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PLANT-DERIVED PHYTOCHEMICALS AS OSTEOCLASTOGENIC MODULATORS: MECHANISTIC PATHWAYS AND CLINICAL IMPLICATIONS IN ORTHODONTICS AND OSTEONECROSIS OF JAWS

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ABSTRACT
Osteoclasts are crucial elements of bone remodelling and orthodontic tooth movement, yet their therapeutic stimulation remains little explored by pharmaceuticals and plant-based phytochemicals. This review amalgamates the current mechanistic evidence on plant-derived phytochemicals that promote osteoclastogenesis through convergent molecular pathways. Four key signalling clusters were identified—hypoxia–VEGF, MAPK/NFATc1, cytokine-mediated, and vascular modulatory axes—linking phytochemicals such as 6-Shogaol, Salvia miltiorrhiza, Asperosaponin VI, Akebiasaponin D to controlled osteoclast activation. This integration also shows that these compounds can enhance bone resorption in a selective manner which is required for accelerated orthodontic tooth movement and treatment of medication-related osteonecrosis of the jaw. By combining these findings, this review introduces a novel framework of "phytochemical-induced osteoclastogenic modulation," highlighting therapeutic possibilities and safety considerations for targeted bone remodeling.

KEYWORDS: Osteoclasts, orthodontic tooth movement (OTM), bisphosphonate related osteonecrosis of the jaw (BRONJ), receptor activator of nuclear factor-kappa B ligand (RANKL), macrophage colony-stimulating factor (M-CSF)

1.INTRODUCTION
Bone is a dynamic tissue that remodels constantly to maintain structural integrity and functionality. This remodelling process is mediated by two processes: osteoblasts, derived from mesenchymal stem cells, which form bone, and osteoclasts, derived from monocyte-macrophage lineage hematopoietic cells, which resorb bone. These interactions occur in a cyclical manner within the Basic Multicellular Unit (BMU).[1]
Although enhancing osteoclast activity may initially appear counterintuitive because of its well-established relation with pathological bone resorption seen in conditions such as osteoporosis [2] and periodontitis[3],recent findings suggests that stimulation of osteoclastogenesis in a controlled manner can be beneficial in specific physiological and therapeutic contexts.[4] One such context is in accelerated orthodontic tooth movement (OTM) where osteoclast activation is essential for timely bone resorption on the compression side, thereby facilitating effective tooth displacement.[5] Likewise, in bisphosphonate-related osteonecrosis of the jaw (BRONJ), excessive suppression of osteoclasts disrupts normal bone turnover and delays healing. [4] Stimulation of osteoclasts in such cases can help restore balance and promote bone regeneration.
Systematic reviews suggests that in spite of promising results for various bio functional molecules in stimulation osteoclasts in animal models, their translation to clinical use remains limited for several reasons such as limitations in methodology, heterogeneity of the study, lack of definitive evidence, challenges in administrative method, lack of detailed pharmacological knowledge, such as their pharmacokinetics and properties. [6,7] Alternatively, herbal plant extracts present a promising alternative due to their rich bioactivities, low toxicity, cost-effectiveness, and ease of extraction. With their antioxidant, anti-inflammatory, and antimicrobial properties, phytochemicals may offer a sustainable therapeutic strategy.[8] This review explores the potential of such compounds in osteoclastogenesis. With the above perspective, this review summarizes the phytochemical compounds which have been used for osteoclastogenesis.

2. The Biology of Osteoclastogenesis
To appreciate on how phytochemical compounds can influence osteoclastogenesis, a thorough understanding of the basics of osteoclast differentiation is required.

