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REVIEW article

Immunomodulatory effects of curcumin on receptor activator of nuclear factor-kappa B ligand in periodontitis

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Abstract: Periodontitis is a chronic inflammatory disease of the tooth-supporting structures, often causing alveolar bone loss due to increased osteoclast activity mediated by receptor activator of nuclear factor-kappa B ligand. Curcumin is believed to have immunomodulatory effects and has been proposed as a natural therapeutic agent targeting receptor activators of nuclear factor-kappa B ligand expression. This study aims to evaluate and review the immunomodulatory effects of curcumin on receptor activators of nuclear factor-kappa B ligands in periodontitis. This systematic review followed the PRISMA 2020 guidelines. A search of published literature in PubMed, Scopus, ScienceDirect, and Google Scholar was employed. Risk of bias assessment was performed using three different tools, including QUIN for *in vitro* studies, SYRCLE's RoB for animal model studies, and Cochrane RoB 2 for clinical trials. All studies evaluating curcumin's effects on receptor activator of nuclear factor-kappa B ligand levels, both membrane receptor activator of nuclear factor-kappa B ligand and soluble receptor activator of nuclear factor-kappa B ligand, were considered for inclusion in this review. Of the 307 potentially eligible studies, four studies were ultimately retrieved. This study found that there is a significant decrease in receptor activator of nuclear factor-kappa B ligand levels after curcumin administration. The immunomodulatory effects of curcumin are believed to be through modulation of macrophage polarization and inhibition of the nuclear factor kappa-B signaling pathway, and possibly indirectly through inhibition of autophagy. Thus, curcumin shows promising potential as an adjunct agent for periodontitis through the mechanism of decreasing receptor activator of nuclear factor-kappa B ligand levels which then reduces alveolar bone loss. Large-scale clinical trials with rigorous methods are warranted to determine the optimal dosage, formulation, and long-term safety for clinical application in periodontal therapy targeting receptor activators of nuclear factor-kappa B ligand.

Introduction

Periodontitis (PD) is a chronic inflammatory condition resulting in the degradation of periodontal tissues and resorption of the alveolar bone [1]. Dysbiosis of periodontal microbes and dental plaque, followed by an

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immune response, are the main causes of PD [2]. Globally, PD is one of the most common diseases, as evidenced by the total number of severe PD cases of 1.1 billion in 2019 [3] and it is projected that 1.5 billion people will experience severe PD by 2050 [4], making PD a global public health concern. Furthermore, numerous papers showed that PD is associated with general health and with various chronic systemic diseases [5-15]. This is a strong reason for PD to be addressed comprehensively so that it does not cause new systemic problems. One of the severe impacts of untreated PD is alveolar bone loss (ABL), which will then result in tooth loss due to damaged supporting tissue. Tooth loss has a negative impact on unstable occlusion, temporomandibular disorders, and decreased quality of life due to pain and psychological factors [16, 17]. The mechanism of ABL due to PD is excessive osteoclast activity and bone resorption so bone formation by osteoblasts is disrupted [18]. Osteoclast differentiation, activation, and survival are regulated by receptor activators of nuclear factor-kappa B ligand (RANKL), its receptor RANK, and feedback receptor osteoprotegerin (OPG) [19-21]. Increased RANKL/OPG ratio that occurs in PD is associated with ABL [19]. At present, the most frequently performed and considered effective PD treatment is scaling and root planning (SRP) [21]. However, SRP does not directly target the molecular mechanisms that modulate alveolar bone resorption, including the RANKL/OPG pathway. Thus, in addition to SRP, adjuvant therapy that can inhibit osteoclastogenesis is needed to prevent further ABL. Several pharmacological agents, including bisphosphonates and denosumab, have been reported to inhibit osteoclast activity by modulating RANKL [22-24]. However, adverse effects such as osteonecrosis of the jaw exist from these agents [25, 26]. Thus, there is a need for safer therapeutic agents, based on natural compounds, which can modulate RANKL without the risk of long-term adverse effects.

