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REVIEW

HERBAL THERAPY SUPPRESSES INTERLEUKIN-1β IN PERIODONTITIS AND TYPE 2 DIABETES MELLITUS

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ABSTRACT

Introduction: *Interrelated pathological conditions such as periodontitis and Type 2 Diabetes Mellitus (T2DM) remain a mystery to solve. Excessive production of Interleukin-1β (IL-1β) damages periodontal tissue and pancreatic β cells, leading to insulin resistance. Herbal therapy is one of the potential treatments to manage the periodontitis and T2DM bidirectional relationship. This scoping review explores the potential of herbal therapy and decreasing IL-1β in periodontitis and T2DM treatment.* ***Aim:*** *This study aims to elaborate on the effects of herbal therapy on decreasing IL-1β cytokines as potential targeted therapeutic targets for both periodontitis and type 2 diabetes conditions.* ***Methods:*** *Literature research was conducted from 2013 to 2023 to find relevant articles according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines. A search was conducted in PubMed, Scopus, Web of Science, and Science Direct using search terms based on PCC (Population, Concept, Context) predefined research questions related to T2DM, Periodontitis, Interleukin-1β expression, Natural Products or herbs or herbal or herbal therapy. Open access, primary study designs, and English language publications were included. Non-animal studies, non-final studies, reviews, and book chapters were considered as exclusion.* ***Result:*** *Initial literature search yielded 2886 articles, and after removing duplicates and ineligible manuscripts, 32 articles were assessed for eligibility, with the final 9 studies included in the review.* ***Conclusion:*** *Several herbal therapies were effective in decreasing Interleukin-1β and correlated to systemic and periodontal conditions. Herbal therapy is effectively decreasing Interleukin-1β as a potential therapeutic target in periodontitis and Diabetes Mellitus Type 2 management.*

Keywords: *cytokine; herbs; interleukin-1β; periodontitis; type 2 Diabetes Mellitus*

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) and periodontitis are both chronic diseases, and the linkage of these two diseases indicates the presence of one condition resulting in the severity of the other disease, and vice versa.[1] Type 2 diabetes mellitus (T2DM) is a metabolic disorder with a very high prevalence rate and increases from year to year globally.[2] The International Diabetes Federation in 2019 stated that T2DM

cases globally have reached 463 million.[3] The prevalence of diabetes between 20-79 years is 9.3% of the world's population. T2DM occurs due to dysfunction of the insulin-producing organ, the pancreas, in terms of secretion, action, or both.[4] Impaired insulin regulation results in impaired insulin function, and elevated blood glucose which is known as a hyperglycemia condition.[5,6] Uncontrolled hyperglycemia conditions lead to various destructive even life-threatening complications.[7]

The most common complications of T2DM include cardiovascular disease, retinopathy, neuropathy, and impaired wound healing.[8] Chronic inflammation plays an important role in the development and progression of T2DM.[5,9] Inflammatory mediators such as IL-1β, IL-6, and TNF-α are associated with T2DM in forming reactive oxygen species (ROS) and hyperglycemia.[5,9,10] The release of inflammatory mediators triggered by hyperglycemia and mediated by oxidative stress confirmed the link between diabetes mellitus, oxidative stress, and inflammation.[5]

Hyperglycemic conditions result in the production of secondary metabolite *products advanced glycation end* products (AGEs), and pro-oxidant products that can increase intracellular oxidative stress (Figure 1).[11] The secondary metabolite of AGEs binds to one of its most researched receptors, RAGEs.[9,11] The binding of AGEs-RAGEs mediates oxidative stress and inflammation, and results in systemic atherosclerosis to local periodontal tissue damage of the oral cavity.[12,13] A systematic review in 2022 showed that periodontitis can modulate systemic and local levels of AGEs even without hyperglycemia.[14] This explains the two-way relationship between periodontitis and T2DM, namely periodontitis plays a role in the development of prediabetes, diabetes, low glycemic control, and insulin resistance.[14–17]