2.1 Osteoclast differentiation
Osteoclasts develop from bone marrow monocyte/macrophage lineage cells regulated by two crucial cytokines. The binding of the macrophage colony-stimulating factor (M-CSF) to cell surface receptor c-Fms provides signals

required for proliferation and survival of osteoclast precursor cells, whereas the interaction of receptor activator of nuclear factor-κB ligand (RANKL) with receptor activator of nuclear factor-κB (RANK) triggers signals necessary for the differentiation of osteoclasts, their resorptive activity, and the survival of developed osteoclasts. [9,10] (Figure 1)

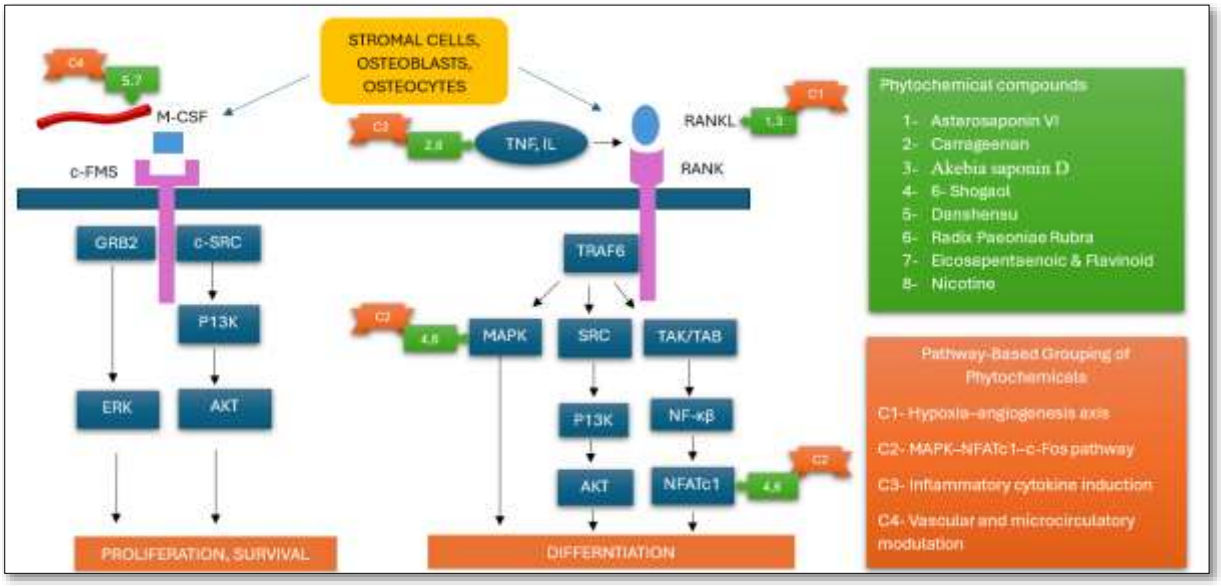

Figure 1: Osteoclastogenesis action of phytochemical compounds (PCC) and their mechanism of action on signalling pathways of osteoclast differentiation. PCC 1, 3 act through C1- Hypoxia-Angiogenesis Axis by enhancing the RANKL expression by elevating HIF-1α AND VEGF. PCC 4, 6 act through MAPK–NFATc1–c-Fos pathway by increased expression of TRAF, cathepsin K and osteoclast specific genes. PCC 2, 8 act through C3- Inflammatory cytokine induction by production of TNF-1 α, IL-8. PCC 5, 7 act through C4- Vascular and microcirculatory modulation by improving local circulation, in turn increasing osteoclast precursors and M-CSF signalling.

2.2 Conditions requiring stimulation of osteoclasts

Osteoclasts, beyond their role in bone resorption, are integral to physiological bone remodelling, fracture healing, and the maintenance of the bone marrow microenvironment. In this context, carefully regulated osteoclastogenesis may offer novel approaches to promote skeletal health and repair. Thus, a balanced and context-specific understanding of osteoclast function is essential to harness their potential while avoiding deleterious effects.

1. Accelerating orthodontic tooth movement

Orthodontic treatment duration poses challenges, often due to slow tooth movement (0.8–1.2 mm/month). [7,11] A proven method to accelerate this is the Regional Acceleratory Phenomenon (RAP), a tissue response to noxious stimuli that enhances healing by increasing the activity of BMUs in alveolar bone remodelling. [12] (Figure 2) Long, H. et al.,2013 have assessed and determined that of all the methods, corticotomy is both effective and safe for enhancing OTM speed. [13] Corticotomy effectively triggers RAP, boosting OTM speed, though it is invasive. As a result, research is shifting toward less invasive alternatives—such as local application of hormones, ligands, growth factors, and herbal compounds—to safely induce RAP and reduce overall treatment time while preserving oral health. [14] (Figure 2A)