Curcumin from turmeric (*Curcuma longa*) is a polyphenol that has many health effects through its antioxidant, anti-inflammatory, and immunomodulatory properties [27-32]. In PD, curcumin has been reported to be effective as an adjuvant therapy through its anti-inflammatory properties and through immune modulation [33]. In addition to curcumin being reported to be effective in inhibiting various proinflammatory cytokines in PD, including nuclear factor-kappa B (NF-κB) and tumor necrosis factor-α (TNF-α) involved in RANKL-induced osteoclastogenesis [31], it also has promising effects in reducing PD-induced ABL [34, 35]. More specifically, various preclinical evidence reported that curcumin has the potency as a natural RANKL inhibitor [36-39]. Thus, in addition to curcumin exhibiting a promising effect on inflammatory conditions in PD, it also has the potential as an adjuvant therapy to inhibit and treat PD-induced ABL through modulation of RANKL. Most previous studies discussing the effects of curcumin on RANKL expression were conducted in the context of osteoporosis and/or osteoarthritis, not PD. In addition, studies often focus on the anti-inflammatory effects of curcumin on PD without specifically evaluating the modulation of RANKL as a major target in alveolar bone resorption. To our knowledge, a systematic review exclusively analyzing how curcumin modulates RANKL in PD models or subjects has not been performed. Therefore, this study was conducted to analyze and summarize the evidence on the effects of curcumin on RANKL in PD. By understanding how curcumin works in suppressing RANKL, this study may help in the development of curcumin-based therapeutic strategies for PD.

Materials and methods

Research question: This systematic review study was conducted by the PRISMA 2020 guidelines [40]. The research question addressed in this study was “What is the immunomodulatory effect of curcumin on RANKL in PD?”. In addressing this focused question, the population, intervention, comparison, outcomes, and study (PICOS) model was used, as described in **Table 1**.

Search terms: Literature evaluating the effects of curcumin on RANKL related to ABL in PD was searched electronically in PubMed, Scopus, ScienceDirect, and Google Scholar, were selected in this search. We

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applied the following keyword combination: curcumin or diferuloylmethane or Curcuma or turmeric and ABL or PD or periodontal or periodontal disease or osteoclast or osteoclastogenesis or RANKL. The search process was carried out by two authors (FMR & WE) in October 2024.

Table 1: PICOs model

Element	Details
Population	Cell line, animal models, or individuals with PD
Intervention	Curcumin from turmeric
Comparison	Cell line, animal models, or individuals treated with standard periodontal treatments, placebo control, or untreated
Outcomes	RANKL levels
Study	Preclinical or clinical studies

Eligibility criteria: The inclusion criteria we set to determine included studies followed PICOS, which included: 1) preclinical animal or cell studies, or clinical trials with PD given curcumin intervention in any form; 2) studies that analyzed RANKL levels, either membrane RANKL (mRANKL) or soluble RANKL (sRANKL), or both; 3) articles written in English; and 4) full-text articles that have been peer-reviewed. Meanwhile, the exclusion criteria included: 1) studies that only evaluated the effect of curcumin on ABL without specifically referring to RANKL levels; 2) studies that were review articles, editorials, commentaries, and expert opinion; and 3) studies that were not published or were preprints. All papers published from inception to October 2024 were considered for inclusion.

Risk of bias assessment: Studies were further evaluated for quality using the quality assessment tool for in vitro studies (QUIN) for *in vitro* studies [41], the systematic review center for laboratory animal experimentation's risk of bias (SYRCLE's RoB) for *in vivo* studies [42], and the Cochrane RoB 2 for RCT [43]. In the QUIN tool, a score of 2 was given for the answer "adequately specified", 1 for "inadequately specified", and 0 for "not specified", with the final results assessed as low, medium, and high risk if the results were >70%, 50-70%, and <50%, respectively. Meanwhile, for the evaluation using SYRCLE's RoB, the judgment was "Yes" for low, "No" for high, and "Unclear" for unclear risk. Finally, Cochrane Rob 2 provided a judgment of "low risk of bias", "some concerns", or "high risk of bias". The risk of bias summaries was visualized using RevMan software v-5.4 to facilitate the reading of the results. Independently, this process was performed by two authors (FMR & ADN) and validated by one author (RA). During the evaluation process, in-depth discussions and careful conclusion-making were conducted to address any discrepancies.

Data extraction: Two authors (AN & ARH) read all included studies and independently extracted essential data using Microsoft Excel 2019 for Windows. The extracted data included reference, study design, subjects, curcumin (dose and mode), control, duration of treatment, and findings related to the effect of curcumin on RANKL levels. Finally, all data were analyzed qualitatively with the support of other relevant evidence.

