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Resolvins: The resolving mediators divulged

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Abstract
Resolution pharmacology has gained paramount importance in the field of medicine. Resolvins are specialized pro-resolving lipid mediators (SPMs). They are natural bioactive agents involved in the resolution of inflammation. They function when uncontrolled inflammatory processes are developed. Lipoxins, resolvins, protectins, and maresins are families of mediators that are under SPM. In recent years it has become evident that periodontitis is a multifactorial inflammatory disease initiated by oral microbial biofilm. This review focuses on understanding the role of resolvins, endogenous lipid mediators in overall oral health, and periodontal inflammation that modulate cellular fate and resolution.

Keywords: Resolvin, inflammation, lipid, pro-resolving, oral health, periodontal

Introduction
Our body's healing mechanism involves inflammation which is considered a vital process**.** An imbalance in the cardinal signs of inflammation leads to a diseased state. More recent studies have shown that advanced molecular mechanisms govern the fate of the inflammatory process. Acute inflammation is considered a physiological response that helps the host to defend and maintain homeostasis [1].

It was a breakthrough when Metchnikoff found that, acute inflammation resolves when neutrophils are ingested by tissue macrophages [2].

The first leukocyte responders to accumulate in the inflamed site are polymorphonuclear neutrophils followed by mononuclear cells, monocytes, and macrophages. They enter the inflammatory site and contribute to clearing the cellular debris, phagocytizing the apoptotic polymorpho nuclear neutrophils thereby perpetuating inflammation [3]. However, a failure to remove toxic metabolites of neutrophils and apoptotic inflammatory cells leads to the chronicity of the lesion, resulting in chronic periodontal diseases [4].

Until now, inflammation was focused in terms of induction. But, attention to attenuation was never put in the spotlight; how is inflammation turned off? What are the possible mechanisms involved? Inflammation was always thought to be a passive process until the discovery by Charles N. Serhan in the late 20th century regarding inflammation which unveiled the molecules that mediate the resolution of inflammation [5]. Specialized immunoresolvents include a group of endogenous molecules, namely resolvins, lipoxins, protectins, and maresins, which actively drive the cessation of inflammation [6]. In this context, the role of specialized pro-resolving mediators (SPMs), especially resolvins in periodontal disease holds the limelight of this review.

Specialized Pro resolving Lipid mediators
Specialized Pro resolving Lipid mediators are the derivatives of essential fatty acids which can serve as futuristic pharmacological aids for resolving chronic inflammations. They include

- RvE1-RvE3 which are EPA-derived E-series Rvs
- RvD1-RvD6 belongs to the DHA-derived D-series.
- LXA4 and LXB4 are Arachidonic acid-derived lipoxins
- Protectins, neuroprotectins (PD1/NPD1 and PDX),
- Maresins (MaR1 and MaR2)
- Docosapentaenoic acid (DPA)-derived 13-series Rvs (RvT1-RvT4)

- Aspirin-triggered epimeric forms (AT-RvD1-AT-RvD6), are SPMs derived from PUFAs, such as ω-3 PUFAs and ω-6 PUFAs, present in dietary sources [7].
- Prostaglandins, leukotrienes, and thromboxanes also derive from arachidonic acid, an ω-6 PUFAs

A plethora of animal model studies demonstrates anti-inflammatory along with pro-resolving properties of resolvins [8].

What are resolvins?

A major quantum leap in the field of medicine has been the discovery and introduction of the role of resolvins in the resolution of inflammation.

Resolvins are derivatives that are considered to be critically involved in the phase of inflammation resolution. They are enzymatically generated from eicosapentaenoic acid EPA, and DHA, which are enriched in fish oils. They are further divided into the EPA-derived E-series resolvins, and DHA-derived D-series resolvins [9].

Resolvins-metabolism

In humans, peripheral blood, cerebrospinal fluid, sputum, placenta, urine, synovial fluids, lymphnodes, and spleen produce SPMs enzymatically[10]. However dietary uptake and liver sources help to maintain DHA and EPA levels in the brain [11].

The LOX /Lipoxygenase and COX-2 (Aspirin-triggered cyclooxygenase) pathways synthesize resolvins majorly.

D-series Resolvins

RvD1 and RvD2 are synthesized from 15-lipoxygenase (15-LOX) and 5- lipoxygenase (5-LOX) catalysis [12]. Cells like neutrophils, macrophages, leukocytes, and endothelial cells provide an apt environment for the synthesis of resolving. Aspirin-acetylated COX-2 pathway has also been known to synthesize RvDs. Formation of AT-RvDs includes epoxidation, lipid oxidation, and hydrolysis [13]. However, the pathway of the RvD3-RvD6 synthetic pathway is not been reported to date.