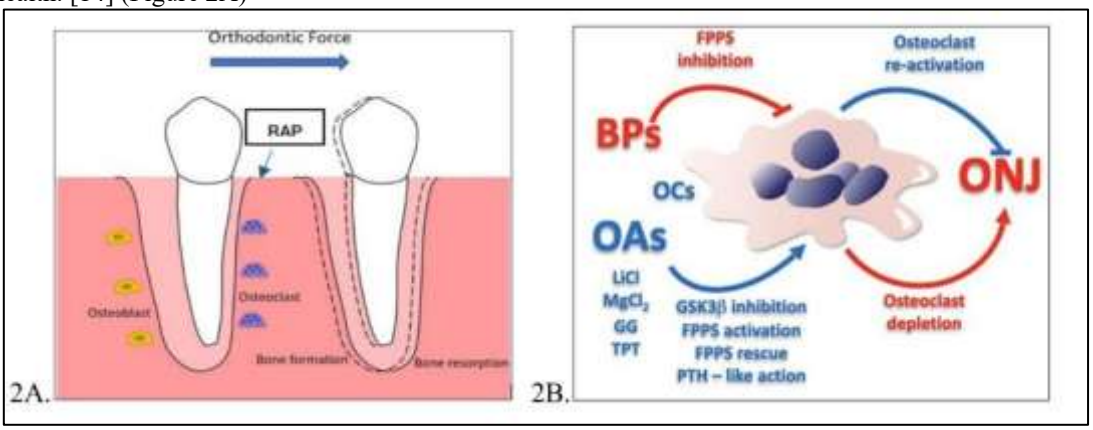

Figure 2A. Regional Acceleratory Phenomenon (RAP) response facilitates orthodontic toot movement by increasing bone resorption on the pressure side, marked by the presence of osteoclast, and enhancing bone formation on the tension side, indicated by the presence of osteoblasts. This coordinated bone remodelling accelerates the repositioning of the tooth.

Figure 2B. Schematic representation of the potential effect that might be determined by Osteoclastogenic Agents in the prevention and treatment of Osteonecrosis of the Jaw. BPs, Bisphosphonates; OAs, Osteoclastogenic Agents; ONJ, Osteonecrosis of the Jaw; OCs, Osteoclasts; LiCl, Lithium Chloride; MgCl2, Magnesium Chloride; GG, Geranyl– Geraniol; TPT, Teriparatide; GSK3b, Glycogen synthase kinase-3 beta; FPPS, Farnesyl Pyrophosphate Synthase; PTH, Parathyroid hormone. Arrow and hammer-headlines respectively mean stimulation and inhibition.

2. Bisphosphonate-related osteonecrosis of the jaw (BRONJ)

Bisphosphonates inhibit farnesyl pyrophosphate synthase (FPPS) in the mevalonate pathway, disrupting osteoclast function and leads to osteoclast apoptosis. As an adverse effect, this mechanism suppresses bone turnover and promotes accumulation of necrotic bone. Additionally, it also inhibits angiogenesis, reducing vascular supply to the jawbone and impairing tissue repair. These effects compromise the jaw's ability to respond to trauma or infection, resulting in persistent non-healing lesions and exposed bone—hallmark features of ONJ.[15] Thus, treatments that locally counteract osteoclast inhibition without affecting systemic benefits are of interest. Literature suggests three potential strategies: inhibition of Glycogen Synthase Kinase-3 beta (GSK3β), administration of geranyl-geraniol (GG), and local application of magnesium (Mg). Topical use of GG and Mg may mitigate bisphosphonate-induced local effects in the jaw while preserving systemic efficacy, offering a promising approach to prevent or treat BRONJ through targeted modulation of osteoclast differentiation. [4] (Figure 2B)

3. OTM in bisphosphonate therapy patients

A systematic review highlighted that systemic bisphosphonate use during orthodontic treatment reduces the rate and extent of tooth movement, thereby prolonging treatment duration. [16] This effect is therapeutically applied to enhance anchorage and prevent relapse. The reduction in tooth movement is due to decreased osteoclast activity and structural alterations, including disrupted cytoplasmic polarity and cell margins. These changes impair the localization and expression of bone-resorbing proteins like H(+)-ATPase and cathepsin K. Experimental studies suggest that bisphosphonates delay bone turnover, leading to extended orthodontic timelines. [17] To counter this, localized reactivation of osteoclasts around moving teeth may serve as a promising strategy to restore bone remodelling.