Results

Study selection: 307 potentially eligible research were identified after 85 records were excluded due to duplicates. The initial screening resulted in 212 papers being excluded, the remaining 95 studies. The results of the screening of titles and abstracts obtained 39 articles after 56 reports were excluded due to irrelevance to our study topic. Furthermore, the remaining 39 studies underwent an eligibility assessment. At this stage, we excluded several studies for the following reasons: review articles, irrelevant aim, unavailable full text, incomplete data, and studies testing RANKL mRNA. Finally, four articles were retrieved in this review, as shown in **Figure 1**.

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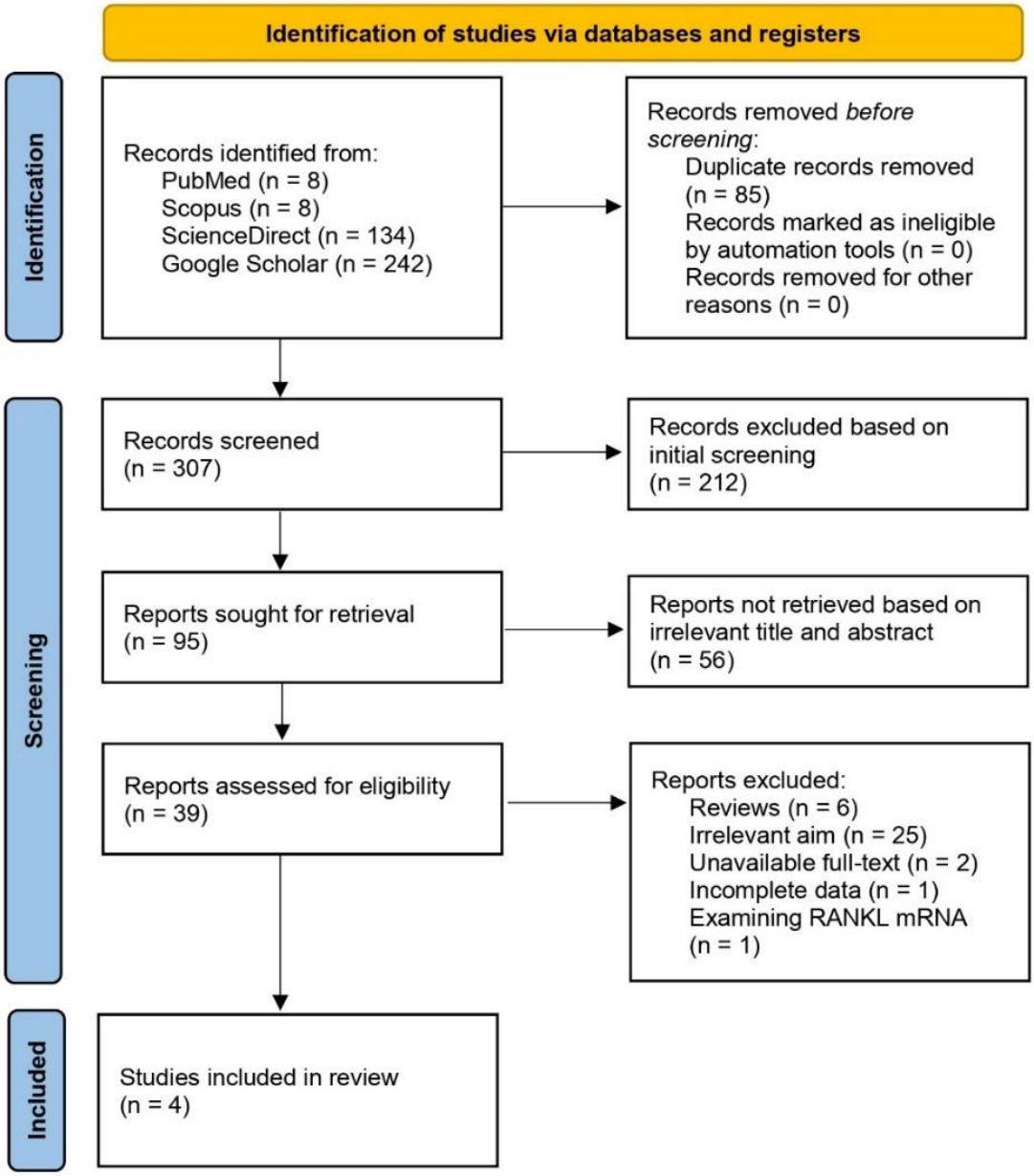
Characteristics of included studies: Four articles were finally included in this study, including one *in vitro* study [38], two *in vivo*/animal model studies [44, 45], and one randomized-controlled trial (RCT) [46]. All studies used natural curcumin, with dosage forms in the form of dissolved curcumin [38, 45], gel [46], and tablets [46]. The duration of curcumin administration in in vivo studies and RCT was 30 days [44, 45] and six weeks or around 42 days [46]. Three studies tested the RANKL level [44-46] and one study tested the sRANKL level [38]. The test was carried out using the ELISA [38, 44, 46] and immunohistochemistry methods [45]. **Table 2** summarizes all study characteristics and main findings.