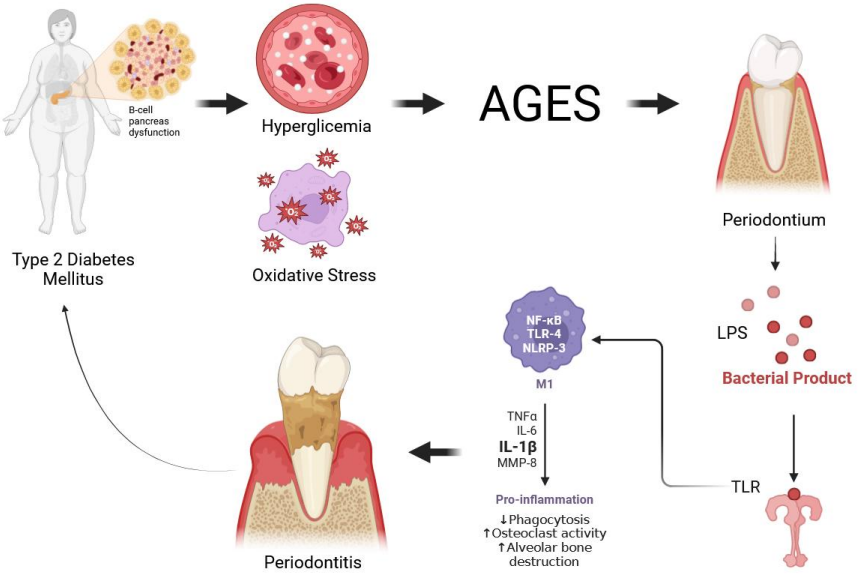

Figure 1. Two-Way Pathophysiological Mechanism of Type 2 Diabetes Mellitus and Periodontitis (Illustration generated using https://www.biorender.com/)

Immunohistochemical studies of gingival tissue in patients with T2DM and chronic periodontitis show that hyperglycemia conditions improve the inflammatory condition of the gingival tissue by activating the NLRP3 pathway. This abnormal inflammatory response results in tissue damage.[18] T2DM complications also have an impact on bones, including increased bone fragility and impaired bone healing.[19,20]

Oxidative stress that persists and for a long time disrupts biological processes, damages cellular macromolecules, and triggers inflammation and degenerative diseases.[21] Oxidative stress is an imbalance between the oxidation system and cellular antioxidants caused by excess free radical production and reactive oxygen species, better known as ROS. Hyperglycemia in people with T2DM increases markers of chronic inflammation, further contributing to increased ROS and ultimately leading to complications of T2DM including vascular dysfunction.[22] This explains that inflammation is a determining factor in the onset and progression of T2DM and its complications.[23]

A prospective clinical study was conducted from April 2011 to November 2013 involving patients diagnosed with T2DM without primary treatment. The results showed a qualitative disruption of IL-1β cytokine production by circulating monocytes in patients with T2DM, possibly due to NLRP3 inflammatory disorders and increased IL-6 cytokine production.[24] Levels of pro-inflammatory cytokines IL-1β accompanied by TNF-α and LPS measured using ELISA were shown to increase alveolar bone loss in T2DM and periodontitis-induced mice and a more severe impact was observed histopathologically. These data suggest that T2DM can increase the production of inflammatory cytokines IL-1β and TNF-α and even LPS in periodontal tissue. Hyperglycemia conditions are also involved in the increased inflammatory response especially IL-1β associated with periodontitis as it is explained in Figure 2.[25]

Salivary levels of IL-1β along with IgA and MMP-8 showed a significant decrease after 12 weeks of oral prophylaxis administration in adult subjects accompanied by chronic periodontitis compared to subjects with healthy periodontium. This means IL-1β can act as a biomarker with a good degree of accuracy for screening, early diagnosis, and management of periodontal disease.[26–28]

The inflammation associated with T2DM and its progression has to do with the balance between pro-inflammatory and anti-inflammatory cytokines. Anti-cytokine therapy is known to provide promising anti-cytokine potential as T2DM therapy but not without limitations[9]. There has been some study done using herbal therapy to overcome the bidirectional relationship between periodontitis and T2DM through the inflammatory pathway.