4. Positive contributor to the bone microenvironment and skeletal health.

The start of bone remodelling at a specific bone location is crucial for renewing an old or damaged bone matrix. Failure to trigger bone remodelling may cause the accumulation of microdamage and hypermineralization, resulting in decreased bone quality and a higher risk of fractures. The commencement of osteoclastogenesis primarily relies on the interaction between osteoclast precursor cells and the osteoblast lineage cells. Evidence underscores the primary regulatory function of osteocytes during the early phase of bone remodelling. [18] Being the most numerous cells in bone, osteocytes influence osteoclasts, which are primed to resorb bone first via a system of osteocyte canaliculi. Osteocytes can sense microfractures and microcracks in bone and contact osteoblasts on the bone surface. Nakashima et al., 2011 [19] showed that osteocytes express significantly more RANKL and are more effective in facilitating osteoclastogenesis compared to osteoblasts and bone marrow stromal cells. Thus, for initiating the bone remodelling, retaining the crosstalk between osteoclasts and osteocytes is beneficial for skeletal health.

3. Information Sources and Search Strategy:

A comprehensive and systematic search was conducted across multiple electronic databases to identify relevant studies. The following databases were searched: PubMed, Scopus, Web of Science, Additional sources included Google Scholar and reference snowballing from relevant articles and reviews to ensure comprehensive literature coverage. No date restrictions were applied to allow for a comprehensive inclusion of all relevant studies regardless of their publication year.

The search strategy was developed using a combination of Medical Subject Headings (MeSH) and free-text keywords. Keywords and Boolean operators were used in combinations such as:

1. ("osteoclastogenesis" OR "osteoclast differentiation" OR "osteoclast proliferation") AND ("phytochemicals" OR "herbal compounds" OR "plant extracts")
2. ("bone resorption" OR "resorption rate" OR "accelerate orthodontic tooth movement" or "enhance orthodontic tooth movement) AND ("in vitro" OR "animal studies" OR "clinical trials" OR "experimental study").

Table 1 presents an overview of plant-derived phytochemicals reported to stimulate osteoclast differentiation and activity, along with their associated molecular mechanisms of action.

TABLE 1: Phytochemicals from plants stimulating osteoclasts and their mechanism of action

Sl	Phytochemical compounds	Plant source	Type of study	Methodology	Key findings	Mechanism of action/ Hypothesis	Conclusion	Author	Year & place of study
1.	Asperosaponin VI (ASA VI)	Dipsacus asper Wall	In vivo - rats	Effect of local injection of asperosaponin VI (ASA VI) on the orthodontic tooth movement in rats.	10 mg/lg of ASA VI was injected locally, submucoperiosteally, showed a significant increase in OTM in comparison with the control group on day 7 (1.44-fold) and day 14 (1.54-fold).	ASA VI promote angiogenesis and accelerate wound healing by upregulating the HIF-1a/VEGF pathway. This pathway promotes the activity of RANKL promoter and enhanced osteoclastogenesis in the compression side of orthodontic tooth movement.	ASA VI increases bone resorption on the pressure side shown by an increased expression of RANKL while also aiding in bone deposition on the tension side, shown by an increase in bone density and trabecular spacing	Ma D et al. [20]	2020, China
2.	Carrageenan (CN)	Chondrus crispus species of seaweed - Rhodophyceae	In vivo - rats	Effect of 40 mg of CN on OTM speed during 21 days of Incisor retraction in rat(test group) vs control with saline	Twenty-one days after saline and CN injection, OTMs were 0.7 and 1.1 mm, respectively, Twenty-one days after saline and carrageenan injection, mean osteoclast counts were, respectively, 4.87 and 7.143 per field	Expression of cyclooxygenase (COX)-2, prostaglandin E2 (PGE2) and its receptors, numerous cytokines, suchas tissuenecrosis factor (TNF)-a, IL-1, IL-6	Local injection of CN can induce inflammation after 6 hours. It can increase approximately 1.6-fold (58%) the speed of OTM, and increase the osteoclast count 1.5-fold (40%) after 21 days of space closure.	Kavoli S et al. [21]	2107, Iran
3.	Akebia	Rhizome of	In viv	Effect of local injection of ASD	The distance between the first	ASD solution at the dose of 10	Increases bone	Cui	2018, China

