

# Soy Isoflavone Mediated Modulation of IL-1 $\beta$ Related Inflammatory Pathways in Oral Mucosal Cells: A Scoping Review of Experimental Studies

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## Article Info

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## ABSTRACT

Background: Soy isoflavones, particularly genistein, have been widely studied for their anti-inflammatory properties. However, evidence regarding their modulatory effects on interleukin-1 $\beta$  (IL-1 $\beta$ )–related inflammatory pathways in oral mucosal tissues remains limited. Objective: This scoping review aimed to map the available experimental evidence on the effects of genistein on inflammatory responses associated with IL-1 $\beta$  in the oral cavity. Methods: A scoping review was conducted following a comprehensive literature search of PubMed and ScienceDirect databases. Articles published in English between 2016 and 2026 were screened using predefined keywords related to soy isoflavones, genistein, IL-1 $\beta$ , inflammation, and oral or periodontal tissues. Original experimental studies focusing on inflammatory modulation in oral or periodontal contexts were included. Results: From the literature search, only one experimental study met the inclusion criteria. The included study investigated a genistein-loaded folic acid–modified liposome-hydrogel composite for periodontitis treatment. The findings demonstrated that genistein exerted anti-inflammatory effects by modulating inflammatory cytokines, including IL-1 $\beta$ , and inhibiting the TLR4/MyD88/NF- $\kappa$ B signaling pathway. The study also reported improved inflammatory regulation through macrophage phenotype modulation and interaction with periodontal ligament stem cells. Conclusion: Current experimental evidence on the role of genistein in modulating IL-1 $\beta$ –related inflammation in the oral cavity is scarce. The limited findings suggest that genistein has potential anti-inflammatory effects in periodontal inflammation; however, further well-designed experimental studies focusing specifically on oral mucosal cells and inflammatory pathways are needed to support its therapeutic application.

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## INTRODUCTION

Inflammation of the oral mucosa plays a critical role in the pathogenesis of various oral diseases, including aphthous stomatitis, periodontitis, peri-implantitis, and oral mucosal wound healing disturbances. Among pro-inflammatory cytokines, interleukin-1 $\beta$  (IL-1 $\beta$ ) is recognized as a key mediator that initiates and amplifies inflammatory responses in oral epithelial and connective tissues. IL-1 $\beta$  promotes leukocyte recruitment, matrix degradation, and activation of downstream signaling pathways such as NF- $\kappa$ B and MAPK, which are closely associated with tissue destruction and delayed mucosal healing (Dia et al, 2008). Inflammation of the oral mucosa plays a critical role in the pathogenesis of various oral diseases, including aphthous stomatitis, periodontitis, peri-implantitis, and disturbances in oral mucosal wound healing. Among pro-inflammatory cytokines, interleukin-1 $\beta$  (IL-1 $\beta$ ) is recognized as a key mediator that initiates and amplifies inflammatory responses in oral epithelial and connective tissues. IL-1 $\beta$  promotes leukocyte recruitment, extracellular matrix degradation, and activation of downstream signaling pathways such as nuclear factor- $\kappa$ B (NF- $\kappa$ B) and mitogen-activated protein kinases (MAPKs), which are closely associated with tissue destruction and delayed mucosal healing (Graves et al., 2016; Hajishengallis, 2015).

Oral mucosal cells, particularly oral keratinocytes, actively contribute to innate immune responses by producing IL-1 $\beta$  following exposure to microbial components, mechanical injury, and oxidative stress. Sustained or excessive IL-1 $\beta$  expression has been shown to impair epithelial barrier integrity, delay re-epithelialization, and exacerbate inflammatory tissue damage in the oral cavity, thereby compromising mucosal homeostasis and healing capacity (Groeger and Meyle, 2019; Loo et al., 2020).

Soy isoflavones, mainly genistein and daidzein, are biologically active polyphenolic compounds derived from *Glycine max* that exhibit estrogen-like, antioxidant, and anti-inflammatory properties. Accumulating experimental evidence demonstrates that soy isoflavones can suppress the production of pro-inflammatory cytokines, including IL-1 $\beta$ , TNF- $\alpha$ , and IL-6, primarily through inhibition of NF- $\kappa$ B activation and modulation of MAPK-related signaling pathways (Rietjens et al., 2017; Zhang et al., 2021).

Experimental studies in epithelial and immune cell models have shown that genistein attenuates IL-1 $\beta$ -induced inflammatory responses by reducing reactive oxygen species generation, inhibiting phosphorylation of MAPKs, and down-regulating NF- $\kappa$ B nuclear translocation. Although many of these studies were conducted outside the oral cavity, oral keratinocytes share similar inflammatory signaling mechanisms, supporting the biological plausibility of soy isoflavone-mediated modulation of IL-1 $\beta$  signaling in oral mucosal cells (Valsecchi et al., 2016; Ahmed et al., 2022).