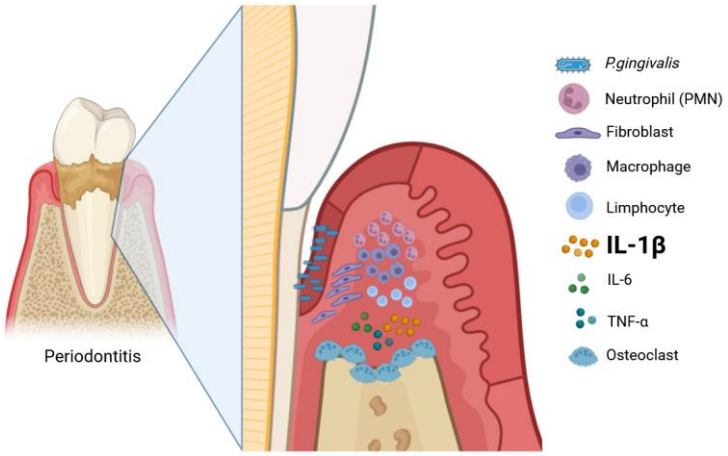

Figure 2. Chronic Inflammatory Cellular Response in Periodontal Tissue (Illustration generated using https://www.biorender.com/)

METHODS

Protocol and registration

A scoping review was done using herbs or natural products therapy on IL-1β expression in Periodontitis and Type 2 Diabetes Mellitus settings. A systematic search was conducted in PubMed, Google Scholar, and Scopus. Two authors screened references independently. Data extraction was performed iteratively, and results were presented for each included comparison. The inclusion and exclusion criteria were defined.

Study design

This scoping review was developed in five stages, namely: (i) definition of the research questions, (ii) literature search strategies, (iii) assessment of study eligibility and duplicates removal, (iv) data extraction, and (v) summary of findings. The study report was structured in a way to contemplate all items of the PRISMA extension for scoping reviews (PRISMA-ScR).[29]

Definition of the Research Questions

Research questions were done using PCC questions, namely population, concept, and context. Predefined research questions are:

Population: T2D and Periodontitis

Concept: Interleukin 1B expression

Context: Natural Products or herbs or herbal or herbal therapy

Search Strategies

Data search strategies were conducted in PubMed, Science Direct, Web of Science (WOS), and Scopus using keywords: ((Type 2 Diabetes) **AND** (Periodontitis)) **AND** (natural products) OR (herbs) **OR** (herbal therapy) **OR** (Herbal) **AND** (Interleukin 1 beta expression).

Eligibility Criteria, Study Screening and Data Extraction

Inclusion and exclusion criteria were iteratively defined along data extraction, as previously recommended by Arksey and Levac.[30,31] Different types of primary study designs, such as randomized controlled trials, non-randomized trials, were considered for inclusion. Open-access journals and articles were considered for inclusion. Studies conducted before 2013 were not considered for inclusion, given that they might not reflect the current standard of practice due to

the fast evolution of the field over the last two decades. Non-animal studies, non-final studies, reviews, and book chapters were considered as exclusion. Other languages except English were excluded.

Data Extraction

Data extraction was performed in a Microsoft Excel® spreadsheet (2021). The framework for data extraction was *a priori* defined in a way to reflect the research questions. The final framework was achieved after incorporating relevant aspects.

Summary of Findings

Study screening was documented and presented in a PRISMA flow diagram in Figure 3.[32] Results were presented by author, published year, study design, natural products that have been used, methods, results, mainly in inflammatory cytokines, and also the source of the database.

RESULTS

Electronic searches retrieved 2,886 references. After removing duplicates, outdated articles, titles, and abstracts of 2,168 references were screened, 910 non-English records were excluded and 1225 records were not retrieved leading to a selection of 32 studies. Identification of studies via databases was done using Prisma 2020 flow diagrams by Haddaway et al., (2022) as presented in Figure 3.[32] Nine studies were included after the assessment of full texts and presented in Table 1.