	saponin D (ASD)	the plant Dipsacus asper Wall.	o - rats	with different concentrations on the rate of orthodontic tooth movement in rats and compared with PGE2	and second molar was successively increased compared with the control group. On H & E staining, under microscope, the number of osteoclasts was increased on the tension side, reaching a peak on day 21st, and decreased later.	mg/kg can accelerate orthodontic tooth movement efficiently like PGE2 solution	resorption on the pressure side shown by an increased expression of RANKL	et al. [22]	
4.	6-Shagoal	Ginger	In vivo - rats	Actions of 6-shogaol on osteoclast differentiation and function on osteoclastogenesis-induced mouse bone marrow macrophages in vitro and on rats. control (CON) (orthodontics only), IPinj (orthodontics + Intraperitoneal injection of 100 mg/kg 6-shogaol), and Localinj (orthodontics + local Intragingival injection of 25 mg/kg 6-shogaol) (n=6 per group).	Average OTM of the CON group, IPinj group and Localinj group was 0.58, 0.68 and 1.1mm respectively. Expression level of osteoclast marker genes was significantly enhanced with increasing doses of 6-shogaol. TRAP cells were more on locinj site than that in the control group and IPinj.	6-shogaol enhances RANKL-induced osteoclast differentiation by promoting JNK activation and NFATc1 expression. & increased expression of sclerostin (bone formation inhibitory factor secreted by the PDL cells.	6-shogoal accelerates tooth movement by inducing osteopenia by a mechanism similar to surgically induced bone injury	Zhu et al. [23]	2021, China
1.5.	Danshensu	Salvia miltiorrhiza	In vivo - rats	Effects of aqueous extract of S.miltiorrhiza (SM) on the promotion of OTM and healing of periodontal ligament in 150 rats divided as control group (saline inj), SM group (0.75 g/kg/day of crude drugs) and Danshensu (phytochemical compound in	The expressions of RANKL and OPG in the treatment groups were enhanced compared with control group. Increase rate of OPG expression was slower than that of RANKL. But RANKL decreased conspicuously after no orthodontic pressure was applied, especially in the treatment groups. ESM groups promoted osteoclasts	SM can improve local microcirculation of periodontal ligament, leading to the re-opening of blood vessels with structural disorder and atresia in the periodontal ligament of orthodontic tooth, which might make it faster and more capable of recruiting	ESM or pure Danshensu promoted the movement of orthodontic tooth and shortened the course of plateau period during orthodontic movement, which might be	Xiao et al. [24]	2018, china

