

Results

Morphology of HOMFs following PMC treatment

Representative microscopic images of HOMFs following 72-hour treatment are shown in Figure 1. Cells in the negative control, 6.25 µg/mL PMC-treated group, and positive control displayed spindle-shaped, fibroblast-like morphology. No obvious morphological evidence of cytotoxicity was observed in the 6.25 µg/mL PMC-treated group compared with the control groups.

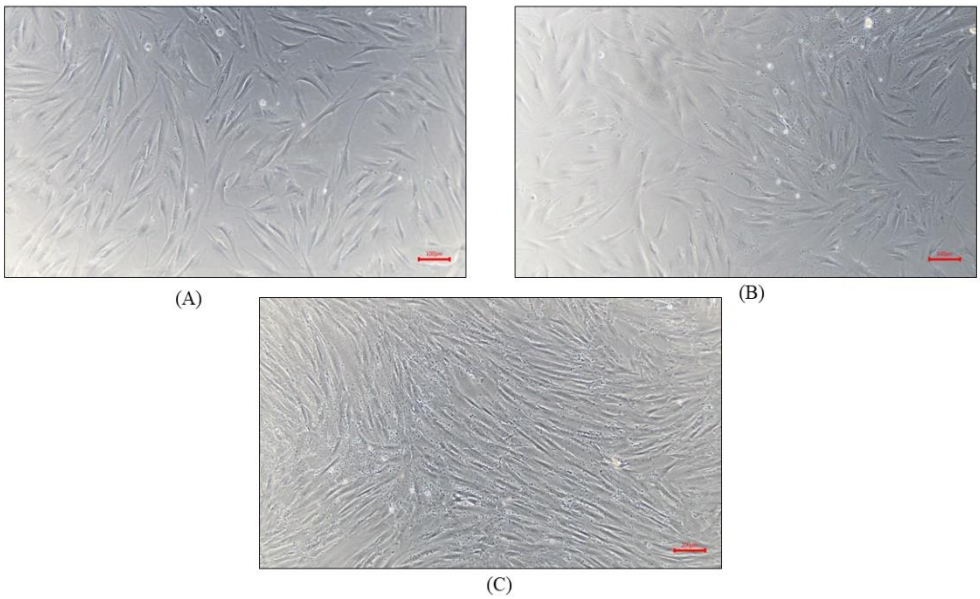

Figure 1. Representative microscopic images of human oral mucosal fibroblasts following 72-hour treatment. (A) Negative control (0 µg/mL palm mixed-carotenes, PMC); (B) 6.25 µg/mL PMC; and (C) positive control (10% fetal bovine serum). The 6.25 µg/mL PMC group was selected because it showed the highest MTT viability response among the PMC-treated groups. Cells displayed spindle-shaped, fibroblast-like morphology across the selected groups, with no obvious morphological evidence of cytotoxicity such as marked cell rounding or detachment in the 6.25 µg/mL PMC-treated group. Scale bar = 100 µm.

Effect of PMC on HOMF viability

The positive control group showed a viability value of 257% relative to the negative control. Among the PMC-treated groups, the highest cell viability was recorded at 6.25 µg/mL, reaching 153%, which was significantly higher than the negative control ($p = 0.005$). Treatment with lower PMC concentrations also increased viability, with values of 123% and 129% observed at 1.56 µg/mL and 3.13 µg/mL, respectively. Although viability remained above the control level at higher concentrations ranging from 12.5 to 100 µg/mL, the response was lower than that observed at 6.25 µg/mL, with values ranging from 111% to 121% (Figure 2). Pairwise analysis showed that viability at 6.25 µg/mL was significantly higher than that at 25 µg/mL ($p = 0.049$), 50 µg/mL ($p = 0.03$), and 100 µg/mL ($p = 0.04$).

Effect of PMC on HOMF cytotoxicity

All PMC-treated groups showed cell viability values above 100%. These values were higher than the 70% viability cut-off specified in ISO 10993-5, indicating that none of the tested PMC concentrations exhibited cytotoxic effects on HOMFs (Figure 2).

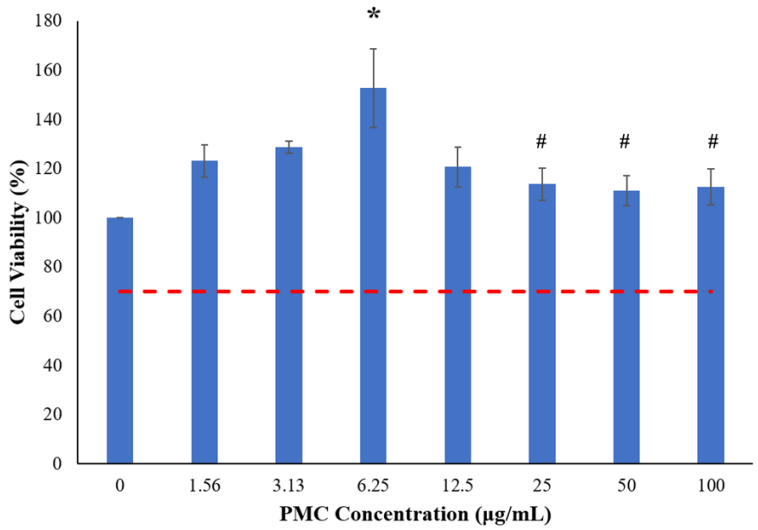

Figure 2. Percentage viability of human oral mucosal fibroblasts following 72-hour exposure to palm mixed-carotenes (PMC) at concentrations of 1.56 –100 µg/mL, as determined by the MTT assay. Values are presented as mean ± SEM from three biological replicates. *$p < 0.05$ compared with 0 µg/mL PMC; #$p < 0.05$ compared with 6.25 µg/mL PMC. The dashed red line indicates the 70% viability reference value for non-cytotoxicity based on ISO 10993-5.