E-series Resolvins

RvE1 and RvE2 are formed from EPA through COX2 and 5-LOX pathway. Endothelial cells interact with leukocytes hence promoting their synthesis. The cytochrome P450-driven pathway which is an aspirin-independent mechanism of EPA also attribute to the synthesis of E series Resolvins. The synthesis of RvE1 and RvE2 is enhanced during inflammation in response to increased 5-LOX concentrations. On the contrary, RvE3 is synthesized through the 12/15-LOX pathway in the eosinophils [14].

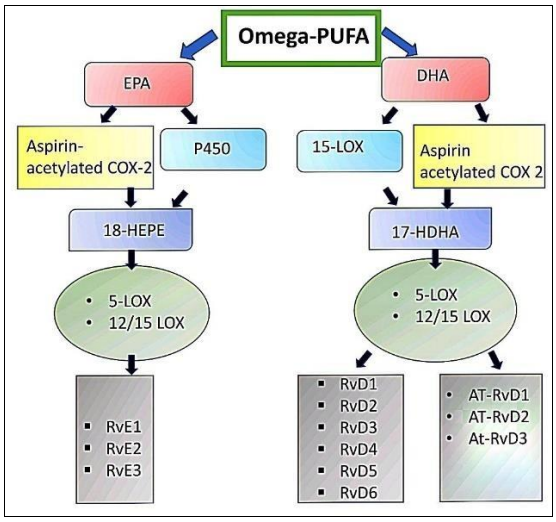

Fig 1: Show the Omega-PUFA different of EPA and DHA

Oxidation, hyperoxydation, and epoxidation processes affect stability of resolvins reducing their biological half-life *in vivo*.

Mechanism of Rvs in the Resolution of Inflammation

1. Mitogen-activated protein kinase (MAPKs) signaling pathway

In eukaryotes, MAPKs are serine and threonine protein kinases which are involved in signal transduction. MAPK signaling pathways which are identified till now have been stimulus-dependent. They are

1. (ERK) Extracellular-signal-regulated kinase,
2. Stress-activated protein kinase /The c-Jun N-terminal kinase (JNK),
3. p38MAPK pathways [15].

Resolvins modulate the resolution of inflammation following MAPK pathway. Lung tissues in a murine model, when treated with RvD1 has demonstrated reduced production of proinflammatory cytokines through the activation of ERK1/2, p38MAPK, and JNK. RvD1 produced through signaling pathways of p38MAPK and JNK, inhibited the proinflammatory production in Interleukin (IL)-1 Beta induced osteoarthritis [16].

2. NF-κB(Nuclear factor Kappa B) Signaling Pathwa

NF-κB is a protein transcription factor. It regulates the expression of monocyte chemoattractant protein 1, IL-6, IL-8, tumor necrosis factor-α (TNF-α), E-selectin and adhesion molecules. These factors contribute to cellular resistance by providing a connection between pathogenic signals and cellular danger signals.

Anti-inflammatory action of Resolvin was achieved by inhibiting the NF-κB signaling pathway at specific sites [17].A study by Wang et al. (2011) on mice lung tissue showed inhibition of I-KB activation as well as production of IL-6 and TNF – α by pretreatment with RvD1. A decrease in adhesion molecule COX-2 and inducible nitric oxide synthase (iNOS) in lung tissues was also noted. In animal models treated with

AT-RvD1 and RvD2 predominantly decreased NF-κB mRNA expression and protein activation. On the contrary dextran sulfate sodium treatment proved to be ineffective in reducing the levels. In a study done on HEL293 cells by Ishida et al. (2010) concluded that RvE1 can inhibit nuclear translocation of NF-κB induced by TNF-α- in a Chem R23-dependent manner.

The occurrence and development of autoimmune diseases, tumors, and inflammation are regulated by Phosphatidylinositol-3-Kinase Signaling Pathway. They regulate cell proliferation, transcription, differentiation, and translation. Studies have shown that Resolvins have the potential to prevent the proliferation of fibroblasts in murine models as they can reduce the activity of ERK pathways. RvE1 enhances the resolution of inflammation by binding to Chem R23, thereby initiating PI3K signaling [18]. Similarly, LY294002, a PI3K selective inhibitor abrogates a cardioprotective effect of RvD1, showing that the protective mechanism of RvD1 is associated with the activation of the PI3K/Akt signaling pathway [19].

Other Signaling Pathways

Micro RNA (miRNA) are small single-stranded, non-coding RNA molecules containing 21 to 23 nucleotides. They play a major role in cell differentiation as well as cell apoptosis.