				SM) (250, 500, 750 mg/kg/day of body weight).	proliferation in the first 20 days.	phagocytic cells to remove necrotic tissue and shorten the time of the plateau period to accelerate movement of orthodontic tooth. It also increases the expression of TGF-β1, which is thought to play a role in accelerating tooth movement	related to its role on promoting microcircu lation		
2. 6.	Radix Paeoniae Rubra	Paeonia lactiflora Pall. or Paeonia veitchii Lynch	In vitro	A dose-dependent design was used to demonstrate RPR's action on osteoclastogenesis. Effects of RPR on stimulation of osteoclast differentiation in RAW264.7 cells and peripheral blood mononuclear cells was studied.	•RPR was shown to induce monocyte/macrophage lineage precursor cells to differentiate into osteoclast-like cells in both murine RAW264.7 cells and human PBMCs after 7 and 14 days •Western blotting showed that RPR treatment induced phosphorylation of JNK, ERK, and p38 in RAW 264.7 cells. •Real-time RT-PCR showed higher levels of c-Fos and NFATc1, calcitonin receptor, OSCAR, TRAP. RPR were similar to RANKL.	Kinase inhibitors were employed to reveal NF-κB, p38 MAP kinase, ERK, and JNK as signaling pathways of RPR's osteoclastogenic impact. Stimulation of MAP kinases caused expression of NFATc1 and c-fos, helping clarify that RPR function is similar to RANKL in osteoclast differentiation.	RPR stimulates osteoclast differentiation through a signaling pathway of MAP kinases,	Tzeng et al. [25]	2018, china
3. 7.	Eicosapentaenoic (EPA) & Flavinoid (mg/100g)	Stichopus hermani(SH),	In vivo - rats	Investigation of the active ingredients of nanopowder Stichopus hermanii promoting bone resorption in tension area orthodontic tooth Movement on 32 rats divdided as control (K-), OTM only (K+), OTM+3% SH (P1), OTM +3.5 % SH(P2)	•OTM achieved after 7 days In the K(+) group, the mean was 0.45 mm, while the mean of the P1 group was 0.496 mm, and the mean of P2 group was 0.498 mm •The statistical results of one-way Anova showed that there was a significant difference of TRAP-6 expression as a osteoclast marker in the tension area between K(-), K(+)	Epa can increase trafm 6 AP-1 is a cell biosensor that can change extracellular signaling for cell function. When there is no AP-1 expressed in osteoblast, this can induce osteoclastogenesis through TRAP-6. Flavonoid is one active ingredient of	Nanopowder Stichopus hermanii 3.5% has an active ingredient that could increase osteoclast activity to resorb periodontal ligament and alveolar bone in tension areas of orthodonti	Prameswari, Brahmanta [26]	2017, indonesia

					groups and the P1 and P2 groups, with P2 group having the highest. (13.17 cell/ field of view)	Stichopus hermanii that can inhibit AP-1 and induce osteoclastogenesis.	c tooth movement		
8.	Nicotine	Nicotiana tabacum	In vivo - rats	Assessment of the effect of nicotine on orthodontic tooth movement using the amount of OTM, b) histological changes in bone cells, c) bone cell distributions using immunohistochemical staining on 4 groups of 32 rats. group A: 0.37 mg/kg, group B: 0.57 mg/kg, and group C: 0.93 mg/kg. group D) - 0.5 mL saline inj	•Group C had highest OTM (0.82 ± 0.063 mm), Group B (= 0.52±0.043 mm), group A (0.50±0.057 mm) and group D (0.23 ± 0.043 mm) •Increased osteoclast cell distribution and activity in the nicotine groups on both the non-operated and operated sides with a complex remodelling pattern. Osteoblastic activity was diminished in the tension site of the experimental group when compared with the control group in the current study. •Experimental group given the highest nicotine dose (0.93 mg/kg) showed decreased bone density around the mesiobuccal and distobuccal roots of the upper first left molar and a complicated remodelling pattern.	Nicotine accelerated orthodontic tooth movement with unbalanced bone resorption and apposition patterns around the moving teeth.	Nicotine stimulates osteoclast differentiation and resorption of calcium phosphate, which is the principal component of bone. It stimulates the resorption process that occurs during osteoid turnover by increasing the production of matrix metalloproteinases. and nicotine increasNumber of TRAP-positive multinucleated osteoclasts significantly increased with nicotine.	Bakathir et al. [27]	2016, Egypt

4.DISCUSSION

Osteoclastogenesis is a complex multi-step process where myeloid cells/macrophages are first committed as osteoclasts precursors and differentiated near the bone surface. Although it is covered by M-CSF and RANKL, it can be further modulated by a variety of signalling pathways and microenvironmental cues such as hypoxia, angiogenesis, inflammation, and oxidative stress. In recent years, plant-derived phytochemicals as modulators of osteoclast differentiation and activity have been researched particularly in the context of OTM. Instead of examining the findings of each phytochemical in isolation, this discussion integrates the mechanistic insights of all of them to reveal underlying patterns and correlations that position them within the broader biological

framework of osteoclast regulation. Figure 1 (numbers in green boxes) represent the action of the phytochemicals from plants in the osteoclastic differentiation.