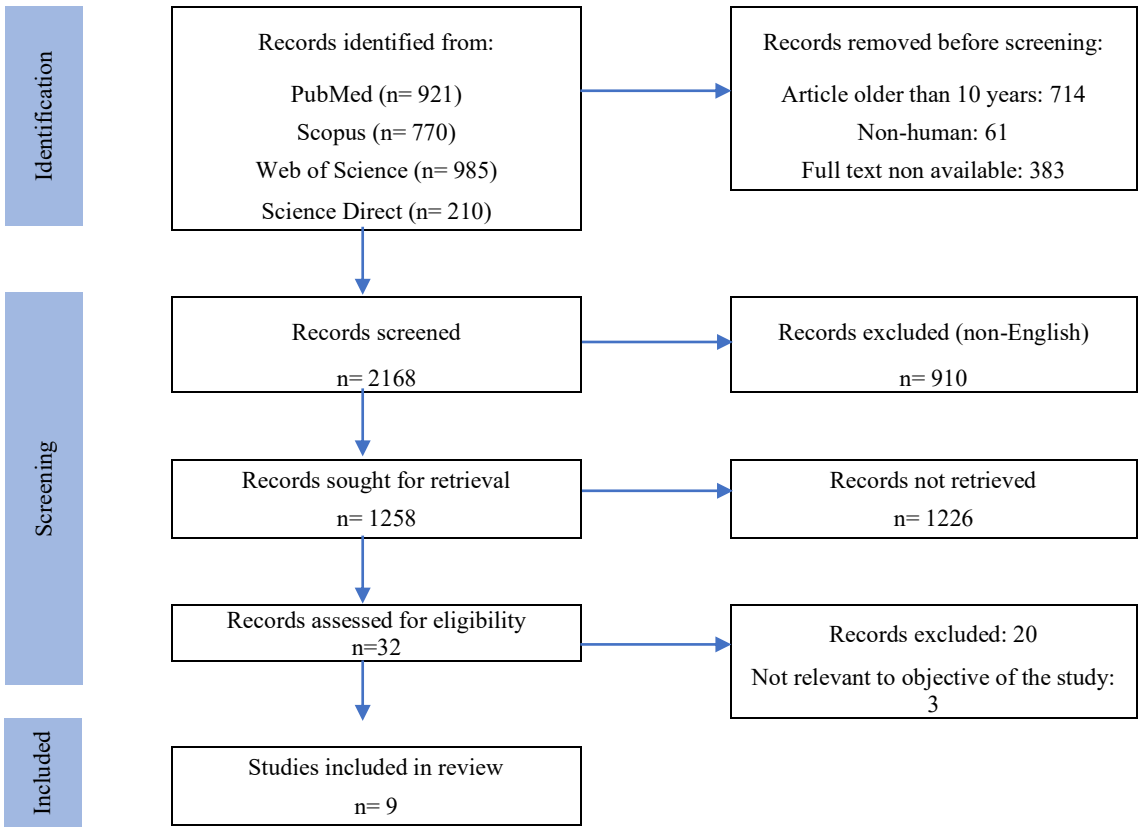

Figure 3. Identification of Studies Via Databases using Prisma Flow Diagram 2020.[32]

Table 1. Summary of Scoping Review

No.	Author, Year	Study Design	Natural Products	Methods	Result	Decreasing IL-1β	Source
1.	Harikrishnan et al, 2018.[33]	In vitro	Phyllanthus amarus Schum. & Thonn.	ELISA, qRT-PCR	↓↓ TNF-α , ↓↓ IL-1β, ↓↓ PGE2	Yes	WOS
2.	Choi et al, 2022[34]	In vivo, Animal study	MSF and L. plantarum K8 lysates combined with LPS	ELISA	Inhibit TNF-α and synergistic effect of IL-1β	Yes	WOS, Science direct
3.	Alanazi et al, 2023[35]	In vivo, Animal study	Dodonaea viscosa extract	ELISA	↓↓ serum insulin levels in diabetic rats ↓↓ the serum TNF-α ↓↓ IL-1β ↓↓ caspase-3 ↓↓ NO ↓↓ PG-2	Yes	WOS, Science direct
4.	Zhang et al, 2020[36]	In vivo, Animal study	*Scutellaria baicalensis* and *Coptis chinensis (SC)*	ELISA	↓↓ IL-1*β* ↓↓IL-6 ↓↓ TNF-*α*	Yes	WOS, PubMed
5.	Ryuk et al., 2017[37]	In vivo, Animal study	Tetragonia tetragonioides (Pall.) Kuntze (TTK)	IHC, RT-PCR	↓↓ serum concentrations of the proinflammatory cytokines ↓↓ TNF-α ↓↓monocyte chemoattractant protein-1 ↑↑ β-cell masses ↓↓ β-cell apoptosis ↓↓ Il-1β expressions	Yes	WOS, PubMed
6.	Li et al., 2018[38]	In vitro and in vivo study	Ursolic acid	ELISA, WB, Histological	↓↓ TNF-α, IL-1β, IL-6 and IL-18 levels	Yes	PubMed
7.	Hu et al, 2021[39]	In vivo, Animal study	Angelica Dahurica	Histology and Immunofluorescence; WB	↑↑ wound healing Regulates the polarization of M1 and M2 subtypes of macrophages. ↓↓ inflammation ↑↑ angiogenesis ↓↓ CD68, IL-1β, TNF-α, and IL-6 ↑↑ VEGF and TGF-β1protein	Yes	PubMed
8.	Sha et al, 2021[40]	In vivo, Animal study	Curcumin	ELISA	↓↓ inflammatory cells infiltration ↓↓ probing depth ↓↓ osteoclast numbers the improvement of PDL ↓↓ RANKL ↓↓IL-1β serum concentration	Yes	PubMed; Science Direct
9.	Ahmad et al, 2018[41]	In vivo, Animal study	Zingerone (4-(4-hydroxy-3-methylphenyl) butan-2-one)	ELISA	↓↓ NF-kB ↓↓ IL1-β, IL-2, IL-6 ↓↓ TNF-α improved the insulin levels	Yes	PubMed; Science Direct