Figure 1: PRISMA flowchart



Risk of bias assessment of included studies: In the evaluation of *in vitro* studies, the study by Xiao et al. [38] obtained a final score of 70.83%, indicating a low risk (>70%). In the *in vivo* study assessment, the blinding domain, both in performance bias and detection bias, was assessed as unclear to high bias. In addition, both studies were assessed as unclear for the other sources of bias domain because both studies did not explain other possible biases. Finally, for the RCT study, the results showed that the study by Bhavanam et al. [46] was assessed as having a low risk. The summary of the results can be seen in **Figure 2**.

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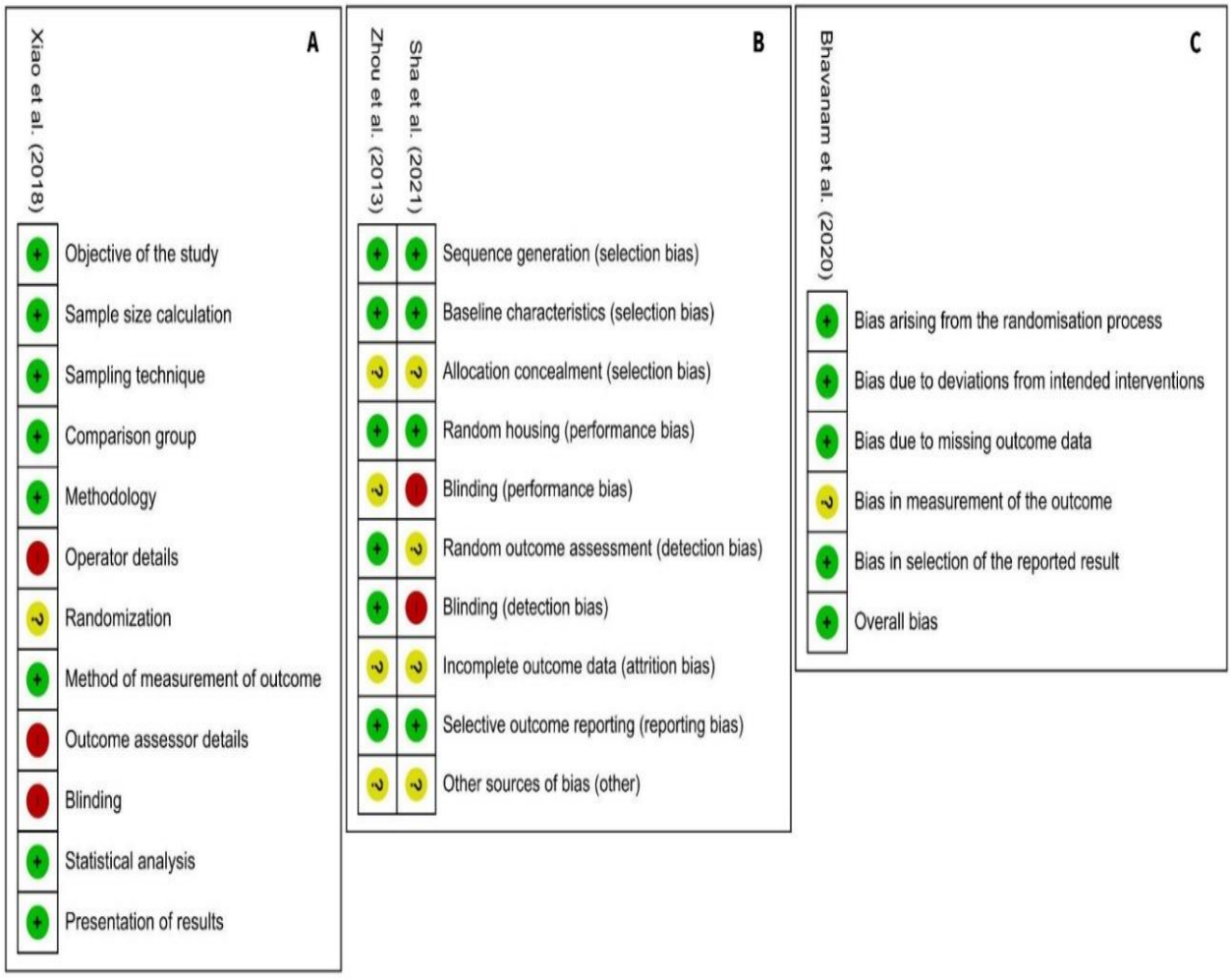
Table 2: Characteristics of included studies