1. Resolvins modulate microRNAs (miRNAs) and markers of apoptosis-like lactic dehydrogenase (LDH) and B-cell lymphoma-2 (Bcl2) [20].
2. Studies have shown that RvD1 decreases miR-219, miR-21, and miR-146b expression and reduction of miR-146b and miR-21 expression is by RvD2 [21].
3. Rvs act in the resolution of inflammation by regulating the expression of miRNAs [22].
4. RvD1 has shown an anti-inflammatory effect by blocking apoptotic markers such as caspases and decreasing LDH release [23].
5. By activating the Rac/eNOS pathway, RvD2 enhances the binding of Rac to GTP via the GPR18 receptor [24].
6. Antioxidant enzymes, such as heme oxygenase-1, superoxide dismutase and nuclear factor-E2-related factor expression can additionally be modulated by Resolvins [25].

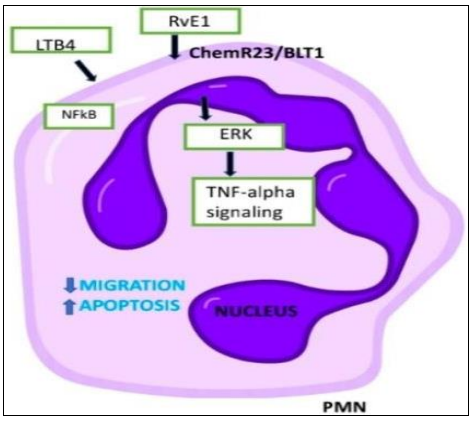

Fig 2

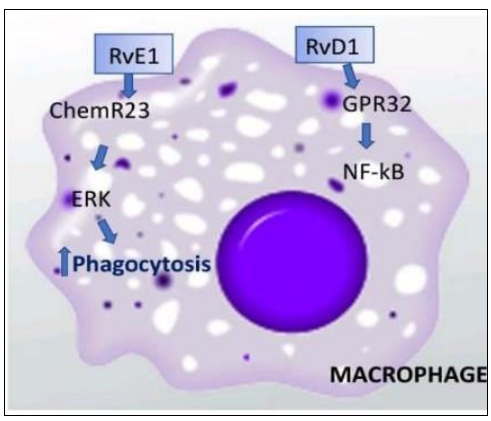

Fig 3

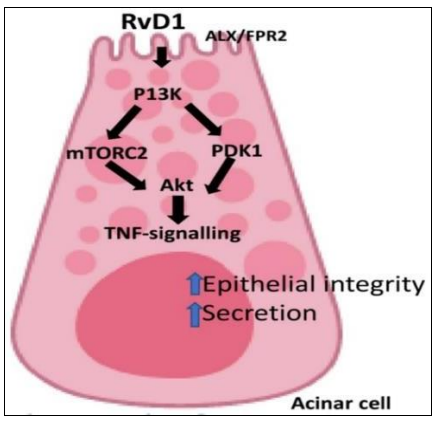

Fig 4

Fig 2-4: Pathways in PMN, Macrophage and Acinar cell structures.

Role of Resolvins

1. Coagulation

Blood clotting is an inevitable mechanism involved in one's body to help with injured blood vessels and to stop bleeding. It encompasses processes of blood vessel constriction, platelet aggregation, and wound stabilization [26].

- The selective blocking of thromboxane-stimulated platelet aggregation and adenosine diphosphate (ADP) with RvE1 has been noted in human-rich plasma which was concentration-dependent [27].
- RvE1 has also shown to possess regulatory actions by demonstrating the reduction of ADP-stimulated P-selectin surface mobilization [28].
- RvE2 has been shown to maintain homeostasis by down-regulating the expression of leukocytes in human whole blood [29].

2. Pain

Pain management is a crucial aspect in terms of medical as well as dental healthcare.

1. Resolvins have been shown to inhibit NF-κB and COX-2 in the peripheral nervous system illustrating an anti-hyperalgesic effect.
2. In a study done on murine models, aspirin-triggered resolvin D1 (AT-RvD1) and its precursor, 17(R)-hydroxy- 4Z, 7Z, 10Z, 13Z, 15E, 17R, 19Z-docosahexaenoic acid (17(R) HDoHE), has shown the possible anti-hyperalgesic effects [30].
3. Inhibition of TNF-α synthesis release and downstream signaling is also a possible mechanism shown by RvE1 to reduce neuropathic pain.
4. Studies have proven that they can enhance the phagocytic activity of macrophages and thereby reducing peripheral inflammation [31].

3. Immune System

A strong network of biological mechanisms that protect the body from outside invaders is imperative in every aspect of health. When there is an acute inflammation the white blood cells, especially PMNs will produce oxygen radicals and produces proteolytic and hydrolytic enzymes. Even though these metabolites can kill bacteria, they need to be repeatedly removed from the inflammation site, failing to would lead to chronicity [32]. Anti-inflammatory cytokines such as IL-10 also regulate the suppression of inflammation [33].