A. Pathway-Based Grouping of Phytochemicals

The analysed phytochemicals converge on a limited set of master signalling pathways known to regulate osteoclastogenesis, despite being from different plant sources. This clustering provides a more integrative way to understand their action.

The first cluster (C1 in figure 1) involves the hypoxia–angiogenesis axis, where compounds such as Asperosaponin VI[20] and Akebiasaponin D[22] primarily act through the upregulation of hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF). During OTM, localized hypoxia is created at the compression sites of the periodontal ligament. By increasing HIF-1α expression, these compounds boost the hypoxia response, leading to greater VEGF release. Sequentially, VEGF enhances vascular permeability, recruitment of osteoclast precursors, and RANKL expression, thereby osteoclast differentiation is accelerated. Both substances are triterpenoid saponins produced from Dipsacus asper Wall, showing that plants from this genus may contain similar structural chemicals that systematically alter the hypoxia-VEGF-RANKL cascade.

The MAPK–NFATc1–c-Fos pathway, which symbolizes the intracellular signaling cascade downstream of RANKL-RANK binding, is the focus of a second cluster (C2 in figure 1). Phytochemical compounds such as 6-Shogaol (from ginger) [23] and Radix Paeoniae Rubra(RPR) [25] directly springs on action on the mitogen-activated protein kinases ERK, JNK, and p38, inducing the transcription factors c-Fos and NFATc1. These regulators of transcription are viewed as the master switches of osteoclastogenesis, controlling the expression of TRAP, cathepsin K, and other osteoclast-specific genes. These compounds are strong osteoclastogenic stimulators because this pathway acts more directly than the hypoxia-driven cluster and results in a strong induction of osteoclast-specific gene expression.

The third cluster involves inflammatory cytokine induction, (C3 in figure 1) represented most clearly by Carrageenan and Nicotine. Carrageenan is well known in experimental pharmacology for its ability to cause inflammation. In the context of orthodontics, carrageenan promotes the formation of osteoclasts by stimulating macrophages and lymphocytes, which in turn release TNF-α and IL-8. [21] Nicotine is a naturally occurring alkaloid that inhibits osteoblast activity while increasing TRAP-positive multinucleated cells and matrix metalloproteinases to promote osteoclastogenesis. [27] Therefore, both substances indirectly promote osteoclastogenesis by shifting the equilibrium in favor of an environment that promotes inflammation and bone resorption.

The final cluster centres on substances like Salvia miltiorrhiza and Stichopus hermanii that act through vascular and microcirculatory modulation (C4 in figure 1). Salvia recruits osteoclast precursors and aids in their differentiation by increasing local circulation and vessel remodelling within the periodontal ligament. [24] Similar to this, Stichopus, which is high in collagen, glycosaminoglycans, and fatty acids like EPA and DHA, improves the tissue microenvironment and promotes osteoclast fusion and M-CSF signaling.[26] By combining osteoclast activation with ongoing angiogenesis and repair, these substances seem to have a more systemic supportive effect on bone remodeling.

It is clear from rearranging these phytochemicals into mechanistic clusters that, in spite of their varied origins, they all converge on four main pathways: vascular/microcirculatory support, inflammation-mediated cytokine signaling, MAPK/NFATc1 signaling, and hypoxia–VEGF signaling. A deeper comprehension of the ways in which compounds derived from plants affect osteoclast biology is provided by this cohesive clustering.

B. Clinical Correlation: Therapeutic vs. Pathological Effects

Differentiating phytochemicals based on their risk or possible clinical use is a second crucial viewpoint. Compounds that locally and precisely speed up osteoclastogenesis are highly sought after in orthodontics to minimize side effects, shorten treatment times, and ease patient discomfort. Compounds like Asperosaponin VI [20], Akebiasaponin D[21], 6-Shogaol [23], and Salvia miltiorrhiza[24] are promising in this regard because they act locally, encourage osteoclast activity and subsequent remodelling, and have a short-lived effect after application. Additionally, salvia appears to promote osteoclast apoptosis following force release, indicating a self-limiting profile that might stop excessive bone loss.