In the field of dentistry, IL-1 $\beta$ -driven inflammation plays a pivotal role not only in periodontal tissue destruction but also in impaired oral mucosal wound healing following trauma, surgery, or infection. Persistent IL-1 $\beta$  signaling has been associated with delayed epithelial closure and prolonged inflammatory phases, which may negatively affect clinical outcomes in oral inflammatory and regenerative conditions (Kinane et al., 2017; Groeger and Meyle, 2019). Therefore, strategies aimed at modulating IL-1 $\beta$ -related inflammatory

pathways are of considerable interest for improving oral mucosal health and promoting tissue repair.

Despite growing interest in the anti-inflammatory effects of soy isoflavones, evidence regarding their role in modulating IL-1 $\beta$ -related inflammatory pathways in oral mucosal cells remains fragmented across experimental studies employing diverse models, stimuli, and outcome measures. Consequently, a comprehensive synthesis of existing experimental evidence is required to map current knowledge, clarify mechanistic trends, and identify research gaps.

Therefore, this scoping review aims to systematically map experimental studies investigating soy isoflavone-mediated modulation of IL-1 $\beta$ -related inflammatory pathways in oral mucosal cells, with particular emphasis on molecular signaling mechanisms relevant to oral inflammation and mucosal healing.

## METHODS

This study was conducted as a scoping review to map the available experimental evidence regarding the modulatory effects of soy isoflavones on interleukin-1 $\beta$  (IL-1 $\beta$ ) related inflammatory pathways in oral mucosal cells. A comprehensive literature search was performed using the PubMed and ScienceDirect databases to identify relevant peer-reviewed articles. The search strategy employed predefined keywords and their combinations using Boolean operators as follows: ("soy isoflavone" OR genistein OR daidzein) AND ("IL-1 $\beta$ " OR "interleukin-1 beta") AND ("oral mucosa" OR oral epithelial). Articles published in English between 2016 and 2026 were considered eligible. After removal of duplicate records, titles and abstracts were screened based on predefined inclusion and exclusion criteria. Original experimental studies (in vitro and in vivo) investigating the effects of soy isoflavones on IL-1 $\beta$  expression or IL-1 $\beta$ -related inflammatory signaling pathways in oral mucosal or oral epithelial cells were included. Review articles, book chapters, conference proceedings, and clinical studies were excluded to avoid duplication of primary data and to maintain a focus on mechanistic experimental evidence. Relevant data extracted from the included studies comprised author names, year of publication, experimental model, type of soy isoflavone, inflammatory stimuli, signaling pathways involved, and key findings related to IL-1 $\beta$  modulation. The study selection process is summarized in Figure 1.

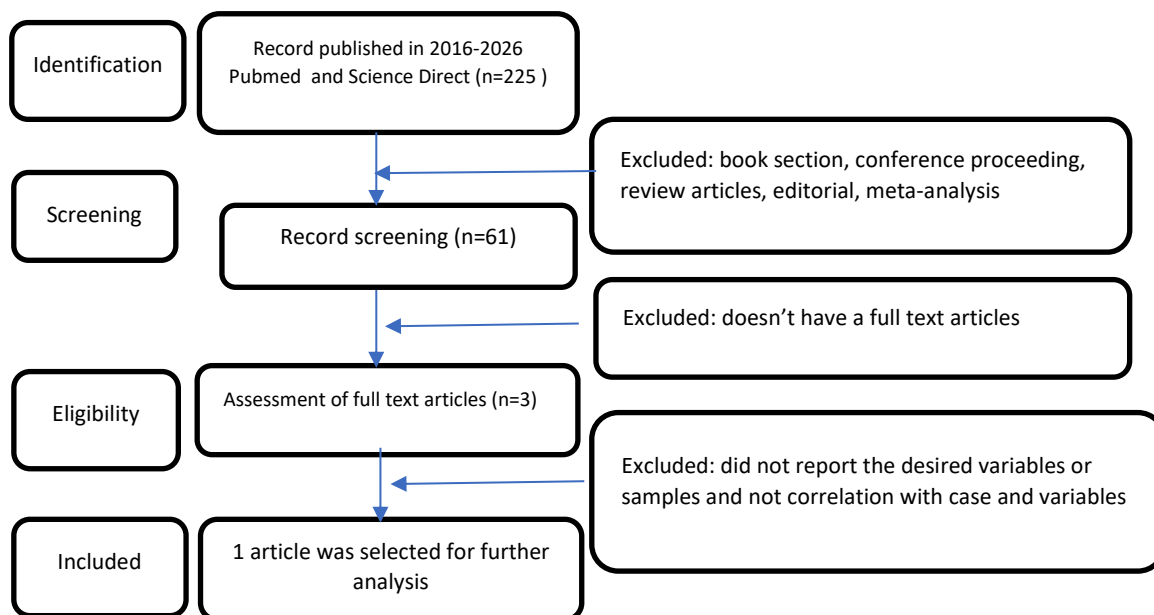


Fig. 1. The article selection process flow diagram

## RESULTS AND DISCUSSION

A total of one experimental study met the eligibility criteria and was included in this scoping review. The main characteristics of the included study are presented in Table 1.