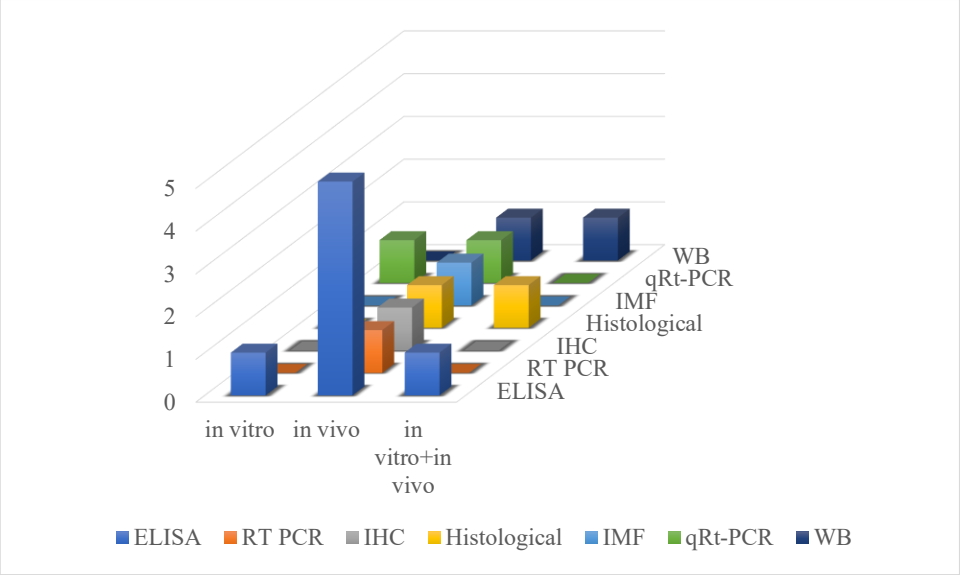

Figure 4. Analysis of summary findings

The results of the literature review are tabulated and analyzed as presented in Figure 4. In vivo research and ELISA are the common study designs and methods used. Most of the in vivo studies were done using an animal model. All the studies using herbal therapy showed a decreased in IL-1β.

DISCUSSION

Understanding of the inflammatory processes associated with periodontitis and diabetes can provide modalities for the treatment and prevention of T2DM.[42] IL-1β cytokine is the main cytokine in local and systemic inflammation. The pathological role of IL-1β is observed in several diseases, including Diabetes Mellitus and periodontitis.[43,44] Despite the many pathological effects of IL-1β found, IL-1β immunomodulatory is also developed in the therapeutic process.[45]

A meta-analysis of 2921 patients from phase I to IV studies targeting IL-1β as diabetes therapy showed a paradigm shift in glycemic therapy in which a combination of symptomatic and causative therapies goes hand in hand with each other. This therapy does not disqualify novel treatments by targeting the pathogenesis processes that occur.[46]