Nicotine[27] and carrageenan[21] , on the other hand, have a more problematic profile. Both cause widespread inflammatory activation, which speeds up osteoclastogenesis, but at the expense of collateral tissue damage. Nicotine suppresses osteoblast function, lowers bone density, and jeopardizes periodontal health in addition to stimulating osteoclast activity. These results highlight the dangers of using inflammatory mediators in clinical settings, even though they are helpful in emphasizing their role in osteoclastogenesis. Rather than being a potential treatment, carrageenan is still mainly used as an experimental tool. [21]

Certain compounds seem to fall somewhere in the middle. Stichopus hermanii promotes osteoclastogenesis while also supplying bioactive substances like collagen and glucosaminoglycans that aid in angiogenesis and tissue repair. [26] The mechanism by which RPR strongly induces osteoclast differentiation is like that of RANKL,

which raises concerns about whether it could be improved as a treatment or if its effects might be too potent for controlled use. These examples imply that to safely utilize such compounds, careful dose optimization and delivery strategies are necessary.

C. Direct vs. Indirect Modulation of Osteoclastogenesis

Differentiating between phytochemicals that directly activate osteoclastogenic transcriptional programs and those that act indirectly through environmental modulation is another method of correlating these substances. RPR, 6-Shogaol, and nicotine are examples of compounds that directly act by upregulating the expression of NFATc1, c-Fos, or TRAP, thus "turning on" the genetic program of osteoclast differentiation. A permissive microenvironment for osteoclastogenesis is created by substances such as Asperosaponin VI, Akebiasaponin D, Salvia, and Stichopus, which act indirectly by changing local vascularity, hypoxia, or growth factor availability. Because it causes inflammation and indirectly increases osteoclast activity through cytokines, carrageenan is a hybrid case.
There are significant ramifications to this distinction. If not properly targeted, direct activators increase the risk of uncontrolled bone resorption even though they may produce a strong and quick osteoclastogenic response. Although they may act more slowly, indirect modulators enable more physiologically aligned, context-dependent remodeling. In orthodontics, where controlled acceleration of tooth movement is desired without pathological bone loss, this balance is crucial.

Implications for Dentistry and Beyond

These findings have dental significance that goes beyond orthodontic tooth movement. Controlled stimulation of osteoclast activity may help resolve necrotic bone and improve turnover in the setting of medication-related osteonecrosis of the jaw (MRONJ). On the other hand, knowing which phytochemicals significantly stimulate osteoclastogenesis could aid in determining the variables that worsen bone loss in periodontal disease. This dual significance emphasizes the necessity of placing osteoclast-modulating phytochemicals in the context of both possible treatments and environmental exposures that could exacerbate disease. Future investigations should concentrate on the following areas:

- Detailed mechanistic analyses to map particular molecular targets of phytochemical compounds.
- Safety profiling and dose optimization in clinical trials and animal models.
- Exploration of synergistic effects between plant compounds and conventional osteoclast modulators.
- The creation of potent phytochemicals that are standardized.
- Investigation of the potential synergistic effects of conventional osteoclast modulators and plant compounds.

5. CONCLUSION

Overall, this review indicates that phytochemicals derived from plants affect osteoclastogenesis via a small number of convergent pathways, mainly involving vascular modulation, MAPK/NFATc1 activation, hypoxia–VEGF signaling, and the induction of inflammatory cytokines. It is feasible to make significant connections between various studies and forecast the possible risks or clinical uses of the phytochemicals by grouping them based on these mechanisms. While substances like nicotine and carrageenan draw attention to the risks of unchecked inflammatory activation, compounds like Asperosaponin VI, Akebiasaponin D, and Salvia miltiorrhiza seem most promising for the controlled, localized acceleration of orthodontic tooth movement. Our knowledge of the possible safety profiles of direct and indirect modulators is further enhanced by this distinction. Future studies ought to look into combinatory effects, optimize localized release delivery systems, and carefully assess long-term outcomes to harness the benefits of these natural compounds in dentistry.

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