Discussion

This study evaluated the response of HOMFs to PMC exposure using an in vitro cell viability model. The findings showed a non-linear, concentration-dependent pattern, in which HOMF viability increased from the lower PMC concentrations and reached its highest response at 6.25 µg/mL, before declining at higher concentrations. Although all PMC-treated groups showed viability values above the untreated control, only 6.25 µg/mL produced a statistically significant increase. This suggests that 6.25 µg/mL may represent the most favorable concentration for supporting HOMF metabolic activity under the present experimental conditions. In addition, all PMC-treated groups remained above the 70% viability threshold recommended by ISO 10993-5 for in vitro cytotoxicity testing, indicating that PMC were non-cytotoxic to HOMFs within the tested range.

The positive control group showed the highest cell viability, which was expected because 10% fetal bovine serum (FBS) contains nutrients, growth factors, attachment factors, and other bioactive molecules that support cell survival and proliferation (Lee *et al.*, 2022). In comparison, PMC are naturally derived carotenoid compounds rather than direct growth factor substitutes. The negative control provided the baseline viability under serum-free conditions, while the FBS-supplemented positive control represented a growth-supportive condition. PMC were tested under serum-free conditions to determine whether they could maintain HOMF viability without inducing cytotoxicity. Therefore, the ability of PMC to maintain or enhance HOMF viability supports their preliminary cytocompatibility in this cell model but does not confirm direct stimulation of fibroblast proliferation.

The present findings are in agreement with previous reports on the biological safety and protective effects of palm-derived carotenes in other human cell types. Meganathan *et al.* (2022) showed that carotenes from palm oil were not cytotoxic to normal human retinal pigment epithelial cells and did not stimulate proliferation in cancer cells, suggesting a favorable safety profile. The same study also

reported that PMC reduced oxidative stress-related injury in an in vitro model of age-related macular degeneration. In differentiated human neural cells, Magalingam *et al*. (2022) demonstrated that PMC attenuated oxidative stress-induced loss of cell viability and influenced antioxidant defense pathways. In another recent study, Yee *et al*. (2025) reported that PMC enhanced human osteoblast viability while suppressing osteoclast maturation, suggesting a possible role in bone-related cellular regulation. Taken together, these studies support the view that PMC may exert cell-protective effects in different human cell models.

The viability-supporting response observed in HOMFs may be partly explained by the antioxidant properties of the major carotenoid components present in PMC, particularly β-carotene and α-carotene, which may help reduce oxidative stress-related cellular damage and support cellular metabolic activity. Sen Gupta and Ghosh (2013) reported that α- and β-carotene isolated from crude palm oil exhibited antioxidant activity in vitro through radical scavenging, metal chelation, superoxide scavenging, inhibition of lipid peroxidation, and protection against protein denaturation. These antioxidant effects were concentration- and assay-dependent, indicating that carotenoid activity may vary according to the biological or experimental system. In fibroblast-related studies, carotenoids such as β-carotene have also been reported to protect dermal fibroblasts from ultraviolet-associated oxidative damage by neutralizing free radicals, enhancing endogenous antioxidant responses, and modulating signaling pathways such as mitogen-activated protein kinase and nuclear factor-kappa B (Flieger *et al*., 2024; Ma *et al*., 2025). However, oxidative stress markers, antioxidant enzyme activity, mitochondrial function, and extracellular matrix-related markers were not directly assessed in the present study.

From a translational perspective, the non-cytotoxic response of HOMFs to PMC suggests that it may be further explored as a potential bioactive candidate for oral soft tissue applications, including topical wound-healing formulations or biomaterial-based approaches in regenerative dentistry.

Several limitations should be considered when interpreting these findings. First, the study used the MTT assay as the sole endpoint. Although MTT is commonly used to assess cell viability and preliminary cytotoxicity, it primarily reflects cellular metabolic activity and does not directly confirm cell proliferation. Future studies should therefore include proliferation-specific assays or markers to determine whether the increased MTT response represents actual cell growth. Second, the study was performed using an in vitro monoculture model, which cannot fully reproduce the complex environment of oral soft tissues, in which fibroblasts interact with epithelial cells, immune cells, extracellular matrix components, and inflammatory mediators. Further work involving functional assays, such as migration, collagen production, oxidative stress analysis, and wound-healing models, would provide a more comprehensive understanding of the effects of PMC on oral fibroblast behavior. Appropriate in vivo studies may also be needed to determine the relevance of these findings for oral tissue repair or regenerative applications.

Despite these limitations, this study is, to the best of our knowledge, the first to investigate the effects of PMC on HOMFs. The findings provide preliminary evidence regarding the biocompatibility of PMC with HOMFs. The use of ISO 10993-5 criteria strengthens the reliability and translational relevance of the findings. Establishing a non-cytotoxic profile is an important first step before advancing toward more mechanistic and functional investigations of PMC in oral tissue research.

Conclusions

This study showed that PMC were non-cytotoxic to HOMFs under the tested in vitro conditions. All PMC concentrations were found to maintain cell viability above the ISO 10993-5 threshold, with the highest viability response observed at 6.25 μg/mL.

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Conflict of Interests

The authors declare that they have no conflicts of interest.

Ethical Approval

Ethics approval for this study was granted by the institutional research ethics committee (JEP-2023-625). All donors provided informed consent before the oral mucosal tissue samples were collected.

Declaration of Generative AI and AI-Assisted Technologies Use

During the preparation of this work, the author(s) used ChatGPT (OpenAI, GPT-5.4) for language editing and clarity improvement. The author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

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