Reference	Study Design	Subjects	Curcumin (dose - mode)	Control	Duration of study	Findings
[46]	RCT	60 patients	500 mg tablets twice a day	Placebo tablets	6 weeks	RANKL levels decreased significantly with curcumin administration (109.1±28 pg/mL) from baseline (254.07±54.5 pg/mL) compared to the decrease in the control group (236.01±47.14 pg/mL) from baseline (254.07±54.5 pg/mL).
[44]	*In vivo*	24 Wistar rats	12.5 µg/mL gel daily, local application	Chlorhexidine gel 0.2%	30 days	A significant difference was observed between RANKL levels in the curcumin group (320±29.09 pg/µL) and the experimental PD group (514.16±44.35 pg/µL). However, it was not significant when compared with the chlorhexidine control (343.33±21.55).
[38]	*In vitro*	LPS-induced rats' gingival fibroblasts	10 and 20 µM	Untreated	-	Curcumin significantly decreased the release of sRANKL compared to control (LPS-induced cells).
[45]	*In vivo*	30 Wistar rats	100 mg/kg daily, intra-gastric administration	I: saline II: vehicle	30 days	RANKL levels were lower significantly in the control receiving curcumin than those in the control group.

Figure 2: Summary of the risk of bias: *in vitro* study using the QUIN tool (**A**), *in vivo* studies using SYRCLE's RoB tool (**B**), and a clinical trial using Cochrane RoB 2 (**C**)



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Discussion

Our systematic review reviewed publications evaluating the effects of curcumin on both overall RANKL, mRANKL, and sRANKL in PD. It is found that curcumin has an immunomodulatory effect in regulating RANKL levels in subjects with PD. *In vitro* studies by Xiao et al. [38] on LPS-induced rat gingival fibroblasts with a curcumin dose of 10-20 µM showed that curcumin decreased the release of sRANKL. Meanwhile, a preclinical animal study by Sha et al. [44] with a curcumin gel dose of 12.5 µg/mL revealed that curcumin was more significant in suppressing RANKL levels. Additionally, in the same study, curcumin was found to be as effective as 0.2% chlorhexidine gel in modulating RANKL levels. This was also revealed in an animal study by Zhou et al. [45] using a curcumin dose of 100 mg/kg that a notable decrease in RANKL levels was observed. Furthermore, an RCT study by Bhavanam et al. [46] on sixty individuals with PD treated with 500 mg curcumin tablets for six weeks showed very promising effects, where the decrease in RANKL levels was considered significant compared to the control group. Thus, three preclinical studies and one RCT included in this study concluded that curcumin is effective in modulating RANKL levels in cells, animal models, and individuals with PD, and even proved to be as effective as the usually used conventional drug, chlorhexidine.