Table 1. Data extracted from included studies

No	Authors/ year	Title	Methods	Result
1	Guichun Wang, Chengjun Peng, Maomao Tang, Yuxiao Wang, Jiaxin Li, Hairong Chen, Xiangwei Chang, Zixuan Shu, Ning He, Jian Guo,	Simultaneously boosting inflammation resolution and osteogenic differentiation in periodontitis using folic acid-modified liposome-thermosensitive hydrogel composites	The study evaluated the anti-inflammatory and osteoregenerative effects of genistein-loaded liposomal thermosensitive hydrogel using in vitro (RAW 264.7 macrophages and periodontal ligament stem cells under LPS-induced inflammation) and in vivo rat periodontitis models. Inflammatory markers, macrophage polarization,	Genistein-based FA-GEN-Lip@Gel significantly reduced periodontal inflammation by suppressing IL-1 $\beta$ -associated inflammatory signaling through inhibition of the TLR4/MyD88/NF- $\kappa$ B pathway and promoting macrophage polarization from M1 to M2. This anti-inflammatory effect improved the periodontal microenvironment,

No	Authors/ year	Title	Methods	Result
	Shuangyi / 2023		osteogenic differentiation, alveolar bone regeneration were assessed using ELISA, RT-qPCR, Western blotting, micro-CT, and histological analyses	enhanced osteogenic differentiation of PDLSCs, inhibited osteoclast-related activity via the OPG/RANKL/RANK pathway, and ultimately supported alveolar bone regeneration

Based on the data extraction summarized in Table 1, only one experimental study was identified that met the inclusion criteria and directly investigated the role of genistein-mediated inflammatory modulation in periodontal tissues. This study demonstrated that inflammation and tissue injury in periodontitis are closely interconnected, with pro-inflammatory cytokines such as IL-1 $\beta$ , TNF- $\alpha$ , and IL-6 playing a central role in sustaining inflammatory responses and disrupting cellular homeostasis. The findings provide preliminary mechanistic evidence that targeting inflammatory crosstalk particularly macrophage-driven cytokine signalling may represent a promising therapeutic approach for modulating periodontal inflammation and tissue regeneration. The majority of existing studies concentrate on the gastrointestinal tract, while research related to the oral cavity remains scarce.

Genistein is a naturally occurring, non-pharmacological compound recognized for its potential geroprotective properties, contributing to the maintenance of health span. It belongs to the isoflavone class and is predominantly found in plants of the Leguminosae family, with soybeans being the primary dietary source, along with other legumes such as fava beans and, to a lesser extent, coffee beans. Structurally, genistein functions as a phytoestrogen due to its similarity to endogenous estrogen, particularly in the presence of a phenolic ring and the spatial arrangement of hydroxyl groups. This structural resemblance enables genistein to interact with estrogen receptors, allowing it to exert both estrogen like and anti-estrogenic effects. Early experimental studies demonstrated that genistein, at higher concentrations, can suppress breast cancer cell proliferation, indicating its potential anticancer activity (Mas Bagues et al 2022). Genistein has been shown to suppress the expression of pro-inflammatory cytokines, including IL-1 $\beta$  and TNF- $\alpha$ , and inhibit the activation of the NF- $\kappa$ B signalling pathway in response to inflammatory stimuli such as lipopolysaccharide (LPS) *in vitro*. This effect is associated with downregulation of Toll-like receptor 4 (TLR4)-mediated signalling and reduced nuclear translocation of NF- $\kappa$ B, suggesting that genistein can modulate mucosal and epithelial inflammatory responses at the molecular level (Fan et al., 2021). In animal studies, genistein improved mucosal barrier function and reduced mucosal inflammation by regulating cytokine expression and tight junction integrity (Zhang et al., 2020). Additionally, genistein's modulation of macrophage phenotypes and systemic inflammatory cytokines further supports its potential role in mitigating mucosal inflammatory

responses. Studies investigating the role of genistein in inflammation, particularly in relation to interleukin-1 $\beta$  and the oral mucosa, remain limited. Therefore, future experimental-level research is required to elucidate the mechanisms by which genistein modulates inflammatory pathways within the oral mucosal environment, so that it may contribute to the development of more effective and targeted therapeutic strategies.

## CONCLUSION

This scoping review highlights the limited availability of experimental studies investigating the role of genistein in modulating inflammatory responses, particularly IL-1 $\beta$ -associated pathways, within the oral cavity. Although the single included study suggests that genistein possesses promising anti-inflammatory properties through regulation of key signaling pathways and cytokine profiles, the evidence remains insufficient to draw definitive conclusions. Future experimental research focusing on oral mucosal cells and inflammatory mechanisms is essential to clarify the modulatory effects of genistein and to support its potential development as a targeted therapeutic agent for oral inflammatory diseases.

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