The favorable role of ω-3 PUFAs in the body's immune response is well recognized and acknowledged in the inflammatory process. A study has shown that RvD1 regulates human macrophage responses to lipopolysaccharides, thereby enhancing antibacterial action [34].

- Whereas, RvE1 modulates inhibition of dendritic cell migration, leukocyte infiltration, and IL-12 production [35].

- A study reported on allergic airway responses demonstrated a RvE1-initiated resolution program.
- Similarly, a crucial action for IL-23 and IL-6, which promote the survival and differentiation of IL-17-producing T helper cells, in maintaining inflammation was also reported with Resolvin [36].
- A murine study has shown that resolvin E2 (RvE2) is endogenously produced in both the initiation and resolution phases during self-limited murine peritonitis [37].
- Study showed that 8,18- dihydroxyeicosapentaenoic acid and 11,18-diHEPE which are metabolites of EPA have shown anti-inflammatory properties [38]. It was reported to be biosynthesized by eosinophils via the 12/15-lipoxygenase pathway.
- In a murine study on the peritoneum, results demonstrate that specific fatty acids like RvD1 and RvD5 are regulated during E Coli. infections and that they are anti-phlogistic, and thereby enhancing lower antibiotic requirements for bacterial clearance [39].

Hence resolvins block the production of proinflammatory mediators and regulate leukocyte trafficking to inflammatory sites as well as clearance of neutrophils from mucosal surfaces. In particular, resolvins act to protect healthy tissue during an immuno- inflammatory response to infection, injury, or other environmental challenges and then act to resolve inflammation and promote healing after the insult has passed.

Periodontitis

Periodontitis is a chronic inflammatory condition affecting the tooth-supporting structures that can initiate gingival infection and eventually lead to inflammation and infection of alveolar bone and tooth loss [40]. This osteoclastic bone resorption involves different factors, including prostaglandins, which mediates its number and action [41]. RvE1 inhibits osteoclast growth and bone resorption in that context by interfering with its differentiation. These bone-sparing actions of RvE1 are in addition to inflammation resolution [42].

- RvE1 was effective in the treatment of induced periodontitis when applied locally in rabbits [43].
- Resolvin series have demonstrated an impact on PMN infiltration thereby inhibiting oxygen radical production [44].

Hence, these studies have paved a novel treatment pathway in the treatment of periodontitis.

Resolvins and Salivary Gland Function

Sjögren's Syndrome (SS) autoimmune disease with xerostomia (dry mouth) and Keratoconjunctivitis sicca (dry eyes) which challenged the present treatment modalities has benefitted with resolvin.

In salivary epithelium, RvD1 receptor activation has shown to have therapeutic value in salivary gland dysfunction associated with SS by resolving inflammation and promoting tissue repair [45]. They have also prevented TNF- α mediated salivary epithelium formation in Par -C10 cells. RvD1 amplified cell polarity and migration of Par-C10 cells via PI3K/Akt signaling.

The studies endorse that RvD1 can be effective in tissue repair and regeneration of damaged salivary glands in addition to the resolution of inflammation by activation of ALXR/FPR2 [46].

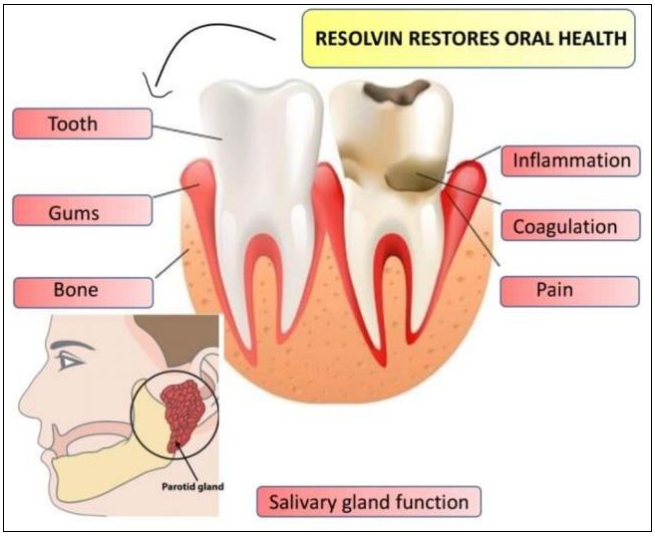

Fig 5: Resolvin restores oral health

Conclusion

Resolvins are a novel class of lipid mediators, which not only harbour anti-inflammatory and pro-resolution properties but also enhance and restore tissue integrity. They would be a therapeutic tool in an ideal clinical setting with its analgesic, anti-inflammatory, host modulatory and reparative properties. Hence, more emphasis must be given to utilizing resolvin in the treatment of periodontitis, thereby utilizing the resolution of inflammation in combatting the disease.

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Author's Contribution

Not available

Conflict of Interest

Not available

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