The developed therapeutic mechanisms of T2DM and periodontitis focus on inhibiting the inflammatory process by regulating factors such as cytokines.[47,48] Neutralization of IL-1β cytokines can prevent pancreatic B cell damage and can be used as a preventive treatment.[49] Several IL-1β cytokine inhibitory agents in the form of IL-β antagonists such as rilonacept, anti-IL-1β monoclonal antibodies, and canakinumab have been shown to have potential as therapeutic agents. Inhibition of the cytokine IL-1β provides benefits for clinicians in understanding the role of these pro-inflammatory cytokines in reducing the disease burden of many patients.[48]

The process and application of human antibodies that bind closely to IL-1β neutralization has a potency 10-fold higher than already marketed antibodies such as canakinumab.[50] The potential of human IL-1β monoclonal antibodies shows high affinity and potency in vivo and in vitro, making human anti-IL-1β as a potential

therapeutic agent.[50] Literature review Cheng et al. in 2020 stated that IL-1β is a pro-inflammatory cytokine that plays an important role in periodontitis conditions. The impact of prolonged production of IL-1β is continuous bone damage due to the role of this cytokine as a stimulator of bone resorption. Conventional therapies such as SRP, surgical therapy, and antibiotics have a limited inhibitory effect on IL-1β. Herbal therapy research is needed on the importance of IL-1β inhibition in periodontal treatment or as an adjunct therapy in the future.[51]

Hyperglycemia as a manifestation of T2DM is suspected of inhibiting the effects of nonsurgical periodontal therapy on the cytokine concentration of the gingival sulcus fluid.[52,53] This statement is supported by the research of de Sousa Rabelo et al. (2020) which states that periodontal therapy decreases local markers of inflammation, especially IL-1β and IFN-γ regardless of diabetic conditions. Double-blind randomized clinical trial intervention studies showed that there was a decrease in IL-1β levels, malondialdehyde (MDA), plaque index, periodontal depth, and clinical attachment loss in the treatment group accompanied by chronic periodontitis and DM after nonsurgical periodontal therapy with symbiotic supplementation added.[54]

Herbal ingredients have been widely used since ancient times to the present day and are widely considered for use in treating diseases related to inflammation, including periodontitis. Its use was widely developed as an adjunct to modulating immune system responses in the treatment of T2DM and periodontitis. Natural ingredients have a variety of pharmacological qualities that vary such as anti-oxidative, anti-inflammatory, anti-osteoclastogenesis, and antibacterial. Natural ingredients possess the potential of medication in dealing with hyperinflammatory components of sufferers. Herbal ingredients with beneficial pharmacological effects are usually found in foods and drinks consumed regularly, as well as plants that are often found around us.[55]

Diabetes therapy derived from herbs recommended by the WHO as an antihyperglycemic agent can restore the function of pancreatic tissue by increasing insulin concentrations. Research on antidiabetic therapy from this herbal plant is still ongoing around the world along with the growing challenges of diabetes. This is a challenge for clinicians as well as researchers.[56] In vitro studies of curcumin gel application in rats suggest curcumin is potentially as effective as chlorhexidine in treating periodontitis in rats. The way it works is by regulating RANKL and serum IL-1β levels to stop bone destruction associated with periodontitis.[57]

The future of treatment innovations by modulating cytokines such as IL-1β by various supplements with herbal ingredients is still widely researched, supported by this review. Periodontal tissue repair and decreased blood glucose levels demonstrate the therapeutic effect of IL-1β, indicating that modulation of this cytokine has potential as a target for treating the bidirectional relationship between periodontitis and type 2 diabetes mellitus (T2DM).

CONCLUSION

The inflammatory process is a pathway that confirms the relationship between periodontitis and the pathological conditions of T2DM.

Decreasing IL-1β expression is potentially a dual therapeutic target for treating both periodontitis and T2DM. Herbal therapies and supplements are capable of modulating the immune response, and their extensive pharmacological effects have the potential to lower IL-1β cytokine levels in the management of various diseases, including periodontitis and T2DM. More research is needed to explore IL-1β reduction using other potential herbal substances as therapeutic alternatives.

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