As a pivotal cytokine, RANKL regulates the differentiation, activation, and survival of osteoclasts, being a major regulator in the process of osteoclastogenesis. In pathological conditions such as PD, RANKL expression increases which then causes an imbalance in the RANKL/OPG ratio, promoting excessive osteoclast activity and accelerating alveolar bone destruction [18, 47]. RANKL consists of two forms, namely mRANKL and sRANKL. However, sRANKL released from the surface of osteogenic cells also has biological activity in stimulating osteoclastogenesis [48]. In addition, sRANKL found in gingival crevicular fluid in PD showed that sRANKL levels are associated with the severity of PD [49]. Therefore, our study reviewed studies that evaluated both overall RANKL, mRANKL, and sRANKL. It has been reported that curcumin exerts immunomodulatory effects on RANKL-induced osteoclastogenesis through macrophage polarization from the M1-M2 phenotype and suppression of NF-κB pathway activation [39]. A transition from M1-M2 macrophage polarization entails altering their phenotype and function from pro-inflammatory to anti-inflammatory roles. M2-type macrophages then express Toll-like receptor, transforming growth factor-β (TGF-β), interleukin-10, and interferon-γ (IFN-γ) which function as anti-inflammatories, producing healing effects on periodontal tissues [50]. Furthermore, inhibition of RANKL by curcumin through suppression of NF-κB can be explained, where the decrease of RANKL causes the RANKL-RANK interaction to be prevented. This inhibits the NF-κB, mitogen-activated protein kinase (MAPK), and phosphatidylinositol 3-kinase (PI3K)/AKT signaling, resulting in a nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1) not being induced. This results in inhibition of osteoclast precursor differentiation [51, 52]. Overall, through modulation of macrophage polarization and inhibition of NF-κB signaling, curcumin contributes to decreased RANKL levels, which in turn inhibits osteoclast formation and activity, and helps prevent excessive PD-induced alveolar bone destruction. Another possible mechanism is through inhibition of autophagy. Recent evidence suggests that curcumin directly suppresses autophagy in RANKL-promoted osteoclast precursors and leads to enhanced anti-osteoclastogenic effects of curcumin [36, 53]. Suppression of autophagy results in decreased expression of tartrate-resistant acid phosphatase (TRAP), NFATc1, and cathepsin K in osteoclasts [54]. Thus, this decrease has an impact on decreasing osteoclast differentiation and function, which in turn results in reduced bone resorption. In other words, curcumin intervenes in the process by which RANKL would normally induce osteoclast precursors to undergo autophagy and differentiate into active osteoclasts. By inhibiting this autophagy, curcumin can reduce excessive osteoclast formation and osteoclastogenesis in alveolar bone. The mechanism of autophagy inhibition by curcumin does not reduce RANKL itself but disrupts the signaling pathways and cellular processes triggered by RANKL, thereby inhibiting osteoclast differentiation and function.

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The results of our study provide opportunities for curcumin use as an adjuvant therapy, especially in preventing and deceleration ABL in PD. Considering RANKL's pivotal role in bone destruction through stimulation of osteoclastogenesis, the ability of curcumin to decrease RANKL expression shows significant potential for application in periodontal therapy protocols. However, these implications emphasize the need for clinical trials such as RCT to further evaluate the optimal dose, dosage form, and safety of long-term use, so that curcumin can be widely integrated into modern dental practice, especially in molecular-based and immunomodulatory therapeutic approaches. Our study has several strengths, one of which is the specific and underexplored focus of this study, namely the evaluation of the effect of curcumin in modulating RANKL levels in PD. This study also integrates findings from several experimental models, both from cell and animal studies, to RCT, thus providing a holistic perspective on the clinical potential of curcumin as an immunomodulatory agent. However, this study acknowledges several limitations, including the limited number of studies retrieved, which limits the ability to draw strong conclusions. Variations in dose, dosage form, and duration of curcumin administration also add to the heterogeneity of studies, making it difficult to conduct meta-analyses. Moreover, as the majority of existing evidence is derived from preclinical studies, further studies with stronger clinical designs, such as double-blinded RCTs, are essential to establish the effectiveness and safety profile of curcumin in managing PD.

Conclusion: This study concludes that curcumin shows strong potential as an immunomodulatory agent in inhibiting RANKL expression in PD. The effectiveness of curcumin has been consistently confirmed in various models, including in vitro cells, experimental animals, and individuals with PD. Thus, curcumin holds considerable promise as a natural compound-based adjuvant therapy in PD, particularly in preventing RANKL-induced ABL. However, more large-scale RCT with rigorous methods is essential to ensure the optimal dose, best dosage form, and safety profile in long-term clinical applications.

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