






# Immunomodulatory roles of gut-derived short-chain fatty acids in periodontal inflammation and homeostasis

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## Abstract

Short-chain fatty acids (SCFAs), primarily acetate, propionate, and butyrate, are microbial metabolites generated through the fermentation of dietary fibers by the gut microbiota and are increasingly recognized as critical regulators of host immune homeostasis. Beyond their metabolic roles, SCFAs exert potent immunomodulatory effects across mucosal tissues, including the periodontium, by shaping both innate and adaptive immune responses. This review synthesizes current evidence on the dual roles of SCFAs in periodontal health and disease, with particular emphasis on the contrasting effects of systemically derived versus locally accumulated SCFAs within periodontal tissues. Gut-derived SCFAs absorbed into the circulation modulate immune function through activation of G protein-coupled receptors (GPR41, GPR43, and GPR109A) and inhibition of histone deacetylases. These pathways promote regulatory T cell differentiation, skew macrophage polarization toward anti-inflammatory M2 phenotypes, and regulate neutrophil and dendritic cell activity. These effects support immune tolerance, epithelial barrier integrity, and resolution of inflammation, thereby contributing to periodontal homeostasis. In contrast, SCFAs produced locally within periodontal pockets can reach millimolar concentrations that disrupt epithelial and fibroblast function, induce oxidative stress, and amplify inflammatory signalling, ultimately driving tissue destruction and disease progression. Emerging evidence links gut microbial composition and systemic SCFA availability to periodontal inflammation through immune and neuroimmune crosstalk, supporting a biologically plausible gut-oral axis. Translational strategies aimed at harnessing the immunoregulatory properties of SCFAs are critically evaluated in this review. While these approaches are promising, challenges related to dosing, delivery, inter-individual variability, and limited human interventional data remain, underscoring the need for rigorously designed translational studies.

## Keywords

short-chain fatty acids (SCFAs), macrophages, butyrate, periodontitis, immunomodulation, G protein-coupled receptors (GPCRs)

